FUTURE DIAGNOSTICS IN ORTHOPAEDIC INFECTIONS

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I.INTRODUCTION:

Ortho means upright, correct, and straight. Child is a Paios. The term was first used in 1841 by French physician Nicolas Andry in his book "Orthopaedia: the science to treat and avoid abnormalities in children." The medical discipline of orthopaedics, deals with musculoskeletal disorders and trauma, commonly referred as trauma and orthopaedic surgery The spinal column, muscles, tendons, ligaments, joints, spinal cord and peripheral nerves and associated nerves make up the column of vertebra.

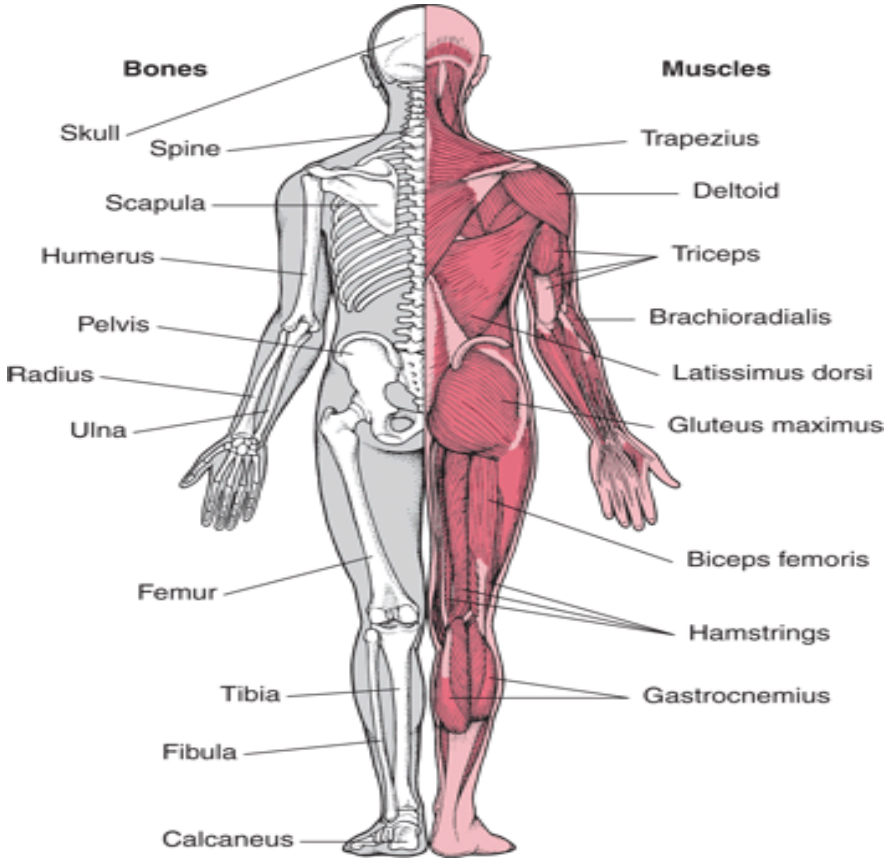

Figure 1: Musculo-skeletal system

The diagnosis and treatment of diseases of the musculoskeletal system, which includes the skeleton and the soft tissues that surround it are the focus of contemporary orthopaedics. Orthopaedic surgeons treat non-traumatic diseases as well as musculoskeletal injuries, particularly fractures throughout the world. Orthopaedic sub-specialization is becoming more prevalent and can be characterized by patient age (for instance, children orthopaedics), by location (for instance, Surgery of hip), or by disease (e.g. rheumatoid surgery). Alternately, one might think of orthopaedics in terms of the structures that it mostly deals with.. A knowledge of the anatomy, physiology and pathology of these structures and tissues gives a suitable starting place for researching the subject's clinical aspects. (1)

