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Review

The use of nanomaterials to treat bone infections

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ABSTRACT

A new era of osteomyelitis treatment has been taking strides towards efficient, local administration of antibiotics at the site of infection. By having them localized to the site of infection, this toxicity is no longer an issue and actually has shown to be a more productive treatment for osteomyelitis. Researchers have focused the production of non-biodegradable, antibiotic, infused bone cements specifically designed for proficient osteocyte binding, useful antibiotic release over a desirable period of time, and promotion of bone regeneration. These cements are then surgically placed on the infected site following debridement and irrigation. The problem, however, is that the use of ineffective cements and the overuse of antibiotics has led to the development of resistant bacteria. Due to this, further research is being done in the field of antibiotic discovery and delivery. Specifically, the development of biodegradable materials capable of efficiently delivering antibiotics and also eliminating the need for follow-up surgery to remove the delivery material is being done, thus reducing exposure risk. Nanoparticles have been developed in the forms of scaffolds and injections to deliver a higher degree and longer lasting duration of antibiotic release, while promoting bone regeneration.

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1. Introduction

Since the invention of prosthetic joints, some engineers and physicians have spent their careers trying to not only improve the materials which make up these prosthetics, but the manner they are utilized in order to make sure their use is as beneficial, comfortable, and long lasting as possible. One problem with this fact is the possibility of bone infection or osteomyelitis. It was concluded as recently as 2015 that infection following knee or hip arthroplasty has an incidence rate of 2 to 2.4%, with the infection burden for each (knee or hip) being slightly under 1% [1,2].

Clinically, physicians are able to classify bone infection in to two different categories including chronic and acute cases. The most common form of acute cases is due to blood vessel weakness or damage more commonly known as hematogenous infection. Due to the high vascularization of bone in children, they are the most commonly infected individuals from this mechanism. Chronic cases are less common but when diagnosed have been shown to present for over 80 years, in some

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cases [3]. Additionally, chronic cases are becoming much more prevalent now than previous years due to the more frequent use of prosthetics for joint replacements and fracture repair. During surgery or, in many cases, a fracture, the periosteum of the bone is disturbed allowing for increased access to the osteocytes by bacteria resulting in a more severe form of infection [4].

However, the increased frequency of these types of surgeries is not the only reason for the increased prevalence of bone infections. The major influence is due to the damage inflicted upon the vascular and skeletal system by diabetes and cardiovascular diseases. Now, more than ever, the prevalence and incidence of such diseases are escalating. It has been stated by the Center for Disease Control (CDC) [5] that 9.3% of the United States population is affected by diabetes whether they are diagnosed or not. Additionally, the American Heart Association (AHA) [6] estimates that 35% of the United States population expresses greater than or equal to three out of the seven heart disease risk factors, which is the most up to date standard in recognition of susceptibility. Reviews published by Namba et al. [7,8] also found that men and people suffering from obesity or arthritis also have an increased prevalence of osteomyelitis, but they were unable to find a connection among people suffering from rheumatoid arthritis like other reviews [9–12].

In order to combat the reality of bone infections it is important to first understand what is going on biologically during an infection before it is possible to find ways to prevent, treat, or even cure such manifestations. During an infection, the body's first immunological response is to signal the collection and focus of immunologic cells to the site of injury or infection. This begins with the function of the non-specific system involving macrophages, neutrophils, and other phagocytic cells at the site, and the recognition of the infection by the body signals associated T-cells and B-cells of the specific immune system to produce the necessary antibodies [13]. This concentration of cells and immunologic agents like histamine trigger an immune response resulting in pain, swelling, redness, heat, and loss of function. Though this is generally a beneficial response, if the infection is substantial or persistent, this response can eventually lead to cell and tissue necrosis and the most severe forms of osteomyelitis [3]. During an immune response, there is a transition of cells between certain stages, by utilizing this fact, researchers are able to monitor the impact of the materials being tested for effectiveness and completion of treatment. One example of this is the transference of macrophage from a type 1 form to type 2. Each of which has a different impact favoring type 1 for less severe infection cases [14].

