ANTIMICROBIAL ADVANCED WOUND CARE DRESSING

Roy Carr[1], Bernd Liesenfeld[1], Gregory Schultz[1,2], Christopher Batich[1,2], David Moore[1], Jillian Vella[1], William Toreki[1], Gerald Olderman[1,] [1]Quick-Med Technologies, [2]University of Florida, [*]corresponding author*

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Summary

QuickMed Technologies (QMT) has developed a patented process (NIMBUS™) that permanently attaches a quaternary ammonium-based polymeric microbicidal agent onto a range of physical substrates. The process has been shown to provide effective protection against pathogenic bacteria (including *Staphylococcus aureus* and *epidermidis, Pseudomonas aeruginosa, MRSA, VRE*), viruses and fungi. NIMBUS™ dressings have been prepared on a range of substrates that include cellulosics (cotton, rayon) as well as more advanced wound dressing substrates such as foams, hydrocolloid and hydrogel components, and superabsorbents.

The NIMBUS process offers an effective alternative to silver based dressings at less than 10% of the cost. The NIMBUS human and environmental safety profile is also superior to silver and other competitors. NIMBUS dressings can be used throughout the wound healing cycle.

Current commercially available antimicrobial dressings have clearly demonstrated improved healing on chronic wounds, translating into improved patient outcomes. High cost, and the possibility of patients developing resistance to leached agents such as silver or antibiotics, has made prophylactic use of these materials potentially problematic. NIMBUS technology addresses these problems and was recently featured in TIME magazine (**Vol 167**, issue #12, 2006, p57), in an article that profiled Quick-Med scientist Greg Schultz as part of a series on technology innovators pioneering societally relevant scientific advances.

Infection and Inflammation in Wounds

Wound Bed preparation. The modern paradigm for the optimal treatment for wounds is summarized neatly by the concepts of wound bed preparation: the elimination of necrotic tissue and fibrinous exudate, controlling infection, establishing moisture balance, and optimizing the epidermal margin.[1] Control of infection is a critical parameter in this process, and can be achieved with the help of antimicrobial/antibacterial wound dressings.

Antimicrobial Wound Dressings as a barrier. A primary function of antimicrobial dressings is to provide a barrier between the wound (an easy point of entry for opportunistic pathogens), and the environment. This barrier functions both ways: i) protecting the wound from environmentally present pathogens and ii) preventing the spread of bacteria exuding from colonized wounds by suppressing them in the dressing, the discharge of which might otherwise spread through patient contact with caregivers, other patients, linens, etc. The emergence of resistant bacteria (i.e. MRSA, VRE…) and increasing awareness of the dangers associated with nosocomial infections highlight the usefulness of antimicrobial dressings for patients, caregivers, and health facilities as a whole. See images of **Figure 3**.

The suppression of infection and inflammation helps wounds heal faster. The bacterial colonization of a wound initiates a cascade of events that lead to a reduced rate of healing. As bacterial load grows, the inflammatory response is stimulated, which increases protease levels, and in turn drives down the rate at which extracellular matrix (ECM) is formed, and suppresses growth factors, all of which leads to decreased healing.[2] NIMBUS™ materials have been shown in laboratory tests not only to have bacteriocidal efficacy, but also to bind proteases, thus providing two methods by which the wound healing rate can be improved. Clinical evidence shows that silver based antimicrobial dressings demonstrate significantly improved rates of healing in chronic wounds by suppressing the bacterial challenge to the wound.

The role for antimicrobial wound dressings as prophylaxis and protection. Wounds in at-risk patients can progress from initial acute wounds with low levels of bacteria to critically colonized or infected wounds. This risk is exacerbated by conventional dressings that do not suppress bacterial growth in the dressing: bacteria shed from the wound can grow in the rich medium provided by wound fluid absorbed into common dressings (gauze, foams, alginates etc.) The bacteria growing in the "reservoir" within these simple dressings can shed back into the wound and promote progression (**Figure 1**) to critically colonized levels of bacteria. Wound healing is delayed not only through the indirect retardation of healing from inflammation induced protease elevations at the wound, but also through direct production of proteases, as has been characterized from the presence of *pseudomonas aeruginosa* (one of the most prevalent wound pathogens.) This sequence of events illustrates the difficulties faced within the chronic wound environment, and supports clinically observed successes associated with the treatment of chronic wounds with antimicrobial dressings.

