ANTIMICROBIAL WOUND DRESSINGS: MECHANISMS AND FUNCTION

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Introduction

Antimicrobial dressings provide a number of important benefits to both the patient and the caregiver. Antimicrobial dressings act as a barrier to the transmission of microbial pathogens, and enhance both the health of the patient and the safety of the public. This type of dressing can be an important element in a strategy to minimize hospital acquired infections (HAIs).

The most obvious benefit of an antimicrobial dressing is as a barrier to the growth and spread of pathogens. The barrier function prevents infection of the patient from external bacteria, and also protects caregivers and fellow patients from bacteria residing in the covered wound. Additionally, a dressing that draws fluid from a colonized wound pulls in bacteria. In a conventional dressing these bacteria would grow and multiply in the dressing, and could be shed back into the wound to increase the bacterial population (see **Figure 2**), as well as spread to caregivers, other patients, and onto surfaces.

Antimicrobial technologies

Silver based. Silver is used as an antimicrobial in many different forms, from silver nitrate to nanocrystalline silver. The fundamental mechanism by which silver kills bacteria is by disruption of metabolic processes. This requires internalization of discrete particulates: thus all forms of silver function by leaching. Silver dressings have proven very effective, particularly in addressing chronic wounds and are therefore very popular. Silver ions have a degree of toxicity to mammalian cells, and may discolor skin. There is laboratory proven incidence of silver resistant bacteria (although several silver resistant genes have been indentified, this is not a major clinical factor for dressings with at-use concentrations of silver agents).

Iodine. Iodine has long been used as an antiseptic, and acts on bacterial cells through an oxidative degradation of the cell components and by interruption of protein function. This oxidative mechanism is broadly effective against a wide range of pathogens. Since the agent functions on multiple cell components, it is difficult for bacteria to develop resistance to iodine. The use of iodine in wound dressings is mainly as a water soluble, polymerically stabilized povidone-iodine. Long term exposure to iodine has been reported to induce skin irritation and staining.

Antibiotics. Consumer over the counter products including “Band-Aids” (J&J trademark) are available with antibiotics, though the use of antibiotics for wound dressings in clinical settings is rarer due to the widely publicized incidence of antibiotic resistant bacterial strains. The most widely consumer utilized antibiotic is triclosan, which is understood to target a gene (Fab1) involved in the synthesis of fatty acids; at high concentrations triclosan can act on multiple cytoplasmic and membrane targets. Triclosan is utilized in sutures, as well as in household products including antiperspirants, soaps, and toothpaste. There is concern about the formation of dioxins as triclosan degradation products.

Cationic biocides. Biguanides and quaternary agents. In general these function by coordinating to the cell membrane, and compromising the cell wall. The specific activity depends on structure, and size: larger polymeric agents act solely on the cell wall, while smaller monoquats can enter the cell. Cationic biocides with lower charge densities can be susceptible to inactivation by proteinaceous bodily fluids. Instances of bacterial resistance have been documented for monoquats (small molecules with a single quaternary charge center), but not for polyquats (larger polymeric structures with many quaternary charge centers).

Designing a wound dressing

The design of the NIMBUS® dressing was conceived with the goals of maximizing antimicrobial efficacy, while at the same time minimizing the chances of permitting bacterial resistance to evolve. Adaptive resistance is generated when bacteria are exposed to sublethal doses of biocidal agents, so we built a bound microbicide technology using a long-chain polymeric quaternary agent that uses a non-leaching mode of activity. The high charge density of the polymeric agent ensures fast and durable antimicrobial activity, which is unimpeded by the presence of protein-rich bodily fluids (blood, serum, wound exudates). The bound agent acts on the cell membrane, thus disabling known bacterial mutation strategies to generate resistance.

This technology was reviewed by FDA and cleared as a deNovo device (novel device with no clear predicate), and is being commercialized as **Derma Sciences’ Bioguard™ product line.** This technology is a platform capable of integration into further products.

Tables 1 and 2 at right show the results of efficacy testing: both for antimicrobial efficacy against specific bacteria, and for durability to repeated challenge.

