2.5. DIAGNOSIS: IMAGING

Authors: Jiří Gallo, Peter Sculco, Milan Kaminek, Eva Nieslanikova, Libuse Quinn

QUESTION 1: What imaging modalities are available to help evaluate the extent of an infection and guide bone resection?

RECOMMENDATION: Imaging methods have a potential to demonstrate the extent of soft-tissue/bone involvement in patients with periprosthetic joint infection (PJI). The use of computed tomography, magnetic resonance imaging (MRI) or nuclear medicine techniques may help to delineate the extent of bone and soft tissue involvement and may guide bone resection.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 86%, Disagree: 8%, Abstain: 6% (Super Majority, Strong Consensus)

DEFINING THE STRENGTH OF THE RECOMMENDATIONS

Assigning the strength of the recommendations was provided by concise presentation of the literature quantity and quality while accounting for the trade-off between the clinical experience and their limitations. In order to standardize the approach across the consensus document/specialists from different medical branches, we adopted the methodology of defining the strength of the recommendations and evaluating the evidence from the American Academy of Orthopaedic Surgeons (AAOS) Clinical Practice Guideline and Systematic Review Methodology v2.0 [1].

The selected studies might be flawed in a number of parameters. For example, study design (randomized-control/prospective/retrospective), type of study (diagnostic/case-control/ observational/case reports), primary purpose, population, study inclusion/exclusion criteria, definition of PJI, gold standard for diagnosis of PJI/distinct clinical entities (abscess, presence of soft-tissue edema, periprosthetic fluid collections, bone damage), data collection/analysis/ interpretation etc. Therefore, methods for assigning the quality of the selected studies were appraised in accordance with the GRADE recommendations [2]. In the GRADE approach randomized trials start as high-quality evidence and observational studies as low-quality evidence. Five factors may lead to rating down the quality of evidence: study limitations or risk of bias, inconsistency of results, indirectness of evidence, imprecision and publication bias [3]. In accordance with the AAOS manual [1], high-quality diagnostic studies cannot have any substantial flaw,
moderate-quality studies can have less than two flaws, low-quality diagnostic studies less than three flaws and very low-quality studies have more than three substantial flaws. Observational studies were classified as follows: high-quality studies have less than two flaws, moderate-quality studies have between two and four flaws, low-quality studies from four to six flaws and very low-quality studies have more than six flaws.

RATIONALE

Removal of all infected/necrotic tissues is pivotal in the treatment of PJI. In practice, surgeons are guided mainly by experience of what constitutes infected and/or necrotic tissue that must be excised. Tissue color/structure/consistency can guide the degree of resection, in addition to active bleeding from apparently healthy tissue and bone surfaces. Surgeons may use specific dyes (e.g., methylene blue) as a visual aid to differentiate between necrotic tissue and healthy soft tissue. Currently, there is no consensus on whether imaging modalities could be used preoperatively to better define the location of infected soft tissue and bone or be used to guide the degree and depth of surgical debridement. While imaging methods, such as Indium labeled bone scans, have been used for diagnosis of PJI in very select cases, whether a preoperative imaging modality can provide the spatial resolution and accuracy to determine the exact regions of soft tissue involvement of osteomyelitis that require debridement is still debated [4]. The primary question of this paper is to determine, based on the available evidence, if preoperative imaging, and which type of imaging, could best define the border between the infected and non-infected soft tissue and bone and quantitatively and qualitatively assess the extent of associated soft tissue and osseous damage associated with chronic PJI.

The literature search was conducted utilizing databases such as PubMed, Embase, Cochrane Library, Scopus, ScienceDirect and Google Scholar. The search strategy utilized the following Medical Subjection Headings (MeSH) terms: “hip arthroplasty,” “hip replacement,” “hip prosthesis,” “knee arthroplasty,” “knee replacement,” “knee prosthesis,” “infection,” “periprosthetic infection,” “prosthetic joint infection,” “nuclear imaging,” “leukocyte imaging,” “antigranulocyte imaging,” “18F-fluorodeoxyglucose,” “positron emission tomography,” “ultrasound,” “computed tomography,” “magnetic resonance imaging,” “conventional radiography” and “best match” for each database.

