**The 2018 International Consensus Meeting on Musculoskeletal Infection: Summary from the Biofilm Workgroup and consensus** **on Biofilm related Musculoskeletal Infections**

**ICM 2018 Biofilm workgroup**

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**Abstract**

Biofilm-associated implant-related bone and joint infections are clinically important due to the extensive morbidity, cost of care and socioeconomic burden that they cause. Research in the field of biofilms has expanded in the past two decades, however, there is still an immense knowledge gap related to many clinical challenges of these biofilm-associated infections. This subject was assigned to the Biofilm Workgroup during the second International Consensus Meeting on Musculoskeletal Infection held in Philadelphia USA (ICM 2018) (<https://icmphilly.com>).

The main objective of the Biofilm Workgroup was to prepare a consensus document based on a review of the literature, prepared responses, discussion and vote on thirteen biofilm related questions. The Workgroup commenced discussing and refining responses prepared before the meeting on day one using Delphi methodology, followed by a tally of responses using an anonymized voting system on the second day of ICM 2018.

The Working group derived consensus on information about biofilms deemed relevant to clinical practice , pertaining to: 1) surface modifications to prevent/inhibit biofilm formation, 2) therapies to prevent and treat biofilm infections, 3) polymicrobial biofilms, 4) diagnostics to detect active and dormant biofilm in patients, 5) methods to establish minimal biofilm eradication concentration for biofilm bacteria, and 6) novel anti-infectives that are effective against biofilm bacteria. It was also noted that biomedical research funding agencies and the pharmaceutical industry should recognize these areas as priorities.

**Keywords**

Biofilm, International Consensus Meeting, Musculoskeletal Infection, periprosthetic joint infection, Surgical Site Infection, osteomyelitis

**Introduction and Background**

Around two thirds of all human infections are believed to be biofilm related. Biofilm-associated implant-related bone and joint infections, or biofilm-associated musculoskeletal (MSK) infections, are clinically important due to the extensive morbidity, cost of care and socioeconomic burden that they cause 1–3.  A biofilm can be described as a complex and well-structured aggregation of microorganisms, of single or multiple species. Biofilms are found adherent to biotic (host tissue) and abiotic (implant/biomaterial) surfaces, or as floating aggregates, all of which are encased in a self-produced matrix of polymeric substances. Biofilm thickness can vary between a single cell layer to thick, three dimensional communities with columns and channels. Biofilms are tolerant to antimicrobials and evade the host immune system. Biofilm formation is central to the pathogenesis of implant-related infections which develop after microorganisms, bacteria or fungi, attach to the protein conditioned surface. All the materials used in orthopaedic implants are vulnerable to attachment of biofilm forming bacteria. Bacterial attachment is known to occur intraoperatively, post operatively, and on a delayed basis. The propensity for biofilm formation at any of these time points places implants at risk for surgical site infections (SSIs). Following attachment there is a stepwise progression of biofilm formation and maturation leading to an established infection.

Biofilm associated infection is one of the most common causes for failure of orthopaedic implants. Clinically, biofilm-associated infections can exist innocuously with few symptoms or signs 4. With currently available diagnostic tests, clinical diagnosis can be challenging unless dispersed microorganism are virulent enough to incite a host response. Diagnostically, the sensitivity of conventional microbiologic culture methods can be low, due to the inability of microorganisms to propagate in the sessile phenotype.  Failure to isolate and identify the pathogen is not only associated with challenges in antimicrobial management, but also can lead to continuation of the infection and failure following revision surgery, and lead to a falsely low incidence of implant-related infections. Surgical debridement is an important part of treatment. Many times the debridement is intralesional, making it difficult for the surgeon to be certain removal of biofilm is complete and biofilm fragments remaining in the surgical site have the potential to propagate the infection 5–8.

Although research in the field of biofilms has expanded in the past two decades, there is still an immense knowledge gap related to many clinical aspects of biofilm-associated infections. Given this, and the great clinical and financial impact of biofilm infections, this subject was assigned to the Biofilm Workgroup during the second International Consensus Meeting on Musculoskeletal Infection held in Philadelphia USA, July 25-27, 2018 (ICM 2018) (<https://icmphilly.com>).

