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RESEARCH ARTICLE

Definition of Periprosthetic Hip and Knee Joint Infections and the Economic Burden

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Abstract: Periprosthetic Joint infection (PJI) following hip and knee replacements is an important complication causing major concern for patients, operating surgeons and healthcare systems. Therefore, a standardized definition of PJI is required to improve communication and allow for valid comparisons of various diagnostic and treatment strategies. This review summarizes the most commonly used definitions for PJI and the current consensus. It also highlights the economic burden related to PJIs and the importance of a multidisciplinary approach to managing those infections.

Keywords: Consensus, Definition, Periprosthetic Joint Infection, Total Hip Arthroplasty, Total Knee Arthroplasty.

INTRODUCTION

Since the introduction of joint arthroplasty, infection has been a distressing complication associated with huge implications [1]. In fact, Sir John Charnley considered stopping hip replacement surgery in the 1960s because of the consequences of periprosthetic joint infection (PJI) [2]. Over time, various definitions and classification systems of PJI have been devised [3 - 8] to provide a platform for communication and improve treatment outcomes. However, a number of challenges deemed it impossible to reach a universal definition due to the variability of the 1) infecting organisms and their virulence, 2) hosts immune response, 3) criteria used for defining PJI including the time of onset (early *vs*. late), source of infection (postoperative *vs*. hematogenous) and tissues involved (superficial *vs*. deep) and 4) diagnostic tools utilized to establish a diagnosis [1, 9]. With so many variations of definitions and classification systems, it has been internationally recognized that there is a need for a universal definition in order to compare practice and drive research and to determine the optimum strategies for prevention and management of PJIs. Consensus decision making depends on general agreement and is particularly useful in such circumstances when available research fails to answer a specific question as it offers the benefit of protecting surgeons from guidelines which may potentially be narrow in scope or based on flawed or limited data [10]. Working parties formulate evidence based proposals in relation to a topic of interest after reviewing the literature and put those proposals forward for the consensus groups meeting to obtain experts opinion. Consensus requires a spirit of cooperation to welcome different viewpoints, consolidate ideas and address concerns with an ultimate goal of an acceptable, workable solution to the topic of interest [10].

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Accordingly, working parties have been set up and consensus meetings held in the United States and Europe to establish a communicable definition, and a gold standard for the prevention and management of PJI.

This paper provides an overview of common PJI definitions and the outcomes of recent consensus meetings. It also highlights the economic burden related to PJIs and the importance of a multidisciplinary approach to managing those infections.

DEFINITIONS OF PJI

Numerous definitions and classification systems for PJI have been described in the European and American literature. Some of the more common definitions and classification systems are detailed in Table **1** [3 - 5, 7 - 9, 11, 12].

Table 1. A summary of consensus group meetings.

Study	Definition	+ve	-ve
ASEPSIS 1986 [11]	A scoring method for post operative wound infections for use in clinical trials A score of 1 to 5 is given for each of the following parameters dependent on the proportion of wound affected: 1-serous exudate 2-erythema 3-purulent exudate 4-separation of deep tissues Additional points are then given for: 1-antibiotic use 2-drainage of pus under local anaesthetic 3-debridement of wound under general anesthetic 4-serous discharge 5-erythema 6-purulent exudate 7-separation of deep tissues 8-isolation of bacteria 9-inpatient stay more than 14 days **Score** **Meaning** 0 to10 No infection Normal healing 11 to 20 Disturbance of healing 21 to 30 Minor infection 31 to 40 Moderate infection ≥ 41 Severe infection	Recognized by NICE as a valid measure for assessment of surgical site infection	Score is time consuming to carry out in daily clinical practice
SPLIF 2010 [5]	Classification according to etiology, location and duration Diagnosis: Presence of a fistula close to the prosthesis confirms infection until proven otherwise Post operative signs suggestive of infection: 1- unusually strong pain or its recurrence after a symptom free period 2- purulent discharge from a surgical wound 3- disunion, necrosis or scar inflammation 4- general signs of fever 5- radiological appearance of loosening Biological signs: White cell count (WCC) is not a good positive or negative predictor of infection Normal Erythrocyte Sedimentation rate (ESR) and C-reactive protein (CRP) do not exclude infection CRP should be used for monitoring of infection Suspect infection with ESR >30mm and CRP >13.5mg/l Imaging modalities: CT, MRI, US and nuclear medicine imaging suggestive of infection	Includes physical signs Provides biological parameters Describes imaging techniques for diagnosis	Specificity and sensitivity of biological parameters not given High level of clinical suspicion may lead to over diagnosis of PJI

(Table 1) contd.....

