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REVIEW ARTICLE

Prosthetic joint infections: radionuclide state-of-the-art imaging

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Abstract Prosthetic joint replacement surgery is performed with increasing frequency. Overall the incidence of prosthetic joint infection (PJI) and subsequently prosthesis revision failure is estimated to be between 1 and 3%. Differentiating infection from aseptic mechanical loosening, which is the most common cause of prosthetic failure, is especially important because of different types of therapeutic management. Despite a thorough patient history, physical examination, multiple diagnostic tests and complex algorithms, differentiating PJI from aseptic loosening remains challenging. Among imaging modalities, radiographs are neither sensitive nor specific and cross-sectional imaging techniques, such as computed tomography and magnetic resonance imaging, are limited by hardware-induced artefacts. Radionuclide imaging reflects functional rather than anatomical changes and is not hampered by the presence of a metallic joint prosthesis. As a result scintigraphy is currently the modality of choice in the investigation of suspected PJI. Unfortunately, there is no true consensus about the gold standard technique since there are several drawbacks and limitations inherent to each modality. Bone scintigraphy (BS) is sensitive for identifying the failed joint replacement, but cannot differentiate between infection and aseptic loosening. Combined bone/gallium scintigraphy (BS/GS) offers modest improvement over BS alone for diagnosing PJI. However, due to a number of drawbacks, BS/GS has generally been superseded by other techniques but it still may have a role in neutropenic patients. Radiolabelled leucocyte scintigraphy remains the gold standard technique for diagnosing neutrophil-mediated processes. It seems to be that combined in vitro labelled leucocyte/bone marrow scintigraphy (LS/BMS), with an accuracy of about 90%, is currently the imaging modality of choice for diagnosing PJI. There are, however, significant limitations using in vitro labelled leucocytes and considerable effort has been devoted to developing alternative radiotracers, such as radiolabelled HIGs, liposomes, antigranulocyte antibodies and fragments, as well as more investigational tracers such as radiolabelled antibiotics, antimicrobial peptides, bacteriophages and thymidine kinase. On the other hand, positron emission tomography (PET) is still growing in the field of PJI imaging with radiotracers such as ^{18}F-fluorodeoxyglucose (FDG), ^{18}F-FDG white blood cells and ^{18}F-fluoride. But unfortunately this superb tomographic technique will only receive full acceptance when specific PET uptake patterns can be successfully developed. The emergence

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of hybrid modality imaging using integrated single photon emission computed tomography (SPECT) and PET with computed tomography (SPECT/CT and PET/CT) may also have a contributing role for more accurate assessment of joint replacement complications, especially combined with new radiotracers such as ^{68}Ga and ^{64}Cu. Finally, in searching for infection-specific tracers, currently there is no such diagnostic agent available.

Keywords Prosthetic joint infection · Preoperative diagnosis · Radionuclide imaging · Hybrid imaging

As life expectancy increases, prosthetic joint replacement is becoming a more frequently used procedure to improve quality of life of the aging population. Total joint arthroplasty is one of the most reliable and cost-effective surgical procedures performed [1]. Complications of prosthetic joint surgery such as heterotopic ossification, fracture and dislocation are relatively uncommon. Aseptic or mechanical loosening and polyethylene wear is nowadays the major cause of arthroplasty failure, which can occur in more than one quarter of patients [2]. Although occurring infrequently, prosthetic joint infection (PJI) nevertheless is a serious complication of joint replacement surgery that results in substantial morbidity and decline in functional outcome. Moreover, it is associated with significant clinical, psychological and financial costs. Furthermore, surgeons are faced with an increasingly complex mix, with a higher prevalence of immunocompromised patients, increased co-morbidities and antibiotic-resistant bacteria, along with several known patient-related and surgical risk factors [3].

Classifications, pathogenesis and clinical scenarios

Classification schemes encompass the pathophysiological and pathogenetic pathway of the development of PJI and on the other hand a distinction between early, delayed and late presentation may be clinically useful. Some of the currently used classifications are explained in Table 1 and Fig. 1 [1, 4].

Today's prosthesis, a combination of metal (cobalt-chromium or titanium) and plastic (ultrahigh molecular weight polyethylene), can be attached to native bone in numerous ways. In aseptic and septic conditions, initially, the prosthetic implant is surrounded by a bone and fibrous tissue membrane, leading to osseous integration. Only rarely does bone directly interface with the metal or plastic of the prosthesis; usually it is separated by a thin layer of reactive fibrous tissue situated between the host and the implant or its anchoring cement, known as the "membrane" by orthopaedic surgeons. Even well-fixed implants may have these membranes, but in a failed prosthetic joint, this membrane becomes thickened by inflammatory cells, collagen and blood vessels. In infection, in which microbial colonization of the prosthesis occurs at the time of implantation or thereafter (e.g. as a result of haematogenous seeding), a low inoculum appears to be sufficient. The presence of a foreign body, the prosthetic joint, and the formation of a biofilm contribute to the susceptibility to infection. The responsible pathogens attach to the devices by proteinaceous cell wall and capsular polysaccharide-associated adhesins and remain subsequently protected from antibiotics and the host immune response by secreted biofilms.

The *clinical scenarios* of PJI depend upon the time of infection, similar to the pathogenesis, summarized in Table 1 [4].

More recent studies reported a shift from acute/early to more chronic/late PJI, reflecting changes in surgical practice, including the use of prophylactic antibiotics and improvements in the operating room environment [3].

Preoperative workup

Preoperative diagnosis of PJI relies on clinical history, physical examination and investigations including serum markers of inflammation [white blood cell count, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR)], joint aspiration and several imaging modalities (Table 2).

A thorough evaluation of medical and surgical history as well as physical examination is an excellent screening tool for PJI and helps guide subsequent diagnostic evaluation.

Establishing the presence of acute infection or, in the presence of a sinus tract communicating with the prosthesis, chronic infection, is rather uncomplicated. Furthermore, the diagnosis of PJI is straightforward in some patients in whom joint aspiration is diagnostic and the clinical signs of infection are obvious. The most challenging diagnostic situation, however, is a persistent slight elevation of the CRP level or persistent pain after surgery. In these circumstances, the distinction between delayed infection and failure related to prosthetic wear debris can be very difficult.

Acute phase reactants must be interpreted cautiously in patients with coexistent chronic inflammatory rheumatic diseases that can produce the same response. In addition, a normal ESR or CRP level does not completely rule out a low-grade infection, although false-negative results may occur in patients who have been treated with antibiotics or present with indolent delayed-onset infection [5].

If blood cultures are not positive, joint aspiration may allow confirmation of the diagnosis [6].

Finally, due to substantial lack of any definite preoperative tests for detecting PJI with high certainty, a variety of imaging modalities (such as radiological and nuclear

Table 1 Classification schemes of PJI (including pathogenesis and clinical presentations)

Classification according to the route of infection	Pathogenesis	According to the onset of symptoms	Microorganisms
Perioperative	Inoculation of microorganisms into the surgical wound during implantation or immediately thereafter	Early PJI (< 3 months): acute onset of symptoms with fever—systemic symptoms—wound secretion, typical for surgical site infection	> ¾ staphylococci; other gram-pos. species; gram-neg. bacilli
		Delayed PJI (3–24 months): prolonged indolent course with a subtle presentation, persistent joint pain, mimicker of aseptic condition	Low-virulence organisms such as CNS and *Propionibacterium acnes*
Contiguous	Wound contamination due to penetrating trauma (open fractures) or from an adjacent focus of infection (skin and soft tissue lesions)	Delayed PJI (3–24 months): subacute presentation with sometimes sinus tract formation, prolonged wound secretions	Low-virulence organisms such as CNS and *Propionibacterium acnes*; gram-neg. rods
Haematogenous	Microbial spread through blood or lymph from a distant focus of infection (e.g. skin, lung, dental & urinary tract)	Late PJI (> 24 months): acute onset of symptoms of infection in a previously well-functioning joint	> Staphylococci (*S. aureus* in 50%), *Escherichia coli*, polymicrobial and exotic organisms

CNS coagulase-negative staphylococcus

medicine techniques) have been developed for further evaluation of the suspected PJI [2].

