Wound Infections: The Microbial War Is Raging

Clinical RM

Introduction
Since 2003, there has been a healthy debate over the role the United States has chosen to play in the Middle East, specifically, over the choice to engage in two wars with somewhat nebulous goals. Nine years later, we still have soldiers deploying and are now saddled with the escalating cost of precious lives, wounded, and resources; yet, it remains precarious to withdraw too early jeopardizing the missions. However, regardless of military and long-term strategic outcomes associated with the conflicts in Iraq and Afghanistan, another war has been raging, behind the scenes and at a much smaller level: the microbial one, and here, there is no debate. We need to engage to combat wound infections.
U.S. servicemen and women (and our allies) who have been traumatically injured (typically from improvised explosive devices or rocket propelled grenade attacks) are suffering from devastating wound infections caused primarily by opportunistic bacteria and fungi [1,2,3]. What makes this all the more troubling is that these infections occur after a surgeon has already taken great strides to repair the damage caused by the initial trauma, which then leads to significant morbidity such as revised amputation and extended hospital care. Probably, the most bothersome and frustrating to caregivers is that the bacteria and fungi causing the infection are harmless to healthy individuals. So why is this happening to our Wounded Warriors?

The answer is speculative as the research surrounding the topic is far from exhaustive. However, based on the ongoing research that is being performed in the Dept. of Wound Infections at Walter Reed Army Institute of Research and by other laboratories in academia and pharmaceutical companies, we can start to make some interesting hypotheses. For one, as with all wars, a significant amount of wounded accompany the tribulation and so wound infections are not a new problem [4]. However, with better medical care, body armor, and rapid evacuation, some wounded are now surviving what would have once killed them [2,5,6]. The wounds themselves are often large and unwieldy; require numerous blood transfusions, and extensive surgery [5,6]. Therefore, the patient is in more of a compromised state, some would also say immunocompromised [7] making them vulnerable to nosocomial, opportunistic infection.

Part of the immunosuppression that accompanies these traumatic wounds may come from an unfortunate side-effect of pain treatment. Morphine is often the painkiller used with large traumatic injuries; however, the drawback is that morphine also drives down the innate immune system, which can sensitize the patient to many bacteria [8]. Another contributing factor could be massive transfusions that wounded soldiers receive, which more often than not contain older blood. Research from Eldad Hod’s laboratory has shown that those who receive old blood (animal models or human patients) also receive a bolus of free iron, the iron released from dead or dying blood cells [9,10]. Therefore, the unfortunate side effect of the transfusion is that this free iron help “feed” the bacteria and fungi that require this limited cofactor for survival.

A third significant contributing factor with respect to difficult-to-treat infections is antibiotic resistance. In past conflicts, wound infections were a problem, but a clinician could rely upon penicillin or other antibiotics as they were developed to clear the infection [4]. However, since the clinical introduction of penicillin in the 1940’s, bacteria have found numerous ways to acquire antimicrobial resistance, and the rate at which it is acquired is staggering. As each
It appears that the bacteria are winning the war, and really it is not just a military wound infection problem; but also a civilian one, especially with respect to diabetics and hospital-acquired infection [12,13,14,15]. Perhaps, there is a way forward, and we can turn the tables. Groups such as the IDSA (www.idsociety.org) and the Union of Concerned Scientists (www.ucsusa.org) as well as individual concerned clinicians and researchers are trying to draw awareness to the problem and urge lawmakers to action in the United States. Brad Spellberg also wrote a book for the lay audience entitled “Rising Plague: The Global Threat from Deadly Bacteria and Our Dwindling Arsenal to Fight Them” and has testified in front of Congress. Another group, championed by the British Society for Antimicrobial Therapy and Laura Piddock, established a group called Antibiotic Action (antibiotic-action.com), to open the eyes of British lawmakers. Besides awareness, which will hopefully increase research dollars, there are some promising and possible therapies on the horizon. As stated previously, large companies devote only 1% of research dollars to antimicrobial approaches; nonetheless, 1% of a billion dollar plus research program is still a significant amount of money. Pfizer, Inc. has a promising new molecule that attacks lipopolysaccharide synthesis in gram negative bacteria [16], and other companies such as Rib-X Pharmaceuticals, Microbiotix, Inc., Basilea Pharmaceutica, and Achaogen, Inc. all have impressive lead compounds in Phase I and Phase II trials. However, we have seen this before, haven’t we? Resistance is assuredly on
the horizon for these molecules even if they are eventually FDA approved and used. In fact, Glaxo-Smith Kline (who acquired a compound from Anacor, Inc.) just had a Phase II trial fail because of resistance (Gordon Research Conference, 2012). So maybe it is time to try novel antimicrobial strategies, “out-of-the-box” thinking, and not the same old, single antibiotic, small molecule chemotherapy approach. The last paragraph will highlight some of these pursuits.

