Wound Infection: How Are We Solving The Problem?
Introduction
A great number of wounded warfighters survive their initial injuries because the personnel are protected with the latest body armor and personal protection. Similarly, outside the military arena, our ability to repair the human body has taken us to places we never imagined. What we are seeing in the stead of trauma recovery is a longer and more serious pattern of recovery with respect to wounds, and in particular wound infection.
The pervasiveness of antibiotic treatment coupled with the adaptability of organisms has made wound infection patients likely to be infected with multiple antibiotic resistant (MDR) bacteria. It is interesting that a number of personnel with wound infections tend to be infected with MDR during their (often multiple hospital stays), rather than in Theater.

At Military tertiary care facilities in the U.S., the most frequently isolated bacteria from traumatic war wounds is Acinetobacter baumannii-calcoaceticus (ABC) complex; the majority of these isolates have been MDR. About 65% of these isolates have eight (8) or more resistance determinants representing a very broad range of resistance. Most of the ABC complex isolates are found in blood-stream infections and at least two-thirds of the patients with ABC complex isolates are critically ill or on ventilators.

The spread of these organisms into Military hospitals, and even into the general population, remains worrisome. Other organisms of interest in wound infections include Klebsiella pneumoniae, Escherichia coli, other members of the Class Enterobacteriaceae, Pseudomonad aeruginosa, Methicillin –resistant Staphylococcus aureus (MRSA), as well as other organisms. All of them can be multiple-resistant organisms (MRO). Many are notorious in their ability to pass resistance factors among one another. Because of the complexity of the problem, wound infections are being addressed across a wide spectrum of disciplines, as well as military commands. Wound infections impact the War-fighter, the Unit, the Command, as well as the family of the Combatant.

We, at ClinicalRM are not only interested in the outcomes to each impacted concern, but are actively involved in trying to solve the impacting problems. We provide support for the Joint Theater Trauma System (JTTS) and the Joint Theater Trauma Registry (JTTR). By assisting the DoD in the development of data and other evidence-based information, ClinicalRM personnel at USAISR have contributed to the provision of clinical practice guidelines within the JTTS. These guidelines have reportedly decreased the post injury complication rates by 54%.

Our personnel at WRAIR and elsewhere have significantly contributed to the continuing development of the Multidrug-resistant Organism Repository and Surveillance Network (MSRN). The MSRN provides a mechanism for the acquisition of MRO from all sources of the military and VA system. Once organisms are confirmed and clinical data acquired, these data can provide researchers with the tools to assess resistance, determine biomarkers and provide the basis for projections in response to antibiotic resistance patterns in theater, segments of theater and at the individual point of care. Further, with the greater understanding of
biomarkers, the responses to infections can be addressed in very direct and improved ways.

Our researchers in the Wound Infection Department at WRAIR are looking at genotypic and phenotypic characterization of organisms, antimicrobial resistance mechanisms, molecular epidemiology and surveillance, biofilm research, wound healing and immune modulation, surgical intervention, and chronic care management. These studies focus on the ability of species, or specific strains within species groups, to facilitate antibiotic resistance gene transfer, and take into consideration the modes where the organisms are growing (e.g., infection or biofilm), especially when trying to recreate the host environment. The WRAIR’s genomic sequencing capability is leveraged to identify relationships of chromosomai and plasmid-encoded antibiotic resistance genes among isolates at the single-nucleotide polymorphism (SNP) level. This approach allows differentiation between the selection of resistant organisms from the primary wound infection and nosocomial super infection with drug resistant organisms. Our bio-informaticists are highly trained in the interpretation of genomics data and assist our investigators to develop analyses that assist the Government in their decision making.

The issue of surveillance at the molecular/genomic level can be illustrated by a recent paper published by military personnel as well as ClinicalRM employees. In 2008 a new resistance plasmid called New Delhi metallo-β-lactamase gene 1, bla(NDM-1) was isolated from Klebsiella pneumoniae. This plasmid is horizontally transferred to related genera. Soon the plasmid was found in E. coli and other members of the family Enterobacteriaceae. This resistance factor provides organisms with a broad range of beta-lactam resistance, including to carbapenems. As a routine screening procedure, the MSRN surveys all carbapenem-resistant isolates for this gene. In April 2012, investigators at the MRSN described the appearance of this plasmid in two strains of Providencia stuartii. As reported, the strains were identical by pulse-field gel electrophoresis (PFGE). The bla(NDM-1) gene was carried on a gene that was sequenced by emulsion PCR and pyrosequencing (such as with Roche 454). Analysis of the plasmids indicate similarity to plasmids from E. coli and has retained resistance genes for other antibiotics.

The significance of this finding cannot be underestimated. P. stuartii is intrinsically resistant to colistin and related agents. Thus the organisms are resistant to virtually all available antibiotics. The structure of the plasmid surrounding the bla(NDM-1) gene makes it highly transferable. As such, spread of this gene to other organisms is likely. These kinds of information are important in planning and directing future endeavors to protect our Warfighters and advance our scientific knowledge.

As we have seen, wound infections provide a difficult and diverse research area of concern. Because of the problems we encounter with antibiotic resistance, our personnel are continuously looking at new modalities for treatment of wounds. Examples include novel uses of bacteriophage as therapeutic agents.
Other novel modalities include iron starvation using gallium and iron chelators, and the use of predatory bacteria where a bacterium harmless to humans can invade and kill infectious bacteria. Such bacteria include *Bdellovibrio* and *Micavibrio* that can invade many gram-negative bacteria including Enterobacteriaceae and pseudomonads.

Our Business Development personnel are continuously looking at the need for research into wound infections. We have seen a marked increase in the need for wound infection research by our military and other Government venues such as NIH. ClinicalRM researchers are ready to assist the Government in this important research endeavor.
About Clinical Research Management, Inc.
Clinical Research Management (ClinicalRM) is not only involved in the testing of new antibiotics in Phase I, II, III studies, monitoring protocol development, site selection, and assistance with FDA approvals, but is also involved in responding to the challenges of antimicrobial resistance. Our epidemiologists track resistance patterns around the globe and they evaluate how the observed resistance appears, where it emanates from, and how we can best contain the spread of the new resistance factors.

Our scientists work with the Government and academia to develop new responses to the ever-growing threat of multiple-resistant super-bugs. They use in silico techniques, as well as information from genomics, to determine sites on, or in, these organisms that are most likely to be vulnerable to engineered antimicrobials. ClinicalRM is committed to developing new responses to disease and the challenges presented by these super-bugs. If you feel ClinicalRM can add value to your research efforts, we are interested in speaking with you. Call toll free at (800) 431-9640 or visit www.clinicalrm.com

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You can read more of Dr. Boyer’s writings at www.clinicalrm.com