Imaging techniques and features

Nuclear medicine compared to radiographic techniques

Plain radiographs should always be performed for the evaluation of the painful arthroplasty. Radiographic findings such as radiolucency, osteolysis and migration are observed in both infection and aseptic loosening and, therefore, they may be neither sensitive nor specific for diagnosing PJI. Periosteal new bone formation or an adjacent soft tissue collection are highly suggestive of infection but are infrequently present. In the early stages of infection plain radiographs will be normal in appearance. Plain radiographs, therefore, have the greatest utility when serial studies are performed over time. They often demonstrate loosening of the prosthesis in delayed-(onset) infections, but signs of loosening are usually absent in patients with early-(onset) and acute-(onset) haematogenous infections. Finally, conventional radiographs can rule out other conditions such as dislocation and periprosthetic fractures [7].

Ultrasonography may detect the presence of periprosthetic collections and joint effusions around the prosthesis and can be used to guide joint aspiration and drainage procedures. It is especially helpful in prosthetic hip infection in which effusion cannot be clinically diagnosed [7].

Cross-sectional imaging techniques, such as *computed tomography* and *magnetic resonance imaging*, are of limited value in the presence of metallic prosthetic implants owing to beam hardening and dephasing artefacts [7]. Nevertheless, advances in multidetector CT and several MRI techniques have improved the image quality by further minimizing metallic artefacts. MRI displays greater resolution for periprosthetic soft tissue abnormalities than CT or radiography. On the other hand, CT is useful in detecting joint effusion, sinus tracts, soft tissue abscesses, bone erosion and periprosthetic lucency, especially in the case of total hip arthroplasty. In addition, similarly to ultrasonography, it may assist in guiding joint aspiration and selecting the surgical approach [4, 7].

Radionuclide imaging, which is, in general, not affected by metallic hardware, is the current imaging modality of choice for evaluation of suspected joint replacement infection [2]. The two oldest radionuclide imaging modalities used for this purpose are bone scintigraphy (BS) and gallium citrate scintigraphy [8] (Table 3).

Bone scintigraphy BS is widely available, relatively inexpensive, easily performed and rapidly completed. Uptake of bone-seeking tracers such as ^{99m}Tc-labelled diphosphonates MDP or HDP, which accumulate on the surface of the bone mineral matrix, depends on blood flow and especially on the rate of new bone formation [9]. The main reason is that accumulation of labelled diphosphonates occurs inconsistently in periosteal new bone. Moreover, uptake of those bone-seeking radiopharmaceuticals is also well known in areas of sterile inflammation, such as osteolysis induced by polyethylene wear debris. Also, any cause of accelerated new bone formation, including postoperative physiological bone remodelling, as well as pathological conditions such as fracture, heterotopic ossification, aseptic loosening and infection all may present as increased periprosthetic activity on BS. Subsequently, tracer uptake around the prosthesis greater than the background level can occur as a physiological

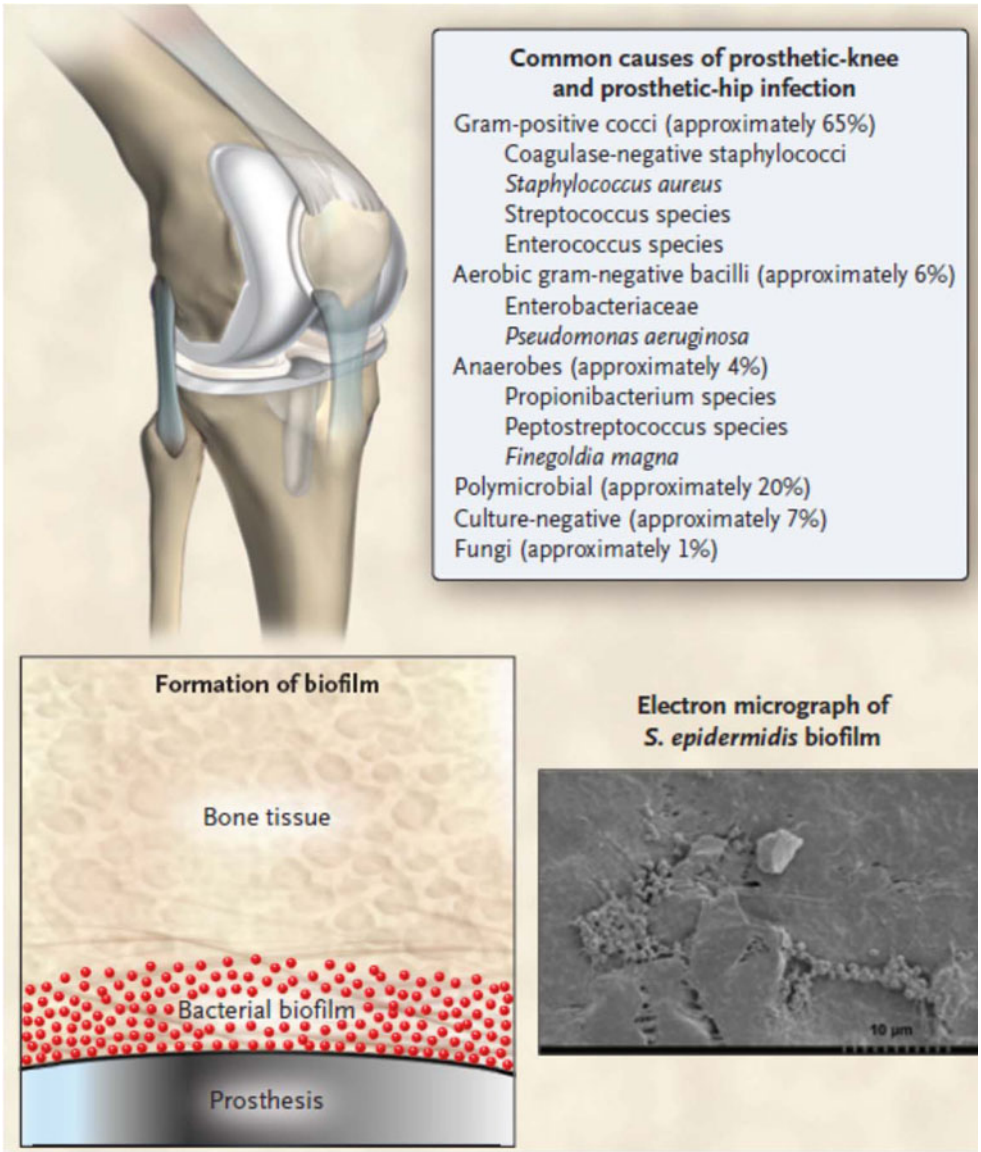

Fig. 1 Causes of infection associated with prosthetic joints. There are two basic pathogenetic concepts of PJI. PJI related to surgery including a small number of otherwise non-virulent bacteria contaminating the implant during surgery and persisting as a biofilm despite a functional immune system and antimicrobial treatment. Secondly, haematogenous PJI whereby bacteria invade into the sterile encapsulated joint space through a process of bacteraemia, acquired from any remote infectious process in the body elsewhere. Commonly and less frequently isolated microorganisms are shown (adapted with permission from [132])