To ensure accurate diagnosis, effective treatment, and improved results, diagnostics must be enhanced due to the wide clinical range of orthopaedic infection.The main stays of management include early identification of the clinical condition, proper diagnostic sampling, and antimicrobial therapy.It can be difficult to get representative samples, and invasive sampling is frequently required. Comorbid inflammatory conditions and immunosuppressive medications, among other host characteristics, make it more difficult to detect and diagnose infection.Two fundamental ideas form the basis of the diagnosis for orthopaedic infection.:

a) Detecting the pathogen and
b) Detecting the host inflammatory response

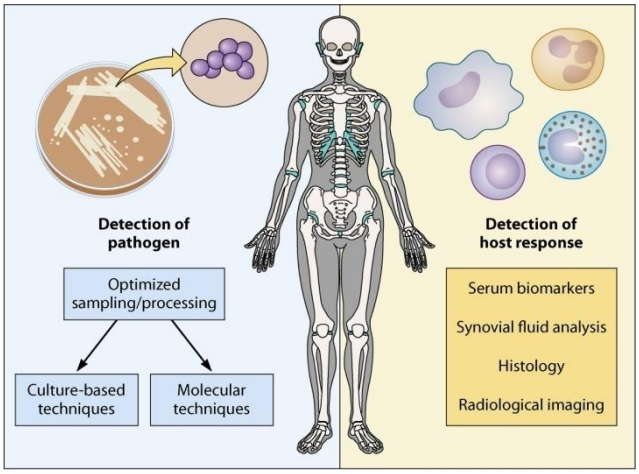

Figure 2: Principles of diagnostics in orthopaedic infections.

II. DETECTING THE PATHOGEN:

a) Culture based techniques:

For the accurate diagnosis of infections of the bones and joints, sampling is necessary. Although peripheral blood cultures are an important diagnostic tool, it is typically necessary to sample synovial fluid, bone, or periprosthetic tissue in order to confirm a diagnosis of orthopaedic infection. The objective is to collect samples through a way it reduces contamination from skin flora. The samples must be taken strictly aseptically and without introducing the needle via sinus or fistula tracts in order to prevent contamination. To prevent cross contamination with occurrence of infections in prosthetic joint (PJI), many periprosthetic samples should be taken using different sterile tools (2).

Swabs used for culture specimens are useless for diagnosing orthopaedic infections because they have lower sensitivity than tissue samples and have poor microbiologic concordance with deeper samples (3). (4). Low Gram stain sensitivity for infection identification in orthopaedic samples (5). Orthopaedic samples should only be cultured for fungi and mycobacteria when there is a clinical suspicion for it; routine testing is not required (6). The most significant warning indicator for an infection with a culture negative outcome is pre sampling antibiotic medication, which decreased the yield of culture specimens (7). Systemic antibiotics must to be avoided whenever possible for at least two weeks before culture ascertainment.

With PJI, where common commensal organisms may potentially be implicated in infection, separating contaminants from real pathogens is very challenging. Differentiating between a pathogen and a contaminant may be facilitated by detecting these organisms in multiple samples separately collected. As a reference standard for infection diagnosis, histology samples from individuals receiving surgical repair were used in their prospective analysis to determine the optimum amount of samples required to detect PJI. According to mathematical modelling, 5 to 6 surgical specimens must be collected for culture in order to achieve appropriate sensitivity and specificity. In more recent research (8, 9, 10), tissue samples were inoculated in bottles cultured with blood together with clinical rather than histological criteria. Particularly relevant to PJI is the duration of bacterial culture incubation as slow-growing species like *Cutibacterium* acnes may be involved.

Advantages: primary method of pathogen identification in joint infection. Synovial fluid, periprosthetic tissue, and sonicate fluid samples were injected into bottles containing blood cultures to increase production, allows for the profiling of identified species' antimicrobial susceptibility widely accessible

Limitations: Multiple samples were required in the PJI environment because of limited sensitivity of a single sample and the difficulty in distinguishing contaminants from genuine pathogens. Pre-sampling antibiotic treatment reduces yield Long-term incubation is necessary for the identification of sensitive organisms**.**

Molecular techniques:

PCR: PCR has been applied to several infection sites. One of two broad approaches is typically used when using PCR to diagnose infections of the bones and joints

(i) Broad-range 16S PCR followed by sanger or next-generation sequencing (NGS) to determine the causative agent of positive results.

(ii) PCR with primers that are specific to one or more prevalent pathogenic organisms or a multiplex panel of species.

Advantages: It can identify both live and nonviable bacteria and the sensitivity should be less influenced by antibiotic administration prior to collection. The rapidity of bacterial identification can enable prompt application of the right pathogen-directed anti-microbial medication. It could also find organisms that are hard to cultivate or picky. (11)

Limitations: Diagnostic panels using multiplexing will not pick up uncommon illnesses.