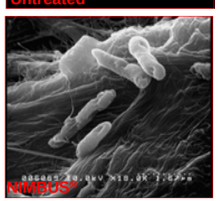

Figure 1 (left). Scanning Electron microscope images of *E. coli* on untreated gauze wound dressing (top) and on NIMBUS® treated wound dressing (bottom). NIMBUS® materials destabilize the cell wall structures and induce cellular collapse, as shown in the high resolution SEM images at left. *E. coli* bacteria that grew in contact with control substrate has intact membranes and full rod shape (top image). In contrast, after 1 h exposure to the NIMBUS® treated surface the individual *E. coli* bacteria show clear changes in membrane appearance and general morphology. Some cells show indentations and even small holes on the sides with exuding intracellular content.

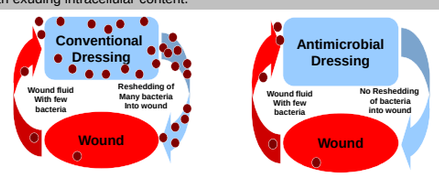

Figure 2 (left). Reshedding of bacteria into a wound from a conventional dressing (left) compared to an antimicrobial dressing (right). Wound fluid absorbed by a non–antimicrobial dressing serves as nutrient to grow bacteria shed by the wound, which can in turn recolonize the wound. This scenario is interdicted by the use of an antimicrobial dressing.

Antimicrobial Resistance

In addition to resistances to antibiotics (MRSA, VRE), bacterial resistance to silver has also been documented, particularly in the UK. Both antibiotics and silver attack metabolic processes in microbes and corrupt steps in the replication process after they enter through the cell wall. Various microbes have found ways to resist these processes, either through small changes in metabolic steps, or through an effluent pump mechanism, in which the bacteria can expel small antimicrobial molecules before they are able to be effective. An additional concern is that bacteria can communicate genetic information to each other through plasmid sequences, and impart their acquired resistance to other bacteria.

NIMBUS® materials employ polymeric quaternary ammonium chemistry; the very large polymers physically damage the cell membrane from external to the cell. **Figures 1** illustrate this process, showing bacteria whose cell wall structures have collapsed after destabilization induced through contact with NIMBUS® treated surfaces (bottom image shows holes in cell walls). All known resistance mechanisms to other antimicrobials (including silver, monoquats and antibiotics) are based on bacterial cells developing the ability to expel or inactivate internalized agents. NIMBUS® materials are not internalized due to the very large size of the antimicrobial molecules (high molecular weight polyquat), and because these molecules are permanently bound to the substrate material.

Bactericidal Efficacy Testing

Table 1

Organism	% killed	*ATCC#*
The most common wound-associated bacteria		
Staphylococcus aureus	>99.9999%	12600, 6538
Staphylococcus epidermidis	>99.9999%	12228
Enterococci spp	>99.9999%	19433
Escherichia coli	>99.9999%	15597, 8739
Pseudomonas aeruginosa	>99.9999%	51447, 15442, 9027
Enterobacter spp	>99.9999%	13048
Proteus spp	>99.9999%	13115
Klebsiella pneumoniae	>99.9999%	13833
Streptococci	>99.9999%	10096
Candida albicans	>99.9995%	
Additional common bacterial species associated with burn wounds		
Serratia marcescens	>99.9999%	13880
Additional common bacterial species associated with [body] odor		
Corynebacterium xerosis	>99.9999%	7711
Corynebacterium diptheriae	>99.9999%	43145
Micrococcus luteus	>99.9999%	21102
Proteus vulgaris	>99.9999%	13115

**CDC, 1996, common bacterial species associated with wound infections

Table 2 (below) shows long term efficacy of antimicrobial activity, as measured in 10 % fetal bovine serum (fbs.)

Sample	Staph. aureus (cfu/ml)	E. coli. (cfu/ml)
18 hour control	3.8 x10^6	1.2 x10^6
18 hour QMT sample	< 3 (6 log kill)	<3 (6 log kill)
3 day control	4.3x10^6	6.0 x10^6
3 day QMT sample	<3 (6 log kill)	<3 (6 log kill)
7 day control	6.5 x10^6	3.7 x10^6
7 day QMT sample	<3 (6 log kill)	4.4 x 10^2 ~4 log kill

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