Study	Definition	+ve	-ve
AAOS 2010 [12]	High probability of infection: One or more symptom AND at least one or more of the following: Risk factors (supported by evidence or expert opinion), physical exam findings (*e.g.* warmth, effusion, redness, swelling or a sinus tract associated with the joint) or radiological evidence of implant loosening/osteolysis Low probability of infection: Pain or joint stiffness only and no risk factors, physical examination findings or radiological evidence of implant loosening /osteolysis Algorithm provided for clinical tests: If ESR and CRP raised joint aspiration is recommended If joint aspiration provides positive differential cell count and positive culture – infection is likely If only one of the above is positive repeat aspiration and if positive infection is likely If second aspiration is negative and surgery is planned frozen section is recommended	Applicable to hip and knee surgery only Risk factors included Physical signs included Useful algorithm	Amount of samples for aspirate/culture may miss diagnosing some PJIs
IDSA 2012 [4]	Definite: 1) Sinus tract communicating with the prosthesis 2) There is purulence around the prosthesis without any other known cause Highly suggestive: 1) Acute inflammation on histopathologic examination of periprosthetic tissue at the time of surgical debridement OR prosthesis removed is highly suggestive of PJI as defined by the attending pathologist 2) ≥2 Intra-operative cultures yielding same organism, OR combined aspiration and culture 3) Cultures grow a virulent microorganism from tissue or synovial fluid samples **Additional information** - PJI can be present if the given criteria are not met. All available information should be taken into account when diagnosing PJI - Intra-operative diagnosis is reliable when interpreted by a skilled pathologist	Clear information stipulates that at least 3 or optimally 5 periprosthetic samples OR explanted prosthesis should be submitted for anaerobic and aerobic cultures Antibiotics should be withheld for 2 weeks prior to cultures being taken if possible	In the absence of a skilled pathologist PJI may be missed
MSIS 2011 [15]	Major criteria: 1) There is a sinus tract communicating with the prosthesis; or 2) A pathogen is isolated by culture from 2 or more separate tissue or fluid samples obtained from the affected prosthetic joint; or Minor criteria: 3) When 4 of the following 6 criteria exist: a. Elevated ESR and CRP b. Elevated synovial WCC c. Elevated synovial polymorphonuclear percentage (PMN%) d. Presence of purulence in the affected joint e. Isolation of a microorganism in one culture of periprosthetic tissue or fluid, or f. Greater than 5 neutrophils per high-power field in 5 high-power fields observed from histologic analysis of periprosthetic tissue at ×400 magnification **Additional Information** Please note that a PJI may be present if less than 4 of these criteria are met		

(Table 1) contd.....

Study	Definition	+ve	-ve
International consensus group 2014 [16]	Major criteria: 1) A sinus tract communicating with the joint; or 2) 2 positive phenotypically identical organisms on cultures taken in periprosthetic sampling; or Minor Criteria: 3) when 3 of the following 5 criteria exist: a. Elevated ESR & CRP b. Elevated synovial fluid WCC OR ++ change on leucocyte esterase test strip c. Elevated synovial fluid PMN% d. A single positive culture e. Positive histological analysis of periprosthetic tissue	Accompanying declaration states infection may be present when these criteria are not met Further stipulation of values of the minor criteria is given according to acuteness or chronicity of infection	
CDC 2015 [7]	Major Criteria: 1) A sinus tract communicating with the joint; or 2) 2 positive periprosthetic tissue or fluid cultures with matching organisms; or Minor Criteria: 3) when 3 of the following 5 criteria exist: a. CRP >100mg/L AND ESR >30mm/hr b. Synovial fluid WCC >10,000 cells/μL OR ++ change on leucocyte esterase strip test of synovial fluid c. Elevated synovial fluid PMN percentage (>90%) d. A single positive periprosthetic tissue or fluid culture e. Positive histological analysis of periprosthetic tissue (more than 5 PMNs per high power field) **Additional Information** Further details given about: 1) Definition of matching organism 2) Positive cultures of hardware from a hip or knee can be used to meet criterion 2 3) Definition of sinus given	Specific for hip and knee replacement only	

The National Institute of Clinical Excellence (NICE) in the United Kingdom provides guidelines on the management of surgical site infections (SSI) and bases its definition of an SSI on that agreed by the Center for Disease Control (CDC) [13]. NICE also recognizes the ASEPSIS wound scoring system which was devised by Dr Wilson at University College London Hospital in 1986 for postoperative surveillance of wound healing and effectiveness of antibiotic treatment after infections [11, 14]. ASEPSIS provides the advantage of a very detailed assessment of the surgical wound but can be quite time consuming to fill out on day to day clinical assessment (Table **1**).