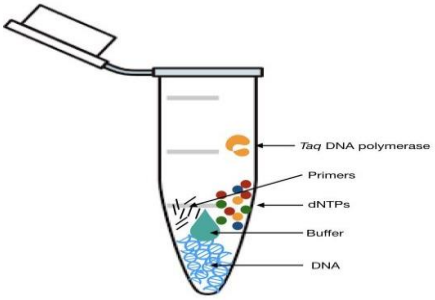

Figure 3: PCR (polymerase chain reaction)

Shotgun metagenomics: The process known as "metagenomic shotgun sequencing" involves extracting and sequencing every nucleic acid present in a sample, usually utilising next-generation sequencing methods to characterize a wide range of specimen-types, including those in environmental and microbiome studies (12, 13)

Limitations: Substantial expense linked complicated workflow technique susceptible to bacterial contamination at several production stages.

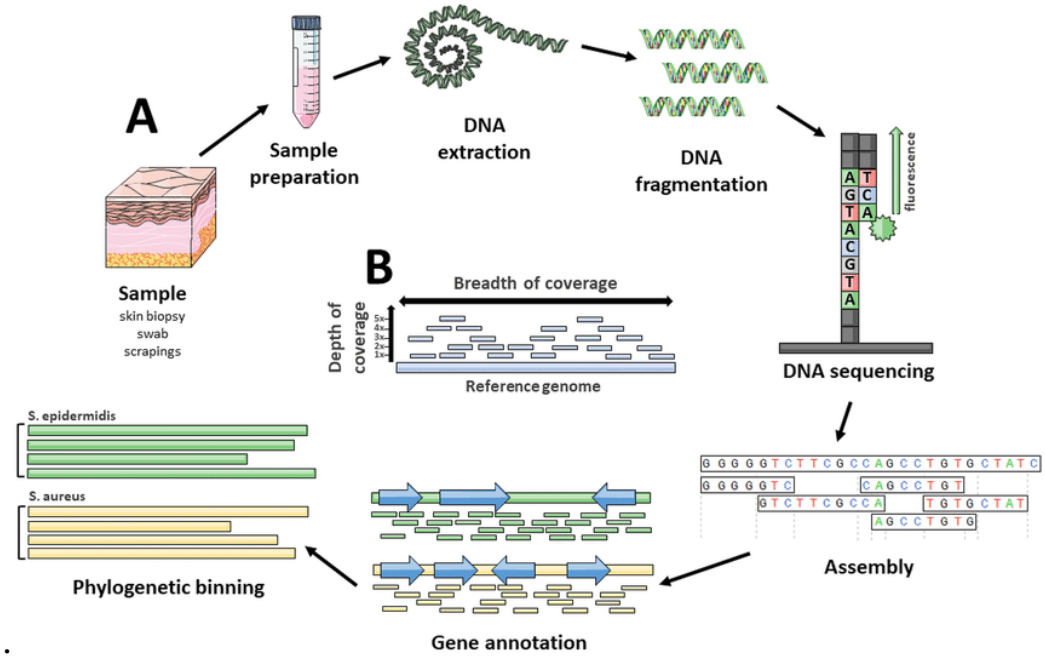

Figure 4: Shotgun (Meta) genomic sequencing study

III. DETECTING THE HOST RESPONSE

a) Serum biomarkers: C-reactive protein and Erythrocyte sedimentation rate are most affordable and accessible serum inflammatory markers (CRP). They may be raised in various systemic disorders, inflammatory states, cancer, or post surgical intervention, but they lack the specificity of an ideal diagnostic test. Indicators of significance for orthopaedic infection include procalcitonin and interleukin 6 (IL-6). Activated macrophages and monocytes create IL-6, which promotes the synthesis of a number of other acute phase reactants. In comparison to white cell count, ESR, and CRP, IL-6 had the highest diagnostic accuracy, according to a comprehensive evaluation of inflammatory markers in PJI (14); its reported pooled sensitivity and specificity were 97% and 91%, respectively.

b) Synovial fluid analysis: Standard of care for suspected septic arthritis of the native and prosthetic joints is to sample the synovial fluid. Synovial fluid white cell count of 50,000/mL is typically used as the cutoff for native joint septic arthritis (15). Prosthetic and native joint arthritis present with inflammatory arthropathies, making synovial fluid analysis interpretation difficult. Prosthetic and native joint arthritis present with inflammatory arthropathies, making synovial fluid analysis interpretation difficult. Therefore, while interpreting the results of a synovial fluid analysis, it is important to take into account the medical field, the patient's co-morbidities, immune state, and, in the case of artificial joints, the duration of symptoms, timing in relation to surgery, and the implicated joint.