Table 2 Preoperative and intraoperative non-imaging tests for the diagnosis of PJI

Category	Diagnostic tests	Caveats
Preoperative		
Haematological tests	White blood cell count and differential ESR, CRP and/or combination testing	Neither sensitive nor specific tests can remain elevated for several months; CRP level returns to the preoperative level within 2 months; cut-off levels of both ESR and CRP seems to be most useful
Synovial fluid aspiration	White blood cell count and differential; gram stain and culture; IL-6	A critical point to obtain such positive cultures is to strictly avoid any antimicrobial therapy before sampling fluids for microbiological analysis
Intraoperative		
Periprosthetic tissue	Histopathology; gram stain and culture	Broad-range PCR is an innovative procedure but is not routinely incorporated
Explanted prosthesis	Sonication; culture	

PCR polymerase chain reaction

Table 3 Radiotracers used for imaging PJI

Non-specific radiotracers for imaging of PJI	Specific radiotracers for imaging of PJI
• ^{67}Ga-citrate	• Antibiotics such as quinolone family (SPECT or PET)
• In vitro labelled leucocytes (^{111}In, ^{99m}Tc)	• Antimicrobial peptides such as UBI (SPECT or PET)
• Antigranulocyte antibodies or fragments (^{99m}Tc)	• Bacteriophages (SPECT)
• Human immunoglobulins (^{111}In, ^{99m}Tc)	• Thymidine kinase (PET)
• Liposomes (^{111}In, ^{99m}Tc)	
• Biotin (^{111}In)	
• Cytokines such as IL-8 (^{99m}Tc)	
• Chemotactic peptides such as LTB_4	
• Apoptosis markers such as annexin V (^{99m}Tc)	
• ^{18}F-fluorodeoxyglucose (FDG)	
• ^{18}F-FDG-labelled WBCs	
• ^{18}F-fluorine	
• Other PET tracers such as ^{68}Ga, ^{64}Cu, ^{124}I	

response for several months following joint replacement. Therefore, any new bony uptake (focal or diffuse) around a prosthesis can be caused by both septic and aseptic loosening. Persistent uptake more than 12 months after surgery is usually abnormal; however, in clinical practice, tracer uptake is known to persist for an even longer period of time. In general BS is highly sensitive but not very specific as it cannot differentiate between infection and aseptic loosening (Figs. 2 and 3).

Moreover, the data in the literature about its diagnostic efficiency show a considerable variability and to some extent, this inconsistency is caused by several factors, such as (1) the use of different scan interpretation criteria (quantitative analysis versus qualitative approach), (2) performing a three-phase study instead of only a delayed bone scan, (3) the type of prosthesis (knee versus hip, cemented versus cementless, old versus new ones) affecting both the degree and the pattern of periprosthetic bone uptake, and last but not least, (4) the fact that during the first year after implantation, when nearly two thirds of all PJIs occur, periprosthetic bony uptake is so variable that only a completely normal BS, which in clinical practice is uncommon, provides us useful information [10–19]. Nonetheless, BS is more sensitive than plain radiographs [20]. Lieberman et al. suggested, therefore, that BS is useful only when conventional radiography is inconclusive [21]. Others have suggested that the role of BS should be limited to that of a screening test, or that it should be performed as a part of a combined study with gallium or labelled leucocyte scintigraphy (Table 4).

Sequential bone/gallium scintigraphy In an effort to enhance the radionuclide diagnosis of PJI, ^{67}Ga-citrate scintigraphy (GS) often is improved in addition to BS and the two studies are interpreted together using standardized

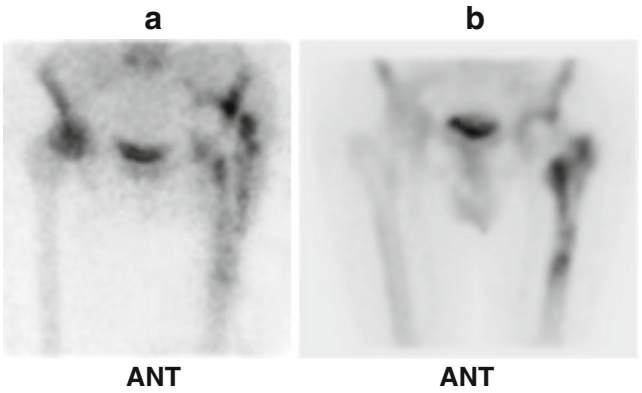

Fig. 2 **a** Infected 3-year-old cementless revised left hip prosthesis. There is diffusely increased activity around the femoral component of the prosthesis. Intraoperative cultures grew *S. aureus*. **b** Aseptically loosened 4-year-old cementless left hip prosthesis. There is diffusely increased activity around the femoral component of the prosthesis. Compare with **a**. Periprosthetic uptake patterns on bone scans do not reliably differentiate between infection and aseptic loosening

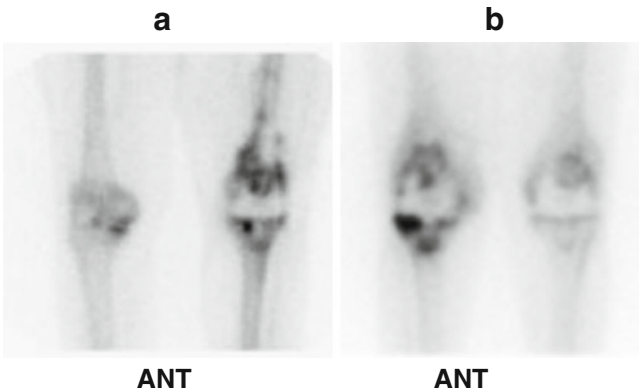

Fig. 3 **a** Aseptically loosened 6-year-old knee prostheses. Note the striking bony uptake around the left knee prosthesis, compared to the right. **b** One-year-old infected right knee prosthesis. Intraoperative cultures grew *S. hominis*. Periprosthetic uptake pattern is virtually indistinguishable from that in Fig. 3a

Table 4 Interpretation criteria, advantages and disadvantages of radionuclide imaging techniques for PJI

Imaging technique	Interpretation criteria	Advantages	Disadvantages
(Three-phase) bone scintigraphy	1. Quantitative versus semi-qualitative analysis 2. Technique used (three-phase scan or only delayed bone scan)	Sensitive, high NPV, screening tool, easily performed, widely available, cheap	Low specificity, low accuracy, not useful within 1 year postoperatively
Sequential bone/gallium scintigraphy	Uptake congruency of the spatial distribution and intensity	Improved specificity versus bone scan alone, use in neutropenic patients	High additional radiation dose of 18 mSv, many equivocal cases, not widely performed
In vitro leucocyte and/or bone/marrow scintigraphy	1. Quantitative versus semi-qualitative analysis 2. Uptake congruency of the spatial distribution and intensity 3. Serial or delayed imaging	Highly sensitive and specific when combined with sulphur colloid imaging	Additional radiation dose, discomfort and inconvenience for the patient, laborious—risk of blood handling— not useful in neutropenic patients, expensive especially when combined
Antigranulocyte scintigraphy	1. Quantitative versus semi-qualitative analysis 2. Serial or delayed imaging	In vivo imaging method (use of kits)	AGS overall lower accuracy compared to in vitro LS, expensive, possibility for allergic reaction, not widely practised, role in prosthetic joint imaging not yet fully established
[^{18}F]FDG PET and/or PET/CT	1. Quantitative versus semi-qualitative analysis 2. Several FDG uptake patterns available in the literature	Highly sensitive for the inflamed prosthetic joint, improved spatial resolution especially when combined with CT, fast imaging technique	Limited specificity for infection, not useful within 1 year postoperatively, attenuation artefacts (metallic implants), lower accuracy for knee prostheses, expensive technique, not widely available, role in prosthetic joint imaging not yet fully established
SPECT/CT	Coregistered analysis of the images	Improved specificity versus SPECT alone, can differentiate between bone versus soft tissue infection	Attenuation artefacts (metallic implants), often low counts of in vitro leucocyte/gallium studies, role in prosthetic joint imaging not yet fully established