**Methodology**

The main objective of ICM 2018 was to bring together experts in MSK infections from around the world to assimilate the best available data on management of patients afflicted with implant-related, bone and joint infections (MSK Infections), including SSI and Periprosthetic Joint Infections (PJI), to ultimately derive a consensus document (<https://icmphilly.com>). The first step, led by ICM 2018 co-chairs, Drs. Javad Parvizi and Thorsten Gehrke, was to identify and recruit 869 MSK infection experts from 92 countries. These experts agreed to serve as delegates tasked to identify the controversies and challenges related to prevention, diagnosis and treatment of MSK infection, then seek consensus on those issues using Delphi methodology 9, which have emerged as a critical tool by which thought leaders debate all existing knowledge to derive “general agreement” in response to clinical care driven questions. The complete details for the Delphi methods and timelines of the thirteen specific steps used to complete the 2018 ICM have been published10. All of the consensus questions, voting responses and additional information on the 2018 ICM are available online (<https://icmphilly.com>), or on the iOS and Android App (ICMPHILLY). Only delegates with an established expertise in the field of MSK infection were invited. These distinguished delegates generated 652 questions addressing clinical issues related to MSK infection. These questions were grouped into 18 clinical and basic science areas, each addressed by separate workgroups, including a workgroup to address issues related to biofilms. Over 24 months, each question was assigned to 2 or more delegates to prepare responses. Response preparation consisted of a systematic literature review, data summary and an independent narrative response written from the perspective and experience of each authoring delegate. These responses were reviewed by a facilitator and combined into a single document. The compiled response was then edited by both authors to an agreed response to be posted to the ICM web site for review and comment by all 869 delegates.  The authoring delegates then refined their responses based on the comments in preparation for discussion and voting at the in-person meeting that was held on July 25th -27th 2018, in Philadelphia, USA. The controversial questions and responses were discussed and further edited on the initial day of the meeting. The delegates who attended the meeting in person then voted to: 1) agree, 2) disagree or 3) abstain, on each response during the latter two days of the meeting, following Delphi methodology 9 and the voting results were rated as: a) Simple majority (50.1%-59%) : No Consensus; b) Majority (60%-65%) : Weak Consensus ; c) Super Majority (66%-99%) : Strong Consensus and d) Unanimous (100%) : Unanimous Consensus.

Among the 18 workgroups there was one made up of the 28 authors of this consensus document dedicated to biofilms. This group consisted of biofilm experts from backgrounds including both basic and clinical science in microbiology, immunology, biomedical engineering, infectious diseases and orthopaedic surgery. The biofilm workgroup was tasked with discussion, response editing and voting on the thirteen biofilm related questions that were deemed to be relevant to clinical practice. While the majority of the responses to the ICM questions were focused with the intent to provide clinical recommendation for prevention, diagnosis or treatment, the biofilm responses were more basic science in nature, given as informative narratives without clinical recommendations.

The Workgroup emphasizes that consensus was reached without compulsion, undue influential power or expressiveness, inability to comprehend another course of action, or impatience with the process of debate. Discussion was carried out in a moderated open forum were everyone had opportunity to study the wording of the questions and responses, review the available evidence and voice their opinion before  voting  occurred. Below is a summary of the thirteen biofilm related questions, responses and/or recommendations with HTML links to a downloadable PDFs for each question, response, consensus and post-meeting rationale.

**Results**

The Biofilm Workgroup’s response to the 13 questions is summarized in Table1, which covers biofilm microbiology, life cycle, structure, quorum sensing, susceptibility to host immune response and antimicrobials, and novel therapy technologies. All of the questions and responses were considered with an eye to identifying opportunities for clinical intervention, either now or in the future. The vast majority of the data were basic science in nature with minimal low-level clinical outcome data in isolated areas, making responses to the questions narrative opinions about the current state of knowledge. These narrative responses are felt to be foundational to clinical judgement for management of MSK infections rather than clinical recommendations. We provide an interpretive discussion of the responses. The strength of evidence assigned to each response is based on the collective judgement of the Workgroup about the scientific validity of the data because reports on basic scientific data cannot be categorized by the Level of Evidence methodology used for clinical data. High level clinical outcomes data were not available to address any of the 13 questions. Thus, the audience is encouraged to read the rationale for each question in the ICM 2018 document (<https://icmphilly.com>) to gain a deeper understanding of the available data.

