FUTURE DIAGNOSTICS IN ORTHOPAEDIC INFECTIONS

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I.INTRODUCTION:

Ortho = Straight, Upright, Correct. Paios = Child. First used by Nicolas Andry; a French doctor (1841) in a book titled "Orthopaedia: the art to correct and prevent deformities in children".

Orthopaedic specialty is the branch of medicine which manage trauma and disease of musculoskeletal system, it is also known as: Trauma and Orthopaedic Surgery. It consists of the vertebral column, muscles, tendons, ligaments, joints, peripheral nerves, and spinal cord and its nerves.

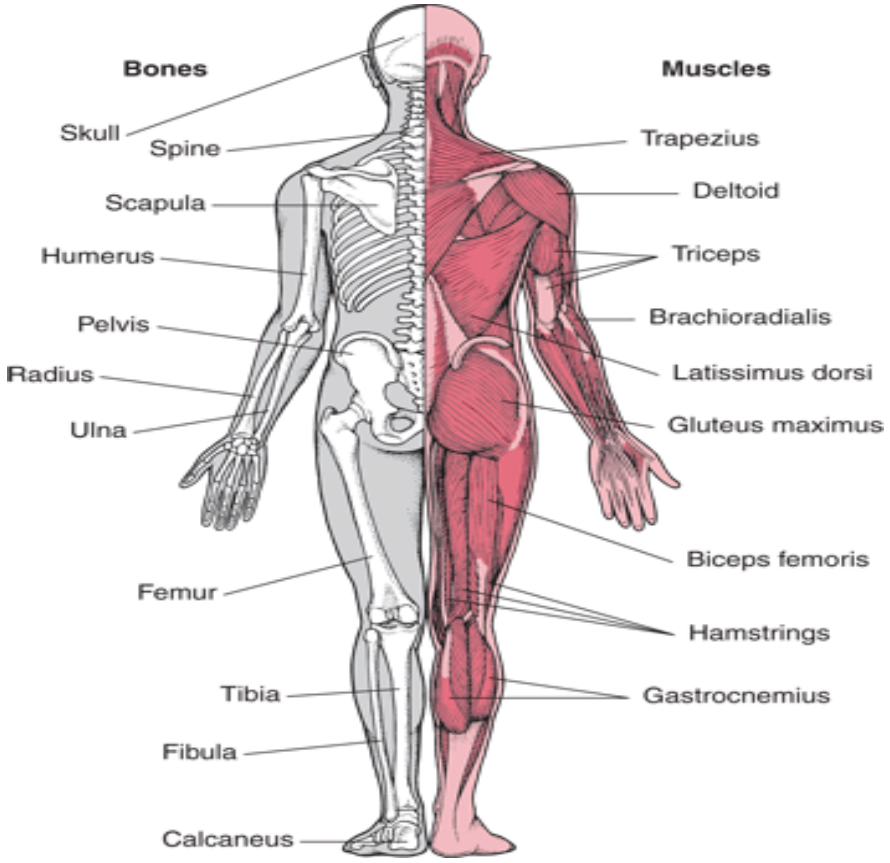

Figure 1: Musculo-skeletal system

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. (e.g. paediatric orthopaedics), by region (e.g. hip surgery) or by condition (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.. Obtaining representative samples can be challenging and often requires invasive sampling. Comorbid inflammatory conditions and immunosuppressive medications, among other host characteristics, make it more difficult to detect and diagnose infection.The central tenets of diagnostics in orthopaedic infection revolve around two core principles:
a)Detection of the pathogen and
b) Detection of the host inflammatory response

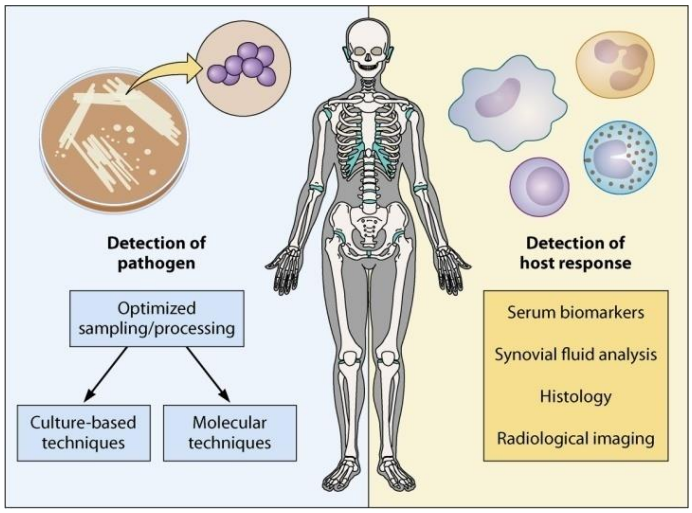

Figure 2: Principles of diagnostics in orthopaedic infections.