NPV negative predictive value

criteria [22–24]. Since both gallium and diphosphonates are bone-seeking radiopharmaceuticals, ^{67}Ga-citrate is not accurate enough to image PJI. Similar to diphosphonates, gallium also accumulates not only in infection, but also in the postoperative patient, in heterotopic or periosteal new bone formation, aseptic loosening, fractures and even granulomatous reaction to prosthetic cement [24, 25]. Images are therefore interpreted by established criteria comparing congruity of the spatial distribution and intensity of the two scans. Although sequential BS/GS, with an accuracy ranging from 65 to 80%, provides somewhat better results than BS alone, it seems to be of limited value for diagnosing PJI, also in combination with a number of drawbacks inherent to ^{67}Ga-citrate [14, 24, 26, 27] (Fig. 4).

Labelled leucocyte scintigraphy (LS) Targeting leucocytes that migrate to sites of infection and inflammation may represent the single most important achievement in radionuclide diagnosis of infection to date. Commonly used tracers include ^{111}In-oxine and ^{99m}Tc-hexamethyl propyleneamine oxime (HMPAO). The introduction of in vitro labelled autologous leucocytes has dramatically improved the accuracy of the radionuclide diagnosis of PJI [28–30]. Labelled leucocytes do not accumulate at sites of increased bone turnover or remodelling in the absence of infection. Uptake of labelled cells depends on intact chemotaxis, the number and type of cells labelled, and the principal cellular component of a given inflammatory response [31]. Since circulating neutrophils are predominantly labelled and neutrophils are inconsistently present in the infected prosthetic joint, LS is the gold standard for imaging this purpose. Moreover, at least in theory, LS is particularly well suited to distinguish between the infected prosthesis and the inflamed aseptically loosened prosthesis, in which neutrophils are generally absent [31–34] (Fig. 5).

Some investigators reported that the technique was sensitive, but not specific, while other investigators found that the test was specific, but not sensitive. These relatively unsatisfactory results reported for LS, performed as the only radionuclide imaging technique, have been attributed to several factors, such as (1) the presence of a chronic or low-grade infection with fastidious microorganisms and the presence of a biofilm around the infected prosthesis (decreasing its sensitivity) [35, 36], (2) the possible negative

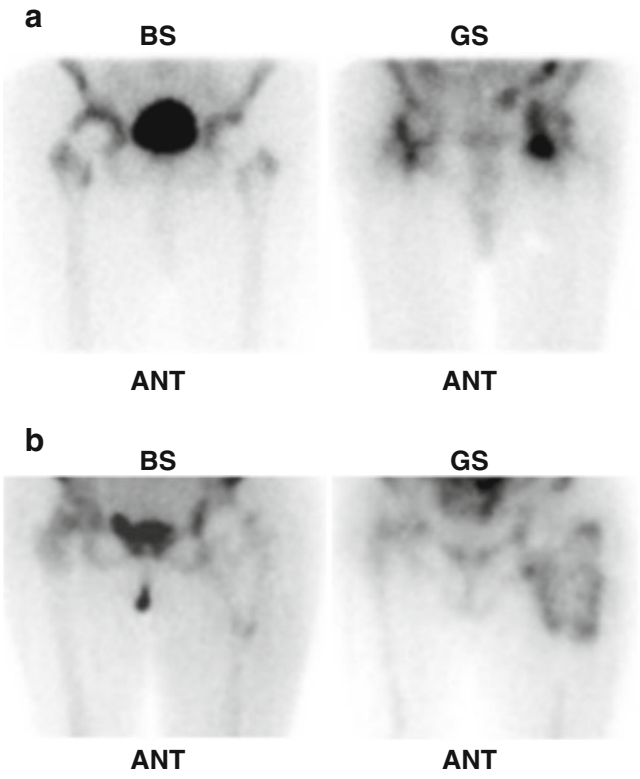

Fig. 4 **a** Bilaterally infected 10-year-old cementless hip prostheses. The distribution of activity on the bone and gallium images is spatially incongruent and the combined study is (true) positive for infection. Intraoperative cultures grew *S. aureus*. **b** Aseptically loosened 3-year-old cemented left total hip replacement. Periprosthetic uptake on the gallium study is similar in distribution to that on the bone scan, but is much more intense and the combined study is (false) positive for infection. Combined bone/gallium imaging is only slightly more accurate than bone imaging alone for diagnosing PJI

influence of administered antibiotics (decreasing its sensitivity) [37], (3) the non-specific inflammation in the neighbouring soft tissues (decreasing its specificity), (4) the interfering problem of ectopic bone marrow present in the appendicular skeleton, particularly induced by prosthetic surgery (decreasing its specificity) [38–41], and last but not least (5) the inability to develop a generally accepted acquisition protocol in combination with the lack of a satisfactory analysis method for interpretation of the images [2, 42, 43].

Moreover, the cell labelling technique is labour intensive, requires appropriately trained staff and there is handling of blood products which entails a risk for contamination. Finally, in neutropenic patients there may also be too few leucocytes available for harvesting and for labelling.

Conventional radionuclide imaging: enhanced techniques

Therefore, to overcome those limitations of in vitro LS, for many years, a combination of two or even three radiopharmaceuticals and/or modifications of the scanning protocol have (largely) been adopted in clinical practice (Table 4).

Leucocyte/bone scintigraphy The combination of BS and LS did not significantly improve accuracy, as expected. Diagnostic criteria for a positive study were non-congruent bone and leucocyte uptake, either in spatial distribution or in intensity [44] (Fig. 6).

In the largest retrospective study on suspected hip prostheses comprising 116 patients, Teller et al. found, besides a lower sensitivity of 64% and a *moderate high* specificity of 78%, that a positive ^{111}In LS only increased the likelihood of infection from 14 to 30%, although negative results decreased the likelihood to 7% [45].

Leucocyte/bone marrow scintigraphy (BMS) Because leucocyte uptake around prostheses can be secondary to bone

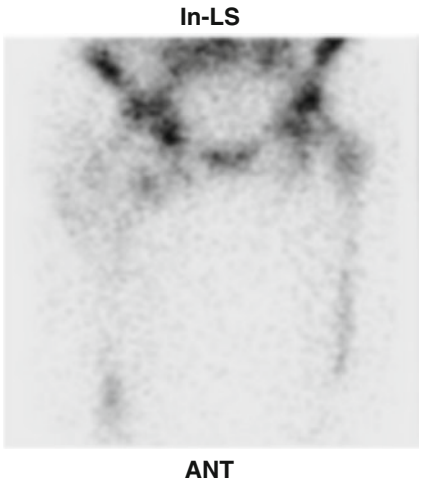

Fig. 5 Infected right hip prosthesis, suspected on bone scan (not shown). The indium-labelled leucocyte study is unremarkable and therefore the study is negative for infection

