Medical Xpress

New twist on old medical technology may prevent amputations

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Old technologies, bone cement and a well known antibiotic, may effectively fight an emerging infection in soldiers with compound bone fractures, according to a study published online today in the *Journal of Orthopedic Research*. An urgent search for solutions is underway as 20,000 additional American soldiers head for Afghanistan, and as evidence emerges that the infection studied may set the stage for more dangerous infections that can lead to amputation.

Osteomyelitis is (OM) a bone infection caused by various bacteria, and usually occurs in severe fractures when bone is exposed to open air. Although Acinetobacter baumannii rarely causes OM in the United States, it is very prevalent in the Middle East, and is now present in more than 30 percent of soldiers recovering from open fractures in field hospitals in Iraq and Afghanistan. Past studies have established that one in four severe war wounds in Iraq is a fracture, more than 80 percent of which are open, where the bone is exposed to airborne bacteria.

Not common in the United States and not potentially fatal, A. baumannii OM had been largely ignored until recently by physicians and the pharmaceutical industry, which focuses on life-threatening infections that affect millions, not hundreds. Then military outbreaks of the infection started among American soldiers returning from Iraq in 2003, with the number of A. baumannii OM infections seen in field hospitals, and in stateside facilities receiving injured soldiers, growing. At the same time, data began to emerge from hospitals treating soldiers suggesting that easily contracted A. baumannii may be arriving first at the fracture site and "priming" it so that it becomes more vulnerable to methicillin-resistant Staphylococcus aureus (MRSA), which recently surpassed HIV as the most deadly pathogen in the United States despite nearly universal use of the best available antibiotics.

"If you apply the findings from two small studies to the entire U.S. military, which is a leap, perhaps 2,000 soldiers come into field hospitals with compound fractures each year that become infected with A. baumannii," said Edward Schwarz, Ph.D., professor of Orthopaedics within the Center for Musculoskeletal Research at the University of Rochester Medical Center. "About a third of them go on to get a staph infection after they reach the hospital, with about a third of those, perhaps 200 soldiers, suffering infectious complications that could cost them a limb. Studies already underway in our lab seek to clarify how the initial infections could gradually be replaced by catastrophic MRSA, and to prove that we can save limbs by putting an established antibiotic into bone cement for the first time."

Current antibiotics often kill a strain of bacteria responsible for a disease, only to create a vacuum quickly filled by related strains. The widespread overprescribing of antibiotics and the speed of bacterial evolution have greatly increased the likelihood that the strains most able to resist antibiotics will thrive. Multi-drug resistant (MDR) bacterial strains are now widespread in all hospitals.

MDR strains tend to cluster in hospitals, where patients may pass the infection to each other no matter how sterile the environment, although the exact cause is not known. Multi-drug resistant Acinetobacter baumannii (MDRAB) infections is oftentimes treated with an older class of drugs known as polymyxins, including colistin, one of the last-resort antibiotics for multidrug resistant A. baumannii. Approaches commonly used to overcome MDR infections after orthopaedic injuries include applying a large dose of antibiotic locally to the site of infection via bone cement. Bone cements composed of Plexiglas (polymethyl methacrylate or PMMA) have been used for decades for plastic surgery, to anchor in bone prostheses and to fill in holes in bone caused by trauma. Such materials became even more useful when researchers realized decades ago that they could load them with antibiotics to deliver large doses of drug directly to the injury site without subjecting the whole body to toxic levels of antibiotic. While bone cements laced antibiotics against staph and strep infections are common (e.g. vancomycin), no group had ever developed a bone cement treatment using colistin against A. baumannii.

To begin the process of providing such a treatment for soldiers, a team of orthopaedic, military and pharmaceutical researchers came together to conduct the current study, the results of which argue for a human clinical trial with colistin-laced bone cement, researchers said. Such a trial would likely proceed within the military medical system, where treatments for maladies suffered specifically by the troops are pursued under military research contracts, which use with the same standard required by the U.S. Food and Drug Administration when approving medications and devices for civilian use.

Schwarz and colleagues developed a group of mice infected with drug resistant A. baumannii strains isolated directly from soldiers wounded in Iran and Afghanistan. The mice were then treated with either colistin by injection, local colistin via PMMA bead bone cement or a bone cement control with no drug. Researchers measured the amount of bacteria in the mice as they responded to treatment with a new test of parC gene activity, a gene known to be present only in A. baumannii. Experiments confirmed that all study mice were infected with the bacteria, and that 75 percent of the strains were resistant to multiple antibiotics. Importantly, the bone cement containing colistin significantly reduced the infection rate such that only 29.2 percent of mice had detectable levels of parC after 19 days (p

Along with Schwarz, Daniel Crane, Kirill Gromov, Dan Li, Matthew Hilton and Regis O'Keefe led the study effort within the Center for Musculoskeletal Research in Rochester, along with Kjeld Søballe from the Department of Orthopedics at Aarhus University Hospital in Denmark. Christian Wahnes and Hubert Büchner led the effort within Research & Development with Heraeus Medical GmbH, which donated the colistin for testing. Clinton Murray of the Infectious Disease Service at Brooke Army Medical Center in San Antonio made available to researchers the strains of A. baumannii taken from soldiers. The work was supported by research grants from the U.S. Army Medical Research Acquisition Activity (USAMRAA) Orthopaedic Trauma Research Program, and the National Institutes of Health Public Health Service Awards.

The team also took the first close look at the effect of A. baumannii and S. aureus osteomyletis on bone biochemistry. When bacteria infect bone, they uncouple delicately balanced biochemical signaling responsible for the recycling of bone to preserve its strength, typically resulting in bone loss (osteolysis) that can be seen as a hole on X-rays. In the current study, researchers found that staph infection did indeed encourage bone breakdown, but were surprised to find that A. baumannii infection did the opposite, encouraging bone formation.

"These findings have implications for clinical care, as imaging technologies that capture unusual bone cell growth may be used to diagnose A. baumannii earlier," Schwarz said.

Source: University of Rochester Medical Center