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What's New in Musculoskeletal Infection: Update on Biofilms.

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SPECIALTY UPDATE

What's New in Musculoskeletal Infection: Update on Biofilms

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Infections involving orthopaedic surgical implants present unique challenges when compared with infections that do not involve implants. Microorganisms have a high affinity for adhering to foreign materials commonly used in orthopaedics, including cobalt-chromium, titanium, polyethylene, and polymethylmethacrylate (PMMA) cement. When bacteria adhere to these surfaces, they can form a complex structure surrounded by a self-generated extracellular polymeric substance (EPS) matrix formed by multiplex agents of biopolymers consisting of proteins, polysaccharides, lipids, nucleic acids, and humic substances¹⁻³. The term “biofilm” is commonly used to describe this network of microorganisms, a term popularized by Dr. J. William Costerton et al. in 1978⁴.

Biofilms are formed by a confluence of bacteria commonly encountered in orthopaedic infections. Up to 65% of bacterial infections are caused by biofilm-producing organisms⁵. Staphylococci, specifically *Staphylococcus aureus* (*S. aureus*) and *Staphylococcus epidermidis* (*S. epidermidis*), are the most common biofilm-forming bacteria found in orthopaedics, and, when combined with *Pseudomonas aeruginosa* (*P. aeruginosa*), they represent nearly 75% of biofilm infections observed in medical devices⁶. *Propionibacterium acnes* (*P. acnes*), an organism commonly found in shoulder infections, has also been shown to form biofilm. Biofilms can be composed of a single organism or can be polymicrobial; polymicrobial biofilms are more difficult to eradicate⁷.

Once bacteria adhere to the surface of implants, they may replicate and may form a complex network of microorganisms that communicate with one another via cell-to-cell signaling that facilitates the participation of bacteria in quorum sensing⁷. Quorum sensing serves as an elementary endocrine system whereby bacteria sense the local cell population density and regulate gene expression by releasing extracellular molecules to facilitate synchronized changes in the bacteria within the biofilm. These transcriptional changes can occur with the exchange of plasmids between bacteria, which can confer genes for virulence factors and antibiotic resistance, and can commence the formation and secretion of the EPS matrix that supports the biofilm⁸. This matrix not only anchors bacteria to orthopaedic implants, but it also provides a nearly impenetrable defense mechanism as a result of the matrix serving as a protective physical barrier for bacteria against the host immune system⁹. This barrier also limits the flow of fluid within the biofilm, which reduces the amount of available nutrients; this leads bacteria to enter a no-growth or diminished-growth state that resists growth-dependent antimicrobial agents and renders it difficult for antibiotics to penetrate and eradicate biofilms¹⁰.

There have been numerous new technologies developed to detect biofilms, to prevent biofilm formation, or to disrupt biofilms to make them more susceptible to treatments. Detecting planktonic, or free-floating, bacteria can be achieved by traditional culturing; however, biofilm bacteria may be easier to detect using molecular methods, such as polymerase chain reaction (PCR), fluorescence in situ hybridization (FISH), and DNA microarrays¹¹. Some antibiotics, including rifampicin,

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TABLE I Microorganisms Used in Quorum-Sensing Studies

Microorganism	No. of Reports and References
<i>Pseudomonas</i>	20 ^{20,23-25,28-30,32,36,97-107}
<i>Staphylococcus</i>	8 ^{19,20,24,27,35,37,108,109}
<i>Acinetobacter baumannii</i>	3 ^{26,31,110}
<i>E. coli</i>	3 ^{28,111,112}
<i>Vibrio</i>	4 ¹¹³⁻¹¹⁶
<i>Candida</i>	3 ^{18,21,22}

which inhibits transcription, and meropenem, which inhibits cell wall biosynthesis, demonstrate antibiofilm activity^{12,13}. Other medications with different mechanisms, such as those that inhibit quorum sensing and bacteriophage therapy to disrupt the biofilm's extracellular matrix, have shown some promise against biofilms and remain an active area of investigation^{14,15}. Physical methods to disrupt biofilms using ultrasound and electrotherapy may be used in conjunction with other chemical methods of treating biofilms¹⁶.

There are numerous avenues by which the prevention and treatment of biofilm infections continue to be explored in orthopaedics. The purposes of this orthopaedic infection update are to describe the basic science of biofilm formation, to detail published guidelines for the diagnosis and treatment of biofilm infections, and to explain modifiable factors in biofilm formation after orthopaedic trauma and total joint arthroplasty. We reviewed literature published in the past 24 months to identify the studies most relevant to orthopaedics in both basic science and clinical practice with regard to musculoskeletal infection, and they are presented below.

Biofilm Basic Science

In 2015, biofilm research was robust, with more investigations published than any one clinician could keep up with. There were 4,817 publications cited in PubMed during 2015, plus another 907 in the first 2 months of 2016. For publications on the biology of biofilms, there were 870 citations from January 2015 to February 2016 that crossed multiple disciplines, including medicine (implant, bone, lung, urological), dentistry (periodontal disease), industry (waste water sludge), agriculture (plant, animal), and marine (fish, coral). Most of the basic science reports were not in the orthopaedic literature. PubMed identified only 82 citations as orthopaedic in 2015, plus 20 citations in January and February 2016. Myriad investigations studying all aspects of biofilm biology were reported; however, 3 important areas were noted: (1) quorum quenching (anti-quorum sensing), (2) persister cells, and (3) use of anti-cancer chemotherapy drugs to eradicate biofilms.

Quorum sensing was identified in 246 citations in 2015, with another 56 citations in January to February 2016; these citations were dominated by ways to interrupt or to alter

quorum sensing as a strategy to prevent or disperse biofilms, using six microorganisms (Table I). Although acyl homoserine lactone (AHL) from *Pseudomonas* was the dominant quorum-sensing molecule (autoinducer) studied, quorum-quenching strategies were all different. The theme was novel ideas involving unstudied compounds that all had therapeutic potential. None of the strategies presented were near clinical use, and none had corroboration. There were 19 molecular compounds¹⁷⁻³⁴, 19 plant-based compounds, 2 microorganism-generated compounds (Table II), and 2 nanoscale surface treatments (titania nanotubes³⁵ and zinc oxide nanoparticles³⁶). Another strategy that was investigated was quorum quenching to interrupt virulence factors rather than to prevent microorganism growth and biofilms³⁷. Attention to small-molecule anti-quorum-sensing agents carries the hope that resistance will not occur; however, resistance to some agents has already occurred³⁸.

Persister cells with inherent tolerance to antimicrobials were first described in the 1940s in planktonic bacterial populations. There were only 40 PubMed citations for persisters and antimicrobial tolerance from 2006 to 2014. During 2015, there were 15 citations covering the characteristics of persisters, how they are formed, and potential eradication strategies³⁹. One major point is that surface adhesion is important for persister cells to be present in biofilm⁴⁰. Two misconceptions that permeate the literature need consideration. The first

TABLE II Quorum-Quenching Compounds

Plant origin
<i>Centella asiatica</i> (spadeleaf) ¹⁰⁶
<i>Piper delinatum</i> flavonoids ¹¹⁴
<i>Leucetia chagosensis</i> ¹¹³
Tannic acid ¹⁰³
Cannabinoid HU-210 (medical marijuana) ¹¹⁶
Chamomile ¹⁰²
<i>Nymphaea tetragona</i> (water lily) ¹⁰⁰
Green tea polyphenols ¹⁰⁷
Pomegranate ¹¹²
Cranberry ¹⁰⁵
Rosmarinic acid (rosemary) ¹¹⁷
<i>Petiveria alliacea</i> ¹⁰¹
<i>Berberis aristata</i> , <i>Camellia sinensis</i> , and <i>Holarrhena antidysenterica</i> ¹¹¹
Quercetin (fruit and vegetable flavonol) ¹⁰⁴
Clove bud oil ⁹⁹
Phytochemicals of various medicinal plants ¹¹⁸
<i>Coriandrum sativum</i> (coriander) ¹¹⁹
Microorganism origin
<i>Glycyrrhiza glabra</i> ¹¹⁰
Halophilic marine <i>Streptomyces</i> ¹²⁰

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misconception is that persister cells cannot be killed. This is not true, as they are reliably killed when the antimicrobial concentration is high enough⁴¹. *Minimum biofilm eradication concentration* (MBEC) is widely used to refer to the concentration needed to kill all persister cells^{41,42}. Interestingly, the MBEC is lower when antimicrobial exposure is continuous and prolonged⁴¹. The second misconception is that a decreased number of microorganisms after a specific intervention, either in biofilm or attached to a surface, is a measure of success. Although this is considered good, it is not good enough. For cure or prevention, total elimination of all viable microbes is required. When any viable microbes remain, infection can propagate.