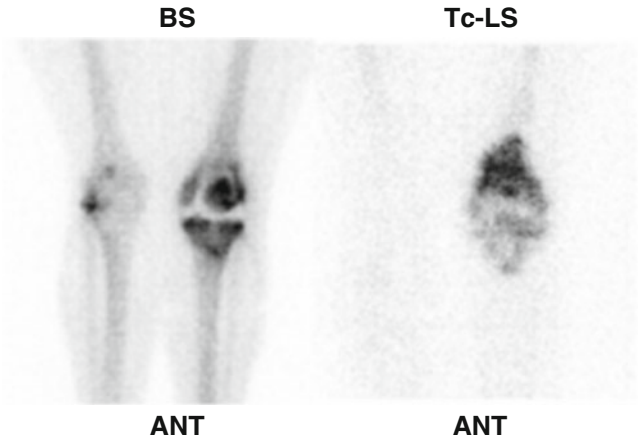

Fig. 6 Infected 5-month-old left knee replacement. The distribution of activity around the prosthesis on the bone and Tc-labelled leucocyte images is spatially incongruent, the usual criterion for infection

marrow displacement or activation by surgery, the combination of LS and BMS with ^{99m}Tc-sulphur colloid has been introduced [46]. The principal of combined LS/BMS is thus based on the fact that LS and BMS both reflect radiotracer accumulation in the reticuloendothelial system of the marrow [38]. While the distribution of marrow activity is similar on LS and BMS in normal individuals and in those with underlying marrow abnormalities, on the other hand in osteomyelitis, LS and BMS are not similar due to the fact that infection stimulates uptake of leucocytes but suppresses uptake of sulphur colloid. Therefore, LS and BMS are spatially incongruent in PJI [31] (Fig. 7).

Over the years the results of LS/BMS, with few exceptions, have been remarkably consistent, with reported accuracies ranging from 86 to 98%. In most of the LS/BMS series reported to date, leucocytes have been labelled with ^{111}In-oxine. Recent data, however, suggest that comparable results can be achieved using leucocytes labelled with ^{99m}Tc-HMPAO [11, 46–51].

Late leucocyte scintigraphy Some investigators have found that the accuracy of LS for diagnosing PJI is improved by performing early and *late* imaging. Larikka et al. reported improved sensitivity (83 vs 50% and 100 vs 87% for hip and knee prostheses, respectively) and specificity (100 vs 90% and 82 vs 77% for hip and knee prostheses, respectively) by comparing early (4–6 h) and late (20–24 h) ^{99m}Tc LS [35, 36]. Fernandez et al. came to similar conclusions, in a study with 49 prosthetic joint implants. Those results show again an improvement of specificity (87 vs 72%) and also a greater inter-observer reproducibility, for 4-h/24-h compared to 4-h ^{99m}Tc LS [52] (Fig. 8).

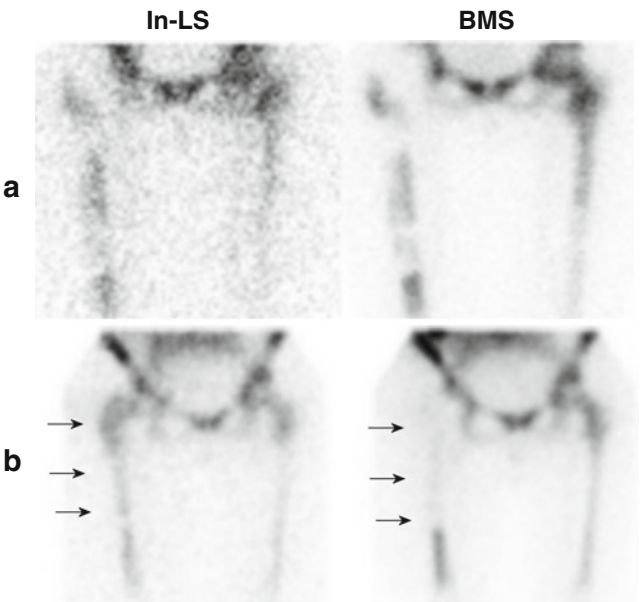

Fig. 7 **a** Aseptically loosened right hip replacement. The distribution of activity around the prosthesis on the labelled leucocyte (*left*) and sulphur colloid (*right*) images is spatially congruent, and the combined study is negative for infection. **b** Infected right hip replacement. There is activity around the femoral component on the labelled leucocyte study (*left*). On the bone marrow image (*right*), however, activity is present only distal to the tip of the prosthesis. The distribution of activity on the labelled leucocyte and sulphur colloid images is spatially incongruent (*arrows*), and the combined study is positive for infection

Serial time point or multiphase leucocyte scintigraphy - Other investigators have used dual or serial time point LS as a surrogate for BMS. The hypothesis is that early leucocyte images reflects white blood cell uptake in marrow, since neutrophil uptake in the bone marrow, as in the spleen, is immediate and the result of extensive physiological margination in sinusoids, while the late leucocyte images reflect white blood cell uptake in infection [53, 54]. Subsequently, incongruence between early and late images, analogous to conventional LS/BMS, is indicative of infection.

Pelosi et al. studied the accuracy of a serial time point (50 min, 4 h and 20 h) imaging protocol with ^{99m}Tc LS in 78 patients suspected of having infected hip-knee arthroplasties. They found that the accuracy of the technique, using visual analysis, was about 75%. Using semi-quantitative analysis, considering a 10% up ratio positive for infection, the accuracy improved to about 95% [55]. Simonsen et al. retrospectively reviewed 76 painful hip prostheses studied with ^{99m}Tc LS and found in agreement with Pelosi et al. that serial (LS) imaging improved the accuracy of the technique [56].

In vivo labelled leucocyte scintigraphy or antigranulocyte scintigraphy (AGS) Reducing or eliminating the need for a separate bone marrow study would be an improvement over combined LS/BMS, but there are other limitations to the technique as well, responsible in some part to the fact that LS/BMS is not widely used in clinical practice and the poor availability of sulphur colloid in Europe. Considerable

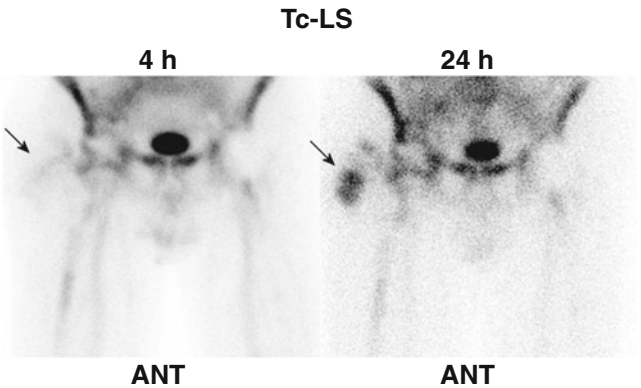

Fig. 8 Infected right hip replacement: 4-h (*left*) and 24-h (*right*) labelled leucocyte images. The abnormal labelled leucocyte activity (*arrows*) is seen clearly only on the later images

efforts, therefore, have been devoted to developing in vivo methods of labelling leucocytes with promising results (Table 4).

Granuloscint/Scintimun® and sulesomab/LeukoScan® are a murine whole monoclonal G1 immunoglobulin and, on the other hand, a 50-kDa fragment antigen binding (Fab′) portion, that bind respectively to the non-specific cross-reacting antigen (NCA) 95 and NCA 90 present on activated leucocytes [57]. The technique involves injection of a prepared agent (kit) into the patient relying on in vivo trafficking of leucocytes. Therefore, similarly to in vitro labelled leucocytes, both radiopharmaceuticals are proposed as promising agents for imaging of inflammation and infection. The results of these agents for diagnosing PJI, however, have been variable [58–63].

Similarly to in vitro LS, some investigators have also made adaptations to the scanning protocol of AGS, in order to improve the specificity of this modality [64–67] (Fig. 9).

SPECT/CT bone, leucocyte and gallium imaging modalities

The main drawback of radionuclide imaging is the limited spatial resolution and subsequently the poor anatomical detail compared to morphological modalities, such as CT and MRI [7, 68].