Biomarkers: found in synovial fluid Synovial fluid has been evaluation for a number of biomarkers that measure the host inflammatory response at the location. Leukocyte esterase and alpha defensin have received the most attention among the known biomarkers. Leukocyte esterase, which is readily available as a colorimetric test strip, is an enzyme found in neutrophils. Blood in the sample has a negative impact on the efficacy of leukocyte esterase testing strips (16), which is problematic because many synovial fluid samples will contain blood. Both an ELISA and a lateral flow test for alpha defensin are available, with results available in a matter of minutes. Comparing alpha defensin to CRP, IL-6, and leukocyte esterase, it is reported to have superior sensitivity.

Limitations: Costly red cell presence affects the effectiveness of the leukocyte esterase test. Compared to ELISA, lateral flow alpha defensin has a lesser sensitivity.

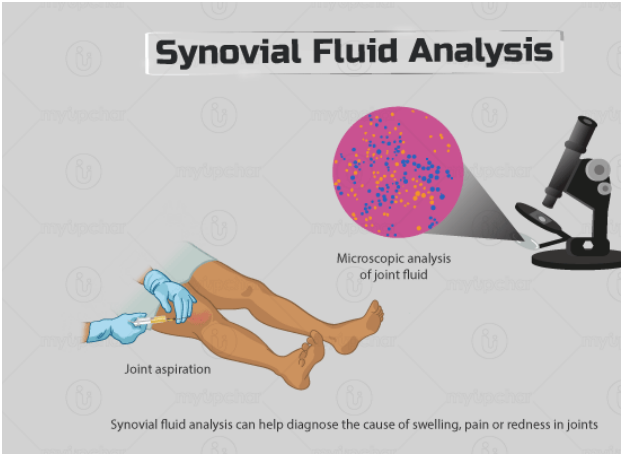

Figure 4: Synovial fluid analysis

c) Histology: The existence of an inflammatory infiltration is confirmed by histological examination of bone and synovial tissues, which might reveal crucial details about the underlying aetiology. Histology alone does not, however, have a high enough sensitivity to completely rule out prosthetic joint infection. The histological analysis of intraoperative frozen sections may serve as a basis for surgical approach recommendations**.**

Limitations: Sensitivity is insufficient to use this test alone to "check out" infection.

Radiological imaging:

The diagnosis of an orthopaedic infection and the evaluation of complications are both improved by radiological imaging. Particularly in implant-related infections where clinical symptoms may be minor, suggestive radiography findings may be useful in providing information to support and guide more extensive diagnostic collection.

Ultrasonography also avoids ionising radiation and has the advantage of being widely available. However, it can direct synovial fluid aspiration and is useful in assessing joint effusions, adding extra crucial diagnostic data. In general, it is useless for diagnosing osteomyelitis.

Computed tomography (CT):

Although it is less sensitive to osteomyelitis than magnetic resonance imaging, it gives a more accurate spatial examination of the soft tissue and the bone (MRI). It might display fluid remains or soft tissue deformities that suggest an infection. In the case of implant-associated orthopaedic infections, artifactual alterations from prostheses interfere with both CT and MRI scans. Because it has more sensitivity in CT and can identify alterations associated to bone marrow oedema early in the course of infection, MRI is the imaging modality of choice in the assessment of osteomyelitis. Following treatment, MRI alterations can last for weeks or even months.

Nuclear imaging:

It can screen for inflammatory changes while avoiding the artifact-related issues that other modalities experience, which makes it a possible diagnostic aide in the evaluation of PJI.

Bone scintigraphy:

It is one of these methods that is most frequently used to evaluate prosthetic joints, but its reported accuracy varies from 50 to 70% (17).

