



CLINICAL UTILITY OF SEROLOGICAL AND GENETIC BIOMARKERS IN ORTHOPEDIC INFECTIONS: ADVANCES IN DIAGNOSIS AND TREATMENT MONITORING

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ABSTRACT

Orthopedic infections such as osteomyelitis and prosthetic joint infections (PJIs) are difficult to diagnose and treat. The conventional diagnosis methods, i.e., microbiological cultures and imaging studies, are usually restricted by prolongation of results and false-negative results. In the recent past, the clinical value of serological and genetic biomarkers has emerged for enhancing the specificity of diagnosis, treatment efficacy, and monitoring disease activity in orthopedic infections. These biomarkers, including inflammatory markers, cytokines, and genetic signatures, provide a faster and more accurate alternative to traditional diagnostic techniques. Serological biomarkers, such as C-reactive protein (CRP), procalcitonin (PCT), and interleukins, may predict the severity of infection and inform therapy. Genetic biomarkers, especially those involving microbial resistance or host immune responses, reflect the behavior of the pathogen and the immune profile of the patient and help form more tailored treatment plans. Progress in genomics and proteomics is further facilitating the discovery of new biomarkers that would make effective diagnostic and prognostic markers. Additionally, these biomarkers are critical for the identification of recurrences, monitoring the efficacy of interventions, and forecasting long-term outcomes. This review documents recent progress in serological and genetic biomarkers, their applications in enhancing diagnostic efficacy, informing treatment options, and improving patient outcomes in orthopedic infections. Although these biomarkers show great promise, more clinical validation is needed for them to have standardized protocols and be widely used in clinical settings.

1. INTRODUCTION

Orthopaedic infections such as osteomyelitis, periprosthetic joint infection (PJI), and deep musculoskeletal infection (MSKI) are therapeutically and diagnostically challenging and usually necessitate prolonged hospitalization, multiple surgery, and heightened

morbidity [1]. Conventional testing techniques, especially culture-based assays, have the drawbacks of false positives in polymicrobial infections and false negatives in antibiotic preconditioning. Hence, there is increased interest in using serological and genetic biomarkers for improving diagnostic

accuracy and therapy guidance. Biomarkers like C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and procalcitonin (PCT) have been well established as effective inflammatory markers, but newer developments in immunoassays, e.g., MENSA (Medium Enriched for Newly Synthesized Antibodies), have already demonstrated a remarkable potential for the diagnosis of certain pathogens like *Staphylococcus aureus* and *Streptococcus agalactiae* (Group B *Streptococcus*, GBS). In addition, convergence of genetic and genomic tools made it possible to identify novel biomarkers with higher sensitivity and specificity. Of note, soluble tumor necrosis factor receptors (sTNF-R1, sTNF-R2) and B-cell activating factor (BAFF) were useful for PJI detection with high diagnostic accuracy [2][3]. The progress not only supports the detection of pathogens but also helps monitor treatment, recurrences, and outcome. This is a review of the clinical usefulness of genetic and serological biomarkers for orthopedic infections, their ability to improve diagnostic accuracy, treatment guidance, and patient outcomes, and the future directions and challenges to implementing these biomarkers in practice [4].

2. OVERVIEW OF ORTHOPEDIC INFECTIONS

2.1 Types of Orthopedic Infections

Orthopedic infections, including osteomyelitis, prosthetic joint infections (PJIs), and septic arthritis, are complex and challenging due to the formation of a biofilm that protects bacteria from both the immune system and antibiotics as mentioned in [Figure 1]. PJIs and septic arthritis are most often caused by *Staphylococcus aureus* and coagulase-

negative staphylococci, and these infections can progress rapidly to joint destruction or systemic infection, unless identified and diagnosed early in its presentation. Successful management of PJIs and septic arthritis requires that the diagnosis is made early and an aggressive treatment strategy is implemented. To optimize treatment strategies, it is vital to understand the development of biofilm [5].