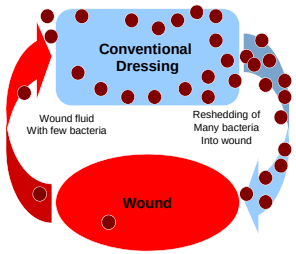


Figure 1. Reshedding of bacteria into a wound from a conventional dressing. Wound fluid absorbed by a non–antimicrobial dressing serves as nutrient to grow bacteria shed by the wound. The bacteria grown in the dressing can shed back into the wound to provide reinoculation.

Antimicrobial Resistance

Resistant organisms are a growing concern in the modern health care environment. Resistant strains of particular concern are the antibiotic resistant strains MRSA, VRSA and VRE. In addition to resistances to antibiotics, bacterial resistance to silver has also been documented, particularly in the UK. Both antibiotics and silver attack metabolic processes in microbes and corrupt replication after they enter through the cell wall.[3] Various microbes have found ways to resist these processes (and ways to pass this acquired resistance on to other microbes through plasmid sequences.) Quaternary ammonium compounds ('quats' or polyquats in the case of polymeric structures) have a fundamentally different mechanism of antimicrobial activity. Quats chemically destabilize the cell wall structures, inducing cellular collapse, as illustrated in **figures 2 a and b**. Since the chemistry of the cell wall is relatively immutable, the generation of resistance to this mechanism is extremely unlikely, making NIMBUS materials a safe alternative.

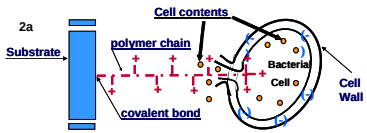
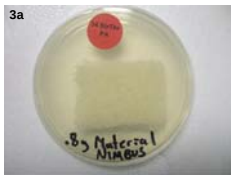


Figure 2: a and b. Mechanism of microbicidal activity of quaternary polymer. The image at left depicts the compromise of a bacterial cell wall by the NIMBUS polymer. The charged polymer chains compromise microbial cell walls, and induce cell lysis, as depicted in the before and after frames of E. coli bacteria that have had their cell walls compromised in the manner depicted, as can be seen from their appearance which resembles empty bags, or burst balloons.

Normal bacterial membranes are stabilized by Ca^{2+} ions binding anionic charged phospholipids. NIMBUS quat-polymer rapidly displaces Ca^{2+} leading to loss of fluidity and eventual phase separation of different lipids. Domains in the membrane then undergo a transition to more smaller micelles leading to membrane disruption. Ref: Antimicrobial Techniques for Medical Nonwovens - A Case Study by C White & J Olderman



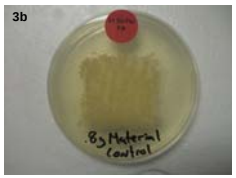


Figure 3: a and b. Strikethrough test demonstrating microbial barrier function of NIMBUS dressing. 0.8 g of NIMBUS gauze were inoculated with 10^6 cfu/ml inoculum (supplemented with 10 % fbs), and checked for growth after 1 and 2 days. Panel A shows no growth on the NIMBUS treated dressing, while the untreated control dressing demonstrates strong growth. The images depict testing with PA: other organisms provided the same results.