A complicated matter in conventional nuclear medicine studies is the absence of anatomical landmarks for delineating the pathological process and for differentiating soft tissue from bone infection, for example differentiating soft tissue involvement from deep-seated prosthesis infection. It is well known that single photon emission computed tomography (SPECT) enables more exact localization of the radiotracer uptake than is afforded by planar imaging alone, resulting in greater specificity [69]. Van Acker et al. and Vanquickenborne et al. investigated the possible role of performing LS SPECT and/or BS SPECT in the setting of the painful knee arthroplasty as well as infected hip prostheses. In both reports, they concluded that performing LS/BS with additional SPECT did indeed increase the accuracy in detecting PJI [70, 71] (Fig. 10).

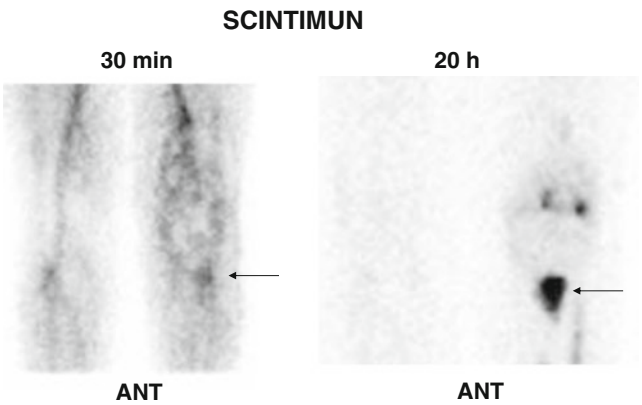

Fig. 9 Infected left knee replacement after revision of the tibial component 1 year earlier. Antigranulocyte antibody scintigraphy: on the early image (30 min p.i.) there is faint focal labelled granulocyte activity at the proximal tibia (*arrow*) and mild diffuse labelled granulocyte activity in the synovium of the knee joint; but on the 20-h image, there is persistent but now intense focal uptake at the proximal tibia (*arrow*), probably localized in the soft tissues near the prosthesis itself, indicating an infected knee prosthesis

These difficulties have been overcome, to a great extent, with the introduction of in-line SPECT/CT systems [72, 73]. The contribution of SPECT/CT with LS or ^{67}Ga-citrate scintigraphy has been evaluated in a variety of clinical indications, demonstrating a definite added value in distinguishing physiological uptake of labelled leucocytes from infectious processes and defining the precise anatomical location of infection in up to 85% of cases [72, 74].

First clinical studies with this integrated hybrid machine in the field of infection and inflammation and in some part of PJI imaging are very promising. In patients with osteomyelitis, LS SPECT/CT can also detect areas of tracer accumulation in surrounding soft tissues, thus defining the precise extent of infection with ensuing relevant clinical impact on patient management. Horger et al. were the first to demonstrate in patients with suspected chronic post-traumatic osteomyelitis imaged with ^{99m}Tc-AGS SPECT/CT, compared to SPECT, that the specificity improved substantially (89 vs 78%) while the sensitivity remained equal. They concluded that ^{99m}Tc-AGS SPECT/CT was therefore of clinical relevance in selecting patients for surgery [75].

In another study, Filippi and Schillaci investigated the value of additional SPECT/CT to ^{99m}T LS in 28 patients with suspected bone (n=15) and joint infections (n=13). They showed that SPECT/CT allowed a correct diagnosis of prosthesis versus soft tissue involvement in five of seven patients with a hip prosthesis. In two of six patients with knee prostheses SPECT/CT correctly localized leucocyte uptake in the synovium and therefore could reliably exclude a PJI [76].

^{18}F-Fluorodeoxyglucose positron emission tomography: current role in PJI

In recent years, ^{18}F-fluorodeoxyglucose positron emission tomography (FDG PET) has been used successfully for assessing a multitude of malignant disorders. FDG, however, also accumulates at the sites of infection and inflammation, including those of the musculoskeletal system [77].

FDG PET has a number of advantages over conventional radionuclide imaging modalities such as LS/BMS or BS/GS of showing no physiological bone marrow uptake [78, 79]. In addition, the PET technique inherently provides high-quality images with improved spatial resolution and imaging is completed within a reasonably short time of 2–3 h [79]. In addition, PET/CT combines PET with a low or

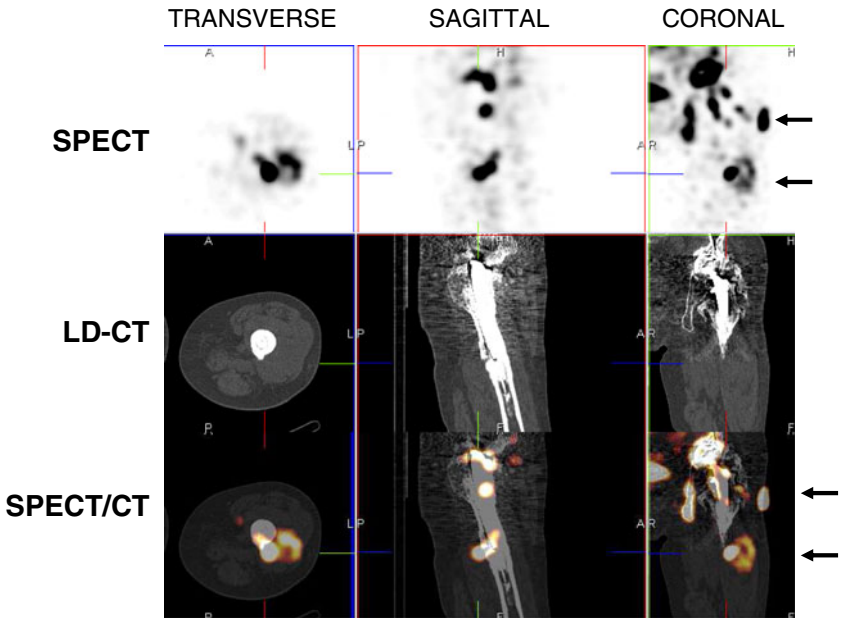

Fig. 10 LS SPECT/CT, performed at 4 h p.i., shows pathological activity at the prosthesis proximal part, the presence of a chronic fistulization in the upper thigh (*arrow*) and an abscess collection near the distal part of the femoral shaft (*dashed arrow*), indicating a chronic infected hip prosthesis. Combining SPECT/CT fusion images enhances the exact localization and, in particular in this case, the extent of the inflamed tissues, probably more accurately than SPECT alone. Subsequently, the orthopaedic surgeon can be prepared for an extended treatment strategy. Finally, note the presence of metal artefacts, generated on the low-dose CT

conventional dose CT scan and provides excellent anatomical correlation of any areas of uptake which increases the accuracy compared to PET alone. Therefore, FDG PET and PET/CT are emerging as important imaging modalities in the management of patients with painful arthroplasty [80].

Published results on the role of FDG PET for diagnosing PJI are however inconclusive due to several factors, such as (1) the lack of uniform interpretation criteria used (quantitative versus qualitative approach by means of standardized uptake values or SUV), (2) different FDG uptake patterns and interpretation criteria, (3) the fact of generating artefacts inherent to the material used as well as introduced by the PET technique and the coregistered CT portion, (4) the important role of activated leucocytes in the inflamed prosthesis, such as neutrophils and macrophages, and the fact that glucose consumption can be even higher in activated macrophages, and (5) the postoperative remodelling conditions involved in arthroplasty surgery and subsequently a-specific FDG periprosthetic uptake up to 6 months after insertion, similarly to conventional tracers [16, 17, 43, 49, 70, 71, 81–86] (Figs. 11, 12 and 13, Table 4).