2.2 Challenges in Diagnosis and Treatment

Diagnosis of orthopedic infections, particularly periprosthetic joint infections (PJIs), remains difficult because of the limitations of the conventional means of diagnosis; cultures, imaging, and inflammatory markers including ESR and CRP, usually lack sensitivity and specificity; they can generate false negatives, nonspecific findings, and the potential impact of confounding factors can hinder timely and accurate diagnosis. Not uncommonly, and of even greater endangerment is that treatments are therefore often delayed, resulting in higher risks of treatment failure, prosthesis loss, or systemic infection. Enhanced early diagnostic tools, in the form of more reliable and accurate biomarkers such as synovial biomarkers, would facilitate diagnosis and treatment and hopefully enhance the outcome of orthopedic infection management [6].

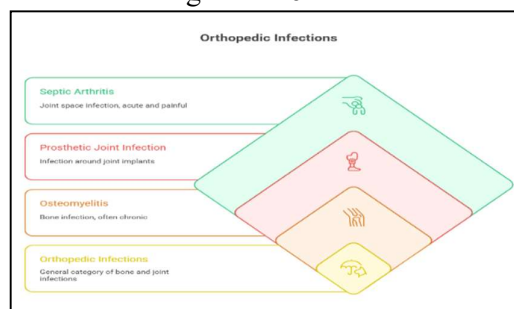


Fig (1): Types of Orthopedic Infections



3. SEROLOGICAL BIOMARKERS IN ORTHOPEDIC INFECTIONS

3.1 Role of Inflammatory Markers

C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are traditional and cost-effective markers that can be used to diagnose orthopedic infections, but they cannot specifically tell you bone from soft tissue infection. Procalcitonin (PCT) has shown increased sensitivity and specificity - this makes PCT more reliable in differentiating osteomyelitis from soft tissue infections, especially in the diabetic foot patient population as mentioned in [Table1]. Although CRP and ESR are good adjuncts for diagnostics, PCT provides greater diagnostic accuracy [7].

3.2 Cytokines and Their Clinical Significance

Interleukins (IL-6, IL-1) and tumor necrosis factor- α (TNF- α) are importantly pro-inflammatory cytokines with biomarker potential in orthopedic infections. IL-6 shows a high level of sensitivity for detecting deep implant

infections, particularly in joint arthroplasty, and improves accuracy when paired with CRP. Alternatively, TNF- α has high specificity with low sensitivity and should thus be regarded more as a secondary marker as opposed to a primary stand-alone test for infection. Collectively, these cytokines help delineate between septic and aseptic joint replacements and offer diagnostic and prognosis guidance. [8].

3.3 Other Serological Markers

Antibody responses and acute phase proteins (CRP, SAA, haptoglobin, C3) can support the diagnosis of orthopaedic infections. Systemic increases occur primarily with acute infection but APPs, most prominently SAA and C3, can be shown to be expressed locally in chronic infections (e.g. osteomyelitis). We presented immunohistochemical evidence for C3 in bone lesions and as such, these markers go beyond research and may have value for the diagnosis and monitoring of chronic infections in the orthopaedic setting. [9].

Table 1: Comparison of Inflammatory Markers in Orthopedic Infections

Marker	Sensitivity	Specificity	Advantages	Limitations	Clinical Use
CRP (C-reactive protein)	High in acute infections	Moderate	Widely available, inexpensive, rapid response to inflammation	Nonspecific; elevated in trauma, surgery, and non-infective inflammation	Initial screening and monitoring treatment response
ESR (Erythrocyte Sedimentation Rate)	Moderate	Low	Cheap, easy to measure, long history of use	Slow to normalize, affected by anemia/age, low specificity	Adjunct marker in suspected osteomyelitis/PJI
PCT	High	High	More specific	Higher cost,	Differentiation



(Procalcitonin)			for bacterial infection, can differentiate soft tissue vs bone infection	limited availability	of osteomyelitis from soft tissue infections
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4. GENETIC BIOMARKERS IN ORTHOPEDIC INFECTIONS

4.1 Microbial Genetic Biomarkers

Microbial genetic biomarkers have the potential to improve the diagnostic ability for orthopedic infections like osteomyelitis and septic arthritis, which can be difficult to diagnose using traditional methods. Serum biomarkers yield the same accuracy with less invasive testing, as not all serum-biomarkers are the same and their accuracy can be striking. CTX-II, TGF- α , MCP-1 and B cell-attracting chemokine 1 are some of the facility's serum biomarker panel markers that exhibited excellent diagnostic accuracies. These provide the ability to distinguish bone and soft tissue infections sooner and reduce the number of invasive or inconclusive culture-based analyses and present timely appropriate therapy^[10].