**Question one** addresses the life cycle of Biofilms, and **Question four** addresses the timeline of biofilm maturation.  These are relevant because diagnosis and treatment options vary by the presence and maturity of biofilms. With biofilm maturity comes the inability to identify bacteria within biofilms using conventional culture and susceptibility testing, and these mature biofilms are resilient to treatment.  The life cycle of biofilm is a complex continuum progressing through four stages: 1) attachment, 2) accumulation, 3) maturation, and 4) dispersal, over a time period that ranges from minutes to hours in vitro, and days to weeks or longer in vivo 11. Biofilms can mature before they present diagnosable findings, because it is the host response to bacteria outside of biofilms that leads to clinical symptoms, physical findings and positive diagnostic tests. This limits the opportunity to intervene before the biofilm is established.  Currently, there is no clinical research available to determine whether the timescale in the development of biofilm formation differs markedly between bacterial species. In vitroexperiments and in vivo animal studies find that progression of biofilms is mediated by the interplay of a number of microbial, host, and environmental factors. These factors can be different across microbial species and even across strains within species. The timeline for biofilm formation may not correlate with the onset of infection symptoms; therefore the concept of acute or chronic biofilm-associated MSK infection is likely to be less pertinent for management decisions than previously thought.

**Questions two, Question five and Question ten** address surface properties that favor attachment and progression to established biofilm.  The available data are mostly basic science in nature from *in vitro* experiments and *in vivo* animal studies, with limited clinical data on iodine surface modification. There is strong consensus that bacterial attachment can occur on essentially all prosthetic and injured or immune compromised biological surfaces, including surfaces of antimicrobial loaded bone cement (ALBC) spacers utilized to locally deliver antimicrobials when treating MSK infection patients during two-stage treatment plans 12,13. ALBC surfaces, which are physically favorable for bacterial attachment, can support the growth of either the original pathogen(s), or a secondary pathogen(s) not present in the initial infection. As the antimicrobial load in ALBC is released, the surrounding antimicrobial levels fall below the minimal inhibitory concentration (MIC), and thus the surfaces become susceptible to microbial colonization.  Additionally, antimicrobial levels can remain sub-therapeutic for years, which increases the risk for the emergence of  microorganisms that are resistant to the incorporated antimicrobial(s), although this has not been realized in clinical practice. The physicochemical properties of materials/implants that are known to affect the time required and robustness of the established biofilms include surface chemistry, surface charge, hydrophilicity/hydrophobicity, micro/nano-topography, and porosity 14–17.  Biofilm formation is affected by surface properties and bacterial attachment to abiotic surfaces is an inherent capability of MSK pathogens. In vitro experiments and in vivo animal models have found that modification of implant surface can decrease bacterial adherence, and thus decrease biofilm formation leading investigators to seek physico-chemical surface modifications and coatings to inhibiting bacterial adhesion to theoretically decrease the risk of infection without limiting osseointegration 18. The ideal implant surface modification should have a long duration of anti-infective effect, mechanical stability and host biocompatibility 19–21.  An innovative technology using iodine to produce porous anodic oxide implant surfaces with the antiseptic properties of iodine was studied in a prospective uncontrolled cohort study for both prophylaxis in high risk patients, and for treatment in confirmed MSK infection cases22. Confirmatory reports on subsets of these patients with hip replacement implants or fixator pins reported no hip implant infections and decreased pin tract infections respectively 23,24.