Bacteriocidal Efficacy Testing

Organism	% wound infection**	% killed	*ATCC#*
The most common wound-associated bacteria			
Staphylococcus aureus	20%	>99.9999%	12600, 6538
Staphylococcus epidermidis	14%	>99.9999%	12228
Enterococci spp	12%	>99.9999%	19433
Escherichia coli	8%	>99.9999%	15597, 8739
Pseudomonas aeruginosa	8%	>99.9999%	51447, 15442, 9027
Enterobacter spp	7%	>99.9999%	13048
Proteus spp	3%	>99.9999%	13115
Klebsiella pneumoniae	3%	>99.9999%	13833
Streptococci	3%	>99.9999%	10096
Candida albicans	3%	>99.9995%	
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
Additional common bacterial species associated with food contamination			
Listeria monocytogenes		>99.9999%	13932
Salmonella choleraesuis		>99.9999%	10708
Additional common bacterial species associated with burn wounds			
Serratia marcescens		>99.9999%	13880

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

NIMBUS Testing Conclusions

The NIMBUS materials detailed have undergone extensive testing for safety, efficacy, durability and production compatibility. Results are presented based on testing by AATCC method 100-1999 unless otherwise noted. The results demonstrate that NIMBUS materials have broad microbicidal efficacy, are long lasting, and can stand up to the specific challenge of resistant strains of organisms. These tests conclusively show that NIMBUS materials make a safe and effective antimicrobial dressing.

Percentage of bacteria killed within in the time indicated.

Time	Log Reduction of species, with ATCC numbers				
	SA(6538)	EC(15597)	PA(15442)	MRSA(BAA-44)	VRE(700221)
1 min	3.76	4.43	3.64	3.87	2.29
10 min	4.21	4.29	3.95	4.22	3.32
1 hr	4.83	5.23	5.31	5.89*	3.28
4 hrs	6.23*	5.72	6.40*	5.89*	5.63

•Denotes full kill; each measurement has an individual control thus inducing some variability in the numbers based on natural differences in the growth rates.
•Testing as per ASTM D-2315, using 10 % FBS as transfer medium.

NIMBUS Embodiments

Materials substrates:
•Traditional wound dressings: Rayon, Cotton, Gauze
•Advanced wound dressings. Polyurethane foam, hydrocolloid components, superabsorbent polymer (SAP), biosynthesized cellulose, composites, hydrogel components, compression wraps

Physical embodiments:
•Medical (traditional): Conventional wound dressings based on gauze, nonwovens, etc.
•Medical (advanced): Advanced wound dressings based on foams and highly absorbent matrix materials
•Medical (nontraditional): Protective garments for secondary and tertiary bandaging (i.e. antimicrobial shirts for burn victims has been a particular request from clinical caregivers).
•Consumer textiles: Socks, T-shirts, various cotton and blended apparel items.

Current research directions:
•Protease inhibition using NIMBUS™ materials.

Treatment costs:
The cost of materials associated with NIMBUS™ treatment is very small, particularly compared to expensive materials such as silver compounds. For many substrates the processing can be integrated readily into current manufacturing techniques, generating a significant added value for a small incremental cost.

Safety Testing

*Testing performed on NIMBUS™ treated cotton gauze, by Toxikon Laboratories, Bedford, MA

NIMBUS materials have passed all standard toxicology tests for prolonged use materials (1-30 days) in direct contact with breached or compromised skin. The FDA is currently reviewing a 510(k) submission on the material.

Safety tests performed and passed, as per ISO 10993.[4]

Cytotoxicity
Primary Skin Irritation
Kligman Maximization (dermal sensitization)
Acute Systemic Toxicity

References

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2. Wright, BJ, Lam, K, Olson, ME, Burrell, RE, Is Antimicrobial Efficacy Sufficient? A Question Concerning the Benefits of New Dressings, *Wounds*, 2003; 15(5):133-142
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4. Test reports from Toxikon on file with Quick-Med Technologies.

WWW.QUICKMEDTECH.COM

David Lerner - President
Email: dlerner@quickmedtech.com (561) 750-4202

Roy Carr – Director of Research & Development, Medical Devices
Email: rcarr@quickmedtech.com (630) 214-9819

Gerald M. Olderman - Ph.D. VP, Research & Development
Email: jolderman@aol.com (781) 271-9893