B31: What conditions must exist for bacteria to become pathogenic within a joint?

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Response/Recommendation:

A list of factors that illustrate the interplay between host vulnerabilities and bacterial survival strategies in joint infections includes:

(a) Host-related factors: Immunocompromised state (diabetes, rheumatoid arthritis, immunosuppressive therapies), anemia, recurrent PJI
(b) Microenvironment factors: Nutrient and oxygen deprivation, increased level of Mg (20 times higher than plasma), joint PMN level and recruited time, capsular integrity, osteoblast-like supernatant cells
(c) Bacterial Pathogenicity Factors: Biofilm formation capacity, intracellular survival capability, special types (Staph aureus and Pseudomonas aeruginosa), escape from quorum sensing and virulence regulation systems, bacterial iron metabolism status (Pseudomonas), polymicrobial infections, properties of extracellular matrix of the biofilm, presence of fungal hyphae, higher initial bacterial load
(d) Implant topography: Rough implant surfaces, cementless implants, and plasma coating all potentially increase the risk of infection, often by creating critically isolated locations where antibiotic delivery may be restricted and where bacteria may be able to persist. When biofilm adheres to these surfaces it can enhance bacterial virulence, increase resistance to antibiotics, and create conditions where infections are more difficult to treat

Evidence: Moderate

Rationale:

Introduction

Periprosthetic joint infection (PJI) remains a major complication following joint replacement surgery, often leading to significant patient morbidity and increased healthcare costs[1,2]. The ability of bacteria to establish infection within a joint depends on a complex interplay between host factors and bacterial pathogenicity[3,4]. Host-related factors include immune competence, local joint microenvironment, and pre-existing conditions, while bacterial factors include virulence mechanisms such as biofilm formation, intracellular survival, and resistance to immune clearance[5]. This systematic review aims to identify the conditions that facilitate bacterial pathogenicity within the joint space, particularly in the context of PJI[6,7].

Methods

Title	Year	Region	Journal	Level of evidence	Intervention	Sample	Results

A comprehensive literature search was conducted using MeSH terms relevant to virulence, pathogenicity, microenvironment, and prosthetic related joint infections on the PubMed/MedLine and Science Direct databases. Of the initial 992 studies identified, 180 met inclusion criteria after abstract screening. The full text of these were reviewed in detail, and 16 studies were selected for inclusion in the systematic review, to evaluate those conditions that predispose to a bacterium to becoming pathogenic within a joint. Data extracted from these publications included the study design, important factors identified, outcomes, and limitations.

Results

The included studies consist of 4 level III and 12 level V studies. Most of the studies were based in Europe (9) or the United States (5), with the others based in China (2). The most relevant findings of the 16 included studies[8-23] are summarized in Table 1.

Discussion

A wide variety of factors contribute to the pathogenicity of bacteria and their ability to proliferate within a joint, resulting in infection and a septic joint (native or prosthetic). One important consideration is the capacity of the host to respond adequately to the presence of bacteria, including the possibility of immune compromise. Conditions like diabetes, rheumatoid arthritis, and immunosuppressive therapies all increase susceptibility to infection by suppressing the capacity of the host to respond adequately. Smoking, excessive alcohol, renal/hepatic insufficiency, cardiac/pulmonary issues, immunosuppressive therapies, anemia, and malignancy are all commonly associated with diminished immune competence of the host. Local skin conditions, when abnormal, can also be considered influential factors and facilitate bacterial seeding, such as psoriasis, active infections, and surgical site contamination. Host nutrient status and local oxygen delivery/deprivation are further aspects that may also be instrumental in the development of an intra-articular infection. Reduced oxygenation and nutrient levels, as a result of peripheral vascular disease, pulmonary/cardiac insufficiency, and malnutrition, may all diminish the host capacity to respond, and avascular or joint spaces promote bacterial persistence and biofilm formation.