Isolated in vitro investigations using chemotherapeutic agents approved by the U.S. Food and Drug Administration (FDA) for specific anti-cancer indications (cisplatin⁴³, 5-fluorocytosine⁴⁴, and mitomycin C⁴⁵) showed eradication of all biofilm-embedded microbes, including persister cells, by mechanisms that are not growth-dependent. This raises the possibility that anti-cancer drugs may have a role in eradicating biofilms.

The extensive growth in research on biofilms is an indication of the need for clinically applicable knowledge. None of the interventions detailed in this basic science review are ready for general clinical application. Although understanding of the fundamental biology of biofilm-based infection is expected to increase the understanding and implementation of current treatment protocols, clinical adoption of basic science knowledge requires carefully designed and conducted clinical trials. Recent reports on clinical treatment protocols are discussed below.

Guidelines for the Diagnosis and Treatment of Biofilm Infections

Biofilms are found in many types of chronic infections, including those involving native tissue (e.g., chronic sinusitis, endocarditis, osteomyelitis) and those that infect indwelling devices (e.g., catheter-associated bloodstream and urinary tract infections, prosthetic valve endocarditis, vascular graft infections, ventriculoperitoneal shunt infections, and ventilator-associated pneumonias). The challenges faced by orthopaedists in treating biofilm infections are also confronted by clinicians in other disciplines. For example, the diagnosis of biofilm infections wherever they occur is challenged by non-planktonic organisms that do not replicate readily in laboratory culture. Decisions about device removal are also faced by surgeons and other interventionalists treating biofilm infections; these individuals must take into consideration the feasibility and morbidity associated with device removal, the likelihood of a cure in the setting of device retention, and the availability of antimicrobials for long-term suppression if a cure is not achieved.

Clinicians treating biofilm infections are often left with controversies about the optimal approach to diagnosis and management of biofilm infections. Guidelines and/or consen-

sus statements have been developed for some biofilm infections in which data are more robust, such as endocarditis⁴⁶; peri-prosthetic joint infection, as stated by the Infectious Diseases Society of America (IDSA)⁴⁷, American Academy of Orthopaedic Surgeons (AAOS)⁴⁸, and International Consensus Meeting on Periprosthetic Joint Infection⁴⁹; catheter-based infections⁵⁰; cardiac device infections⁵¹; otitis media⁵²; and ventilator-associated pneumonia⁵³. However, for some biofilm infections, there are insufficient data to generate meaningful guidelines. Until recently, to our knowledge, there had been no attempt to summarize recommendations on biofilm infections. In 2014, the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) developed guidelines for the diagnosis and treatment of biofilm infections⁵⁴. The multidisciplinary panel of 15 physician-scientists completed a systematic review of questions related to the prevention, diagnosis, and treatment of biofilm infections. The subject included biofilm infections for which other guidelines do not exist and comprised both native tissue infections (chronic lung infections in cystic fibrosis, chronic wound infections) and device-associated infections (orthopaedic devices, endotracheal tubes, intravenous catheters, urinary catheters and urethral stents, tissue fillers). Not surprisingly, although recommendations could be made for some of the questions addressed, many had insufficient data from which to generate conclusions.

In collating data on multiple different types of biofilm infections, common themes nonetheless emerged. Preventive strategies show promise, particularly the administration of topical therapies in the setting of implanted devices. Topical therapies recommended by the panel include the use of antimicrobial PMMA bone cement to prevent infections associated with orthopaedic devices, silver-coated endotracheal tubes to prevent ventilator-associated pneumonia, and chlorhexidine-impregnated sponges around central venous catheters to prevent bloodstream infection. Systemic antimicrobial prophylaxis is not widely effective; its use is only recommended for surgical antibiotic prophylaxis against infections associated with orthopaedic devices. Systemic prophylaxis against other types of biofilm infections has not been demonstrated to be effective.

Diagnostic challenges persist across all types of biofilm infections. Persistent local inflammation may be the only clinical clue to infection; however, this is not always specific for infection. Further, biofilms may colonize devices and may be detected with microbiological means but may not be associated with clinically important infection. Discerning whether infection is the cause of local inflammation is not always straightforward. For infections associated with orthopaedic devices, the guidelines recommended tissue samples rather than swabs, as biofilm organisms may be strongly adherent to tissue. More than one tissue culture is recommended and larger tissue samples (up to 1 cm³) are favored. When orthopaedic and other devices are explanted, sonication is suggested where available to liberate sessile organisms within the biofilm.

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Antimicrobial susceptibility focusing on planktonic organisms should be determined, but it may not represent the heightened resistance of sessile biofilm organisms and may lead to treatment failures. Biofilm-specific antimicrobial susceptibility methods have been designed but have not been clinically validated and are not yet recommended.

Few conclusions could be drawn about optimal treatment strategies, including for infections associated with orthopaedic devices. The ESCMID (European Society of Clinical Microbiology and Infectious Diseases) Guidelines panel concluded that eradication of some biofilm infections is possible without device explantation, although a cure cannot always be predicted in advance⁵⁴. More favorable outcomes are seen when the duration of infection symptoms is short (when the biofilm is young) and when the infecting organisms are susceptible to biofilm-validated antimicrobials, such as rifampicins for staphylococci and fluoroquinolones for gram-negative infections. Combinations of local and systemic therapies can be recommended for some biofilm infections, including orthopaedic infections. Unfortunately, no tests are available that inform when a biofilm infection is clinically cured, as the available surrogate tests can be inaccurate in the face of antibiotic therapy.

Although many questions remain unanswered, it is hoped that the experience gained by this guideline review may facilitate research into solutions that apply to multiple types of biofilm infections and thereby can transcend disciplines.

Biofilm in Orthopaedic Trauma

In the field of orthopaedic trauma, open fractures are injuries in which there is concern of biofilm formation from initial presentation⁵⁵ and are aptly described as “the race for the surface” by Gristina et al.⁵⁶. Implants also represent a surface on which biofilm may easily develop. With open fractures, biofilm can develop on bone and in soft tissues within a matter of hours, especially when either is devitalized, and it competes with the ability of bone to heal after a fracture.

Open fractures represent a broad spectrum of injury because of the multitude of local and systemic host factors that can potentially influence outcomes. Local host factors include, but are not limited to: the extent of contamination; the size of the open wound, including undermining; soft-tissue injury and/or loss; previous implants and/or surgical procedures; periosteal stripping; bone vascularity and/or loss; and blood supply. Systemic host factors consist of age, nutrition, hypothermia, immune function, smoking history, diabetes, comorbid chronic conditions, hypoxia, and endothelial dysfunction⁵⁷.

Acute and/or surgically modifiable factors for open fractures can also influence outcomes and can include the type of surgical procedure⁵⁸, the stability of the fracture, the timing of the surgical procedure⁵⁹⁻⁶¹, the duration of antibiotics⁶², the timing of systemic antibiotics^{62,63}, local antibiotic delivery^{64,65}, the type of irrigant⁶⁶⁻⁶⁸, the length of hypotension, anemia, the

quality of debridement (reduction of local bioburden), the type of wound closure^{69,70}, the timing of wound closure⁷¹, and avoidance of the second-hit phenomenon⁷². Recent literature has suggested that these modifiable factors may directly or indirectly affect biofilm formation and thus represent immunomodulation factors that can optimize healing of the injury by the host's immune system even in the presence of presumed biofilm.