We used the Boolean operators “AND” and “OR” to identify the intersection and union of the terminology sets. References for all the selected articles were cross-checked.

Two of the authors (EN and LQ) performed the literature search. First, articles were screened by title and abstract; 495 potentially interesting studies were identified. Of them, 229 relevant publications including reviews and meta-analyses were then selected for data extraction.

Study Selection

Based on the clinical question, we proposed inclusion and exclusion criteria to be applied when reviewing the search results of each database. An initial review of titles and abstracts was carried out to identify potential studies. The inclusion criterion was human studies. The exclusion criterion was “studies limited to the English language.” This study is based on 49 full texts that have been analyzed to date.

Data Extraction

Once the study selection was completed, the relevant data (number of patients, age, gender, location of PJI, type of PJI, single/multi-center study, study period, type of study, design of study, type of imaging, definition of PJI, gold standard, characteristics of particular imaging methods, limitations of the study) from the included studies were extracted. A spreadsheet was customized to the specific question. After the data extraction and

completion of the tables, the senior authors (JG and MK) assessed the quality of the particular studies used in assigning the strength of the recommendations.

Conventional radiography (CR) can show "signs of damage" in the bone surrounding infected arthroplasty as well as in swollen soft-tissues [5,6]. However, these changes are not specific for PJI, and these are seen only in a minority of PJIs. We did not find any diagnostic study supporting the role of CR in showing the bone/soft-tissue extension of PJI. The conclusion should therefore be *no evidence* for using CR as a tool for visualization of tissues affected by PJI. The only exception is when radiography shows clear presence of osteomyelitis, periosteal reaction and so on and may provide some degree of confidence in planning the extent of bone resection needed during resection arthroplasty.

Ultrasonography can demonstrate collections of fluid inside and around an infected joint as well as it can distinguish between solid and fluid lesions. Sdao et al. reported superficial collections, subcutaneous fistulae, as well as deep periprosthetic collections of fluids around total hip arthroplasty [7]. However, these are not specific for infection. Ultrasound guided aspiration (biopsy) of a hip joint improves reliability of aspiration [8]. Here we suggest concluding the strength of *evidence as low (limited)*. A support for that conclusion is predominantly on anecdotal (case reports) and small-series studies of low quality [9–11].

Computed tomography (CT) is excellent for evaluating bony structures, but it can also contribute to assessment of soft tissue pathology [12]. However, this is not specific for infection. CT can detect abscesses around total joint arthroplasty, which is clinically very useful as a psoas abscess can also mimic PJI [13]. On the other hand, CT arthrography can reveal bone erosions, radiolucency, fistulae, extra-articular extensions of PJI or communications between fluid collections [14,15]. In addition, CT can show displacement of the external iliac vessels with venous compression [11]. Taking these findings into account, alongside the clinical value of CT findings (either positive or negative), we conclude the strength of the recommendations for abdominal/hip CT as *moderate* despite the fact that it is based on anecdotal [16,17] to small-series study evidence [15,18,19]. Therefore, CT should be combined with other imaging/laboratory methods in order to visualize the extension of the soft-tissue/bone damage associated with PJI.

Magnetic resonance imaging (MRI) can detect bone marrow changes, cavities and soft-tissue extension of PJI (edema, fluid collections). In addition, the new metal artifact reduction sequences (MARS) enabled a more reliable assessment of periprosthetic tissues [14]. Contrast MRI can contribute to detection of psoas abscesses [20]. In contrast to radiography, MRI might be more specific for hip PJI as it can differentiate between fluid collections (serous, purulent or hematomas) [21]. Further, progress might lie in optimized MRI parameters with and without view angle tilting (VAT) correction at 1.5 T in coronal fast-spin-echo T2-weighted MRI [22]. Intravenous gadolinium contrast MRI demonstrates improved specificity for abscess detection, despite the fact that non contrast-enhanced MRI with diffusion-weighted imaging has recently achieved comparable performance [23]. Despite that, MRI should be still combined with other imaging/laboratory methods in order to demonstrate the true extension of soft-tissue/bone damage associated with PJI. We suggest concluding the strength of the recommendations for MRI in this specific clinical question as *moderate*, similar to CT.