4.2 Host Genetic Response

Host genetic response determines the susceptibility of individuals to orthopedic infections including periprosthetic joint infection (PJI). Various immune-related genes such as toll-like receptors, cytokines, chemokines, mannose-binding lectin, vitamin D receptors, and human leukocyte antigens (HLA) all play a role in determining risk of infection. Polymorphisms in IL-1 and MBL, and certain HLA subtypes, have been specifically associated with PJI. While evidence is at the infancy, studies

involving transcriptomic approaches or genome-wide studies will likely provide more insight into genetic risk factors, detailing markers that can be beneficial in implementing ASIR (i.e., the clinical management of patients with genetic risk factors) and translating genetic risk into patient-centred prevention in orthopaedic practice^[11].

4.3 Genetic Biomarkers for Antimicrobial Resistance

Genetic biomarkers will be valuable to manage antimicrobial resistance in orthopedic infections because they will identify microbial mutations and resistance genes that vary and affect treatment outcomes. Their use will allow for individualized antibiotic selection while increasing chances of therapeutic success, reducing recurrence, and improving rational antibiotic use when matched with patient specific information. When guided by infection prevention/control and potential emerging antimicrobial methods, genetic biomarkers could be advantageous means of counteracting the emergence of multidrug resistant pathogens within orthopedic practice^[12].

5. ADVANCES IN DIAGNOSTIC TECHNIQUES USING BIOMARKERS

5.1 Next-Generation Sequencing (NGS) for Pathogen Detection

Next generation sequencing (NGS) is increasingly recognized as a potential future diagnostic tool in orthopedic



infections, particularly in the setting of infections involving prosthetic joints and implants. NGS is more sensitive than various culture and direct detection based methods and can identify a variety of pathogens including polymicrobial infections, resistant organisms, and organisms that are often missed using conventional methods. NGS is used to rapidly and extensively characterize microbial samples, adding value by optimizing diagnostics, personalizing treatment options and improving the use of antibiotics. Various technical challenges to routine clinical practice exist including cost, access to specialized expertise and complex data analysis; however ongoing technological developments will likely mitigate many of these challenges and support the full potential NGS can offer to improve the detection and management of pathogens in orthopedic practice ^[13].

5.2 Multiplex PCR for Simultaneous Detection

Multiplex PCR (mPCR) provides a rapid capacity to assess antimicrobial resistance genes directly from synovial and sonication fluid samples in orthopedic infections. This method provides results to multiple resistance mechanisms simultaneously, offers a high specificity, and reliably suggests that positive results are predictive of resistance to antimicrobial therapy. While the overall sensitivity of mPCR is limited—specifically to coagulase-negative staphylococci—it is effective enough to result in false negative outcomes. Given its current limitations, we believe that mPCR may have potential as an adjunct diagnostic. Future studies exploring mPCR with universal primers and sequencing options are warranted since mPCR has the potential to improve accuracy and the

utility of mPCR to guide future antimicrobial therapy ^[14].

5.3 Biomarker Panels for Enhanced Diagnostic Accuracy

Biomarker panels are becoming increasingly important in enhancing the diagnostic accuracy of orthopedic infections through simultaneous strategies related to host immune response and pathogen detection. While culture-based methods are still the backbone of diagnostic testing, traditional methods are not sufficient due to often low sensitivity and length of time for results. New methods of molecular testing and continual development of systemic and localized testing now offer the capability to document host inflammatory activity in conjunction with pathogen detection. The biomarker panels described above will allow multiple biomarkers to inform diagnostic testing allowing for greater reliability, less uncertainty and better clinical decision-making for antimicrobial therapy and surgical management ^[15].