Investigational/experimental tracers

Interleukin-8 Small diffusible molecules, such as small proteins and peptides, which can readily cross the activated endothelium, are used for the development of new tracers including radiolabelled chemokines and cytokines, respectively targeting circulating and migrating neutrophils, lymphocytes and mononuclear cells [87]. One of them is the acute phase cytokine, interleukin-8 (IL-8). Initial clinical investigations with ^{99m}Tc-labelled IL-8 in patients with various infections have recently been reported. The sensitivity, specificity and accuracy were 83, 100 and 90%, respectively, and there were no adverse events [88]. These results are encouraging, but the value of this agent in PJI is not known.

^{111}In-Biotin scintigraphy is based on the non-specific accumulation of biotin at sites of infection, partly linked to increased transcapillary leakage of macromolecules and to interstitial oedema at these sites [89]. On the other hand biotin, known as vitamin H, is a compound of low molecular weight and it is suggested that biotin is partly utilized by growing bacteria at the

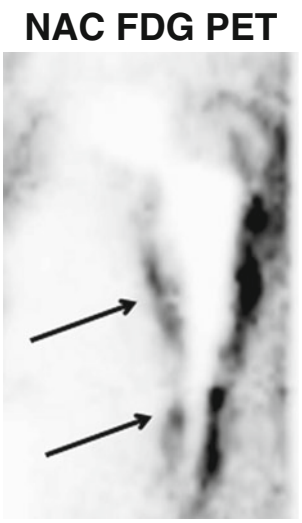

Fig. 11 Aseptically loosened left hip prosthesis. On non-attenuation-corrected FDG PET image, bone-prosthesis interface uptake (*arrows*) can be associated with aseptic loosening and/or inflammation, instead of infection

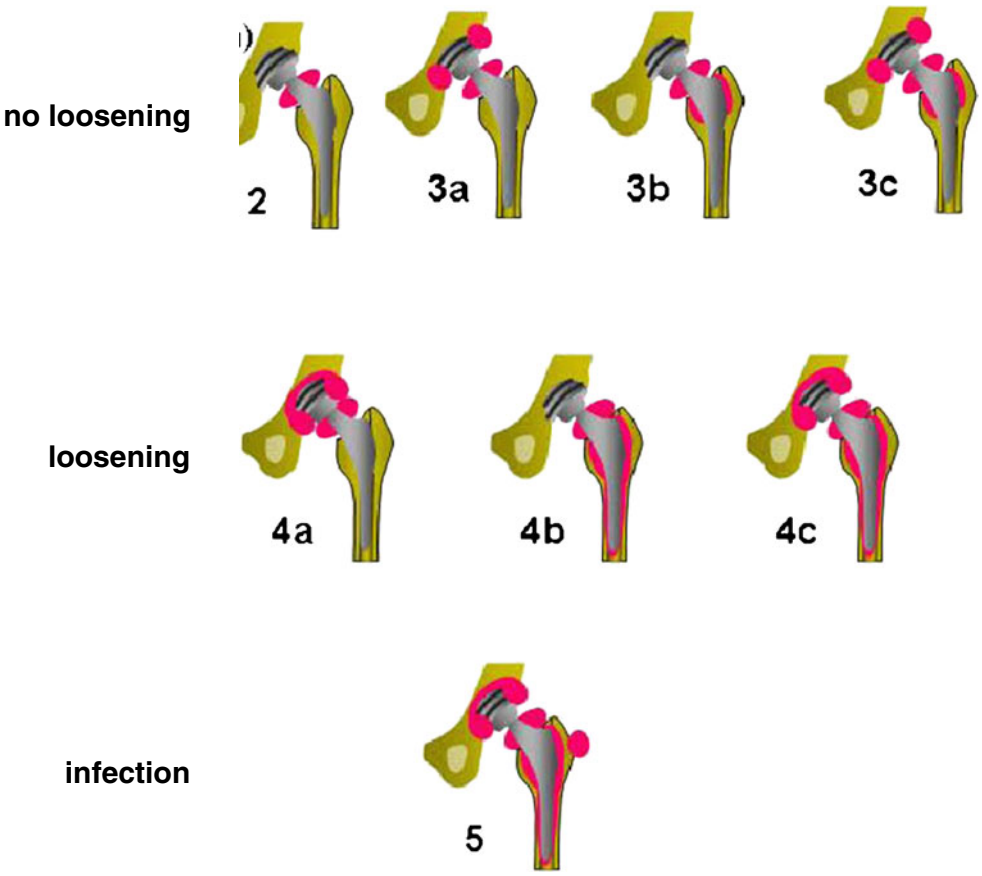

Fig. 12 Qualitative analysis of FDG uptake according to the classification system of Reinartz et al. demonstrate several patterns differentiating PJI (type 5) from aseptic loosening (type 4), physiological remodeling (types 2–3), and normal findings (type 1, no uptake, not shown), in patients scanned with an interval of 6 months after hip arthroplasty (adapted with permission from [17])

site of infection according to the rate of their metabolism [90, 91]. Therefore, biotin is now used as a single agent as ^{111}In-biotin for imaging infection and inflammation [92].

Annexin V scintigraphy Radiolabelled annexin V is a marker of apoptosis and cellular stress or activation and has already been used as a non-invasive tracer for detection of acute, subacute and chronic inflammation in several animal models and humans. In a preliminary study of seven patients undergoing revision surgery for hip (n=5) or knee (n=2) prostheses, Lorberboym et al. reported for the first time on ^{99m}Tc-recombinant annexin V scintigraphy [93]. They found four true-positive, two true-negative and one false-positive annexin V images. They also found that annexin V

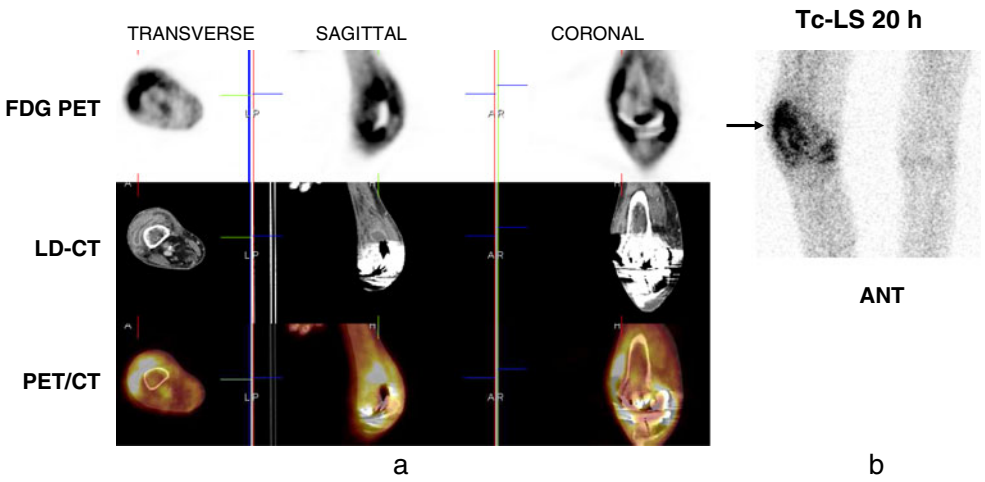

Fig. 13 Infected 4-month-old right knee replacement. Patient with persistent elevated inflammatory parameters after recent total knee arthroplasty was sent for both dedicated PET/CT (**a**) and LS (**b**). Both studies were rather congruent, namely diffuse pathological uptake around the soft tissues and the knee joint, probably indicating an acute infected knee arthroplasty. Intraoperative findings revealed gross purulence and cultures grew *S. aureus*. Note again, similarly to SPECT/CT, the presence of metal-induced CT artefacts. Performing a PET/CT study was, in this particular case, not contributive

uptake in the periprosthetic region is more common and intense in infected prostheses than in aseptic loosening [93].