Bacterial load is an important consideration, and higher initial bacterial load increases the risk of successful joint infection and immune evasion. Inherent bacterial pathogenicity is another critically important aspect that contributes to the likelihood bacteria will become pathogenic within a joint. Staphylococcus aureus, Staphylococcus epidermidis, and other bacterial strains form biofilms that enhance antibiotic resistance and promote immune evasion. Sessile bacteria form colonies capable of quorum sensing, that can influence their collective behavior including virulence regulation. Bacteria communicate to regulate virulence, making quorum-sensing inhibitors a potential target for reducing infection. In addition, S aureus can persist inside osteoblasts, sometimes the etiology of recurrent infections.

1.Intracellular ***Staphylococcus aureus*** in bone and joint infections: A mechanism of disease recurrence, inflammation, and bone and cartilage destruction	2023	Italy	Int J Mol Sci	V	Evaluation of different implant topography and different species on immune response and infection within the joint	74	1.Immune response is depend on the type of bacteria and the topography of the implant surface. 2. *S. epidermidis* seems to be able to hide better from the attack of the immune system when cultured on rough surfaces (indicative of uncemented prostheses). 3. *S. aureus* reacts differently depending on the contact surface 4.Higher biofilm formation on rough surfaces. 5. Cementless implants tend to promote bacterial colonization and a pro-inflammatory environment in association with potential acute infections
2.Bacterial communications in implant infections: a target for an intelligence war	2007	US	Int J Artif Organs	V	Evaluation of the role of growth regulatory systems in gram positive and gram negative organisms	N/A	Attenuation of bacterial virulence by quorum-sensing inhibitors, rather than by bactericidal or bacteriostatic drugs, is a highly attractive concept because these antibacterial agents are less likely to induce the development of bacterial resistance.
3.Cutibacterium acnes biofilm formation is influenced by bone microenvironment, implant surfaces and bacterial internalization	2024	France	BMC Microbiology	V	Comparison of *C. acnes* biofilm on plastic, titanium using microscopy, qPCR, viability assays		*C. acnes* biofilm varies by material and strain, with plastic enhancing gene expression and osteoblast internalization reducing adherence but increasing polysaccharides and gene activation on titanium.
4.Characterization of periprosthetic environment microbiome in patients after total joint arthroplasty and its potential correlation with inflammation	2023	China	BMC Infectious Diseases	III	Samples were analyzed using mNGS and bioinformatics to characterize the periprosthetic microbiota and develop a classification system based on the Random Forest model.	77	1.Staphylococcus and Pseudomonas microbiota types were associated with increased inflammatory responses and higher rates of clinical PJI. 2. The increase of bacterial biodiversity can potenttially indicate a relatively “healthier” periprosthetic environment.
5.Biofilm Microenvironment Activated Antibiotic Adjuvant for Implant Associated Infections by Systematic Iron Metabolism Interference	2024	China	Advanced Science	V	Developing a deferiprone (DFP)-loaded nanomedicine (DFP@Ga-LDH) to target Fe-rich environments in implant-associated infections (IAIs) disrupting bacterial iron metabolism.		Nanomedicines that targets bacterial iron metabolism in implant-associated infections in addition to antibiotics shows strong antimicrobial properties against *Pseudomonas aeruginosa* and helped delay the emergence of antibiotic resistance.
6.Bacterial communications in implant infections: a target for an intelligence war	2007	Italy	The International Journal of Artificial Organs	V	Use of quorum-sensing inhibitors to attenuate bacterial virulence.		Quorum-sensing inhibitors, such as furanone analogs and RNAIII-inhibiting peptide (RIP), effectively attenuate bacterial virulence, reducing infections in *Pseudomonas aeruginosa* and *Staphylococcus aureus*.
7.Bone Environment Influences Irreversible Adhesion of a Methicillin-Susceptible Staphylococcus aureus Strain	2018	France	Frontiers in Microbiology	V	The influence of the bone environment on surface adhesion by a methicillin-susceptible Staphylococcus aureus strain		1. Increasing Mg2+ concentration also enhanced biofilm formation at a high concentration (20x plasma concentration). 2. Lack of oxygen. 3. Osteoblast-like cell supernatants significantly increase *Staphylococcus aureus* adhesion. 4. In a nutrient-deficient microenvironment, most free bacteria preferred to adhere, in a biofilm.