II. DETECTION OF PATHOGENS:

a) Culture based techniques:

For the accurate diagnosis of infections of the bones and joints, sampling is necessary.Peripheral blood cultures are an important diagnostic tool, but confirming a diagnosis of orthopaedic infection generally requires synovial fluid, bone, or periprosthetic tissue sampling. The goal is to obtain samples in a way which minimizes contamination by skin flora.In order to prevent contamination, samples should be taken strictly aseptically and without passing the needle through sinus or fistula tracts.. In the case of prosthetic joint infections (PJI), multiple periprosthetic samples should be obtained using separate sterile instruments to avoid cross contamination (2).

Use of swabs for culture specimens is unhelpful in diagnosis of orthopaedic infection, as the sensitivity is lower than that of tissue samples (3) and microbiologic concordance of superficial swabs with deeper samples is poor (4). Sensitivity of Gram stain for pathogen detection in orthopaedic samples is low (5). Fungal and mycobacterial cultures should be done on orthopaedic samples in select cases based on clinical suspicion and are not necessary as a routine practice (6). Pre sampling antibiotic therapy reduced yield of culture specimens and is the most important risk factor for culture-negative infection (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. In their prospective study to evaluate the optimum number of samples required to diagnose PJI (8) used histology of samples from patients undergoing revision surgery as a reference standard for infection diagnosis. According to mathematical modelling, 5 to 6 surgical specimens must be collected for culture in order to achieve appropriate sensitivity and specificity. More recent studies (9, 10) utilized clinical rather than histopathological criteria as well as inoculation of tissue samples into blood culture bottles. Particularly relevant to PJI is the duration of bacterial culture incubation as slow-growing species like *Cutibacterium* acnes may be involved.

Advantages: Mainstay of pathogen detection in orthopaedic infection Increased yield with inoculation of synovial fluid, periprosthetic tissue, and sonicate fluid samples into blood culture bottles Allows for antimicrobial susceptibility profiling of identified organisms Widely available.

Limitations: In setting of PJI, multiple samples required due to low sensitivity of single sample as well as difficulty distinguishing contaminants from true pathogens Yield diminished by pre sampling antibiotic administration Prolonged incubation required for detection of fastidious organisms.

b) Molecular techniques:

PCR: PCR has been used in numerous areas of infection diagnostics. One of two broad approaches is typically used when using PCR to diagnose infections of the bones and joints

i) PCR with primers that are specific to one or more prevalent causal organisms or a multiplex panel of organisms or

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

Advantages: The speed of bacterial identification can allow prompt initiation of appropriate pathogen-directed antimicrobial agent, it can detect both viable and nonviable bacteria, the sensitivity should be less affected by antibiotic administration prior to sampling. It may also detect difficult-to-culture or fastidious organisms (11)

Limitations: Use of multiplex diagnostic panels will miss atypical pathogens

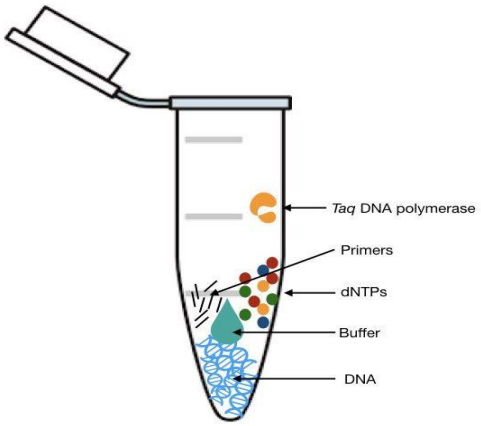

Figure 3: PCR (polymerase chain reaction)

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: Significant cost Complex associated workflow Technique susceptible to bacterial contamination at multiple steps during processing.