The nuclear medicine techniques are regularly used in some clinical settings to diagnose particular infections of the musculoskeletal system [24]. They are based on various principles (radio-labelled cells, peptides, antibodies or (18) fluorodeoxyglucose (FDG) to detect patterns highly associated with infected tissues. Recent systematic reviews and meta-analyses show great diagnostic potential in terms of the likelihood ratio for positive/negative results and diagnostic odds ratio for radio-labelled white blood cells [4]. Anti-granulocyte scintigraphy and combined radio-labelled leukocyte and bone marrow scintigraphy appear to be highly-specific imaging modalities in confirming knee PJI. FDG-PET (positron emission tomography) may not be the preferred imaging modality because it is more expensive and not more effective in confirming periprosthetic knee infection [4]. However, much of the evidence is dated and recent innovations in nuclear medicine technology that have improved image quality and sensitivity of investigations (particularly SPECT/CT – single photon emission computed tomography) are not fully represented in this review.

To date, there is a little knowledge of the capability of these methods to visualize the extent of infection across periprosthetic tissues. Radio-labelled leukocyte or antigranulocyte SPECT/CT imaging has been used to differentiate aseptic loosening from infection [4,25].

Filippi and Schillaci [26] described the usefulness of hybrid SPECT/CT in technetium (99mTC)-hexamethylpropleneamineoxime (^{99m}TC-HMPAO)-labelled leukocyte scintigraphy for bone and joint infections. In the sample of 28 consecutive patients (13 of them with suspected orthopaedic implant infection), SPECT/CT differentiated soft-tissue involvement from bone involvement both in patients with osteomyelitis and in patients with orthopaedic implants.

Graute et al. [27] described an added value of the ^{99m}Tc-antigranulocyte SPECT/CT in comparison with SPECT only or planar imaging for detection of low-grade prosthetic joint infections. Joint infections were diagnosed clinically in nine of 31 patients (1 hip and 8 knee prostheses). Hybrid SPECT/CT led to a further increase in sensitivity and specificity to 0.89 and 0.73 (in comparison with 0.89 and 0.45 for SPECT only, and 0.66 and 0.60 for planar imaging, respectively). In the cases presented in this study, SPECT/CT images additionally demonstrated the extent of infection in the bone or bone marrow, revealed infection in patients with a characteristic pattern indicating the presence of synovitis on planar paging, or excluded infection due to physiological uptake in arteria poplitea, etc. Optimal accuracy was obtained through image fusion, which permitted anatomical allocation of foci of pathological tracer accumulation as well as providing information on the extent of infection. By this way this imaging method seems suitable for elimination of both false-positive and false-negative findings.

Trevail et al. [28] similarly described the added value of SPECT/CT for the diagnosis of hip PJI (235 consecutive patients). Imaging comprised Tc-^{99m} bone scintigraphy, Indium-III (In-III) labeled white cell scintigraphy, and bone marrow scintigraphy if required. Similar to previous studies, SPECT/CT allowed more accurate localization of abnormal uptake on bone and white cell scintigraphy. Recently, preliminary results of a study by Liberatore et al. [29] showed potential of white blood cell scan as a guide to open biopsy in the management of hip and knee prosthesis infection.

Tam et al. [30] reviewed the use of SPECT-CT to follow post total hip arthroplasty complications, including aseptic loosening and PJI. The CT component of SPECT/CT may help interpretation of SPECT images. CT may reveal areas of lucency with associated periosteal reaction, which correspond to the increased uptake on scintigraphy. CT can also demonstrate soft-tissues changes, such as joint distension, fluid-filled bursae or collections in muscles.

Also, Palestre et al. [31] suggest the potential impact of SPECT/CT on information about the presence and extent of infection. In patients with positive results, for example, the examination could provide information about the extent of infection as well as other abnormalities involving the native bone and the prosthesis (joint aspiration and culture could be performed at the same time). In patients with negative results, the CT component could provide information about other causes of prosthetic failure.

