Review Article

Diagnosing prosthetic joint infection: traditional and contemporary techniques

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Abstract: Prosthetic joint infection (PJI) has been recognised as a devastating complication for as long as arthroplasty has been performed. Despite this, there is still no universally agreed standard within either PJI literature or clinical practice for the diagnosis of infection following joint arthroplasty. Recently, however, significant efforts have been made by different specialist musculoskeletal societies to move towards this goal. This paper reviews the history of the diagnosis of PJI, examines the current debate on diagnostic criteria and the limitations of a lack of consensus on infection research, clinical practice, and joint registry data. Based on the current situation, we propose that until there is a consensus on existing algorithms for diagnosis, there is need to implement a "minimum standard set of PJI diagnostics" locally by each national orthopaedic/trauma association (focusing on those tests which are included in every specialist musculoskeletal society's recommended list). Since there is still variation not only internationally but at national and sometimes at local level regarding standardisation of PJI testing, a smaller number of universally accepted PJI tests which are implemented and professionally monitored by national musculoskeletal societies will likely to result in significant improvement in PJI management in the short term, whilst the debate regarding the best criteria is still ongoing and is likely to continue for some time.

Keywords: Arthroplasty; prosthetic joint infection (PJI); criteria; standardisation; diagnostics

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Introduction

Prosthetic joint infection (PJI) has been recognised as a cause of arthroplasty failure since joints were first replaced. Early efforts to mitigate this problem included the introduction of ultraclean air and prophylactic antibiotics. These developments seemed efficient in prevention of PJI, and their efficacy was confirmed through the use of multi-centre randomised controlled trials (1), gaining wide spread acceptance and contributing to the fall in infection rates in early arthroplasty (2). However, recent data from international joint registries still indicate infection as one of the most common indications for revision in primary joint replacement (3,4) and PJI rates might still be significantly underreported in national joint registries (5,6). While early or late acute infections often presents with dramatic and "classical" signs of general infection symptoms, such as pain, redness, increased temperature, loss of function with or without discharging wounds and sinuses, even the early arthroplasty practitioners recognised the difficulty in diagnosing the "low virulence" or so called "low grade" infections, and in differentiating between the superficial and deep prosthetic infections (7). This difficulty has resulted in poor diagnosis rates and suspected underreporting of PJI as a cause of arthroplasty failure (5,6,8). Modalities of investigation have involved clinical findings, serum markers,

synovial markers, ultrasound, radiological and nuclear investigation as well as direct culture of blood and tissue, but consensus on diagnosis of PJI remains elusive. Several recent working groups have sought to create consensus statements and algorithms for PJI diagnosis (9-15) however none of these have as yet reached universal acceptance.

In this review, we will discuss the history and development of investigation of PJI, issues arising from a lack of consensus, current criteria, and propose a pragmatic focus to improve the situation in the short term.

Diagnostic strategies in the early years of arthroplasty—from the early years to the 80s

Early studies of PJI employed rudimentary clinical criteria along with microbiological culture for the diagnosis of joint infection. Two examples of historical papers examining PJI from the 1970s use such descriptions: one study presents superficial infection as "obvious signs of suppuration, a significant rise in temperature more than 48 hours post-operatively, and the presence of a positive wound swab". Deep infection was considered as "infection extending down to the prosthesis or related to the material used to hold the trochanter" and late infection was described as "infection which appeared after apparent healing of the wound some months or years later, usually without a prior episode of infection" (16). The a second paper found those who were "febrile more than 7 days without local reaction or abnormal drainage" or "febrile for more than 7 days, had a local wound reaction with erythema or tenderness or abnormal drainage" were more likely to go on to develop deep wound infection as proved on microbiology (7). However, the difficulties of defining infection, its chronicity and depth were apparent at this stage (17). Moving forward the need for more objective criteria, and the employment of emerging technologies drove a change in approach.

The "technical years"—early 1980s till late 1990s

This stage in the development of PJI diagnostics was characterised by the general and relatively rapid "technological" advances that were typical of medical science in general, and arthroplasty in particular during this period. The renewed focus on the diagnosis of PJI was mainly around the use of newly available technologies such as CT-scans, MRI, different types of bone scans. Whilst the basis of PJI investigation still recommended serum CRP, erythrocyte sedimentation ratio (ESR) test and culture and sensitivity tests as a part of PJI diagnostics, the challenge of diagnosing infections remained. Buchholz, writing from the ENDO Klinik stated in 1981: "the proof of deep infection of the arthroplasty rests ultimately on a positive bacterial culture together with appropriate tissue changes". He mentioned serum ESR, radiological loosening and general signs of inflammation as diagnostic signs, and talked about the challenges of obtaining the correct diagnosis by culture: "Positive bacterial culture is not always obtained... in a proportion of cases the result has been negative; subsequently, at operation in some of these, an organism has been found" (18). These findings regarding culture negative infections paved the way for better future understanding the optimal technique of fluid aspiration, culture techniques and length of incubation of microbiological samples from patients with suspected PJI. However, synovial fluid diagnostics were limited to culture and sensitivity, and preoperative joint aspirations as a part of the PJI investigation were not universally recommended: Harris and Barrack in 1993 questioned the use and value of routine aspiration in the investigation protocol of painful total hip replacement (19).