5.4 Points-of-Care Diagnostics in Orthopedic Infections

Orthopedic infection-related diagnoses, especially peri-prosthetic joint infections, must encompass clinical, laboratory, and imaging assessment. A sinus tract remains a relevant clinical finding, and accurate pathogen identification relies on the ability to collect good quality specimens as early as possible. Because of recent advancements, studies using ultrasonography, CT, and MRI have improved our evaluations of bone and soft tissue involvement, although use of nuclear medicine has not significantly increased. New laboratory techniques including molecular techniques and immune markers provide quicker and more

specific results. When first-line studies are inconclusive, multi-disciplinary evaluation at specialized centers maximizes

diagnostic feasibility and treatment planning as overall limitations and advantages are mentioned in [Table2]^[16].

Table 2: Advances in Diagnostic Techniques Using Biomarkers

Technique	Target	Turnaround Time	Accuracy	Advantages	Limitations
Next-Generation Sequencing (NGS)	Pathogen genome	Hours–days	Very high	Detects rare/unculturable organisms, broad-spectrum	Expensive, requires advanced lab setup
Multiplex PCR	Multiple pathogen genes	Few hours	High	Rapid, simultaneous detection of multiple pathogens	Limited to known targets, risk of contamination
Biomarker Panels	Multiple serological/genetic markers	Variable	High	Improves diagnostic accuracy compared to single markers	Still under research, standardization lacking
Point-of-Care Tests	CRP, PCT, or specific biomarkers	Minutes–1 hr	Moderate	Bedside use, rapid results, useful in emergencies	Lower sensitivity/specificity, limited range

6. CLINICAL APPLICATION OF SEROLOGICAL AND GENETIC BIOMARKERS

6.1 Biomarkers in Initial Diagnosis

C-reactive protein (CRP) has been frequently used to detect implant-associated infection (IAI), but it is non-specific. Emerging data suggests cytokines such as IL-6, IL-1ra, IL-8, and IL-12(p70) are potentially stronger markers of infection, especially as IL-6 and IL-12(p70) have been consistently reported as higher in infected patients. Multiplex cytokine assays could help move the field

further by identifying better and more specific, and earlier, IAI diagnosis compared to the CRP^[17].

6.2 Monitoring Treatment Response

The assessment of treatment response in orthopaedic infections is based on a combination of clinical improvement, laboratory parameters (most notably CRP and ESR) and, if enhanced certainty is desired, imaging (although there may be a delay in radiological change as the infection resolves). Microbiological cultures typically provide a guide for initiating therapy with rifampin-based regimens typically used for bacterial



infections with staphylococcus, while a newer agent such as linezolid and daptomycin can also be used for nonresponsive strains. To effectively monitor treatment response, sufficient penetration of the antibiotic prophylaxis (usually in the case of research) should be ensured through a multidisciplinary approach with early identification of treatment failure to avoid chronic infection or functional compromise ^[18].

6.3 Detection of Recurrence and Complications

A recurring infection related to the orthopaedic device is most commonly heralded by ongoing pain, swelling, erythema, and/or drainage, with any corroborating trends in C-reactive protein or erythrocyte sedimentation rate and imaging and repeated cultures if deemed necessary. Male sex and fractures with fixation device-related infections increase the risk of recurrence. The optimum duration of antibiotics is unknown although it has been suggested that even short courses of fluoroquinolones or rifampicin are indicated potentially to minimize the reinfection risk. Chronic infections, loosening of an implant or non-union underscore a need for vigilance with follow-up and multidisciplinary approach to care ^[19].

6.4 Personalized Treatment Strategies Based on Biomarker Profiling

Biomarkers are potentially essential to improve diagnosis and management of both acute and chronic pain. Neuroimaging (MRI, PET), electrophysiological techniques (EEG, MEG), and molecular markers (cytokines, proteomics, and metabolites) have revealed tremendous insights into the mechanisms of pain, with more work required to validate their true

utility. Combining the biological with the psychosocial dimension of patient management, augmented by Artificial Intelligence (AI), will lead to more personalized therapy and prognosis, reducing healthcare systems engagement and expenditure. To facilitate the transition of the biomarkers to clinically meaningful tools, we require large-scale collaborations and standardizations ^[20].

