New Horizon Workshop: Drug Resistance: New Challenges and Opportunities in Biomaterials-Associated Orthopaedic Infection

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Emerging Immunotherapeutic Approaches against Biomaterial-Associated Infection

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Abstract

Antibiotics are critical to the success of surgical procedures including orthopaedic prosthetic surgeries. Unfortunately, there has been a dramatic increase in the emergence of antibiotic resistant bacteria which have led to serious clinical consequences. For instance, in the U.S. alone, antibiotic resistant bacteria have been estimated to cause at least 2 million infections and 23,000 deaths a year. Meanwhile, most clinical cases of orthopaedic surgeries have indicated that patients infected with antibiotic resistant bacteria, such as methicillin resistant Staphylococcus aureus (MRSA), are associated with increased mortality and morbidity. This lecture will review the severity of antibiotic resistance, consequences of antibiotic resistance, and antibiotic resistance mechanisms. This lecture will also highlight the recent development of an innovative immunotherapeutic approach in reducing biomaterial-associated infections.

Antibiotic resistance – a serious global problem: The introduction of antibiotics has dramatically improved the fate of infection in patients and has changed the way various diseases and surgical procedures are treated. The ability of antibiotics to treat and cure infection has dramatically reduced the number of incidences of infection, significantly improving the quality of life for numerous patients, reduced childhood mortality, increased life expectancy, and saved numerous lives.

Unfortunately, the discovery and increasingly widespread use (especially the misuse) of antibiotics have led to the rapid appearance of antibiotic resistant strains today, and more and more infections are caused by microorganisms that fail to respond to conventional treatments. Meanwhile, the discovery and development of antibiotics have been declining rapidly over the past several decades. (1) This decline was due to decreasing antibiotic research and development in major pharmaceutical companies; (1) investment in new antibiotic development has been hampered by the uncertain lifecycles (associated with antibiotic resistance development) of new antibiotic drugs and the government regulations affecting the pace of translational exploitation.
Consequences of antibiotic resistance: The consequences of antibiotic resistance are very serious, and could present a significant impact on morbidity, mortality, and financial burdens for patients and public health systems, as described below:

- Antibiotic resistance likely compromises the safety and efficacy of surgical procedures like implantation and transplantation that require the protection of antibiotics. It is estimated that between 38.7% and 50.9% of microorganisms causing surgical site infections are resistant to standard prophylactic antibiotics in the U.S. (2)
- Antibiotic resistance has a direct effect on treating infections. Patients with infections caused by multidrug resistant (MDR) microorganisms are generally at increased risk of worse clinical outcomes and death, and consume more health-care resources compared with similar infections caused by antibiotic susceptible strains. (3) Approximately a two-fold increase in mortality, morbidity, and cost for patients with resistant versus susceptible infections has been reported. (4) A two-fold higher risk of death was attributed to infections caused by carbapenem-resistant K. pneumoniae compared to infections caused by carbapenem-susceptible strains. (5) Meanwhile, hospitals spend, on average, an additional $10,000-40,000 to treat a patient infected by resistant bacteria versus susceptible strains. (6) According to the Centers for Disease Control and Prevention (CDC), in the U.S. alone, antibiotic resistant bacteria cause at least 2 million infections, 23,000 deaths a year, and $55-70 billion per year in economic impact. (8, 9) In Europe, approximately 25,000 people die annually due to MDR bacterial infections, along with a €1.5 billion per year cost in the economy. (10, 11)
- Antibiotic resistance has led to more death of domesticated animals such as pets and farm animals.

Molecular mechanisms of antibiotic resistance: There are two distinct types of antibiotic resistance: intrinsic and acquired. Microorganisms can be intrinsically resistant to certain antibiotics as a result of inherent structural or functional characteristics. (10) For instance, a particular antibiotic may be structurally unable to penetrate the outer membrane of certain microorganisms or the antibiotic entering the membrane is removed by efflux pumps. Meanwhile, microorganisms have also developed, under the selection pressure from antibiotics, various resistance mechanisms to antibiotics that they were originally susceptible to via deactivating, removing, or circumventing the toxicity of antibiotics. These evolved mechanisms are known as acquired resistance and can be acquired via chromosomal mutations or, more commonly, via the acquisition of an antibiotic resistance gene from another bacterium via mobile plasmids or transposons. A variety of factors including human activities may influence the presence of antibiotic resistance and antibiotic resistance genes are omnipresent in natural environments.

