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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 substances[1-3]. The term "biofilm" is commonly used to describe this network of microorganisms, a term popularized by Dr. J. William Costerton et al. in 1978[4].

Biofilms are formed by a confluence of bacteria commonly encountered in orthopaedic infections. Up to 65% of bacterial infections are caused by biofilm-producing organisms[5]. 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 devices[6]. *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 eradicate[7].

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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 sensing[7]. 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 biofilm[8]. 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 system[9]. 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 biofilms[10].

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 microarrays[11]. Some antibiotics, including rifampicin,

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TABLE I Microorganisms Used in Quorum-Sensing Studies

Microorganism	No. of Reports and References
Pseudomonas	20[20,23-25,28-30,32,36,97-107]
Staphylococcus	8[19,20,24,27,35,37,108,109]
Acinetobacter baumannii	3[26,31,110]
E. coli	3[28,111,112]
Vibrio	4[113-116]
Candida	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 biofilms[16].

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 compounds[17-34], 19 plant-based compounds, 2 microorganism-generated compounds (Table II), and 2 nanoscale surface treatments (titania nanotubes[35] and zinc oxide nanoparticles[36]). Another strategy that was investigated was quorum quenching to interrupt virulence factors rather than to prevent microorganism growth and biofilms[37]. Attention to small-molecule anti-quorum-sensing agents carries the hope that resistance will not occur; however, resistance to some agents has already occurred[38].

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 strategies[39]. One major point is that surface adhesion is important for persister cells to be present in biofilm[40]. Two misconceptions that permeate the literature need consideration. The first

TABLE II Quorum-Quenching Compounds

Plant origin
- *Centella asiatica* (spadeleaf)[106]
- *Piper delineatum* flavonoids[114]
- *Leucetta chagosensis*[113]
- Tannic acid[103]
- Cannabinoid HU-210 (medical marijuana)[116]
- Chamomile[102]
- *Nymphaea tetragona* (water lily)[100]
- Green tea polyphenols[107]
- Pomegranate[112]
- Cranberry[105]
- Rosmarinic acid (rosemary)[117]
- *Petiveria alliacea*[101]
- *Berberis aristata, Camellia sinensis,* and *Holarrhena antidysenterica*[111]
- Quercetin (fruit and vegetable flavonol)[104]
- Clove bud oil[99]
- Phytochemicals of various medicinal plants[118]
- *Coriandrum sativum* (coriander)[119]

Microorganism origin
- *Glycyrrhiza glabra*[110]
- Halophilic marine Streptomyces[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 enough[41]. *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 prolonged[41]. 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 (cisplatin[43], 5-fluorocytosine[44], and mitomycin C[45]) 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 consensus statements have been developed for some biofilm infections in which data are more robust, such as endocarditis[46]; periprosthetic 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 Infection[49]; catheter-based infections[50]; cardiac device infections[51]; otitis media[52]; and ventilator-associated pneumonia[53]. 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 infections[54]. 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 cm^3) 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 advance[54]. 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 presentation[55] 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 dysfunction[57].

Acute and/or surgically modifiable factors for open fractures can also influence outcomes and can include the type of surgical procedure[58], the stability of the fracture, the timing of the surgical procedure[59-61], the duration of antibiotics[62], the timing of systemic antibiotics[62,63], local antibiotic delivery[64,65], the type of irrigant[66-68], the length of hypotension, anemia, the quality of debridement (reduction of local bioburden), the type of wound closure[69,70], the timing of wound closure[71], and avoidance of the second-hit phenomenon[72]. 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 decreased[61]. 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 procedure[58], 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 rates[69]. 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 plating[74].

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 surfaces[77]. 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 biofilms[80]. 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 formation[81], 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 polyethylene[82]. 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 biofilm[83]. 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 formation[84-86]. 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 gentamicin[87]. Antibiotics such as gentamicin can also be loaded in Fe_3O_4/carbonated hydroxyapatite coatings to prevent biofilm formation and to decrease bacterial adhesion, while still allowing the implantation of devices in cementless total joint arthroplasty[88].

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 resistance[89]. 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 bacteria[92].

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 polyethylene[93]. 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 imaging[73]. 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 thickness[94].

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 bacteria[95]. 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 biofilm[96].

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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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 meticillin-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.