The Société de Pathologie Infectieuse de Langue Française (SPILF) organized a consensus meeting with other French speaking recognized bodies including the French Society of Orthopaedics and Trauma Surgery and The French Society of Anesthesiology and Intensive Care. A definition of PJI was agreed and this provided a platform for communication of clinical practice and research within the French speaking orthopaedic world [5] (Table **1**).

In 2010, The American Academy of Orthopaedic Surgeons developed guidelines and an evidence report on the management of PJI [12]. The working party involved in developing these guidelines included members of the CDC and experts in the field. The guidelines described two categories: high and low probability of PJI depending on risk factors and clinical and radiological evidence. An algorithm for clinical tests was provided but without specific cut off values for these tests.

Following that, The Infectious Diseases Society of America (IDSA) described the presence of a sinus tract in communication with the joint as a definitive criterion and histopathological findings when present as highly suggestive of infection. They also described the work up required prior to this including a history with a particular reference to pain and investigations including erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), arthrocentesis and blood cultures. However, specific values suggesting the relevance of these results were not provided.

Almost simultaneously with the IDSA, The Musculoskeletal Infection Society (MSIS) convened to establish a definition of PJI to be used by recognized bodies including the CDC as a gold standard for communication. This definition includes major and minor criteria that can easily be measured and members of the CDC were also on the panel [15] (Table **1**).

Professors Thorsten Gehrke and Javad Parvizi recognized that the longstanding issue with the prevention and treatment of PJIs was that although much research into the topic had been undertaken, there was a failure to answer

fundamental questions about the subject due to lack of high level evidence. Therefore, they organized the International Consensus Meeting on PJI in Philadelphia in 2013 with the aim of answering some of these important questions. The details describing the meeting are impressive [16]. The meeting was preceded by 10 months of preparation, inviting delegates involved in the care of PJIs from multiple medical, veterinary and pharmaceutical research fields. 3,500 articles were evaluated in order to establish a firm evidence base to answer clinical questions. This involved 400 delegates from 51 countries, communicating through an online forum in which over 25,000 entries were exchanged. Methods implemented to prevent PJIs such as theatre environment and prophylactic antibiotics were discussed during this meeting, as well as the definition of a PJI and various diagnostic and treatment strategies. Furthermore, a preliminary draft of the consensus statement was motioned and any concerns were addressed in small groups prior to a larger general assembly discussion of questions and consensus statements. The general assembly saw participants vote on 207 consensus statements with the options of: agreeing with the statement, disagreeing with it or abstaining from voting. The strength of consensus was then based on the number of votes as follows: 1) Simple Majority: No Consensus (50.1-59% agreement), 2) Majority: Weak Consensus (60-65% agreement), 3) Super Majority: Strong Consensus (66-99% agreement), and 4) unanimous (100% agreement). The need to control operating theatre traffic was unanimously agreed upon, whilst 202 of the remaining 206 questions had a super majority strong consensus [16]. An outcome of this meeting was the conception of a definition for PJI, constituting 2 major and 5 minor criteria. This definition was formulated on the basis of existing evidence and a consensus of expert opinions. The presence of at least 1 major criterion or 3 minor criteria is required for a diagnosis of PJI. This includes analyses of tissue and aspirate cultures, laboratory tests such as ESR, CRP, polymorphonuclear (PMN) percentage, and synovial fluid white cell count (WCC) and neutrophil count on microscopy. The same definition was then adopted by the CDC with clarification of the definition of matching organisms and appropriate tissue sampling. CDC also stated that the laboratory cutoffs quoted in this definition should not guide clinicians in the actual clinical diagnosis of infection but instead, they should refer to the MSIS consensus definition for clinical use [7] (Table **1**).