Nano-particulate silver is an example of a surface modification that offers short term protection with some limited local antimicrobial activity in the fluid or tissue adjacent to the surface. However clinical data on silver surface modifications of urinary, vascular and peritoneal catheters, vascular grafts and heart valves, have not reported on biofilm formation, and these technologies have not been applied to orthopaedic devices 25. To date, no surface modification found to have a positive in vitro effect has been translated into the clinical setting. Clinical studies are required to determine the long-term impact and outcomes of modified surface properties on biofilm formation in human patients.

**Question three** addresses biofilm susceptibility to host phagocytosis. While neutrophils and macrophages (10 – 20 µm) have the ability to access the surface and enter the channels of a mature biofilm (100 µm) 26, they are not able to access biofilm encased microorganisms 12,13,27–38. When a fragment of biofilm is small enough, phagocytes can engulf it, but they are not able to destroy the bacteria 39–42. Phagocytized sessile bacteria can persist in peri-implant tissue in vitro, and in the tissues of patients with intravenous catheters colonized by a variety of bacteria 43,44. *Staphylococcus aureus* has recently been shown to invade the osteocytic-canalicular network of cortical bone and to reside within osteoblasts where accessibility to phagocytes is limited 45,46. However, after bacteria are dispersed from biofilms they progressively transform into planktonic phenotypes that are more susceptible to antimicrobials, and have surface properties that are detectable by phagocytes, and are subject to phagocytic killing.

**Question six** addresses the biofilm forming capabilities *of Mycobacterium tuberculosis.*

While there are bacteria that do not appear to form biofilms, essentially all bacteria that cause implant-related infections form biofilms including *Mycobacteriaceae*. The work group only addressed the data related to *Mycobacterium tuberculosis,* not the faster growing non-tuberculous mycobacteria (NTMB). Thus, the consensus statements for infections related to *M. tuberculosis* cannot be extrapolated to infections related to NTMB. *In vitro* experiments find that *M. tuberculosis* can form biofilm on metal surfaces; albeit less than on Polymethylmethacrylate (PMMA), and less than is formed by *Staphylococci spp.*  Based on *in vivo* studies and clinical case reports biofilms in TB infections may contribute to casseous necrosis 47–49. Although no data from clinical trials exist to address this question, the Workgroup felt that the published scientific data are strong enough to warrant consensus opinion on the clinical implications for management of implant-related infections caused by *M. tuberculosis*. Accordingly, we recommend that the fundamental principles for implant-related infections caused by other biofilm forming bacteria should also be followed for *M. tuberculosis*. One of the delegates who was not present for the discussion and voting points out that eradication of implant related infections, due to ‘susceptible’ *M. tuberculosis*, is possible with chemotherapy alone 50, and that depending on the anatomic or functional deficiencies, surgical intervention can be performed at a later time point (e.g. weeks to months after initiating anti-TB treatment). This success may be attributed to weak biofilm formation by *M. tuberculosis* and/or, to anti-biofilm properties of the anti-TB agents. The decision of when or if to proceed with surgical debridement for biofilm associated implant related TB infections may best be made in collaboration with an infectious disease specialist experienced in management of extremity TB infections, taking into consideration each patient’s response to chemotherapy.

**Question seven**  assesses the role of microbial synergy, which means that different species (e.g. aerobic and anaerobic microbes) collaborate to cause disease that neither pathogen could achieve alone. Patients with polymicrobial biofilm-associated MSK infections are more challenging to treat due to the need for broad spectrum antimicrobial coverage. The reason could be multifactorial, including microbial synergy 4,51,52. These microbial interactions include cross feeding, quorum sensing, exchange of virulence genes and exchange of antimicrobial resistance genes, making infection eradication more challenging in clinical practice.