8.Phagocytosis of staphylococci biofilms by polymorphonuclear neutrophils: ***S. aureus*** and ***S. epidermidis*** differ with regard to their susceptibility towards the host defense	2009	Germany	The International Journal of Artificial Organs	V	Evaluation of different susceptibility of *S.aureus* and *S.epidermidis* to PMN phagocytosis		1.*S. aureus* biofilms were more susceptible to PMN attack and phagocytosis, with PMNs moving across and engulfing bacteria, while *S. epidermidis* biofilms restricted PMN mobility. 2. Properties of the extracellular biofilm matrix affecting the motility of PMN on the film and apoptosis.
9.Direct Microscopic Observation of Human Neutrophil-Staphylococcus aureus Interaction In Vitro Suggests a Potential Mechanism for Initiation of Biofilm Infection on an Implanted Medical Device	2019	USA	Infection and Immunity	V	Evaluation the effect of adding human neutrophils to a serum-coated glass surface inoculated with Staphylococcus aureus bacteria		1.Human neutrophils could control bacterial growth when their numbers surpassed the bacteria-to-neutrophil ratio of 1. 2.Delayed neutrophil recruitment allowed bacteria to form biofilm clusters, which neutrophils could not clear.
10.Interaction of Bacteria, Immune Cells, and Surface Topography in Periprosthetic Joint Infections	2023	Italy	International Journal of Molecular Sciences	V	It investigates the immune response to PJIs by analyzing synovial fluids from hip and knee replacement patients and using an in-vitro platform to replicate implant environments	74	Rough implant surfaces, common in uncemented prostheses, help *Staphylococcus epidermidis* evade immune detection more effectively, while *Staphylococcus aureus* shows varied responses depending on the surface. Both bacteria form more biofilm on rough surfaces, indicating that surface roughness may influence biofilm formation and immune responses, potentially increasing the risk of PJIs.
11.In vitro polymicrobial inter-kingdom three-species biofilm model: influence of hyphae on biofilm formation and bacterial physiology	2021	Belgium	Biofouling	V	Biofilm model with *Staphylococcus aureus*, *Escherichia coli*, and *Candida albicans* to explore the impact of fungal hyphae on biofilm formation and virulence in polymicrobial orthopedic infections.		Biofilms with fungal hyphae had greater biomass and increased expression of genes related to bacterial virulence, adhesion, exopolysaccharide synthesis, and stress response.
12.Host and microbial characteristics associated with recurrent prosthetic joint infection	2023	USA	Journal of Orthopaedic Research	III	The study evaluates the use of antibiotic cement spacers in two-stage revision arthroplasty for PJIs, with patients either receiving one or multiple spacers based on whether they had recurrent or single infections.	106	1.Recurrent PJI patients had more polymicrobial infections, greater systemic issues, and were more likely to harbor *S. aureus*. 2.Recurrent PJI shows increased antibiotic resistance even though not having exposed to it. 3. McPherson host grade, polymicrobial infection, and *S. aureus* were at higher risk.
13.***Staphylococcus epidermidis*** in Orthopedic Device Infections: The Role of Bacterial Internalization in Human Osteoblasts and Biofilm Formation	2013	France	PLOS One	III	The study compared *S. epidermidis* strains from orthopedic device infections with commensal nasal carriage isolates, assessing their ability to invade osteoblasts and form biofilms through ex vivo infection models, flow cytometry, and biofilm assays.	37	No significant difference between *S. epidermidis* strains from orthopedic device infections and commensal nasal isolates in terms of osteoblast invasion, adherence, or biofilm formation. This suggests that bone cell invasion is not a key factor in *S. epidermidis* orthopedic device infections, unlike in *S. aureus* infections.

