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Dawn of the Biofilm Disease: Highlights about Biofilm in Bone and Joint & Prosthetic Joint Infections Pathogenesis, Diagnosis and Treatment

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Abstract

I present some key considerations of the biofilm disease as part of two complex pathologies such as bone and joint infections and prosthetic joint infections, taking into account the bacterial pathogenic factors to understand the particular nature of these infections, and to achieve an accurate diagnosis and management beyond the antimicrobial therapy. I mention some personal experience of many years in the medical microbiology laboratory and next to the patient's bed.

Keywords: Bone; Joint; Prosthetic joint; Infection; Osteomyelitis; Septic arthritis; Biofilm

Introduction

Bone and joint infections (BJI) are a major situation with higher morbidity and disability association. The increasing use of biomaterials, invasive procedures, prosthetic joint replacement, indiscriminate use of antimicrobial agents, leads bacteria to the development of a special adaptive mechanism knows as the biofilm production, that becomes an acute infection in a chronic disease [1].

BJI related to biofilm-producer microorganism should be consider as an emergency in some special populations, i.e., children, elderly people and immunosuppressed patients (diabetic foot infections as prototype), due to the potential irreversible damage to the joint cartilages and chronification of an acute osteomyelitis process, with the subsequent bone destruction [2].

The prosthetic joint infection (PJI) represents a very selected and complicated group of BJI associated with a foreign body, where biofilm-producer bacteria has the starring, with a special diagnosis and management due to the particular conditions of halogenic material [3], that brings an amazing adhesive growing surface for the bacteria, and stimulates the biofilm production and quorum-sensing related phenomena [4]. This biofilm production protects bacterial community against external aggression like antimicrobial agents, environmental changes (temperature, nutrients depletion, light, oxidative stress), disinfection agents, physical debridement, etc., so, this increases in adherence, antimicrobial resistance, adaptation capacity to environment challenges, mobility (yes, biofilm moves as metastatic masses to another distant places) and longevity, provides bacteria an evolutionary advantage against its planktonic forms.

Questions & Answers

Many guidelines presents the diagnosis and therapeutics algorithms for BJI and PJI, but a comprehensive approach based on answer questions was used by the Infectious Diseases Society of America (IDSA) in the 2012 Clinical practice guideline for the diagnosis of diabetic foot infections [2] and 2013 Clinical practice guideline for the diagnosis and management of prosthetic joint

infections [3], so, follow this experts way to present the evidence as a guideline, I consider that answer questions from years of clinical daily practice and microbiology day -to-day experience could be a simple and easy way to show information that you'll can use in your clinical setting, so, here I go with the questions and answers:

What really is a biofilm?

I have 3 simple concepts to define it, so you can choose the one that best fits to your practice:

• The biofilm is an adaptive growing form of bacteria, attached to a surface.
• A biofilm is a resilient community of bacteria surrounded by an exopolymer matrix that brings resistance against aggressive factors.
• The biofilm is a dynamic system that evolves with the environmental changes, that communicates within itself, and persists over the measures to destroy it.

Why biofilm production are considered a pathogenic mechanism?

Pathogenicity implicates defense and aggression in the same concept, and biofilm:

• Protects bacteria against physical debridement methods, with an increase of its unspecific and specific adherence.
• Biofilm exopolymers hide antigenic components of bacteria from the immune response system, so, eludes some specific immune response (i.e., opsonization, inflammation).
• Biofilm neutralize antimicrobial drugs penetration inside itself, by kidnapping, efflux mechanisms, impermeability changes.
• Biofilm reduces bacterial sensibility to some drugs, i.e., protein & cell wall synthesis inhibitors loss efficacy because bacterial forms "reduces" its metabolic pathways (or turns into a latent stage, similar to bears hibernation!), so, the targets still present, the binding is effective, but "naturally" the bacteria "choose" to modify its metabolism.
• Metastatic phenomena from the external biofilm surface explains distant infections from the original focus.
• Antimicrobial drug resistance needs a special mention, because the increases in the MIC (Minimum Inhibitory Concentration) of the antibiotic is multiply by a 1000 factor, so, reach the effective antimicrobial concentration inside the biofilm, to inhibit the bacterial grow are almost impossible (without toxicity for the patient).

Why BJI & PJI are biofilm related diseases?