In comparison with leukocyte or antigranulocyte imaging, FDG-PET may not be the preferred imaging modality because it is not more effective in confirming periprosthetic infection [25,31]. Periprosthetic activity of FDG can be seen not only during infection but also in synovitis and aseptic loosening [32,33] thus, the specificity of FDG-PET/CT was very low. FDG-labelled leucocyte PET/CT with its high specificity may be a method more useful than labelled leucocyte scintigraphy in periprosthetic infection imaging [34,35]. However, there are some drawbacks to FDG-labelled leukocyte PET/CT including the relatively long time needed for labelling leucocytes, longer time between injection and imaging (three hours), and the necessity of higher injected FDG doses (double the doses used as compared to standard oncological imaging) [35].

Despite lower specificity of FDG described in earlier studies [32,33], a recent retrospective study [36] showed added value of FDG PET/CT in comparison to conventional tests in diagnosing hip PJI (cultures of joint fluid/periprosthetic tissues or clinical follow-up more than six months served as gold standard). Fukui et al. [37] used FDG-PET in order to make more appropriate decision-making in terms of retention of well-fixed uncemented femoral component in two-stage total hip surgery that included delayed reimplantation of an acetabular component in five patients. FDG-PET was employed to assess whether the infection had invaded the bone around femoral component. By a mean follow-up point of 4.2 years after the second-stage operation, none of the 5 patients experienced recurrence of PJI.

Taken together, we suggest concluding the strength of the recommendations for the nuclear medicine techniques in this specific clinical question as *moderate*.

Future Progress

There is an emerging field of new imaging techniques (e.g., molecular imaging methods) that could visualize the extent of infection in musculoskeletal tissues with promising accuracy. However, clinical value of these methods should be demonstrated in well-conducted diagnostic studies.

REFERENCES

[1] American Academy of Orthopaedic Surgeons. Clinical Practice Guideline and Systematic Review Methodology. https://www.aaos.org/uploadedFiles/PreProduction/Quality/Guidelines_and_Reviews/guidelines/Guideline%20and%20Systematic%20Review%20Processes_v2.0_Final.pdf.

[2] Brozek JL, Akl EA, Jaeschke R, Lang DM, Bossuyt P, Glasziou P, et al. Grading quality of evidence and strength of recommendations in clinical practice guidelines: Part 2 of 3. The GRADE approach to grading quality of evidence about diagnostic tests and strategies. Allergy. 2009;64:1109–1116. doi:10.1111/j.1398–9995.2009.02083.x.

[3] Guyatt G, Akl EA, Oxman A, Wilson K, Puhan MA, Wilt T, et al. Synthesis, grading, and presentation of evidence in guidelines: article 7 in integrating and coordinating efforts in COPD guideline development. An official ATS/ERS workshop report. Proc Am Thorac Soc. 2012;9:256–261. doi:10.1513/pats.201208–060ST.

[4] Verberne SJ, Raijmakers PG, Temmerman OPP. The accuracy of imaging techniques in the assessment of periprosthetic hip infection: a systematic review and meta–analysis. J Bone Joint Surg Am. 2016;98:1638–1645. doi:10.2106/JBJS.15.00898.

[5] Zimmerli W. Infection and musculoskeletal conditions: Prosthetic–joint–associated infections. Best Pract Res Clin Rheumatol. 2006;20:1045–1063. doi:10.1016/j.berh.2006.08.003.

[6] Zajonz D, Wuthe L, Tiepolt S, Brandmeier P, Prietzel T, von Salis–Soglio GF, et al. Diagnostic work–up strategy for periprosthetic joint infections after total hip and knee arthroplasty: a 12–year experience on 320 consecutive cases. Patient Saf Surg. 2015;9:20. doi:10.1186/s13037–015–0071–8.

[7] Sdao S, Orlandi D, Aliprandi A, Lacelli F, Sconfienza LM, Randelli F, et al. The role of ultrasonography in the assessment of peri–prosthetic hip complications. J Ultrasound. 2015;18:245–250. doi:10.1007/s40477–014–0107–4.