Preoperative intravenous prophylactic antibiotic administration is effective, and recent literature pertaining to open fractures has shown that administration of therapeutic intravenous antibiotics within 1 hour of injury leads to improved outcomes. Some delay in formal surgical debridement can be accepted for low-grade open fractures, as the risk for presumed biofilm-related infection is decreased⁶¹. Reduction of the local bioburden in open fractures involves irrigation and debridement of the bone and soft tissues. Research has also demonstrated that high-pressure irrigation does not lead to less reoperation compared with low-pressure irrigation and may lead to additional soft-tissue injury and delayed bone-healing^{66-68,73}.

Assuming that the bioburden has been sufficiently minimized after an open fracture, wound closure can be considered. Lower-grade open fractures can be considered for wound closure at the initial surgical procedure⁵⁸, but for high-grade open fractures, delayed wound closure, including use of adjuncts such as local antibiotics^{64,65} and negative-pressure wound therapy devices, may lead to optimal limb salvage rates⁶⁹. Fracture stability and sufficient fracture reduction minimize soft-tissue shear and tension and can be achieved by a variety of modalities. Intramedullary nailing of select open fractures has been shown to have superior results compared with external fixation or plating⁷⁴.

Because both osseous and soft-tissue injuries contribute to the systemic inflammatory response, it is fair to assume that appropriate surgical techniques can decrease bioburden and can provide fracture stability, resulting in lower local inflammatory response (surgical immunomodulation)^{75,76}. The above comments assume that biofilm can develop following an open fracture, and currently we do not have the technology to noninvasively quantify biofilm activity and presence in a stable open fracture following wound closure. Surgical judgment and experience will be important in selecting the appropriate tools and techniques to optimally treat open fractures.

Biofilm in Total Joint Arthroplasty

Periprosthetic joint infections after total joint arthroplasty are similar to infections in orthopaedic trauma in the sense that an implant is normally present, and there can be a similar race to the surface of implants, in which bone ingrowth competes with bacterial growth. Even in the presence of preoperative antibiotics, staphylococcal and *P. acnes* biofilms can form on implant surfaces⁷⁷. There are 3 main areas of recent investigation in this field: the diagnosis and imaging of biofilms, biofilm prevention, and the treatment of biofilms in periprosthetic joint infection.

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Diagnosis and Imaging

Molecular methods such as PCR have been used to aid in the diagnosis of periprosthetic joint infection. However, recent studies have indicated low sensitivity of detection using soft-tissue and bone samples and have indicated that culture may still be more effective, especially for detecting common organisms (*S. aureus*, *S. epidermidis*, and *P. aeruginosa*)^{78,79}. Imaging may provide improved means for diagnosing biofilm infections, although this requires direct visualization of implants or direct access to implants to obtain samples. Molecular fluorescent staining with 16S rRNA FISH and use of confocal laser scanning microscopy enables scientists to image biofilms⁸⁰. Future methods of diagnosing biofilm infection, including the means to image biofilm without the need for an incision, would substantially improve the ability to detect, identify, and treat these infections.

Prevention

The prevention of biofilm formation in total joint arthroplasty requires impregnating implants with antimicrobials, such as antioxidants, antibiotics, and silver. The antioxidant vitamin E was initially introduced into polyethylene to reduce free radicals and to reduce oxidative wear in total joint arthroplasty. Recent studies were contradictory with regard to biofilm prevention; one study demonstrated that vitamin E-blended ultra-high molecular weight polyethylene was unable to prevent biofilm formation⁸¹, but another study demonstrated that it decreased the adhesiveness of *S. aureus* and *Escherichia coli* to this polyethylene in comparison with standard or oxidized ultra-high molecular weight polyethylene⁸². However, by adding a hydrophilic and antibiofilm layer of poly(2-methacryloyloxyethyl phosphorylcholine) (PMPC)-graft to a vitamin E-blended polyethylene, there was a hundredfold reduction in adherence of biofilm⁸³. Thus, antioxidants and other coatings may hold promise for preventing future implant-associated infections.

Previous studies have demonstrated that covalently bonding antibiotics to titanium implants can inhibit biofilm formation⁸⁴⁻⁸⁶. More recent studies have shown that biofilm growth can be partially inhibited when PMMA cement is combined with vancomycin and can be fully inhibited when PMMA is mixed with both daptomycin and gentamicin⁸⁷. Antibiotics such as gentamicin can also be loaded in Fe₃O₄/carbonated hydroxyapatite coatings to prevent biofilm formation and to decrease bacterial adhesion, while still allowing the implantation of devices in cementless total joint arthroplasty⁸⁸.

Although antibiotics are useful agents for fighting bacterial infections, there has been increased antibiotic resistance and there are potentially harmful side effects from using these drugs. Novel antimicrobial methods, such as the photosensitizer RLP068/Cl, have been developed to disrupt biofilms without leading to antibiotic resistance⁸⁹. Silver is a known antimicrobial, and recent studies have evaluated the use of silver in preventing biofilm infections against *Acinetobacter*

baumannii, *S. epidermidis*, *S. aureus*, and *P. aeruginosa* when coated on the surfaces of titanium alloys^{90,91}. Finally, silver nanoparticles have also been shown to be effective against biofilm formation when incorporated within acrylic bone cement but not effective against planktonic bacteria⁹².

Treatment

Traditionally, biofilm infections have been treated by 2-stage exchange arthroplasty in the United States and 1-stage exchange arthroplasty in certain parts of Europe. Although biofilm from the implant is physically removed by extracting the existing components, the potential exists for persistence of biofilm in the surrounding soft tissue. Most patients undergoing treatment for periprosthetic joint infection also receive concomitant intravenous antibiotics, but a recent in vitro study demonstrated that administering cefazolin even at increased concentrations still resulted in persistent *Staphylococcus* biofilm on cobalt-chromium PMMA and polyethylene⁹³. Additionally, pulse lavage was also demonstrated to be ineffective in fully eradicating biofilm and only provided a less-than-tenfold reduction in biofilm as measured with laser scanning confocal microscopy imaging⁷³. Similarly, low-frequency sonication may not be able to treat biofilm infections as fully as pulse lavage can, and it may actually damage implants by increasing surface roughness and may potentially reduce remaining articular cartilage thickness⁹⁴.

However, utilizing other chemical methods of eradicating biofilm such as 2% to 4% chlorhexidine gluconate with pulse irrigation for methicillin-resistant *S. aureus* biofilm was effective at reducing the colony-forming units of bacteria⁹⁵. In addition, the use of calcium sulfate loaded with vancomycin, tobramycin, or a combination of vancomycin and tobramycin reduced biofilm formation and prevented bacterial colonization but did not eradicate established biofilm⁹⁶.

Biofilms are involved in all orthopaedic infections, especially cases where implants are present. To our knowledge, there are no current guidelines in the United States for treating these infections, and such guidelines will need to be developed as we gain more understanding regarding biofilm development. Novel mechanical methods for disrupting biofilm will need to be developed so that biofilms can be detached from adherent surfaces, such as stainless steel, cobalt-chromium, and titanium. Future developments in pharmaceuticals, including the prevention of quorum sensing, quorum quenching, and use of anti-cancer drugs may provide us with new drugs for our armamentarium against biofilms. The opportunity is ripe to develop novel chemical and mechanical means for treating biofilm infections, and this will be important to aid in the future eradication of orthopaedic infections.

Evidence-Based Orthopaedics

The editorial staff of *The Journal* reviewed a large number of recently published research studies related to the

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musculoskeletal system that received a higher Level of Evidence grade. In addition to articles cited already in the Update, 4 other articles with a higher Level of Evidence grade were identified that were relevant to musculoskeletal infection. A list of those titles is appended to this review after the standard bibliography. We have provided a brief commentary about each of the articles to help guide your further reading, in an evidence-based fashion, in this subspecialty area.