7. INTEGRATION OF BIOMARKERS IN CLINICAL PRACTICE

7.1 Current Clinical Guidelines

The AAOS guideline on periprosthetic joint infection (PJI) of hip and knee stresses an organized, evidence-based approach using a variety of tests instead of a single test. The guideline suggests first using CRP and ESR levels as a screening, with subsequent joint aspiration to assess synovial cell count, differential, and cultures. Since microbiology is complex, multiple intraoperative tissue samples and adjunctive tests (e.g., frozen section, synovial biomarkers) can assist with the diagnosis, imaging will contribute to an assessment but is not a standalone diagnostic image. Documentation of microbiological practices and communication among a multidisciplinary team are imperative. Ultimately, the guideline emphasizes the need for individualized decision making, as recommendations need to be adapted to patient specific circumstances ^[21].

7.2 Multidisciplinary Applications of Biomarkers

The use of biomarkers from multidisciplinary perspectives in orthopaedic infections can enhance the diagnosis, treatment monitoring, and outcomes of patients by combining the

abilities of surgeons, infectious disease experts, microbiologists, radiologists, and lab scientists. Incorporated biomarkers with clinical and radiographic findings allow patient-centered care with more optimal antimicrobial strategies while avoiding many unnecessary interventions. Such a management model provides both group and individual develop to clinician skills through case discussions, and also provides an opportunity to network and improve population health focus on living science principles in infectious disease prevention as mentioned in [Figure2]. Overall, biomarkers can serve as a unifying tool across disciplines to enhance communication and comprehensive management of complex orthopaedic infections [22].

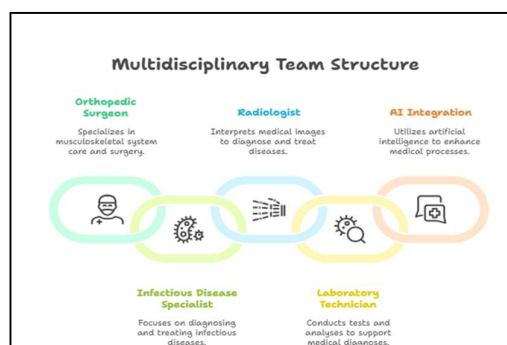


Fig (2): Multidisciplinary Team Structure

8. FUTURE DIRECTIONS AND EMERGING TRENDS

8.1 Genomic and Proteomic Innovations

Developments in genomics and proteomics in orthopedics are able to identify bacterial genes and proteins associated with biofilm formation and antibiotic resistance in bacteria like *Staphylococcus epidermidis*. This information assists in the identification of new diagnostic biomarkers and therapeutic strategies (antibiotic-loaded hydrogels, mesenchymal

stem cells) to advance the prevention and management of orthopedic infections [23].

8.2 Artificial Intelligence in Biomarker Development

AI is being increasingly utilized in orthopaedic infections, particularly in the diagnosis and management of periprosthetic joint infections (PJIs) by detecting infection at earliest and most accurate times; AI can detect subtle differences in complex datasets containing clinical, biomarker, imaging, and molecular data that exceeds traditional detection of infection. AI has potential in machine learning models to predict risk of infection; distinguish septic from asymptomatic failures; and optimize biomarker identification, creation, standardization, testing, and implementation. Limitations to date in the literature include standardized datasets, lack of external validation, and issues related to interoperability, interpretability, and privacy. If we want to create our future in orthopaedic infections, AI has the potential to radically change biomarker design and decision-making towards precision and personalized care [24].

CONCLUSION

The clinical value of serological and genetic biomarkers in orthopedic infections continues to increase, offering unprecedented improvements in both diagnosis and monitoring of treatment for these infections. In some cases, unreported culture and extreme limitations observed with traditional serological tests, culture-based methods and advanced imaging (primarily MRI) have led to the development of a call for accurate biomarkers. Genetic technologies (whole genome sequencing (WGS), next generation sequencing (NGS) etc.) are



making a necessary leap forward in laboratory testing, and providing the ability to rapidly and identify all with a very limited initial sample. If and when practices are able to integrate this continue to test into their normal work flow, they will have to provide training opportunities, however the benefits to patient and provider may be beyond our imagination, including potential quality of care, and patient outcomes. In summary, serological biomarkers working individually are essential however when combined with the emerging genetic technologies, we will be able to rationally and likely improve orthopedic infections to a personal approach, but substantial validation and wide-scale research studies continue to be warranted.

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