Antibiotic resistance likely linked to worse clinical outcomes in orthopaedic biomaterial-associated infections: S. aureus is one of the most common causes of orthopaedic implant-associated infections, with both methicillin-susceptible (MSSA) and resistant (MRSA) strains. As shown in the following table, it seems that orthopaedic biomaterial-associated infections caused by microorganisms resistant to antibiotics likely have a less optimal outcome compared to those caused by antibiotic susceptible microorganisms.
### Table 1. Worse clinical outcomes of patients infected by MRSA compared to those infected by MSSA.

<table>
<thead>
<tr>
<th>Time</th>
<th>Patients</th>
<th>Worse Outcomes</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1995 - 2004</td>
<td>43 patients with periprosthetic joint infections</td>
<td>• Significantly longer hospital durations (median, 15 vs. 10 days)</td>
<td>(12)</td>
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<td></td>
<td></td>
<td>• Significantly higher risk of treatment failure</td>
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<tr>
<td>1997-2001</td>
<td>70 patients with periprosthetic joint infections</td>
<td>• Successfully treated only 48% and 18% of hip and knee replacements, respectively, in MRSA infected patients compared to 81% and 89% in MSSA infected cases</td>
<td>(13)</td>
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<tr>
<td>1998-2004</td>
<td>31 patients with delayed deep infection after total knee arthroplasty</td>
<td>• Significantly higher mean number of surgical procedures per patient</td>
<td>(14)</td>
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<tr>
<td></td>
<td></td>
<td>• Significantly lower proportion of patients with satisfactory outcomes</td>
<td></td>
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<tr>
<td>2000-2002</td>
<td>59 children with musculoskeletal infections</td>
<td>• Significantly longer febrile days and hospital stays.</td>
<td>(15)</td>
</tr>
<tr>
<td>2004-2008</td>
<td>74 children with bone and joint infections</td>
<td>• Significantly longer duration of febrile days, hospital stays, and antibiotic treatment</td>
<td>(16)</td>
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<tr>
<td>2005-2011</td>
<td>30 vertebral osteomyelitis patients</td>
<td>• Significantly higher co-morbidities</td>
<td>(17)</td>
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<td></td>
<td></td>
<td>• Significantly higher rate of patients to undergo surgical procedure within three months (56.3% vs. 14.3%)</td>
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**Emerging antibiotic alternative: Enhancing host immune response to reduce infections:** Innate immunity is the first line of defense against pathogenic organisms and the interface of the interactions between the host and the microbiota. In recent studies, local interleukin 12p70 (IL-12) immunotherapy, which stimulates the host’s immune response, has been shown to be effective in reducing biomaterial-associated infection in animals and to be advantageous over traditional treatments.(18-20)

**Bibliography**


Nanotechnology in Drug-Resistant Biomaterial Infections: Past, Present, and Future

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Abstract

This lecture will describe how nanotechnology can be used to decrease implant infections without using antibiotics. As is well known, antibiotic use has led to the generation of numerous antibiotic resistant bacteria, some of which we have no means of killing. Rather than concentrating on developing new antibiotics, recent efforts have focused on the use of nanotechnology to inhibit bacteria functions on orthopedic implants. Nanotechnology involves the use of materials with at least one dimension in the nanoscale (some refer to less thank 100 nm) (1-2). Such nanomaterials can mimic the natural nanostructured features of tissue (such as bone) and can easily be manipulated to alter medical device surface energetics without changing implant chemistry. This has led to numerous nanofeatured medical devices recently approved by the FDA.

The lecture will highlight such advancements in which distinct nanoscale surface features have been placed on current orthopedic implants (including titanium, poly-ether-ether-ketone, silicon nitride, and others) to both decrease bacteria functions and increase bone growth, without using antibiotics or bone growth factors. In fact, computational models will be discussed which can predict nanoscale surface feature sizes that should be manufactured on medical devices to make such biological events occur. This lecture will also cover what is necessary for the field of nanotechnology in infection control to continue to grow and problems that it faces. In particular, the design and use of internal orthopedic sensors will be covered which in real time can monitor cellular events around and implant and control such events to ensure implant success.