First, combinational therapies are a possible route that shows real promise. Merck and Co. has developed a drug that re-sensitizes methicillin-resistant Staphylococcus aureus to betalactam antibiotics \(^{[17]}\). Christian Melander from North Carolina State University has generated derivatives from sea sponges that also re-sensitize bacteria to already approved antibiotics \(^{[18,19]}\), and work from my lab has found iron chelators can also synergize with conventional antibiotics (unpublished and \(^{[19]}\)).

Second, there is the possibility of using live organisms to eradicate bacteria. Many groups are exploring phage therapy, and two projects in our department are exploring predatory bacteria (next article) and rebooting maggot therapy. Other groups are trying to use antimicrobial peptides (AMPs), either rationally generated \(^{[20,21]}\) or using human AMPs themselves or AMPs based on human structures \(^{[22]}\).

Lastly, human monoclonal antibodies have real promise for two reasons. One, since they are purified from humans, they are not cleared by the human immune system nor are there the typical toxicity issues associated with small molecule therapies i.e. an easier road for FDA-approval \(^{[23,24]}\). Two, they actually work well to clear bacterial infections in animal models, and companies such as Kenta Biotech Ltd., Sorrento Therapeutics, Inc., MedImmune, and Pfizer, Inc. all have antimicrobial teams using human monoclonal approaches that are published \(^{[25,26,27,28]}\) or unpublished but in the works [personal communication].

So while bacteria are currently winning the war, there is hope on the horizon if we keep funding and pushing current antimicrobial research to the next level.
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 superbugs. 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.

References:


About the Author – Daniel V. Zurawski, Ph.D.

Dr. Zurawski has been a primary researcher of pathogenic bacteria for more than 15 years. Specifically, he developed new genetic and molecular tools for Shigella flexneri and Salmonella during his post-doc and thesis, and then, used these tools to identify novel secreted proteins essential for virulence. Dr. Zurawski subsequently joined the Walter Reed Army Institute of Research (WRAIR) targeting Shigella surface proteins as vaccine candidates. Now, Dr. Zurawski is an employee of Clinical RM, Inc. and is contracted by the U.S. Army to manage a lab in the Dept. of Wound Infections at WRAIR. Here, he applies a skill set that includes genetics, biochemistry, and cell biology expertise to study the pathogenesis of and develop drugs/vaccines against MDR-ESKAPE pathogens. He and his colleagues have also developed novel animal models in mice, rats, and swine that incorporate different infection sites, multiple endpoints, and bioluminescent bacteria to address the efficacy of antimicrobials. Dr. Zurawski is the sole PI on grants funded by the Dept. of Defense. In addition, Dr. Zurawski has ongoing research collaborations with experienced laboratories to develop novel antibacterial treatments. This includes, but is not limited to, projects with Luis Actis (NIH-funded A. baumannii investigator), Christian Melander (NIH-funded antimicrobial chemist) and Darrell Irvine (HHMI/NIH-funded drug delivery/nanoparticle investigator). Lastly, Dr. Zurawski played a significant role in establishing the MultiDrug-Resistant Repository Network (MRSN) for the U.S. Army, which is a unique repository that collects every MDR organism isolated from patients in the U.S. military healthcare system, and his lab also has access to these clinical isolates.