IV. Alternative antibiotics for Orthopaedic infections:

In order to evaluate whether alternative antibiotics are comparable to the current clinical workhorses tobramycin and vancomycin, clinicians must first determine the rate of elution, duration of elution rates above MIC, and thermal stability at core temperature. These criteria are mandated by the increasing emergence of resistant pathogens in orthopaedic infections.

Only dalbavancin maintained above-MIC rates while sharing identical elution characteristics to Vancomycin with cefazolin and minocycline.

Amikacin and Meropenem, in contrast, showed good thermal stability as compared to Tobramycin and gradually improved elution profiles and durations of above-MIC activity, making them appropriate substitutes for E. coli and A. Baumannii.

The cyclic lipopeptide antibiotic daptomycin is effective against a variety of gram-positive bacteria. Some intermediate S. aureus that is heteroresistant to vancomycin S. aureus (hVISA) and intermediate- vancomycin S. Daptomycin nonsusceptibility is also present in aureus (VISA) strains. Methicillin-resistant Staphylococcus aureus (MRSA) and coagulase-negative Staphylococci, the most frequent causes of PJI, have traditionally been treated with vancomycin (18,19). Vancomycin is usually only effective against gram-positive bacteria and is usually used in conjunction with an aminoglycoside. In implanted devices, tobramycin is often used instead of gentamicin because it is not commercially accessible in the United States. The addition of an aminoglycoside may have several benefits. Although the clinical significance of this is unknown, combining an aminoglycoside with a cell wall active drug exhibits synergistic efficacy against gram-positive pathogens (20,21) In theory, an aminoglycoside might prevent the development of drug resistance (22). The elution of other antibiotics may be enhanced by an aminoglycoside by increasing the permeability of bone cement.

Conclusion:

It takes a team effort from orthopaedic radiologists, microbiologists, and infectious diseases specialists to improve diagnostic yield given the complexity of orthopaedic infection diagnostic techniques. Strengths and weaknesses of different diagnostic procedures. Although extensive sampling must come before these techniques and they may occasionally be supplemented by molecular methods, culture-based methods remain the foundation of diagnosis. The continued development of innovative molecular diagnostics should be the main emphasis of future research.

A complete assessment of the inflammatory response using radiologic imaging, blood, synovial fluid, and histologic testing is required to establish whether an infectious disease is present. In the end, the diagnosis of orthopaedic infections in the future will still be based on a thorough evaluation of all available microbiological and non-microbiological evidence.

Due to the high local drug concentrations that were used in lethal concentrations for the microorganisms, daptomycin with tobramycin-loaded poly methyl methacrylate beads can be an effective and safe bactericidal local antibiotic delivery system in biofilm-producing bacteria, especially in recurrent or resistant prosthetic joint infections.

REFERENCES:

1) T Duckworth and CM Blundell, Textbook of Orthopaedics and Fracture, Blackwell Publishing, 4th edition 2010 .
2) Larsen LH, Xu Y, Simonsen O, Pedersen C, Schønheyder HC, Thomsen TR, PRIS Study Group. 2014. 'All in a box' a concept for optimizing microbiological diagnostic sampling in prosthetic joint infections. BMC Res Notes 7:1–5
3) Aggarwal VK, Higuera C, Deirmengian G, Parvizi J, Austin MS. 2013. Swab cultures are not as effective as tissue cultures for diagnosis of periprosthetic joint infection. Clin Orthop Relat Res 471:3196–3203. https://doi .org/10.1007/s11999-013-2974-y.
4) Tetreault MW, Wetters NG, Aggarwal VK, Moric M, Segreti J, Huddleston IIJI, Parvizi J, Della Valle CJ. 2013. Should draining wounds and sinuses associated with hip and knee arthroplasties be cultured? J Arthroplasty 28:133–136. https://doi.org/10.1016/j.arth.2013.04.057.
5) Gbejuade H, Elsakka M, Cutler L. 2019. How well does synovial fluid gram staining correlate with cultures in native joint infections? Orthop Rev (Pavia) 11:8156. https://doi.org/10.4081/or.2019.8156.
6) Tai DBG, Wengenack NL, Patel R, Berbari EF, Abdel MP, Tande AJ. 2022. Fungal and mycobacterial cultures should not be routinely obtained for diagnostic work-up of patients with suspected periprosthetic joint infections. Bone Joint J 104-B:53–58. https://doi.org/10.1302/0301-620X.104B1 .BJJ-2021-0876.R1.