**Question eight** asks a clinical question about the importance of mapping the location of the biofilm within a patient for management of biofilm-associated MSK infections. Because biofilm eradication requires physical removal, the extent and location of the biofilm is technically important. However there was strong consensus that there are no clinical methods available to actually identify biofilm before or during surgical debridement. While advanced imaging has been used to spatially locate areas of active infection with good resolution, neither 99mTc  WBC SPECT-CT with concordant 99mTc sulphur colloid marrow map 53,54, nor PET-CT, specifically identify biofilm. Targeted imaging methods which utilize binding of imaging agents to bacteria also do not distinguish between planktonic and sessile bacteria, and it is unknown if these techniques identify dormant cells such as persister cells 55. Optical imaging using fluorescence (fluorescein, indocyanine green and IRDye-800CW) has the potential for identifying microbes on or near a surface. While optical imaging techniques are possible in surgical wounds, none have emerged from the research setting for clinical use 55. Optical dyes (DMMB 1,9-dimethyl methylene blue) can be used to stain the biofilm matrix, but this has yet to gain acceptance for clinical use. There is a major capability gap for these technologies between research and clinical use, which prevents mapping biofilms to specific anatomic sites or a particular implant component/location in clinical practice.

**Question nine** evaluates *in vivo* data on blocking quorum sensing to minimize biofilm formation. While the majority of the data are in vitro, there are somein vivo animal studies that have found that interference with quorum sensing signals/molecules can lead to decreased biofilm formation.56 The workgroup is not aware of any anti-quorum sensing strategies that are available for clinical use, and confirmed that there are no clinical studies investigating the effectiveness of this strategy.

**Question eleven and Question twelve** address antimicrobial susceptibility of microorganisms in both biofilm-associated and non-biofilm-associated states.  The Workgroup identified the need to emphasize the difference in antimicrobial susceptibility between microorganisms in their planktonic form, and the same microorganisms in their biofilm-associated sessile form, noting that biofilm associated phenotypes are hundreds to thousands of times less susceptible to antimicrobials than their free floating planktonic counterparts. This critically important observation is fundamental to the understanding that the MIC used to quantify antimicrobial susceptibility for non-biofilm associated microorganisms has no role in determining the antimicrobial susceptibility of microorganisms in biofilms. There are established validated methodologies for determining MICs, but not for determination of susceptibility of biofilm-associated bacteria 57–59. Determining antimicrobial susceptibility of bacteria within biofilm is not easy. Clinicians need an as yet clinically unavailable test that measures antimicrobial efficacy such as minimum biofilm eradication concentration (MBEC), minimum biofilm bactericidal concentration (MBBC) or minimum biofilm inhibitory concentration (MBIC). Because host defenses have limited ability to kill persister cells within biofilm, a measure of total eradication of the bacteria in the biofilm (MBEC) is favored over methods that measure inhibition of bacterial replication (MBIC), but do not kill the persisters. It was noted that the MBEC assays used in research are not standardized, and that MBEC values for each individual bacteria/antimicrobial pair are dependent on the surface that the biofilm is attached to and the duration the biofilm is exposed to the antimicrobial. Clinically-validated assays of antimicrobial susceptibility (MBEC) are needed to provide guidance for local antimicrobial therapy in biofilm-associated orthopaedic infections. During its early accumulation phase, a growing biofilm has less resistance to antimicrobial therapy than a fully mature biofilm with microorganisms that are quiescent metabolically and not replicating. This relative preservation of antimicrobial susceptibility during the early phase of biofilm formation has led to failed efforts to treat early phase orthopaedic infections without surgical intervention 60.

**Finally, question thirteen** sought data on the role of bacteriophages in treatment of multidrug-resistant PJI. There are several encouraging strategies emerging as potential therapeutic modalities against biofilms, including immunotherapy, nanoparticles with antibacterial effects and antimicrobial peptides along with bacteriophage therapy. The Workgroup discussed the role of bacteriophages in treatment of biofilm-associated implant infections. While this concept is over a century old, currently there is insufficient clinical experience to recommend its use. Moreover, the Workgroup identified several obstacles that have the potential to challenge the scientific premise of phage therapy for treating MSK infections including: 1) phages are neutralized in human serum, although this may depend on the route of the phage therapy and requires more evaluation of clinical efficacy61, 2) phages are strain specific leading to the need for a cocktail of phages to cover all possible bacteria in the biofilm, and 3) CRISPR Cas9 immunity engenders most bacterial pathogens evolutionarily resistance to phages62. While phage therapy costs around $2,000-20,000 USD, and can require more than one round of treatment, this cost is in line with or less than other biologic pharmaceuticals, and is less than surgical debridement. *In vivo* animal studies are required to identify parameters for clinical trials.