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References

- Costerton JW, Stewart PS, Greenberg EP. Bacterial biofilms: a common cause of persistent infections. *Science*. 1999 May 21;284(5418):1318-22.
- Hall-Stoodley L, Costerton JW, Stoodley P. Bacterial biofilms: from the natural environment to infectious diseases. *Nat Rev Microbiol*. 2004 Feb;2(2):95-108.
- Vu B, Chen M, Crawford RJ, Ivanova EP. Bacterial extracellular polysaccharides involved in biofilm formation. *Molecules*. 2009 Jul 13;14(7):2535-54.
- Costerton JW, Geesey GG, Cheng KJ. How bacteria stick. *Sci Am*. 1978 Jan;238(1):86-95.
- Stoodley P, Ehrlich GD, Sedghizadeh PP, Hall-Stoodley L, Baratz ME, Altman DT, Sotereanos NG, Costerton JW, Demeo P. Orthopaedic biofilm infections. *Curr Orthop Pract*. 2011 Nov;22(6):558-63.
- McConoughey SJ, Howlin R, Granger JF, Manring MM, Calhoun JH, Shirtliff M, Kathju S, Stoodley P. Biofilms in periprosthetic orthopedic infections. *Future Microbiol*. 2014;9(8):987-1007.
- Elias S, Banin E. Multi-species biofilms: living with friendly neighbors. *FEMS Microbiol Rev*. 2012 Sep;36(5):990-1004. Epub 2012 Feb 2.
- Bauer TW, Grosso MJ. The basic science of biofilm and its relevance to the treatment of periprosthetic joint infection. *Orthopaedic Knowledge Online Journal*. 2013 Sep;11(9). <http://www.aaos.org/OKOJ/vol11/issue9/SCI003/?ssopc=1>. Accessed 2016 Apr 21.
- Thurlow LR, Hanke ML, Fritz T, Angle A, Aldrich A, Williams SH, Engebretsen IL, Bayles KW, Horswill AR, Kielian T. *Staphylococcus aureus* biofilms prevent macrophage phagocytosis and attenuate inflammation in vivo. *J Immunol*. 2011 Jun 1;186(11):6585-96. Epub 2011 Apr 27.
- Stewart PS, Costerton JW. Antibiotic resistance of bacteria in biofilms. *Lancet*. 2001 Jul 14;358(9276):135-8.
- Tzeng A, Tzeng TH, Vasdev S, Korth K, Healey T, Parvizi J, Saleh KJ. Treating periprosthetic joint infections as biofilms: key diagnosis and management strategies. *Diagn Microbiol Infect Dis*. 2015 Mar;81(3):192-200. Epub 2014 Nov 5.
- Mihailescu R, Furustrand T, Corvec S, Oliva A, Betrisey B, Borens O, Trampuz A. High activity of fosfomycin and rifampin against methicillin-resistant *Staphylococcus aureus* biofilm in vitro and in an experimental foreign-body infection model. *Antimicrob Agents Chemother*. 2014 May;58(5):2547-53. Epub 2014 Feb 18.
- Viganor L, Galdino AC, Nunes AP, Santos KR, Branquinha MH, Devereux M, Kellett A, McCann M, Santos AL. Anti-Pseudomonas aeruginosa activity of 1,10-phenanthroline-based drugs against both planktonic- and biofilm-growing cells. *J Antimicrob Chemother*. 2016 Jan;71(1):128-34. Epub 2015 Sep 27.
- Lu TK, Koeris MS. The next generation of bacteriophage therapy. *Curr Opin Microbiol*. 2011 Oct;14(5):524-31. Epub 2011 Aug 23.
- Tay SB, Yew WS. Development of quorum-based anti-virulence therapeutics targeting gram-negative bacterial pathogens. *Int J Mol Sci*. 2013 Aug 9;14(8):16570-99.
- Yu H, Chen S, Cao P. Synergistic bactericidal effects and mechanisms of low intensity ultrasound and antibiotics against bacteria: a review. *Ultrason Sonochem*. 2012 May;19(3):377-82. Epub 2011 Nov 25.
- Amara N, Gregor R, Rayo J, Dandela R, Daniel E, Liubin N, Willems M, Ben-Tzvi A, Krom B, Meijler MM. Fine-tuning covalent inhibition of bacterial quorum sensing. *Chembiochem*. 2016 Feb 3. [Epub ahead of print].
- Arias LS, Delbem AC, Fernandes RA, Barbosa DB, Monteiro DR. Activity of tyrosol against single and mixed-species oral biofilms. *J Appl Microbiol*. 2016 Jan 23. [Epub ahead of print].
- Brackman G, Breyne K, De Rycke R, Vermote A, Van Nieuwerburgh F, Meyer E, Van Calenbergh S, Coenye T. The quorum sensing inhibitor hamamelitannin increases antibiotic susceptibility of *Staphylococcus aureus* biofilms by affecting peptidoglycan biosynthesis and eDNA release. *Sci Rep*. 2016 Feb 1;6:20321.
- Brackman G, Garcia-Fernandez MJ, Lenoir J, De Meyer L, Remon JP, De Beer T, Concheiro A, Alvarez-Lorenzo C, Coenye T. Dressings loaded with cyclodextrin-hamamelitannin complexes increase *Staphylococcus aureus* susceptibility toward antibiotics both in single as well as in mixed biofilm communities. *Macromol Biosci*. 2016 Feb 18. [Epub ahead of print].
- Feldman M, Ginsburg I, Al-Quntar A, Steinberg D. Thiazolidinedione-8 alters symbiotic relationship in *C. albicans*-*S. mutans* dual species biofilm. *Front Microbiol*. 2016 Feb 10;7:140.
- Fernandes RA, Monteiro DR, Arias LS, Fernandes GL, Delbem AC, Barbosa DB. Biofilm formation by *Candida albicans* and *Streptococcus mutans* in the presence of farnesol: a quantitative evaluation. *Biofouling*. 2016 Mar;32(3):329-38.
- Furiga A, Lajoie B, El Hage S, Baziard G, Roques C. Impairment of *Pseudomonas aeruginosa* biofilm resistance to antibiotics by combining the drugs with a quorum-sensing inhibitor. *Antimicrob Agents Chemother*. 2015 Dec 28;60(3):1676-86.
- Gizdavic-Nikolaidis MR, Pagnon JC, Ali N, Sum R, Davies N, Roddam LF, Ambrose M. Functionalized polyanilines disrupt *Pseudomonas aeruginosa* and *Staphylococcus aureus* biofilms. *Colloids Surf B Biointerfaces*. 2015 Dec 1;136:666-73. Epub 2015 Oct 22.
- Hazan R, Que YA, Maura D, Strobel B, Majcherczyk PA, Hopper LR, Wilbur DJ, Hreha TN, Barquera B, Rahme LG. Auto poisoning of the respiratory chain by a quorum-sensing-regulated molecule favors biofilm formation and antibiotic tolerance. *Curr Biol*. 2016 Jan 25;26(2):195-206. Epub 2016 Jan 14.
- Kostoulas X, Murray GL, Cerqueira GM, Kong JB, Bantun F, Mylonakis E, Khoo CA, Peleg AY. Impact of a cross-kingdom signaling molecule of *Candida albicans* on *Acinetobacter baumannii* physiology. *Antimicrob Agents Chemother*. 2015 Oct 19;60(1):161-7.
- Kratzchvil MJ, Tal-Gan Y, Yang T, Blackwell HE, Lynn DM. Nanoporous superhydrophobic coatings that promote the extended release of water-labile quorum sensing inhibitors and enable long-term modulation of quorum sensing in *Staphylococcus aureus*. *ACS Biomater Sci Eng*. 2015 Oct 12;1(10):1039-49. Epub 2015 Aug 26.
- Nizalapur S, Kimyon Ö, Biswas NN, Gardner CR, Griffith R, Rice SA, Manefield M, Willcox M, Black DS, Kumar N. Design, synthesis and evaluation of N-aryl-glyoxamide derivatives as structurally novel bacterial quorum sensing inhibitors. *Org Biomol Chem*. 2015 Dec 23;14(2):680-93.
- Park S, Kim HS, Ok K, Kim Y, Park HD, Byun Y. Design, synthesis and biological evaluation of 4-(alkyloxy)-6-methyl-2H-pyran-2-one derivatives as quorum sensing inhibitors. *Bioorg Med Chem Lett*. 2015 Aug 1;25(15):2913-7. Epub 2015 May 28.
- Qu L, She P, Wang Y, Liu F, Zhang D, Chen L, Luo Z, Xu H, Qi Y, Wu Y. Effects of norspermidine on *Pseudomonas aeruginosa* biofilm formation and eradication. *Microbiol Open*. 2016 Jan 27. [Epub ahead of print].
- Tay SB, Chow JY, Go MK, Yew WS. Anti-virulent disruption of pathogenic biofilms using engineered quorum-quenching lactonases. *J Vis Exp*. 2016 Jan 1;107.
- Thomann A, de Mello Martins AG, Brengel C, Empting M, Hartmann RW. Application of dual inhibition concept within looped autoregulatory systems towards antivirulence agents against *Pseudomonas aeruginosa* infections. *ACS Chem Biol*. 2016 Mar 1. [Epub ahead of print].