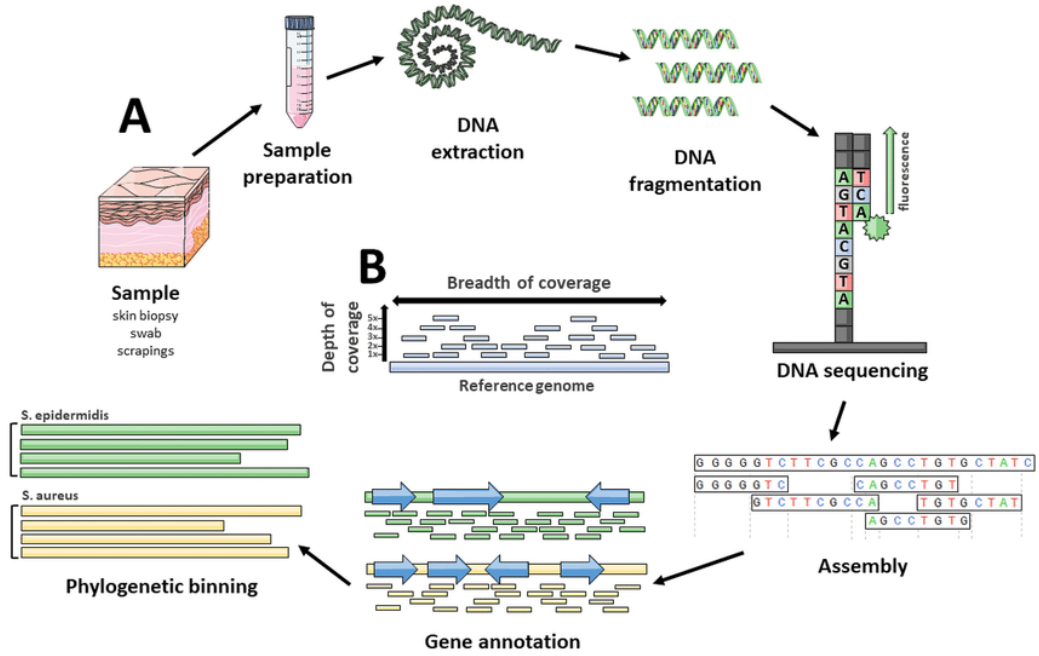

Figure 4: Shotgun (meta)genomic sequencing study

III.DETECTION OF HOST RESPONSE:

a) Serum biomarkers:

The cost-effective and widely accessible serum inflammatory indicators are erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP).However, they lack the specificity of an ideal diagnostic test, as they may be elevated in many systemic illnesses, inflammatory conditions, malignancy, or post surgical intervention.

In addition, procalcitonin and interleukin 6 (IL-6) are additional indicators of importance for orthopaedic infection.. IL-6 is produced by activated monocytes and macrophages and stimulates production of several other acute phase reactants. A systematic review of inflammatory markers in PJI (14) found IL-6 to have the highest diagnostic accuracy compared with white cell count, ESR, and CRP, with a reported pooled sensitivity and specificity for IL-6 of 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). In the presence of inflammatory arthropathies, synovial fluid analysis interpretation is challenging in both native and prosthetic joint arthritis.. Thus, interpretation of synovial fluid analysis should consider the clinical context, patient co morbidities, and immune status and for prosthetic joints, the duration of symptoms, timing relative to surgery, and joint involved.

Synovial fluid biomarkers: Several biomarkers have been evaluated in synovial fluid assessing for the host inflammatory response at the site. Of the known biomarkers, leukocyte esterase and alpha defensin have been studied extensively.Neutrophils contain the enzyme leukocyte esterase, which is easily obtained as a colorimetric test strip. The utility of leukocyte esterase testing strips is

significantly affected by presence of blood in sample (16) which is problematic, as many synovial fluid samples will be contaminated with blood. Alpha defensin available as both a lateral flow test (result available within minutes) and an ELISA Alpha defensin higher reported sensitivity compared with CRP, IL-6, and leukocyte esterase.

Limitations: Utility of leukocyte esterase test affected by presence red cells costly Lateral flow alpha defensin lower sensitivity compared to ELISA.

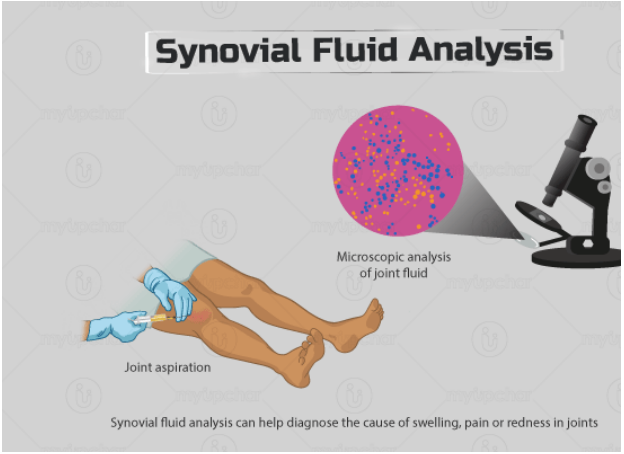

Figure 4: Synovial fluid analysis

c) Histology: Histological analysis of bone and synovial specimens confirms presence of inflammatory infiltrate and can provide important information regarding underlying cause. However, the sensitivity of histology alone is not high enough to rule out prosthetic joint infection. Recommendations on surgical approach might be guided by the histological study of intraoperative frozen sections.