[8] Bureau NJ, Ali SS, Chhem RK, Cardinal E. Ultrasound of musculoskeletal infections. Semin Musculoskelet Radiol. 1998;2:299–306. doi:10.1055/s–2008–1080109.

[9] Baratelli M, Cabitza P, Parrini L. Ultrasonography in the investigation of loose hip prostheses. Ital J Orthop Traumatol. 1986;12:77–83.

[10] van Holsbeeck MT, Eyler WR, Sherman LS, Lombardi TJ, Mezger E, Verner JJ, et al. Detection of infection in loosened hip prostheses: efficacy of sonography. AJR Am J Roentgenol. 1994;163:381–384. doi:10.2214/ajr.163.2.8037036.

[11] Cheung YM, Gupte CM, Beverly MJ. Iliopsoas bursitis following total hip replacement. Arch Orthop Trauma Surg. 2004;124:720–723. doi:10.1007/s00402–004–0751–9.

[12] Chang CD, Wu JS. Imaging of musculoskeletal soft tissue infection. Semin Roentgenol. 2017;52:55–62. doi:10.1053/j.ro.2016.10.001.

[13] Atif M, Malik AT, Noordin S. Psoas abscess masquerading as a prosthetic hip infection: a case report. Int J Surg Case Rep. 2018;42:17–19. doi:10.1016/j.ijscr.2017.11.054.

[14] Blum A, Gondim–Teixeira P, Gabiache E, Roche O, Sirveaux F, Olivier P, et al. Developments in imaging methods used in hip arthroplasty: a diagnostic algorithm. Diagn Interv Imaging. 2016;97:735–747. doi:10.1016/j.diii.2016.07.001.

[15] Jacquier A, Champsaur P, Vidal V, Stein A, Monnet O, Drancourt M, et al. [CT evaluation of total HIP prosthesis infection]. J Radiol. 2004;85:2005–2012.

[16] Buttaro M, González Della Valle A, Piccaluga F. Psoas abscess associated with infected total hip arthroplasty. J Arthroplasty. 2002;17:230–234.

[17] Gunaratne GD, Khan RJ, Tan C, Golledge C. Bilateral prosthetic hip joint infections associated with a Psoas abscess. A case report. J Orthop Case Rep. 2016;6:3–6. doi:10.13107/jocr.2250–0685.472.

[18] Dauchy FA, Dupon M, Dutronc H, de Barbeyrac B, Lawson–Ayayi S, Dubuisson V, et al. Association between psoas abscess and prosthetic hip infection: a case–control study. Acta Orthop. 2009;80:198–200. doi:10.3109/17453670902947424.

[19] Lawrenz JM, Mesko NW, Higuera CA, Molloy RM, Simpfendorfer C, Babic M. Treatment challenges of prosthetic hip infection with associated iliacus muscle abscess: report of 5 cases and literature review. J Bone Jt Infect. 2017;2:127–135. doi:10.7150/jbji.16429.

[20] Volpin A, Kini SG, Berizzi A. Psoas muscle pyogenic abscess in association with infected hip arthroplasty: a rare case of simultaneous bilateral presentation. BMJ Case Rep. 2015;2015. doi:10.1136/bcr–2015–209711.

[21] Aliprandi A, Sconfienza LM, Randelli F, Bandirali M, Di Leo G, Sardanelli F. Magnetic resonance imaging of painful total hip replacement: detection and characterisation of periprosthetic fluid collection and interobserver reproducibility. Radiol Med. 2012;117:85–95. doi:10.1007/s11547–011–0706–5.

[22] Jiang MH, He C, Feng JM, Li ZH, Chen Z, Yan FH, et al. Magnetic resonance imaging parameter optimizations for diagnosis of periprosthetic infection and tumor recurrence in artificial joint replacement patients. Sci Rep. 2016;6:36995. doi:10.1038/srep36995.