WHAT'S NEW IN MUSCULOSKELETAL INFECTION: UPDATE ON BIOFILMS

33. Wholey WY, Kochan TJ, Storck DN, Dawid S. Coordinated bacteriocin expression and competence in *Streptococcus pneumoniae* contributes to genetic adaptation through neighbor predation. *PLoS Pathog*. 2016 Feb 3;12(2):e1005413.
34. Zhou Y, Zhao R, Ma B, Gao H, Xue X, Qu D, Li M, Meng J, Luo X, Hou Z. Oligomerization of RNAIII-inhibiting peptide inhibits adherence and biofilm formation of methicillin-resistant *Staphylococcus aureus* in vitro and in vivo. *Microb Drug Resist*. 2016 Apr;22(3):193-201. Epub 2015 Nov 16.
35. Kumeria T, Mon H, Aw MS, Gulati K, Santos A, Griesser HJ, Losic D. Advanced biopolymer-coated drug-releasing titania nanotubes (TNTs) implants with simultaneously enhanced osteoblast adhesion and antibacterial properties. *Colloids Surf B Biointerfaces*. 2015 Jun 1;130:255-63. Epub 2015 Apr 18.
36. García-Lara B, Saucedo-Mora MÁ, Roldán-Sánchez JA, Pérez-Eretza B, Ramasamy M, Lee J, Coria-Jimenez R, Tapia M, Varela-Guerrero V, García-Contreras R. Inhibition of quorum-sensing-dependent virulence factors and biofilm formation of clinical and environmental *Pseudomonas aeruginosa* strains by ZnO nanoparticles. *Lett Appl Microbiol*. 2015 Sep;61(3):299-305. Epub 2015 Jul 8.
37. Baldry M, Kitiř B, Frøkiær H, Christensen SB, Taverne N, Meijerink M, Franzyk H, Olsen CA, Wells JM, Ingmer H. The agr inhibitors Solonomamide B and analogues alter immune responses to *Staphylococcus aureus* but do not exhibit adverse effects on immune cell functions. *PLoS One*. 2016 Jan 5;11(1):e0145618.
38. Ruer S, Pinotsis N, Steadman D, Waksman G, Remaut H. Virulence-targeted antibacterials: concept, promise, and susceptibility to resistance mechanisms. *Chem Biol Drug Des*. 2015 Oct;86(4):379-99. Epub 2015 Feb 6.
39. Wood TK. Combatting bacterial persister cells. *Biotechnol Bioeng*. 2016 Mar;113(3):476-83. Epub 2015 Sep 3.
40. Sun J, Li Z, Chu H, Guo J, Jiang G, Qi Q. *Candida albicans* amphotericin B-tolerant persister formation is closely related to surface adhesion. *Mycopathologia*. 2016 Feb;181(1-2):41-9. Epub 2015 Sep 18.
41. Castaneda P, McLaren A, Tavaziva G, Overstreet D. Biofilm antimicrobial susceptibility increases with antimicrobial exposure time. *Clin Orthop Relat Res*. 2016 Jan 21. [Epub ahead of print].
42. Overstreet D, McLaren A, Calara F, Vernon B, McLemore R. Local gentamicin delivery from resorbable viscous hydrogels is therapeutically effective. *Clin Orthop Relat Res*. 2015 Jan;473(1):337-47. Epub 2014 Sep 17.
43. Chowdhury N, Wood TL, Martínez-Vázquez M, García-Contreras R, Wood TK. DNA-crosslinker cisplatin eradicates bacterial persister cells. *Biotechnol Bioeng*. 2016 Feb 23. [Epub ahead of print].
44. Sun J, Liu X, Jiang G, Qi Q. Inhibition of nucleic acid biosynthesis makes little difference to formation of amphotericin B-tolerant persisters in *Candida albicans* biofilm. *Antimicrob Agents Chemother*. 2015 Mar;59(3):1627-33. Epub 2014 Dec 29.
45. Kwan BW, Chowdhury N, Wood TK. Combatting bacterial infections by killing persister cells with mitomycin C. *Environ Microbiol*. 2015 Nov;17(11):4406-14. Epub 2015 May 18.
46. Baddour LM, Wilson WR, Bayer AS, Fowler VG Jr, Tleyeh IM, Rybak MJ, Barsic B, Lockhart PB, Gewitz MH, Levison ME, Bolger AF, Steckelberg JM, Baltimore RS, Fink AM, O'Gara P, Taubert KA; American Heart Association Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease of the Council on Cardiovascular Disease in the Young, Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and Stroke Council. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications: a scientific statement for healthcare professionals from the American Heart Association. *Circulation*. 2015 Oct 13;132(15):1435-86. Epub 2015 Sep 15.
47. Osmon DR, Berbari EF, Berendt AR, Lew D, Zimmerli W, Steckelberg JM, Rao N, Hanssen A, Wilson WR; Infectious Diseases Society of America. Diagnosis and management of prosthetic joint infection: clinical practice guidelines by the Infectious Diseases Society of America. *Clin Infect Dis*. 2013 Jan;56(1):e1-25. Epub 2012 Dec 6.
48. Della Valle C, Parvizi J, Bauer TW, Dicesare PE, Evans RP, Segreti J, Spangehl M, Waters WC 3rd, Keith M, Turkelson CM, Wies JL, Sluka P, Hitchcock K; American Academy of Orthopaedic Surgeons. Diagnosis of periprosthetic joint infections of the hip and knee. *J Am Acad Orthop Surg*. 2010 Dec;18(12):760-70.
49. Parvizi J, Gehrke T, Chen AF. Proceedings of the International Consensus on Periprosthetic Joint Infection. *Bone Joint J*. 2013 Nov;95-B(11):1450-2.
50. Mermel LA, Allon M, Bouza E, Craven DE, Flynn P, O'Grady NP, Raad II, Rijnders BJ, Sherertz RJ, Warren DK. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2009 Jul 1;49(1):1-45.
51. Baddour LM, Epstein AE, Erickson CC, Knight BP, Levison ME, Lockhart PB, Masoudi FA, Okum EJ, Wilson WR, Beerman LB, Bolger AF, Estes NA 3rd, Gewitz M, Newburger JW, Schron EB, Taubert KA; American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee; Council on Cardiovascular Disease in Young; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Nursing; Council on Clinical Cardiology; Interdisciplinary Council on Quality of Care; American Heart Association. Update on cardiovascular implantable electronic device infections and their management: a scientific statement from the American Heart Association. *Circulation*. 2010 Jan 26;121(3):458-77. Epub 2010 Jan 4.
52. Lieberthal AS, Carroll AE, Chonmaitree T, Ganiats TG, Hoberman A, Jackson MA, Joffe MD, Miller DT, Rosenfeld RM, Sevilla XD, Schwartz RH, Thomas PA, Tunkel DE. The diagnosis and management of acute otitis media. *Pediatrics*. 2013 Mar;131(3):e964-99. Epub 2013 Feb 25.
53. American Thoracic Society; Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *Am J Respir Crit Care Med*. 2005 Feb 15;171(4):388-416.
54. Højby N, Bjarnsholt T, Moser C, Bassi GL, Coenye T, Donelli G, Hall-Stoodley L, Holá V, Imbert C, Kirketerp-Møller K, Lebeaux D, Oliver A, Ullmann AJ, Williams C; ESCMID Study Group for Biofilms and consulting external expert Werner Zimmerli. ESCMID guideline for the diagnosis and treatment of biofilm infections 2014. *Clin Microbiol Infect*. 2015 May;21(Suppl 1):S1-25. Epub 2015 Jan 14.
55. Nishitani K, Sutjipornpalangkul W, de Mesy Bentley KL, Varrone JJ, Bello-Irizarry SN, Ito H, Matsuda S, Kates SL, Daiss JL, Schwarz EM. Quantifying the natural history of biofilm formation in vivo during the establishment of chronic implant-associated *Staphylococcus aureus* osteomyelitis in mice to identify critical pathogen and host factors. *J Orthop Res*. 2015 Sep;33(9):1311-9. Epub 2015 May 18.
56. Gristina AG, Naylor PT, Webb LX. Molecular mechanisms in musculoskeletal sepsis: the race for the surface. *Instr Course Lect*. 1990;39:471-82.
57. Cierny G 3rd, Mader JT, Penninck JJ. A clinical staging system for adult osteomyelitis. *Clin Orthop Relat Res*. 2003 Sep;414:7-24.
58. Wiss DA, Gilbert P, Merritt PO, Sarmiento A. Immediate internal fixation of open ankle fractures. *J Orthop Trauma*. 1988;2(4):265-71.
59. Hull PD, Johnson SC, Stephen DJ, Kreder HJ, Jenkinson RJ. Delayed debridement of severe open fractures is associated with a higher rate of deep infection. *Bone Joint J*. 2014 Mar;96-B(3):379-84.
60. Jenkinson RJ, Kiss A, Johnson S, Stephen DJ, Kreder HJ. Delayed wound closure increases deep-infection rate associated with lower-grade open fractures: a propensity-matched cohort study. *J Bone Joint Surg Am*. 2014 Mar 5;96(5):380-6.
61. Reuss BL, Cole JD. Effect of delayed treatment on open tibial shaft fractures. *Am J Orthop (Belle Mead NJ)*. 2007 Apr;36(4):215-20.
62. Obremeskey W, Molina C, Collinge C, Nana A, Tornetta P 3rd, Sagı C, Schmidt A, Probe R, Ahn J, Browner BD; Evidence-Based Quality Value and Safety Committee Orthopaedic Trauma Association, Writing Committee. Current practice in the management of open fractures among orthopaedic trauma surgeons. Part A: initial management. A survey of orthopaedic trauma surgeons. *J Orthop Trauma*. 2014 Aug;28(8):e198-202.
63. Gosselin RA, Roberts I, Gillespie WJ. Antibiotics for preventing infection in open limb fractures. *Cochrane Database Syst Rev*. 2004;1:CD003764.
64. Henry SL, Ostermann PA, Seligson D. The antibiotic bead pouch technique. The management of severe compound fractures. *Clin Orthop Relat Res*. 1993 Oct;295:54-62.
65. Lawing CR, Lin FC, Dahners LE. Local injection of aminoglycosides for prophylaxis against infection in open fractures. *J Bone Joint Surg Am*. 2015 Nov 18;97(22):1844-51.
66. Caprise PA Jr, Miclau T, Dahners LE, Dirschl DR. High-pressure pulsatile lavage irrigation of contaminated fractures: effects on fracture healing. *J Orthop Res*. 2002 Nov;20(6):1205-9.
67. Dirschl DR, Duff GP, Dahners LE, Edin M, Rahn BA, Miclau T. High pressure pulsatile lavage irrigation of intraarticular fractures: effects on fracture healing. *J Orthop Trauma*. 1998 Sep-Oct;12(7):460-3.
68. Bhandari M, Jeray KJ, Petrisor BA, Devereaux PJ, Heels-Ansdell D, Schemitsch EH, Anglen J, Della Rocca GJ, Jones C, Kreder H, Liew S, McKay P, Papp S, Sancheti P, Sprague S, Stone TB, Sun X, Tanner SL, Tornetta P 3rd, Tufescu T, Walter S, Guyatt GH; FLOW Investigators. A trial of wound irrigation in the initial management of open fracture wounds. *N Engl J Med*. 2015 Dec 31;373(27):2629-41. Epub 2015 Oct 8.
69. Schlatterer DR, Hirschfeld AG, Webb LX. Negative pressure wound therapy in grade IIIB tibial fractures: fewer infections and fewer flap procedures? *Clin Orthop Relat Res*. 2015 May;473(5):1802-11. Epub 2015 Jan 17.
70. Webb LX, Dedmond B, Schlatterer D, Laverty D. The contaminated high-energy open fracture: a protocol to prevent and treat inflammatory mediator storm-induced soft-tissue compartment syndrome (IMSICS). *J Am Acad Orthop Surg*. 2006; 14(10 Spec No.):S82-6.
71. Hulsker CC, Kleinveld S, Zonnenberg CB, Hogervorst M, van den Bekerom MP. Evidence-based treatment of open ankle fractures. *Arch Orthop Trauma Surg*. 2011 Nov;131(11):1545-53. Epub 2011 Jun 29.
72. Lichte P, Kobbe P, Dombroski D, Pape HC. Damage control orthopedics: current evidence. *Curr Opin Crit Care*. 2012 Dec;18(6):647-50.
73. Urish KL, DeMuth PW, Craft DW, Haider H, Davis CM 3rd. Pulse lavage is inadequate at removal of biofilm from the surface of total knee arthroplasty materials. *J Arthroplasty*. 2014 Jun;29(6):1128-32. Epub 2013 Dec 16.