**Discussion**

The ICM 2018 engaged 869 international experts using the Delphi method to reach consensus on 652 issues related to management of patients with MSK infections, which was the largest orthopaedic consensus meeting in history. However, despite its major strengths, size, scope and inclusiveness, it is recognized that the Delphi method has some inherent weaknesses. First, and greatest among these weaknesses, is the need to follow the process. While the entire ICM 2018 included a large number of individuals that addressed an expansive docket of questions, which could be at risk for distraction and fatigue amongst the delegates, the Biofilm Workgroup was a functional size (28) that addressed 13 questions. All those present actively and respectfully participated in the discussion, while two facilitators effectively ensured that all voices were heard and unhampered by more dominant participants, resulting in a comprehensive vetting of each question. However, the ICM design did not allow for anonymous discussion, which could have impeded free expression by some if it was in a less collegial environment. Secondly, in scientific areas that are advancing rapidly such as biofilm microbiology, a degree of scientific uncertainty and unknowns can be expected. In the case of the 13 biofilm questions it was possible to find common ground based on strong scientific data. Thirdly, inherent to the Delphi method, participants considering questions outside their area of expertise could reach an incorrect consensus with a high level of confidence based on lack of knowledge. The participants in the Biofilm Workgroup included the world leaders in all areas of biofilm science that were covered by the 13 questions posed to them. Thus, it is unlikely there was consensus reached based on lack of knowledge. And finally, the Delphi method is best for addressing single scalar topics. When complex interdependent areas of knowledge such as medicine and biology are considered, the possibility exists that a consensus is impossible, even when some established knowledge exists, or that conflicting consensuses are arrived at by different groups considering similar questions. The Biofilm Workgroup was very precise in refining the wording of the questions and responses to avoid these pitfalls.

As knowledge about biofilms expands and related strategies enter clinical practice the Workgroup expects new questions will arise, and the responses to the current questions will advance justifying clinical recommendations in the future. We anticipate another ICM in the future to update the consensuses from ICM 2018

**Conclusion**

It is anticipated that the data, rationale and response for each question, while not a specific clinical recommendation, will provide caregivers a higher level of understanding of the pathophysiology they are treating, which can lead to better clinical judgement in the absence of high level clinical outcomes data. Studies dedicated to advance our understanding of biofilms and their role in human implant-related infections are urgently required for better diagnosis and eradication strategies. Consensus was reached on currently available data on biofilms deemed relevant to clinical practice and pertained to: 1) surface modifications that prevent/inhibit biofilm formation, 2) therapies to prevent and treat biofilm infections, 3) polymicrobial biofilms, 4) diagnostics to detect active and dormant biofilm in patients, 5) methods to determine antimicrobial susceptibility of biofilm associated bacteria, and 6) novel anti-infectives that are effective against biofilm associated bacteria. It is also noted that biomedical research funding agencies and the pharmaceutical industry should recognize these areas as priorities.

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**Declarations**

* For pre -,meeting rationales, please refer to <https://icmphilly.com/document/icm-2018-biofilm-document/>
* The mention of commercial products, their sources, or their use in connection with material reported herein is not to be construed as either an actual or implied endorsement of such products by the Department of Health and Human Services. The findings and conclusions in this communication have not been formally disseminated by the U.S. Food and Drug Administration and should not be construed to represent any Agency determination or policy.