Two different answers and one common:

• BJI was more frequent in children, related to mechanic trauma (MRSA -Methicillin-Resistant *Staphylococcus aureus*-) capsulated bacterial infections that has hematogenous spread (*Streptococcus pneumoniae*, *Haemophilus influenzae* type B), previous respiratory infections (*Kingella kingae*, *Streptococcus pyogenes*), prematurity (*Escherichia coli, Streptococcus agalactiae*), malnutrition (*Candida albicans*), enteric diseases (*Salmonella* sp.). So, age-related factors mixed with an ineffective immune response, plus previous antimicrobial therapy use that selects more resistant microorganism and stimulates a defensive reaction of bacteria are the blocks that initiate "the bacterial biofilm wall". In elderly people, vertebral tuberculosis is the classical presentation of chronic osteomyelitis (caseous necrosis).
• PJI comes from an foreign body that leads attach of bacteria and stimulates quorum-sensing phenomena, plus the origin of the replacement (previous infection i.e.,) and the history of antimicrobial use (the antimicrobial drugs naïve patient is an endangered species). Elderly comes with osteoporosis, that provides itself a niche for bone damage, and bacteria takes advantage of it to colonize, even in a patient with a limited immune response. You must consider diabetes mellitus as another major risk factor for biofilm diseases.
• Trauma (direct seed) or hematogenous dissemination (indirect seed), plus immune response that doesn't eradicate bacteria, plus previous antimicrobial use, plus foreign bodies, equals to a possible biofilm-disease.

How I diagnose a biofilm-related BJI/PJI?

Some common considerations should be addressed:

• **FIRST**: Clinical diagnosis of BJI/PJI, the most common acute clinical presentation is the **Septic Arthritis** (SA), with a development time among bacterial access to joint of 3 to 7 days, and classical clinical Celso's symptoms: pain, inflammation of the joint, redness, fever and reduction in range of motion. In the **Acute Osteomyelitis (AO),** limp and localized pain, a minor swelling over the affected bone and occasional erythema could be present. The PJI presents with swelling at the prosthetic joint, minor pain, joint loosening and cracking, fistula with hematic/purulent discharge, and afternoon fever in some cases. Sinus tracts also guides to the differential diagnosis of **Chronic Osteomyelitis (CO)**.
• **SECOND**: Imaging techniques could help to differentiation among pathologies.
  - o **A plain radiograph (PR)** should be performed in all patients with suspected BJI/PJI. Space increases in the joint suggest inflammation.
  - o The **ultrasound sonography** helps to identify joint effusion in SA, that could be missed in PR, also identifies subperiostic abscess (CO)
  - o **Vascular Doppler** may detect elevated blood flow in AO and help in early diagnosis.

- The **Scintigraphy/ Technetium radionuclide (Tc)** bone scan needs high radiation dose, but still be useful for the diagnosis of AO & CO (specially in multi-foci diseases).
- **MRI** is the best test for osteomyelitis (acute & chronic).
- **Computerized Tomography (CT) Scan** should be reserved for diagnostic dilemma but availability over MRI in some centers justified its use.

• **THIRD**: Laboratory findings based on hematological sample:

- **Complete Blood Count (CBC):** Differential white blood cell count, hemoglobin/hematocrit and platelet count guides to a bacterial disease and helps to differentiate from hematological malignancies.
- **C Reactive-Protein (CRP):** Quickly diagnosis & follow-up test with high sensitivity for diagnosis. Rapid normalization if treatment is effective (3 to 8 days).
- **Erythrocyte Sedimentation Rate (ESR):** indicates inflammatory response, but recommend use in conjunction with CRP. Slowly normalization (3 weeks or more) if treatment is effective.
- **Procalcitonin (PCT):** Useful to reinforce inflammatory & infectious nature of the disease, but not for prognosis, only shows promising in SA. This test needs to be standardized according to each lab.
- **Novel biomarkers in sinovial fluid:** α-defensin, interleukin-6 & leukocyte esterase determinations improves the diagnosis of PJI, and helps to identify periprosthetic joint infections with more accurately [5].

• **FOURTH**: Microbiological intervention needs a representative sample, obtain by arthrocentesis or by bone or joint biopsy, or a blood sample for culture and special tests.