WHAT'S NEW IN MUSCULOSKELETAL INFECTION: UPDATE ON BIOFILMS

- 74.** Foote CJ, Guyatt GH, Vignesh KN, Mundi R, Chaudhry H, Heels-Ansdell D, Thabane L, Tornetta P 3rd, Bhandari M. Which surgical treatment for open tibial shaft fractures results in the fewest reoperations? A network meta-analysis. *Clin Orthop Relat Res.* 2015 Jul;473(7):2179-92. Epub 2015 Feb 28.
- 75.** Lord JM, Midwinter MJ, Chen YF, Belli A, Brohi K, Kovacs EJ, Koenderman L, Kubes P, Lilford RJ. The systemic immune response to trauma: an overview of pathophysiology and treatment. *Lancet.* 2014 Oct 18;384(9952):1455-65. Epub 2014 Oct 17.
- 76.** Pfeifer R, Darwiche S, Kohut L, Billiar TR, Pape HC. Cumulative effects of bone and soft tissue injury on systemic inflammation: a pilot study. *Clin Orthop Relat Res.* 2013 Sep;471(9):2815-21.
- 77.** Dastgheyb SS, Hammoud S, Ketonis C, Liu AY, Fitzgerald K, Parvizi J, Purtill J, Ciccotti M, Shapiro IM, Otto M, Hickok NJ. Staphylococcal persistence due to biofilm formation in synovial fluid containing prophylactic cefazolin. *Antimicrob Agents Chemother.* 2015 Apr;59(4):2122-8. Epub 2015 Jan 26.
- 78.** Ryu SY, Greenwood-Quaintance KE, Hanssen AD, Mandrekar JN, Patel R. Low sensitivity of periprosthetic tissue PCR for prosthetic knee infection diagnosis. *Diagn Microbiol Infect Dis.* 2014 Aug;79(4):448-53. Epub 2014 Apr 12.
- 79.** Zegaer BH, Ioannidis A, Babis GC, Ioannidou V, Kossyvakis A, Bersimis S, Papaparaskevas J, Petinaki E, Pliatsika P, Chatzipanagiotou S. Detection of bacteria bearing resistant biofilm forms, by using the universal and specific PCR is still unhelpful in the diagnosis of periprosthetic joint infections. *Front Med (Lausanne).* 2014 Sep 16;1:30.
- 80.** Nistico L, Hall-Stoodley L, Stoodley P. Imaging bacteria and biofilms on hardware and periprosthetic tissue in orthopedic infections. *Methods Mol Biol.* 2014;1147:105-26.
- 81.** Williams DL, Vinciguerra J, Lerdahl JM, Bloebaum RD. Does vitamin E-blended UHMWPE prevent biofilm formation? *Clin Orthop Relat Res.* 2015 Mar;473(3):928-35.
- 82.** Banche G, Allizond V, Bracco P, Bistolfi A, Boffano M, Cimino A, Brach del Prever EM, Cuffini AM. Interplay between surface properties of standard, vitamin E blended and oxidised ultra high molecular weight polyethylene used in total joint replacement and adhesion of *Staphylococcus aureus* and *Escherichia coli*. *Bone Joint J.* 2014 Apr;96-B(4):497-501.
- 83.** Kyomoto M, Shobuie T, Moro T, Yamane S, Takatori Y, Tanaka S, Miyamoto H, Ishihara K. Prevention of bacterial adhesion and biofilm formation on a vitamin E-blended, cross-linked polyethylene surface with a poly(2-methacryloyloxyethyl phosphorylcholine) layer. *Acta Biomater.* 2015 Sep;24:24-34. Epub 2015 Jun 4.
- 84.** Antoci V Jr, Adams CS, Parvizi J, Ducheyne P, Shapiro IM, Hickok NJ. Covalently attached vancomycin provides a nanoscale antibacterial surface. *Clin Orthop Relat Res.* 2007 Aug;461:81-7.
- 85.** Antoci V Jr, King SB, Jose B, Parvizi J, Zeiger AR, Wickstrom E, Freeman TA, Composto RJ, Ducheyne P, Shapiro IM, Hickok NJ, Adams CS. Vancomycin covalently bonded to titanium alloy prevents bacterial colonization. *J Orthop Res.* 2007 Jul;25(7):858-66.
- 86.** Parvizi J, Wickstrom E, Zeiger AR, Adams CS, Shapiro IM, Purtill JJ, Sharkey PF, Hozack WJ, Rothman RH, Hickok NJ, Frank Stinchfield Award. Titanium surface with biologic activity against infection. *Clin Orthop Relat Res.* 2004 Dec;429:33-8.
- 87.** Peñaalba Arias P, Furustrand Täfni U, Bétrisey B, Vogt S, Trampuz A, Borens O. Activity of bone cement loaded with daptomycin alone or in combination with gentamicin or PEG600 against *Staphylococcus epidermidis* biofilms. *Injury.* 2015 Feb;46(2):249-53. Epub 2014 Nov 27.
- 88.** Tian B, Tang S, Wang CD, Wang WG, Wu CL, Guo YJ, Guo YP, Zhu ZA. Bactericidal properties and biocompatibility of a gentamicin-loaded Fe3O4/carbonated hydroxyapatite coating. *Colloids Surf B Biointerfaces.* 2014 Nov 1;123:403-12. Epub 2014 Oct 5.
- 89.** Vassena C, Fenu S, Giuliani F, Fantetti L, Roncucci G, Simonutti G, Romanò CL, De Francesco R, Drago L. Photodynamic antibacterial and antibiofilm activity of RLP068/Cl against *Staphylococcus aureus* and *Pseudomonas aeruginosa* forming biofilms on prosthetic material. *Int J Antimicrob Agents.* 2014 Jul;44(1):47-55. Epub 2014 May 21.
- 90.** Cochis A, Azzimonti B, Della Valle C, De Giglio E, Bloise N, Visai L, Cometa S, Rimondini L, Chiesa R. The effect of silver or gallium doped titanium against the multidrug resistant *Acinetobacter baumannii*. *Biomaterials.* 2016 Feb;80:80-95. Epub 2015 Dec 2.
- 91.** Harrasser N, Jüssen S, Banke JJ, Kmeth R, von Eisenhart-Rothe R, Stritzker B, Gollwitzer H, Burgkart R. Antibacterial efficacy of titanium-containing alloy with silver-nanoparticles enriched diamond-like carbon coatings. *AMB Express.* 2015 Dec;5(1):77. Epub 2015 Dec 9.
- 92.** Slane J, Vivanco J, Rose W, Ploeg HL, Squire M. Mechanical, material, and antimicrobial properties of acrylic bone cement impregnated with silver nanoparticles. *Mater Sci Eng C Mater Biol Appl.* 2015 Mar;48:188-96. Epub 2014 Dec 2.
- 93.** Urish KL, DeMuth PW, Kwan BW, Craft DW, Ma D, Haider H, Tuan RS, Wood TK, Davis CM 3rd. Antibiotic-tolerant *Staphylococcus aureus* biofilm persists on arthroplasty materials. *Clin Orthop Relat Res.* 2016 Feb 1. [Epub ahead of print].