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Table 1: Biofilm related questions, responses or recommendations as well as level of agreement by the working group

|  |  |  |  |
| --- | --- | --- | --- |
| Questions | **Response or recommendation** | **Level of Evidence** | **Delegate Vote** |
| **QUESTION 1:** What is the life cycle of biofilm and the mechanism of its maturation? | A biofilm may be defined as a microbe-derived sessile community characterized by organisms that are attached to a substratum, interface, or each other, are embedded in a matrix of extracellular polymeric substance, and exhibit an altered phenotype with respect to growth, gene expression, and protein production. The biofilm infection life cycle generally follows the steps of attachment (interaction between bacteria and the implant), accumulation (interactions between bacterial cells), maturation (formation of a viable 3D structure), and dispersion/detachment (release from the biofilm). The life cycle of biofilm is variable depending on the organism involved. There are characteristics in the life cycle of biofilm formation. These include, attachment, proliferation/accumulation/maturation, and dispersal. Biofilm can either be found as adherent to a surface or as floating aggregates. | Strong (this is a scientific review) | Agree:  100%, Disagree:  0%, Abstain:  0% (Unanimous, Strongest Consensus) |
| **QUESTION 2:** What surface properties favor biofilm formation? | The attachment of bacteria to implant and biological surfaces is a complex process, starting with the initial conditioning film. Roughness, hydrophobicity/hydrophilicity, porosity, pore topology, and other surface conditions are the key factors for microbial adhesion. Because of the huge variety of these factors, most of the studies directed at bacterial attachment to the implant surface were limited to specific surface conditions since it is difficult to examine the plethora of parameters concomitantly. There are variable conclusions among the available basic science and animal studies relevant to this topic, many of which will be described in greater detail below. Bacteria can form biofilm on almost all prosthetic surfaces and biological surfaces. To date, this consensus group knows of no surface that is inimicable to the growth of biofilm *in vivo*. | Strong | Agree:  100%, Disagree:  0%, Abstain:  0% (Unanimous, Strongest Consensus) |
| **QUESTION 3:** Is the biofilm on orthopaedic implant surface permeable to neutrophils and macrophages in vivo? Are these innate immune cells (meaning any macrophages or neutrophils) capable of engulfing and killing bacteria? | A mature bacterial biofilm has limited permeability to neutrophils and macrophages. Those that get through are clinically ineffective at eradicating biofilm bacteria. While neutrophils and macrophages are capable of engulfing and killing planktonic bacteria, they are not innately capable of effectively engulfing and killing sessile bacteria in biofilm. | Strong | Agree:  100%, Disagree:  0%, Abstain:  0% (Unanimous, Strongest Consensus) |
| **QUESTION 4:** Does the timescale of biofilm formation differ between bacterial species? If so, what is the timescale for common causative organisms? | Currently, there is no clinical research available to answer whether the timescale in the development of biofilm formation differs between bacterial species. *In vitro* studies show high variability in biofilm formation based on bacterial strains and conditions. Animal studies have demonstrated rapid (minutes to hours) biofilm formation. The group notes that the timeline of biofilm formation may not correlate with the onset of infection symptoms. | Strong | Agree:  100%, Disagree:  0%, Abstain:  0% (Unanimous, Strongest Consensus) |
| **QUESTION 5:** Do bacteria form biofilm on the surface of cement spacer in a similar fashion to a metallic implant? | Yes. While the vast majority of studies have been *in vitro*, there is clinical evidence that majority of bacteria are able to form biofilm on the surface of cement spacer. | Strong | Agree:  100%, Disagree:  0%, Abstain:  0% (Unanimous, Strongest Consensus) |
| **QUESTION 6:** Does *Mycobacterium tuberculosis* form a biofilm on implants? | Few data from experimental *in vitro* and *in vivo* studies and a limited number of case reports indicate that *M. tuberculosis* has a slow, albeit significant, ability to form biofilm on metal surfaces. The group suggests that management of *M. tuberculosis* implant-related infections should be treated using the same principles as that of other implant-related infections. | Strong | Agree:  100%, Disagree:  0%, Abstain:  0% (Unanimous, Strongest Consensus) |