14.Adhesin genes and biofilm formation among pediatric ***Staphylococcus aureus*** isolates from implant-associated infections	2020	USA	PLOS One	III	The study compares *Staphylococcus aureus* isolates from implant-associated infections (IAIs) and skin and soft tissue infections (SSTIs), focusing on their MSCRAMM profiles, biofilm formation, and genetic characteristics to understand the differences in adhesion mechanisms and infection behavior.	235	1.*Staphylococcus aureus* isolates from implant-associated infections (IAIs) were mostly methicillin-susceptible (MSSA) and non-USA300, with no significant differences in biofilm formation or MSCRAMM profiles compared to skin and soft tissue infection (SSTI) isolates. 2.The cna gene was more frequent in IAI isolates.
15.Biofilm growth on implants: bacteria prefer plasma coat	2011	Germany	The International Journal of Artificial Organs	V	The study compares bacterial adherence to different surfaces, focusing on how plasma or serum protein pre-coating influences adherence. It found that adherence of *S. aureus* and *P. aeruginosa* to titanium, plastic, and cell monolayers is enhanced when titanium is coated with plasma proteins.		1.*S. aureus* and *P. aeruginosa* preferred adhering to non-biological surfaces like titanium over biological ones. 2. Pre-coating titanium with plasma proteins further increased bacterial adherence, indicating that plasma proteins promote biofilm formation on non-biological surfaces. 3. Temperature, the presence of nutrients, the absence of host defense systems is important to virulence
16.Infectious Dose Dictates the Host Response during ***Staphylococcus aureus*** Orthopedic-Implant Biofilm Infection	2016	USA	Infection and Immunity	V	The study compares immune responses and biofilm growth in PJIs caused by different *Staphylococcus aureus* clinical isolates. It also examines how varying bacterial doses (103 or 105 CFU) affect inflammatory responses in IL-12p40 knockout mice, influencing the infection outcome.		All three *Staphylococcus aureus* strains (USA200, USA300, USA400) formed biofilms similarly in a PJI mouse model, with comparable immune responses. Increasing the bacterial dose neutralized immune response differences, highlighting the impact of inoculum size on infection outcomes. Biofilm formation was consistent across the strains.

Polymicrobial infections are of interest, where some bacterial strains act synergistically with one another, or may share resistance factors. Superinfection with fungi is not uncommon, and the presence of fungal hyphae enhances bacterial virulence, making infections more difficult to treat. Of further interest, Pseudomonas aeruginosa is able to exploit iron metabolism within the joint, increasing its virulence.

Finally, rough implant surfaces promote biofilm formation and further contribute to immune evasion. Complex surface geometry naturally results in small, isolated locations where antibiotic delivery may be limited and bacteria can proliferate unrestricted.

Conclusion

A number of critical factors contribute to the complex relationship between host vulnerabilities and bacterial survival strategies; when conditions favor proliferation, bacterial pathogenicity is enhanced and joint infection more likely ensues. Host related factors are a primary consideration, and any comorbid conditions that result in immune compromise; these factors include diabetes, rheumatoid arthritis, smoking, renal/hepatic insufficiency, immunosuppressive therapies, anemia, and malignancy. The local microenvironment is another important consideration, and factors in this domain include nutrient and oxygen deprivation, increased levels of Mg, joint PMN level and recruited time, capsular integrity, and osteoblast-like supernatant cells. Inherent bacterial pathogenicity is a third critical consideration, including biofilm formation capacity, intracellular survival capability, special types or strains (Staph aureus and Pseudomonas aeruginosa), escape from quorum sensing and virulence regulation systems, bacterial iron metabolism status (Pseudomonas), polymicrobial infections, properties of the extracellular matrix of the biofilm, presence of fungal hyphae, and higher initial bacterial load. Finally, the characteristics of the implant itself, particularly surface topography, are a crucial aspect, including rough/porous surfaces, cementless implants, and plasma coatings. Complex surfaces can create isolated locations where antibiotic delivery may be restricted and where bacteria may be able to persist. When biofilm adheres to these surfaces it can increase resistance to antibiotics, and create conditions where infections are even more difficult to treat.

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