Limitations: Sensitivity not high enough to use as a standalone "rule out test" for infection.

Radiological imaging:

Radiological imaging aids in both diagnosis of orthopaedic infection and assessment of complications.Suggestive radiographic findings might be helpful in providing data to support and guide more extensive diagnostic sampling, particularly in implant-related infections where clinical symptoms may be mild.

In addition to avoiding ionising radiation, ultrasonography offers the benefit of being widely accessible. However, it is helpful in evaluating joint effusions and can direct synovial fluid aspiration, providing extra valuable diagnostic information. In general, it is not helpful in the checkup of osteomyelitis.

Computed tomography (CT):

It provides a more accurate spatial evaluation of the soft tissue and the bone, although it is less sensitive to osteomyelitis than magnetic resonance imaging (MRI). It could show soft tissue abnormalities or fluid residues that point to an infection.. Both CT and MRI are impeded by artefactual changes from prostheses in the setting of implant-associated orthopaedic infections. MRI is the imaging modality of choice in assessment of osteomyelitis; as well as enhanced sensitivity over CT, it can detect changes related to bone marrow oedema earlier in the course of infection. MRI changes can persist for weeks and months post-treatment.

Nuclear imaging:

It can screen for changes associated with inflammation while avoiding artifact-related problems encountered with other modalities, making it a potential diagnostic adjunct in the assessment of PJI.

Bone scintigraphy:

It is one of the most widely utilized of these modalities in assessment of prosthetic joints but reported accuracy ranges between 50 and 70% (17)

IV.Alternative antibiotics for Orthopaedic infections:

The increasing emergence of resistant pathogens in orthopaedic infections mandates clinicians to seek new therapeutic options, first criteria including rate of elution, duration of elution rates above MIC, and thermal stability at core temperature as being necessary to determine if alternative antibiotics are comparable to the current antibiotic workhorses used clinically tobramycin and vancomycin.

Dalbavancin, cefazolin, and minocycline all demonstrated similar elution profiles to Vancomycin, but only dalbavancin maintained above-MIC rate.

Meanwhile, amikacin and meropenem demonstrated progressively better elution profiles and durations of above-MIC activity while exhibiting acceptable thermal stability when compared to Tobramycin, making them suitable alternatives to E. coli and A. Baumannii.

A cyclic lipopeptide antibiotic called daptomycin is effective against a variety of gram-positive bacteria. Some heteroresistant vancomycin-intermediate S. aureus (hVISA) and vancomycin-intermediate S. aureus (VISA) strains also show daptomycin nonsusceptibility.. Vancomycin has been the drug of choice for treating methicillin-resistant strains of Staphylococcus aureus (MRSA) and coagulase-negative Staphylococci, the most common causes of PJI (18,19). Vancomycin typically works in conjunction with an aminoglycoside and is only effective against gram-positive bacteria. Due to the lack of commercially available

powdered gentamicin in the United States, tobramycin is typically substituted in implanted devices. The inclusion of an aminoglycoside has a number of potential benefits. The combination of an aminoglycoside with a cell wall active agent has synergistic activity against gram-positive organisms, although the clinical relevance of this is unclear (20,21) An aminoglycoside theoretically may decrease the emergence of resistance to other agents (22). An aminoglycoside may improve the elution of other antibiotics by making bone cement more permeable.

V.Conclusion:

Diagnostic approaches in orthopaedic infection are multifaceted, and enhancing diagnostic yield requires a collaborative approach involving orthopaedic surgeons, radiologists, microbiologists, and infectious diseases specialists. Strengths and limitations of various diagnostic tests.The backbone of diagnostics continues to be culture-based techniques, although they must be preceded by a comprehensive sampling strategy and can occasionally be augmented by molecular approaches.. Future research should focus on further development of novel molecular diagnostics.

To determine whether an infectious condition is present, a thorough evaluation of the inflammatory response must involve radiologic imaging, blood, synovial fluid, and histologic testing. Ultimately, the future diagnosis of orthopaedic infections will continue to rely upon a global assessment of all available microbiological and non microbiological data.

Daptomycin with tobramycin-loaded polymethylmethacrylate beads can be a safe and powerful bactericidal local antibiotic delivery system in biofilm-producing bacteria especially in recurrent or resistant prosthetic joint infections due to the high local medication concentrations that were administered in lethal concentrations for the microorganisms.

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