- 94.** Singh G, Hameister R, Feuerstein B, Awiszus F, Meyer H, Lohmann CH. Low-frequency sonication may alter surface topography of endoprosthetic components and damage articular cartilage without eradicating biofilms completely. *J Biomed Mater Res B Appl Biomater.* 2014 Nov;102(8):1835-46. Epub 2014 Apr 11.
- 95.** Smith DC, Maiman R, Schwechter EM, Kim SJ, Hirsh DM. Optimal irrigation and debridement of infected total joint implants with chlorhexidine gluconate. *J Arthroplasty.* 2015 Oct;30(10):1820-2. Epub 2015 May 15.
- 96.** Howlin RP, Brayford MJ, Webb JS, Cooper JJ, Aiken SS, Stoodley P. Antibiotic-loaded synthetic calcium sulfate beads for prevention of bacterial colonization and biofilm formation in periprosthetic infections. *Antimicrob Agents Chemother.* 2015 Jan;59(1):111-20. Epub 2014 Oct 13.
- 97.** Chua SL, Yam JK, Hao P, Adav SS, Salido MM, Liu Y, Givskov M, Sze SK, Tolker-Nielsen T, Yang L. Selective labelling and eradication of antibiotic-tolerant bacterial populations in *Pseudomonas aeruginosa* biofilms. *Nat Commun.* 2016 Feb 19;7:10750.
- 98.** Guo Q, Wei Y, Xia B, Jin Y, Liu C, Pan X, Shi J, Zhu F, Li J, Qian L, Liu X, Cheng Z, Jin S, Lin J, Wu W. Identification of a small molecule that simultaneously suppresses virulence and antibiotic resistance of *Pseudomonas aeruginosa*. *Sci Rep.* 2016 Jan 11;6:19141.
- 99.** H J, Omanakuttan A, Pandurangan N, S Vargis V, Maneesh M, G Nair B, and B Kumar G. Clove bud oil reduces kynure9 and inhibits pqs A gene expression in *P. aeruginosa*. *Appl Microbiol Biotechnol.* 2016 Apr;100(8):3681-92. Epub 2016 Jan 29.
- 100.** Hossain MA, Lee SJ, Park JY, Reza MA, Kim TH, Lee KJ, Suh JW, Park SC. Modulation of quorum sensing-controlled virulence factors by *Nymphaea tetragona* (water lily) extract. *J Ethnopharmacol.* 2015 Nov 4;174:482-91. Epub 2015 Aug 29.
- 101.** Kasper SH, Bonocora RP, Wade JT, Musah RA, Cady NC. Chemical inhibition of kynureninase reduces *Pseudomonas aeruginosa* quorum sensing and virulence factor expression. *ACS Chem Biol.* 2016 Feb 10. [Epub ahead of print].
- 102.** Kazemian H, Ghafourian S, Heidari H, Amiri P, Yamchi JK, Shavalipour A, Hourii H, Maleki A, Sadeghifard N. Antibacterial, anti-swarming and anti-biofilm formation activities of *Chamaemelum nobile* against *Pseudomonas aeruginosa*. *Rev Soc Bras Med Trop.* 2015 Jul-Aug;48(4):432-6.
- 103.** Mangwani N, Kumari S, Das S. Involvement of quorum sensing genes in biofilm development and degradation of polycyclic aromatic hydrocarbons by a marine bacterium *Pseudomonas aeruginosa* N6P6. *Appl Microbiol Biotechnol.* 2015 Dec;99(23):10283-97. Epub 2015 Aug 7.
- 104.** Ouyang J, Sun F, Feng W, Sun Y, Qiu X, Xiong L, Liu Y, Chen Y. Quercetin is an effective inhibitor of quorum sensing, biofilm formation and virulence factors in *Pseudomonas aeruginosa*. *J Appl Microbiol.* 2016 Apr;120(4):966-74. Epub 2016 Mar 7.
- 105.** Vadekeetil A, Alexander V, Chhibber S, Harjai K. Adjuvant effect of cranberry proanthocyanidin active fraction on antiviral property of ciprofloxacin against *Pseudomonas aeruginosa*. *Microb Pathog.* 2016 Jan;90:98-103. Epub 2015 Nov 24.
- 106.** Vasavi HS, Arun AB, Rekha PD. Anti-quorum sensing activity of flavonoid-rich fraction from *Centella asiatica* L. against *Pseudomonas aeruginosa* PAO1. *J Microbiol Immunol Infect.* 2016 Feb;49(1):8-15. Epub 2014 May 22.
- 107.** Yin H, Deng Y, Wang H, Liu W, Zhuang X, Chu W. Tea polyphenols as an antivirulence compound disrupt quorum-sensing regulated pathogenicity of *Pseudomonas aeruginosa*. *Sci Rep.* 2015;5:16158. Epub 2015 Nov 9.
- 108.** Dastgheyb SS, Villaruz AE, Le KY, Tan VY, Duong AC, Chatterjee SS, Cheung GY, Joo HS, Hickok NJ, Otto M. Role of phenol-soluble modulins in formation of *Staphylococcus aureus* biofilms in synovial fluid. *Infect Immun.* 2015 Jul;83(7):2966-75. Epub 2015 May 11.
- 109.** Heim CE, Vidlak D, Scherr TD, Hartman CW, Garvin KL, Kielian T. IL-12 promotes myeloid-derived suppressor cell recruitment and bacterial persistence during *Staphylococcus aureus* orthopedic implant infection. *J Immunol.* 2015 Apr 15;194(8):3861-72. Epub 2015 Mar 11.
- 110.** Bhargava N, Singh SP, Sharma A, Sharma P, Capalash N. Attenuation of quorum sensing-mediated virulence of *Acinetobacter baumannii* by Glycyrrhiza glabra flavonoids. *Future Microbiol.* 2015;10(12):1953-68. Epub 2015 Nov 19.
- 111.** Thakur P, Chawla R, Tanwar A, Chakotiya AS, Narula A, Goel R, Arora R, Sharma RK. Attenuation of adhesion, quorum sensing and biofilm mediated virulence of carbapenem resistant *Escherichia coli* by selected natural plant products. *Microb Pathog.* 2016 Mar;92:76-85. Epub 2016 Jan 11.
- 112.** Yang Q, Wang L, Gao J, Liu X, Feng Y, Wu Q, Baloch AB, Cui L, Xia X. Tannin-rich fraction from pomegranate rind inhibits quorum sensing in *Chromobacterium violaceum* and biofilm formation in *Escherichia coli*. *Foodborne Pathog Dis.* 2016 Jan;13(1):28-35. Epub 2015 Nov 23.
- 113.** Mai T, Tintillier F, Lucasson A, Moriou C, Bonno E, Petek S, Magré K, Al Mourabit A, Saulnier D, Debitus C. Quorum sensing inhibitors from *Leucetia chagosensis* dandy, 1863. *Lett Appl Microbiol.* 2015 Oct;61(4):311-7. Epub 2015 Aug 14.