THE INCIDENCE AND ECONOMIC BURDEN OF PJI

The United States CDC initiated the National Nocosomial Infection Surveillance (NNIS) in the 1970s to monitor hospital acquired infections [17]. Similarly, the United Kingdom National Healthcare Safety Network developed the Nosocomial Infection National Surveillance System (NINSS) which provides regular reports on the incidence and prevalence of infection [18].

In 2014, The NINSS of England reported that the cumulative incidence of SSI in 198 hospitals performing 180 852 hip arthroplasties between 2009 and 2014 was 0.7%. The same report showed that 0.6% of 188 974 knee arthroplasties were complicated by SSI. In the US, a 27% reduction in SSI following hip arthroplasties has been reported since 2004 with an overall rate of 0.88% infections. A 40% reduction in PJI following knee arthroplasties has also been reported with an overall rate of 0.92% infections [18, 19].

Although the incidence of infection is falling, the cost to healthcare systems is still immense. In an evaluation of the economic burden of PJI in hip and knee arthroplasty, Kurtz *et al*. [20] reviewed data from the United States National Inpatient Survey. The mean length of inpatient stay for total hip arthroplasty (THA) patients was 4.3 days with an average cost of $39 654. This was reported to increase to an average of 9.7 days in those with PJI resulting in a cost of $70 378. Similar increases were seen in total knee arthroplasty (TKA), with hospital stay increasing from 3.9 days in those without infection to 7.6 days for those with PJI, an increase in cost from $35 769 to $56 275.

In fact, the annual cost of infected revisions to US hospitals has increased by $246 million between 2001 and 2009 and it is projected to exceed $1.62 billion by 2020 [19].

Vanhegan *et al*. [21] compared the cost of revision THA surgery according to the reason for surgery in 305 cases from a tertiary referral center in the UK. The cost of revision for aseptic loosening in 194 patients was £11 897, whereas in 76 patients with PJI the cost was £21 937. This dramatic increase in cost was due to a combination of factors including prolonged operating time, increased blood loss, complications and length of inpatient stay. A similar study of 827 THA and TKA patients in Australia reported an increase to the cost of arthroplasty of 61% in the presence of SSI adding an estimated AUS $97 million to Total Joint Arthroplasty costs in the first 30 days following surgery [22].

MULTI-DISCIPLINARY APPROACH TO MANAGEMENT OF PJI

Following the consensus meetings in France [5] and Philadelphia [16] where a panel of experts from various specialties worked synergistically, the need for a multi-disciplinary Team (MDT) approach to the management of PJI

has been recognized [23]. Disciplines which contributed effectively to those meetings included orthopaedic surgery, infectious diseases, musculoskeletal pathology, microbiology, anesthesiology, dermatology, nuclear medicine, rheumatology, musculoskeletal radiology, veterinary surgery and pharmacy [23]. The consensus document derived from the 'Proceedings of the International Consensus Meeting on Periprosthetic Joint Infection' was developed according to the Delphi method [24]. Principles which govern the Delphi method include anonymity allowing participants to contribute opinions without conformity and permitting free expression, iteration permitting the clarification and adjustment of viewpoints and statistical aggregation of a group response allowing for a quantitative analysis [24]. As part of multidisciplinary input, the Delphi method has been employed elsewhere in the PJI discourse.

In a single surgeon review of patients undergoing two-stage revision surgery for infected THA, Ibrahim *et al*. [25] reports the benefits of a MDT approach. The team responsible for the management of the 125 patients (51.2% undergoing their first revision, 16.8% second revision) with infected THA included microbiologists, infectious disease specialists, orthopaedic surgeons, radiologists, physiotherapists and physicians. With this patient focused management strategy at 5 year follow up, an infection control rate was achieved in 96% of the cases. Additionally, the Harris Hip Score improved from a mean of 38 pre-operatively to 81.2. This emphasizes the importance of working as a team to improve patient outcomes in a challenging situation such as the management of PJIs.

CONCLUSION

The excellent work of the consensus meetings has resulted in the conception of a workable diagnosis of PJI. This will deliver a platform for improved international communication and comparison of research as well as refining the strategies implemented in the prevention and management of PJI. A multi-disciplinary team, sharing all the responsibility is needed to reduce this large burden on patients, surgeons and healthcare systems. With the aid of a highly synergistic and well-functioning MDT, great improvements can be achieved in both the prevention and management of PJI.

CONFLICT OF INTEREST

Each author certifies that he or she, or a member of his or her immediate family, has no commercial interests that might pose a conflict of interest in connection with this work.

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