In a 1998 review from the Mayo clinic Hanssen described the ongoing strategies and difficulties around PJI diagnostics, listing serum CRP and ESR, and culture and sensitivity tests, but talking extensively about different bone scan techniques (technecium-99 or indium-111-labelled scans) (20). Although these gave initial encouragement, the promise of these new techniques and modalities did not give the definitive answer to the question of infection diagnosis that had been hoped for, and a return to bacteriological sampling as well as new biomarkers and a focus on the development of protocol driven diagnosis followed.

Back to synovial fluid. The new era of biomarkers, genetical testing and protocols—from the early 2000s until today

Despite the technological advances in the years leading up to mid 2000s, some "developments" in orthopaedics were not without spectacular failures such as the 3M Capital hip and ASR resurfacing system to name just two (21). However, overall implant designs and materials improved for joint replacement procedures. With improving results of arthroplasty surgeries demand also grew exponentially (22,23). The indications and patient selection criteria of joint replacement surgery have also changed and patients

who would have been turned away 15–20 years ago were now offered surgery (24,25). It is therefore not surprising that despite medical-surgical-technical advancement the burden of PJI has gradually become a returning focus point of the orthopaedic profession.

The importance of finding new useful synovial fluid tests, proposing better techniques and more appropriate incubation length for sample culture and sensitivity, establishing classification systems for PJIs, and recognising the need for standardisation regarding diagnosis and management of PJI characterise this most recent period of research and practice. In a relatively short period of time from the early 2000s, several significant new papers were published about the diagnosis and management of PJI which changed practice and improved patient care: the use of synovial CRP and percentage polymorphonuclear cells (%PMN) (26); the classic article from Switzerland on PJI diagnosis and management (27); the significance of extended culture techniques (28); and sonication (29). But with regards to standardised identification of infection a more important trend was emerging.

The inherent difficulties of a lack of definitive diagnostic criteria for infection have been evident since early modern arthroplasty (7). Infection is often identified as a common cause for revision TKA with rates of between 14.6–36.1% (30-35). Registry data frequently gives lower figures (31,35), but have been shown to under report infection in revision arthroplasty compared to source notes and other databases (5,6,8). Overall, a lack of consistency in diagnosis of infection in research methodology and a lack of specificity in infection reporting criteria in national registries results in poor comparability and understanding of the issue.

A key starting point for standardising the diagnosis of PJI was in 2000. The American Academy of Orthopaedic Surgeons (AAOS) put together a recommendation for the diagnosis of infection following total knee and hip arthroplasty, which was scientifically based on a review of literature available at that time. The stated aims of this guideline were to "combat bias, enhance transparency and promote reproducibility" (15). Following this initiative, in the last decade we have seen an exponential increase in the number of different specialist societies developing and proposing their own criteria about the diagnosis and management of PJI: MSIS (2011) (9), IDSA (2012) (11), MSIS/ICM (2013) (10), EBJIS (2014) (36), ICM (2018) (13), MSIS 2018 AAOS (2019) and EBJIS (2019) (14). These efforts are driven by enthusiastic experts looking for consensus in the field of PJI, but due to the nature of medicine as a science, there are sometimes differences of views amongst them.

In the initial AAOS paper fifteen recommendations were produced, including initially testing CRP and WCC to rule out infection, abstaining from antibiotic treatment until aspiration had been performed, and carrying out nuclear medicine imaging in high risk patients in whom repeated joint aspiration was negative for infection (15). The following year, the Musculoskeletal Infection Society (MSIS) devised a new diagnostic criterion based upon expert consensus statements following extensive literature review (9). This involved identification of one of two major diagnostic criteria, or four of six minor criteria, with a caveat that infection could still be present out with these findings. These criteria were modified by further consensus by MSIS in 2013 to remove "purulence" from the diagnostic criteria (37). A new diagnostic criterion was proposed based upon a validation study of 200 patients in 2018 by MSIS (12). The 2nd International Consensus Meeting (ICM) on Musculoskeletal Infection took place in the same year in 2018, and the Delphi consensus process (38) was used by 658 delegates from 92 countries who debated and voted on 652 questions about the prevention, diagnosis and management of a wide variety of musculoskeletal infections (39). During the meeting there was a weak consensus for the proposed investigation panel for the diagnosis of PJI (13).

Taking a different approach, a joint consensus document from the European Association of Nuclear Medicine, European Bone and Joint Infection Society and European Radiology Society, and endorsed by the European Society of Clinical Microbiology and Infectious Diseases, extensively reviewed the literature on diagnosis of PJI and proposed a flow chart for diagnosis based upon a range of laboratory, radiological and Nuclear Medicine imaging studies (14) and listed the different diagnostic options based on their level of evidence (40). No specific thresholds are given for infection, leaving interpretation up to the clinician.