| **QUESTION 7:** What is the role of the microbial synergy in polymicrobial infections? | In polymicrobial infections, a complex environment may be formed in which microbiological interactions exist between microorganisms. Scientific evidence exists to show that combinations of bacterial species may exist whereby these can protect each other from antibiotic action via the exchange of virulence and antibiotic resistance genes, and this may be evident in adverse outcomes for polymicrobial orthopaedic implant-related infections. It is also probable that polymicrobial infections may be more likely in patients with poor immunity and tissue healing. | Strong | Agree:  100%, Disagree:  0%, Abstain:  0% (Unanimous, Strongest Consensus) |
| **QUESTION 8:** Is the mapping of biofilm to a particular component or anatomical location an important consideration in management of implant related infections? | At present, mapping of biofilms is only possible in the laboratory, not in the clinical setting. Therefore, it is of unknown clinical importance in relation to management of implant-related infections. | Consensus | Agree:  100%, Disagree:  0%, Abstain:  0% (Unanimous, Strongest Consensus) |
| **QUESTION 9:** Is there evidence that interference with bacterial communication by blocking quorum sensing molecules can minimize biofilm formation *in vivo*? | *In vivo* animal studies have demonstrated that interference with quorum sensing signals/molecules in some infections leads to decreased biofilm formation. There are contradictory results in *Staphylococcus* species. However, there are no clinical studies demonstrating this phenomenon. | Limited | Agree:  100%, Disagree:  0%, Abstain:  0% (Unanimous, Strongest Consensus) |
| **QUESTION 10:** Can a biomaterial surface be modified to dispel bacterial adherence and biofilms? What are the potential concerns in modifying implant surfaces to combat biofilms? | The purpose of the surface modification is to decrease perioperative bacterial adherence and thus prevent biofilm formation. This has been shown in *in vitro* studies and *in vivo* animal models. There have been numerous strategies devised to alter surfaces. Such modified surfaces may interfere with the expected osseointegration, mechanical stability, and long-term implant survivability.  The duration of long-term anti-infective effects are unknown. To date, no positive *in vitro* effect has been translated into a clinical setting. | Consensus | Agree:  100%, Disagree:  0%, Abstain:  0% (Unanimous, Strongest Consensus) |
| **QUESTION 11:** What is the relevance of Minimum Inhibitory Concentration (MIC) of infecting organisms in biofilm-mediated chronic infection? | The use of Minimum Inhibitory Concentration (MIC) is limited to (1) defining antibiotics that the microorganism is susceptible to in its planktonic state but cannot be used to guide treatment of biofilm-based bacteria, and (2) selecting long-term suppressive antibiotic regimens where eradication of infection is not anticipated.  Alternative measures of antibiotic efficacy specifically in the context of biofilm-associated infection should be developed and validated. | Strong | Agree:  100%, Disagree:  0%, Abstain:  0% (Unanimous, Strongest Consensus) |
| **QUESTION 12:** What is the Minimum Biofilm Eradication Concentration (MBEC) of anti-infective agents? | The minimum biofilm eradication concentration (MBEC) of antimicrobial agents is a measure of *in vitro* antibiotic susceptibility of biofilm producing infective organisms. It is dependent on the surface, medium and the exposure period to an antimicrobial agent. There are no standardized measurement parameters for MBEC. MBEC is currently a research laboratory value and lacks clinical availability. In the group’s opinion, there is value in developing a clinically-validated MBEC assay. | Consensus | Agree:  100%, Disagree:  0%, Abstain:  0% (Unanimous, Strongest Consensus) |
| **QUESTION 13:** Do bacteriophages have a role in treating multidrug-resistant PJI? | Unknown. Although some preclinical and clinical studies have demonstrated a good safety profile as well as promising therapeutic effects using bacteriophages for treating bone and joint infections, further clinical research using bacteriophage therapy in patients with multidrug-resistant PJI is required.  There are known obstacles to bacteriophage therapy, including the fact that bacteriophages are neutralized in serum and relevant pathogens contain CRISPR/cas9 immunity against bacteriophage. Phages are usually bacterial strain specific; thus, a cocktail of different bacteriophage lineages may be necessary to effectively treat biofilm-mediated infections. | Consensus | Agree:  100%, Disagree:  0%, Abstain:  0% (Unanimous, Strongest Consensus) |