7) Berbari EF, Marculescu C, Sia I, Lahr BD, Hanssen AD, Steckelberg JM, Gullerud R, Osmon DR. 2007. Culture-Negative Prosthetic Joint Infection. Clin Infect Dis 45:1113–1119
8) Atkins BL, Athanasou N, Deeks JJ, Crook DW, Simpson H, Peto TE, McLardySmith P, Berendt AR, Group TOCS. 1998. Prospective evaluation of criteria for microbiological diagnosis of prosthetic-joint infection at revision arthroplasty. J Clin Microbiol 36:2932–2939. https://doi.org/10.1128/JCM.36.10.2932-2939 .1998.
9) Peel TN, Spelman T, Dylla BL, Hughes JG, Greenwood-Quaintance KE, Cheng AC, Mandrekar JN, Patel R. 2017. Optimal periprosthetic tissue specimen number for diagnosis of prosthetic joint infection. J Clin Microbiol 55:234–243 https://doi.org/10.1128/JCM.01914-16.
10) Bémer P, Léger J, Tandé D, Plouzeau C, Valentin AS, Jolivet-Gougeon A, Lemarié C, Kempf M, Héry-Arnaud G, Bret L, Juvin ME, Giraudeau B, Corvec S, Burucoa C, Centre de Référence des Infections Ostéo-articulaires du Grand Ouest (CRIOGO) Study Team. 2016. How many samples and how many culture media to diagnose a prosthetic joint infection: a clinical and microbiological prospective multicenter study. J Clin Microbiol 54:385–391. https://doi.org/10.1128/JCM.02497-15.
11) Patel A, Harris KA, Fitzgerald F. 2017. What is broad-range 16S rDNA PCR? Arch Dis Child Educ Pract Ed 102:261–264
12) Qin N, Yang F, Li A, et al. Alterations of the human gut microbiome in liver cirrhosis. Nature 2014; 513(7516): 59-64.
13) Be NA, Thissen JB, Fofanov VY, et al. Metagenomic analysis of the airborne environment in urban spaces. Microb Ecol 2015; 69(2): 346-55
14) Berbari E, Mabry T, Tsaras G, Spangehl M, Erwin PJ, Murad MH, Steckelberg J, Osmon D. 2010. Inflammatory blood laboratory levels as markers of prosthetic joint infection: a systematic review and meta-analysis. J Bone Joint Surg Am 92:2102–2109. https://doi.org/10.2106/JBJS.I.01199
15) Turner EH, Mc Daniel HL, Spiker AM. 2021. A narrative review of the last decade's literature on the diagnostic accuracy of septic arthritis of the native joint. J Experimental Orthopaedics 8:3–11.
16) Wetters NG, Berend KR, Lombardi AV, Morris MJ, Tucker TL, Della Valle CJ. 2012. Leukocyte esterase reagent strips for the rapid diagnosis of periprosthetic joint infection. J Arthroplasty 27:8–11.
17) Palestro CJ. 2014. Nuclear medicine and the failed joint replacement: past, present, and future. World J Radiol 6:446–458
18) Hip and knee section, fungal periprosthetic joint infection, diagnosis and treatment: Proceedings of International Consensus on Orthopedic Infections. Belden K, Cao L, Chen J, et al. *J Arthroplasty*. 2019;34:387.
19) Clinical practice. Infection associated with prosthetic joints. Del Pozo JL, Patel R. *N Engl J Med 361*. 2009;787:794.
20) Aminoglycoside drugs in clinical practice: an evidence-based approach. Leibovici L, Vidal L, Paul M. *J Antimicrob Chemother*. 2009;63:246–251.
21) Initial low-dose aminoglycosides in Staphylococcus aureus bacteremia: good science, urban legend, or just plain toxic? Bayer AS, Murray BE. *Clin Infect Dis*. 2009;48:722–724.
22) Therapeutic monitoring of vancomycin in adults summary of consensus recommendations from the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists. Rybak MJ, Lomaestro BM, Rotschafer JC, *Pharmacotherapy*. 2009;29:1275–1279.