- **Blood culture:** Useful if bacteremia is suspected, helps in cases of occult BJI suspect (MRSA as main pathogen), and helps in newborn, neonates and young infants as a sepsis indicator without local signs in AO.
- **Synovial fluid/bone sample:**
  - **Biofilm–disrupting diagnostic tests:** Increases the recovery of viable colonies with great simplicity, these tests includes sonication, Vortexing and dithiothreitol treatment, that increases bacterial isolates and leads to demonstrated biofilm production [6,7].
  - **Stains**: Gram, Ziehl-Neelsen, Grocott: fast orientation for treatment selection. Very useful if antibiotic was not previously used.
  - **Culture** and Susceptibility Tests: Confirms diagnosis and leads the de-escalation or switch antimicrobial therapy. The use or Congo Red method helps to identify biofilm-producer colonies.
  - **Bacterial** Polymerase Chain Reaction (bPCR): Helps in diagnosis of fastidious microorganisms (*Kingella kingae*) or in demonstration of eubacteria as *Staphylococcus aureus* (ribosomal RNA), especially if the patient received antimicrobial therapy prior to the sample obtain.
    - *Sinus tract culture is not adequate or representative of mainly pathogen, because tract colonization create a distortion in stains & culture results.*

How I treat the biofilm-related BJI/PJI?

Management of biofilm-related BJI/PJI involves more than antimicrobial drugs:

• **A multidisciplinary team:** Join an Infectious Diseases Specialist, a Medical Microbiologist, a Traumatologist, and a head physician (Pediatrician or Internal Medicine Specialist), and the diagnosis success and adequate management is almost guaranteed. A constant follow-up is a must in this process.

• **Who is the suspect?:** Epidemiology & clinical diagnosis of BJI/PJI offers the most frequent infectious agent related to age, co-morbidities, antimicrobial use history.

• **OR (Operation Room) or not OR, that's the question:**

- Avoid if possible, but perform if consider pus or effusion drainage or bone destruction risk.
- Always arthrocentesis/arthrotomy (SA, especially in children -emergency-).
- Prosthetics material should be removed, surgical cleaning & considerations for one or two surgical times may be performed.
  - Use of antimicrobial deliver devices needs to be consider in case of late prosthesis reimplantation.

• **Antimicrobial Treatment:**

- Pathogen-specific
- Not known pathogen: Choose antibiotic spectrum similar to IV. If initial IV response was favorable, switch to oral antibiotic monotherapy following local microbiologic patterns or clinical infectious disease guidelines.
- Always consider MRSA incidence (high: clindamycin±cephalosporin, alternatives for clindamycin could be trimethoprim-sulfamethoxazole, quinolones or linezolid; in low incidence regions consider first/second generation cephalosporin or clindamycin).
- Length of the antimicrobial therapy:

§ Consider use of bactericidal drug + anti-biofilm drug.
§ AO: 4 to 6 weeks.
§ SA: 4 to 6 weeks or longer (up to several months depends of patient response).
§ CO: approximately 10 weeks (4 weeks of attack phase with IV drugs combination, then 6 weeks for consolidation phase with oral drugs combination; always including an anti-biofilm drug such as rifampin or a quinolone or macrolide), maybe more time is necessary in special case such as diabetic foot osteomyelitis.
§ PJI: Anti-biofilm drugs combination guided by susceptibility tests results is the rule, but, the use of antimicrobial release-devices helps to maintain an infection-free tissue. Thermostable agents as daptomycin are useful in bone cement or spacers.
§ *Notes of the author:*

- *Personal experience in CO in diabetic patients with the combinations of Daptomycin (at high dose over 10 mg/Kg/IV/daily)+Rifampicin (600 mg/PO/daily) for 4 to 6 weeks; or Daptomycin (10 mg/Kg/IV/daily)+Rifampicin (600 mg/PO/daily) for 3 weeks follow by 3 weeks of Linezolid (600 mg/VO/BID) + Rifampicin (600 mg/PO/daily); and then a consolidation phase of Moxifloxacin (400 mg/PO/daily) or Levofloxacin (750 mg/PO/daily) +Rifampicin (600 mg/PO/daily) or Azithromycin (500 mg/PO/daily) for 6 to 10 weeks achieves a complete microbiological, clinical & radiological cure. Several years follow-up doesn't demonstrated relapses [8].*
- *In cases when combination therapy couldn't be use, daptomycin monotherapy at higher dose in susceptible bacteria as MRSA is helpful and exhibit anti-biofilm activity [9].*

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