Bibliography

Bacterial biofilm formation, dormancy and medical device-associated infections

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Despite the technological advances in past decades, medical device-associated infections are still on the rise due to the steady increase in the number of patients requiring orthopedic surgeries. Such complications present unique challenges to both diagnosis and therapy; and thus, there is an urgent need to better understand and control these infections. Previous research has shown that bacterial cells causing medical device-associated infections are commonly reside in multicellular structures known as biofilms. These complex structures are attached to implanted materials/devices with sessile cells embedded in a secreted matrix of extracellular polymeric substances (EPS). It is well documented that biofilm cells have up to 1000 times higher antibiotic tolerance (also known as intrinsic antibiotic resistance) compared to planktonic counterparts. Biofilm associated antibiotic tolerance has been attributed to multiple factors such as reduced antibiotic penetration by EPS and the presence of dormant cells such as small-colony variants (SCVs), persister cells, and viable but non-culturable cells (VBNCs) [1-5]. These dormant populations have reduced metabolism and thus marked changes in physiology and culturability, and exhibit extremely high-levels of antibiotic tolerance. While the significance of these dormant variants is well recognized, the mechanism of their formation is still not well understood and the control remains challenging.

In this presentation, we will present a review of current understanding of bacterial biofilm formation and dormancy, with an emphasis on the topics related to medical device-associated infections and antibiotic tolerance, as well as the new developments towards better diagnosis and treatment of such infections.

Bibliography

The Diagnosis and Treatment of Orthopaedic Infections: A Clinician’s Perspective

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Abstract
This lecture will outline the clinician’s perspective in dealing with infections in adult patients, with a specific concentration on infections of total joint replacements. Emphasis is placed on a team approach for early diagnosis and treatment using established, evidence based methods. This approach has been shown to optimize outcome and minimize further complications when treating this devastating condition.

Infections are one of the most common complications seen by the orthopaedic surgeon treating adult patients. Although primary infections, i.e. those not associated with previous surgery, are seen in infants and children, these are extremely rare in adult patients, unless the patient is immune-compromised. Thus most infections seen in adults are associated with previous surgery, especially if the patient has undergone internal fixation of a fracture, spine surgery with fixation, or joint replacement. Although there are commonalities when discussing infections in different anatomical locations and after various surgical procedures, this lecture will concentrate on infections associated with joint replacement (JR) (1-14).

Implant associated infection after JR is the most common reason for further surgery after primary total knee arthroplasty (TKA) and one of the 3 most common causes of infection after total hip arthroplasty (THA). Despite the use of preventative measures such as optimization of the host preoperatively, the use of prophylactic antibiotics, special operating rooms, and distinct surgical gowns and hoods, infection still occurs in approximately 0.39% to 2.5% primary TKAs and 0.2%-2.2% primary THA. Prosthetic joint infection (PJI) may occur at any time after JR surgery, but often the clinical presentation is classified temporally into: < 3 months after surgery, 3 months to 1 year, or occurrence 1 year or more after surgery. The clinical presentation can vary from rapid onset of local ± systemic symptoms and signs, to a slow indolent painful JR without systemic toxicity.

The approach to PJI is algorithmic, including performing a thorough history and physical examination (including searching for and treating predisposing factors in the host), performing laboratory tests and imaging, joint aspiration, and instituting appropriate surgical and ancillary treatments as indicated. In this regard, consultation with an infectious diseases specialist is critical to effective diagnosis and treatment. Indeed, the most efficient and optimal clinical outcomes have been reported using a team approach, in which patients are seen by the surgical and infectious
diseases team together; decisions can then be made in real time with the patient and entire team present.

There are specific criteria for the diagnosis of PJI that have been agreed upon by expert panels; these will be reviewed in the lecture. Furthermore, the sensitivity and specificity of different methods of diagnosis and testing procedures will be enumerated. In fact, there are different laboratory criteria for determination of acute versus chronic PJI when considering the Erythrocyte Sedimentation Rate (ESR), C-Reactive Protein (CRP) and characteristics of cell counts in the joint aspirate.

Once the diagnosis is made, decisions have to be made as a team as to the acuteness or chronicity of the PJI, and whether the prosthesis can be salvaged or needs to be removed. In either case, medical co-morbidities must be optimized pre-operatively. The type of treatment instituted depends on numerous factors involving patient characteristics and desires, the time and mode of clinical presentation, the details of the joint replacement including the integrity of the soft tissues, the type and virulence of the organism and availability of appropriate antibiotics for successful treatment, the experience of the health care team, and other factors. Treatment must be individualized. The main tenets of treatment include early and accurate diagnosis, timely institution of surgical and non-surgical treatments, and meticulous post-operative monitoring to ensure that the treatment pathway has been effective in eradicating or neutralizing the infection.

Bibliography