At the same time as the publication of these different criteria and recommendations by different specialist societies, the last decade also witnessed revolutionary new discoveries and new research potentials such as novel biomarkers (41), next-generation sequencing (42) and genetic analysis (43). It is not within the scope of this paper to describe all in detail, but it is obvious that the research and development around PJI diagnostics have accelerated significantly and currently all the new developments are pushing the boundaries on many fronts across PJI diagnosis and may yet find themselves included in future diagnostic criteria.

Table 1 Summary of tests recommended by ICM2018, MSIS2018, AAOS2019, EBJIS, EBJIS/EANM/ESR/ESCMID

Variable	ICM 2018 (13)	MSIS 2018 (12)	AAOS 2019 (46)	EBJIS (36)	EBJIS/EANM/ESR/ESCMID (14)
Blood test					
ESR[§]	Yes	Yes	Yes	Yes	Yes
CRP[§]	Yes	Yes	Yes	Yes	Yes
Interleukin-6	–	–	Yes	–	–
D-dimer	Yes	Yes	–	–	–
Synovial fluid tests					
Microbiology cultures[§]	Yes	Yes	Yes	Yes	Yes
Synovial WCC[§]	Yes	Yes	Yes	Yes	Yes
Synovial PMN%[§]	Yes	Yes	Yes	Yes	Yes
Synovial leukocyte esterase[§]	Yes	Yes	Yes	Yes	Yes
Synovial alfa defensin[§]	Yes	Yes	Yes	Yes	Yes
Synovial CRP	Yes	Yes	Yes	–	–
Positive histology[§]	Yes	Yes	Yes	Yes	Yes
Positive tissue samples[§]	Yes	Yes	Yes	Yes	Yes
Intraarticular purulence	Yes	Yes	Yes	Yes	Yes
Sonication	–	–	Yes	Yes	Yes
Diagnostic imaging					
Plain X-ray as first imaging	–	–	–	–	Yes
CT	–	–	Yes	–	Yes
MRI	–	–	Yes	–	Yes
PET-CT	–	–	Yes	–	Yes
Labelled bone scan	–	–	Yes	–	Yes
Labelled marrow scan	–	–	Yes	–	Yes
Anti-granulocyte scan	–	–	–	–	Yes

[§], PJI test included by all specialist societies quoted above that could form the basis of a minimum set of PJI laboratory tests (bold text indicating test suggested by all five professional bodies). ESR, erythrocyte sedimentation ratio; PMN, percentage polymorphonuclear cell; PJI, prosthetic joint infection.

The current situation: need for a standardised approach—what can be done?

The various algorithms and different criteria in current use for diagnosis of PJI have been well summarised in a recent review (44). Attempts in the past to standardise the diagnosis of PJI have involved either evidence based, or consensus approach and despite a professional desire from every specialist society to reach a universal agreement regarding the diagnosis of PJI (the specific diagnostic tests involved in the diagnostic protocol, their relevance within the diagnostic group compared to other tests, and the specific threshold for each and every component), so far it has not been possible to reach universal consensus. The ongoing debate regarding the elements of different diagnostic criteria is unlikely to disappear in the near future.

Due to the lack of standardisation in the diagnosis of PJI, currently there is wide variability not only at international, but also at national and sometimes local levels (45). These unwarranted variations in the methods of diagnosis result in varying and incomparable infection rates between centers (30-35), and raises risks of under-reporting in registries (5,6,8). This results in difficulty in reporting comparison of everyday treatment, analysis of results from local and registry reports, and compromises quality of research in PJI.

The table above (*Table 1*) summarises and compares the diagnostic components of PJI criteria of different specialist

societies based on their most recent criteria (without specific thresholds) in the diagnosis of PJI. It can be concluded that although there are variations in the criteria amongst the different societies, there are a number of tests which are listed in every societies recommended test list (*Table 1*). The investigations criteria for the ICM2018 and MSIS2018 seem to have similar elements, but the infection points are calculated differently: in ICM2018 histopathology is a minor criterion, whilst in MSIS2018 intraoperative findings such as histopathology are calculated separately from blood tests, synovial tests and biomarkers (12,13).

We suggest that the main focus of the PJI diagnosis should shift from the competing different international criteria to a position where there are strong coordinated efforts to implement and vigorously monitor the use of "minimum standard set of PJI diagnostics" in each country and this should be driven by the appropriate national orthopaedic/trauma/musculoskeletal societies. There will always be a need for pioneers and researchers to further explore the horizon to find new and better tools for PJI diagnostics. But for the everyday practice of arthroplasty surgeons and their patients all over the world, it is more important to create a series of standardised tests for suspected PJI, which have been accepted by all major specialist societies. This will allow consistency and standardisation of care throughout national societies, reducing unnecessary variation. When reporting their own results, authors and institutions should describe the threshold they used in line with the recommendations by the specialist international society they choose to follow, and this would allow comparison of diagnostic results depending on different thresholds of the same test as well as and further studies (including meta-analysis) using much bigger data sets.

We propose the introduction and professional mandate of a "minimum standard set of PJI diagnostics" using a smaller number of tests which are recommended by all international specialist infection societies is an achievable goal at national level. If this is implemented, it will result in prompt, significant improvement in the diagnosis and management of PJI, help patients and reduce costs, and should be a priority for every national musculoskeletal society.

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Footnote

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