[23] Chun CW, Jung JY, Baik JS, Jee WH, Kim SK, Shin SH. Detection of soft–tissue abscess: Comparison of diffusion–weighted imaging to contrast–enhanced MRI. J Magn Reson Imaging. 2018;47:60–68. doi:10.1002/jmri.25743.

[24] Love C, Palestro CJ. Nuclear medicine imaging of bone infections. Clin Radiol. 2016;71:632–646. doi:10.1016/j.crad.2016.01.003.

[25] Verberne SJ, Sonnega RJ, Temmerman OP, Raijmakers PG. Erratum to: what is the accuracy of nuclear imaging in the assessment of periprosthetic knee infection? a meta–analysis. Clin Orthop Relat Res. 2017;475:1753–1754. doi:10.1007/s11999–017–5327–4.

[26] Filippi L, Schillaci O. Usefulness of hybrid SPECT/CT in 99mTc–HMPAO–labeled leukocyte scintigraphy for bone and joint infections. J Nucl Med. 2006;47:1908–1913.

[27] Graute V, Feist M, Lehner S, Haug A, Müller PE, Bartenstein P, et al. Detection of low–grade prosthetic joint infections using 99mTc–antigranulocyte SPECT/CT: initial clinical results. Eur J Nucl Med Mol Imaging. 2010;37:1751–1759. doi:10.1007/s00259–010–1431–3.

[28] Trevail C, Ravindranath–Reddy P, Sulkin T, Bartlett G. An evaluation of the role of nuclear medicine imaging in the diagnosis of periprosthetic infections of the hip. Clin Radiol. 2016;71:211–219. doi:10.1016/j.crad.2015.10.026.

[29] Liberatore M, Gentile G, Follacchio GA, Frantellizzi V, De Vincentis G, Monteleone F, et al. 99mTc–labeled white blood cell scan as a guide to open biopsy in the management of hip and knee prosthesis infection: preliminary results. Curr Radiopharm. 2017;10:29–34. doi:10.2174/1874471009666161117120358.

[30] Tam HH, Bhaludin B, Rahman F, Weller A, Ejindu V, Parthipun A. SPECT–CT in total hip arthroplasty. Clin Radiol. 2014;69:82–95. doi:10.1016/j.crad.2013.08.003.

[31] Palestro CJ. Nuclear medicine and the failed joint replacement: Past, present, and future. World J Radiol. 2014;6:446–458. doi:10.4329/wjr.v6.i7.446.

[32] Manthey N, Reinhard P, Moog F, Knesewitsch P, Hahn K, Tatsch K. The use of [18 F]fluorodeoxyglucose positron emission tomography to differentiate between synovitis, loosening and infection of hip and knee prostheses. Nucl Med Commun. 2002;23:645–653.
[33] Chacko TK, Zhuang H, Stevenson K, Moussavian B, Alavi A. The importance of the location of fluorodeoxyglucose uptake in periprosthetic infection in painful hip prostheses. Nucl Med Commun. 2002;23:851–855.
[34] Yılmaz S, Ocak M, Asa S, Aliyev A, Ozhan M, Halac M, et al. The different distribution patterns of FDG and FDG–labelled WBC in inflammatory and infectious lesions. Eur J Nucl Med Mol Imaging. 2012;39:1660–1661. doi:10.1007/s00259–012–2170–4.
[35] Aksoy SY, Asa S, Ozhan M, Ocak M, Sager MS, Erkan ME, et al. FDG and FDG–labelled leucocyte PET/CT in the imaging of prosthetic joint infection. Eur J Nucl Med Mol Imaging. 2014;41:556–564. doi:10.1007/s00259–013–2597–2.
[36] Kwee RM, Broos WA, Brans B, Walenkamp GH, Geurts J, Weijers RE. Added value of 18F–FDG PET/CT in diagnosing infected hip prosthesis. Acta Radiol. 2018;59:569–576. doi:10.1177/0284185117726812.
[37] Fukui K, Kaneuji A, Ueda S, Matsumoto T. Should well–fixed uncemented femoral components be revised in infected hip arthroplasty? Report of five trial cases. J Orthop. 2016;13:437–442. doi:10.1016/j.jor.2015.09.006.