WHAT'S NEW IN MUSCULOSKELETAL INFECTION: UPDATE ON BIOFILMS

- 114.** Martín-Rodríguez AJ, Ticona JC, Jiménez IA, Flores N, Fernández JJ, Bazzocchi IL. Flavonoids from *Piper deliense* modulate quorum-sensing-regulated phenotypes in *Vibrio harveyi*. *Phytochemistry*. 2015 Sep;117:98-106. Epub 2015 Jun 10.
- 115.** Phippen BL, Oliver JD. Clinical and environmental genotypes of *Vibrio vulnificus* display distinct, quorum-sensing-mediated, chitin detachment dynamics. *Pathog Dis*. 2015 Nov;73(8):ftv072. Epub 2015 Sep 16.
- 116.** Soni D, Smoum R, Breuer A, Mechoulam R, Steinberg D. Effect of the synthetic cannabinoid HU-210 on quorum sensing and on the production of quorum sensing-mediated virulence factors by *Vibrio harveyi*. *BMC Microbiol*. 2015 Aug 12;15:159.

- 117.** Corral-Lugo A, Daddaoua A, Ortega A, Espinosa-Urgel M, Krell T. Rosmarinic acid is a homoserine lactone mimic produced by plants that activates a bacterial quorum-sensing regulator. *Sci Signal*. 2016 Jan 5;9(409):ra1.
- 118.** Abachi S, Lee S, Rupasinghe HP. Molecular mechanisms of inhibition of *Streptococcus* species by phytochemicals. *Molecules*. 2016 Feb 17;21(2).
- 119.** Alves S, Duarte A, Sousa S, Domingues FC. Study of the major essential oil compounds of *Coriandrum sativum* against *Acinetobacter baumannii* and the effect of linalool on adhesion, biofilms and quorum sensing. *Biofouling*. 2016 Feb;32(2):155-65.
- 120.** Younis KM, Usup G, Ahmad A. Secondary metabolites produced by marine *Streptomyces* as antibiofilm and quorum-sensing inhibitor of uropathogen *Proteus mirabilis*. *Environ Sci Pollut Res Int*. 2016 Mar;23(5):4756-67. Epub 2015 Nov 4.

Evidence-Based Articles Related to Musculoskeletal Infection

Chiang HY, Herwaldt LA, Blevins AE, Cho E, Schweizer ML. Effectiveness of local vancomycin powder to decrease surgical site infections: a meta-analysis. *Spine J*. 2014 Mar 1;14(3):397-407. Epub 2013 Oct 30.

Pooling the risk estimates from the 8 studies that assessed patients undergoing spinal operations, local administration of vancomycin powder appears to protect against surgical site infections, deep incisional surgical site infections, and *S. aureus* surgical site infections.

Dumville JC, McFarlane E, Edwards P, Lipp A, Holmes A, Liu Z. Preoperative skin antiseptics for preventing surgical wound infections after clean surgery. *Cochrane Database Syst Rev*. 2015 Apr 21;4:CD003949.

A review of 13 studies found some evidence that preoperative skin preparation for clean surgical cases with 0.5% chlorhexidine in methylated

spirits was associated with lower rates of surgical site infections than alcohol-based povidone-iodine paint.

Sikorska H, Smoragiewicz W. Role of probiotics in the prevention and treatment of methicillin-resistant *Staphylococcus aureus* infections. *Int J Antimicrob Agents*. 2013 Dec;42(6):475-81. Epub 2013 Sep 7.

The evidence from a few small clinical studies indicates that administration of specific probiotics may minimize methicillin-resistant *S. aureus* carriage.

Vuotto C, Longo F, Donelli G. Probiotics to counteract biofilm-associated infections: promising and conflicting data. *Int J Oral Sci*. 2014 Dec;6(4):189-94. Epub 2014 Sep 26.

Accumulating evidence suggests that probiotics, especially lactobacilli, positively affect oral, wound, and vaginal infections through a competition and counteraction of pathogens.