Antibiotics have been proven to work but problems have been found to exist due to the bacteria's own defenses against the immune cells. Its shown that once the bacteria imbed themselves in the osteocytes, they are able to produce a fibrinogen layer similar to the fibrinogen present in normal tissue and even lower its metabolic rate, both of which help to disguise the bacteria from immune cells and antibiotics [3]. Additionally, some antibiotics proven to be affective have shown to be toxic in other tissues or organs of the body especially when in the concentrations needed for eradication to be successful. These two problems thus bring up two other problems including: the need for a way to localize the antibiotics necessary to the point of infection and to avoid toxicity.

The focus for this review is to provide information on new methods being developed in the field of osteomyelitis treatment and improved developments in the methods already adopted by the medical field both primary and surgical. These include a number of biological and non-biological methods with the latter being of older relevance and the prior consisting of the most recent research focuses.

2. Current status for bone infections

Since the discovery, acceptance, and eventual mass production of antibiotics, there existed a state of mind that antibiotics were “wonder drugs” that finally gave the human race a leg up on the problems that bacterial disease had created over generations. The fact of the matter though is that this way of thinking has led the human race in to a period of overuse (frequency) of prescribing and an under use (duration) during treatment that has led to a new precaution in medicine due to antibiotic resistant bacteria. In the topic of osteomyelitis, the bacteria of biggest concern include *Staphylococcus aureus* and *Staphylococcus epidermidis* [1,3,15]. In a study analyzing the United States incidence of infection caused by these bacteria in 2013, it was concluded that between 1.6 and 29.7 cases per 100,000, and of those cases, 2.8 to 43% of them were infections of the bone, depending on the location, and it has been shown these numbers are only increasing due to the increased frequency of knee and hip arthroplasty in the United States [2,11, 15–17].

A large amount of research has been dedicated to the discovery of the exact mechanisms of osteomyelitis infection and its subsequent treatment but problems exist. In vitro studies have been able to find fairly predictable patterns of infection and colonization among these infections, but once these circumstances are duplicated in vivo the results do not replicate in the same manner. The reason for this being that animal models have a much larger number of variables both environmental and genetic that must be taken in to account. This makes it difficult for researchers to test new antibiotics [18].

Currently, the gold standard antibiotic for the treatment of osteomyelitis is gentamycin, but it is having the potential to be ineffective to resistant bacteria resulting in the need for new affective antibiotics to be discovered [1]. Some of the most popular antibiotic investigations include: doxycycline, tigecycline, levofloxacin, nafcillin, vancomycin, minocycline, amoxicillin, and even silver particles.

In order to test new or already existing antibiotics for their effectiveness with bone infection, there must first be a delivery method. The most traditional method for delivery is through oral intake. The problem, however, is that this method can result in cytotoxicity and/or allergic reactions within body systems beyond the site of infection. This exact problem has been apparent in research measuring the efficiency of the antibiotic bortezomib, which showed potential in cell death and bone regeneration except it has the potential to cause peripheral neuropathy, and a fungal infection treatment method known as fungizone, which, if not isolated, can result in side effects such as fever, chills, hemolysis, and vomiting [19,20]. Ironically, even a derivative of gentamycin (gentamycin sulfate) has been shown to present systemic toxicity when administered orally rather than locally [21].

An answer to decrease toxicity and possibly increase the effectiveness of a treatment is to develop a way in order to localize the administration of a drug or antibiotic to the site of infection. The basis for this is to either directly apply them to an area surgically with the use of scaffolds either biological or non-biological or the use of compounds that demonstrate a high affinity for the site of infection or bone in this case. The detailed information on how this is being done will discussed later on.

By being directly administered to the location of infection, the drug is already at an advantage, but the antibiotic must be released in an efficient manner. Ideally, the delivery method should allow the antibiotic to release in large concentration at the start and then at a lower but still affective concentration over an extended period of time (days to weeks) [20,22]. This allows for efficient prevention of bacterial growth and adaptation to the treatment. Additionally, researchers are trying to find methods that will not only accomplish these goals but to also be able to promote bone growth following the elimination of infection by incorporating agonistic materials in to the delivery systems.

3. Non-biodegradable delivery systems

3.1. Cements

The use of non-biodegradable materials more commonly known as bone cements have been infused with antibiotics in order to effectively localize the administration of the drugs to a target site, with the most widely used composition being polymethylmethacrylate (PMMA) [16,

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