Infection-specific tracers Among the myriad of radionuclide imaging techniques currently available, none truly is specific for infection, and the search continues for new and better agents [94]. Radiolabelled antibiotics have been investigated for their potential as "infection-specific" tracers [95]. Initially there were promising results with ^{99m}Tc-Ciprofloxacin for diagnosing prosthetic hip and knee infection [96–98].

In contrast, results of in vitro binding, animal and clinical studies reported that ^{99m}Tc as well as ^{18}F-Cipro was not specific for bacterial infections and that, although it was sensitive, the technique could not reliably differentiate the infected from the aseptically loosened joint replacement [99–102]. Recently this non-specificity was demonstrated in a single-centre, phase II, prospective clinical trial comparing ^{99m}Tc-Cipro versus combined LS/BMS [103] (Fig. 14).

Antimicrobial peptides play a critical role in the biological defence system of multicellular organisms [104]. They are produced by various cells, including phagocytes, endothelial and epithelial cells and bind to the bacterial cell membrane. Their expression may be constant or induced on contact with microbial organisms; they also may be transported to sites of infection by leucocytes [105]. Radiolabelled synthetic fragments of ubiquicidin (UBI), a naturally occurring human antimicrobial peptide that targets bacteria, possess the ability to differentiate infection from sterile inflammation [106]. Moreover, it seems to be that the amount of radiolabelled UBI 29-41 uptake depends on the number of viable bacteria present at the site of infection, but results of recent data, performed in animal models of several infections

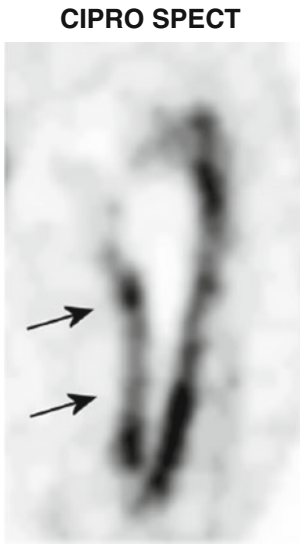

Fig. 14 Aseptically loosened left hip replacement. There is diffuse periprosthetic activity (*arrows*) on the Tc-ciprofloxacin image and the study is false-positive for infection (same patient as illustrated in Fig. 11)

(including PJI), are more controversial [107–111]. Nevertheless, first studies of this agent for diagnosing PJI in humans are encouraging [112].

Another application of a potential infection-specific imaging agent is the introduction of radiolabelled *bacteriophages* which are specific for bacterial species. The binding mechanism consists of the attachment of the phages to specific surface receptors or domains located on the surface of the bacterium and, subsequently, by transferring their genetic material into the host cell dedicated to phage replication/reproduction [113].

Recently, four ^{99m}Tc-labelled bacteriophages against different microorganisms as potential infection-specific imaging tracers were developed. Unfortunately, only one radiolabelled bacteriophage showed any specificity for its host bacteria, indicating this approach needs major evaluation before further studies can be considered [114].

Finally, another approach is the use of enzymatic substrates of bacterial enzymes. These ligands allow the non-invasive detection of bacteria or viruses by targeting thymidine kinase (TK), whose substrate is distinct from that of the major human TK. Because those uracil nucleoside derivatives are incorporated into bacteria rather than into inflammatory cells, it should be specific for the infectious process, as shown in a pilot study of musculoskeletal bacterial infection in humans [115].

Future applications of hybrid imaging with new radiotracers

Following the introduction of new infection imaging agents, such as antigranulocyte antibodies and fragments, ciprofloxacin and biotin, SPECT/CT has demonstrated definite advantages over single-modality imaging [75, 116].

Although ^{111}In-biotin SPECT/CT has been reported to have a high diagnostic value in imaging spinal infections, Graute et al. were the first investigators to evaluate the value of ^{99m}Tc-AGS SPECT/CT in a homogeneous series of patients with suspected low-grade PJI [117]. In a retrospective study of 31 consecutive patients (mainly knee implants), they found that AGS SPECT/CT made a contribution to the final diagnosis in 7 of 31 patients (23%), compared to only 4 cases (13%) for SPECT alone. Thus, they concluded that additional SPECT/CT could provide accurate anatomical as well as precise information on the extent of the infection. Finally, the number of false-positive studies (planar and SPECT) was reduced to six cases when performing additional SPECT/CT, resulting in a moderate positive predictive value of 57%.

In a preliminary study of using PET/CT in hip prosthesis infections, Chen et al. reported a high sensitivity (100%) but a variable specificity (50–87.5%) in predicting residual infection after insertion of an interim spacer [118]. Although the limitations of FDG in imaging arthroplasty are known, on the other

hand given the high negative predictive value, they concluded that PET/CT can be used to rule out persistent infections [118].

The labelling of leucocytes with ^{18}F-FDG has also been investigated in a variety of infections throughout the body with high sensitivity and specificity [119]. Although the results of ^{18}F-FDG-labelled WBCs in initial clinical investigations, including PJI, were encouraging, there are several disadvantages inherent to this procedure [120]. First of all, the labelling efficiency and stability of FDG-labelled leucocytes is significantly less than that for SPECT ligands (such as ^{111}In-oxine and ^{99m}Tc-HMPAO) and it is evident that blood glucose levels affect this labelling procedure. Furthermore, ^{18}F is far from ideal as a radiolabel, quite apart from the instability of ^{18}F-FDG-labelled leucocytes, its half-life of 110 min does not allow sufficient time for imaging of leucocyte migration [121]. For this reason, in the future ^{64}Cu, which has an optimal half-life of 12.7 h, seems to be more suitable [122].

FDG is not the only tracer used in PET imaging nowadays. In a small study of 14 painful knee arthroplasties, Sterner et al. showed a 100% sensitivity for the detection of early aseptic loosening in total knee arthroplasty using the bone-seeking tracer ^{18}F-fluoride [123]. In a recent prospective study, using ^{18}F-fluoride PET in 65 hip prosthetic joints, Kobayashi et al. found a sensitivity and specificity of 95 and 98% for all cases and a sensitivity and specificity of 95 and 88% for surgically treated cases, by using a new uptake pattern classification system for discerning aseptic from septic loosening (Fig. 15). They concluded for the first time that fluoride PET has considerable potential as a method to differentiate septic from aseptic loosening following total hip arthroplasty, since the uptake pattern classification system is relatively simply performed [124]. This first rather large-scale study of fluoride PET suggests a potential role in imaging the failed prosthetic joint but, nevertheless, more studies are warranted in the future.

Radiolabelled targeting of inflammatory cells such as macrophages has shown some promise. For example, Kropholler et al. used PET to monitor macrophage migration into inflamed areas in rheumatoid arthritis using the ligand PK11195 coupled to a PET tracer, ^{11}C, which binds to benzodiazepine receptors on macrophages [125].

The same limitation, as for ^{18}F-FDG, would apply to ^{68}Ga, a generator-produced radiometal with a half-life comparable to ^{18}F-FDG, namely 68 min. Nevertheless, the availability of this PET tracer from a ^{68}Ge/^{68}Ga generator makes it attractive to use in busy nuclear medicine departments, particularly those with limited access to cyclotrons. Furthermore, the addition of targeting small vascular adhesion molecules (VCAM), a vascular peptide protein 1 (VAP-P1), or even transferrin to ^{68}Ga allows specific targeting of molecules of inflammation and

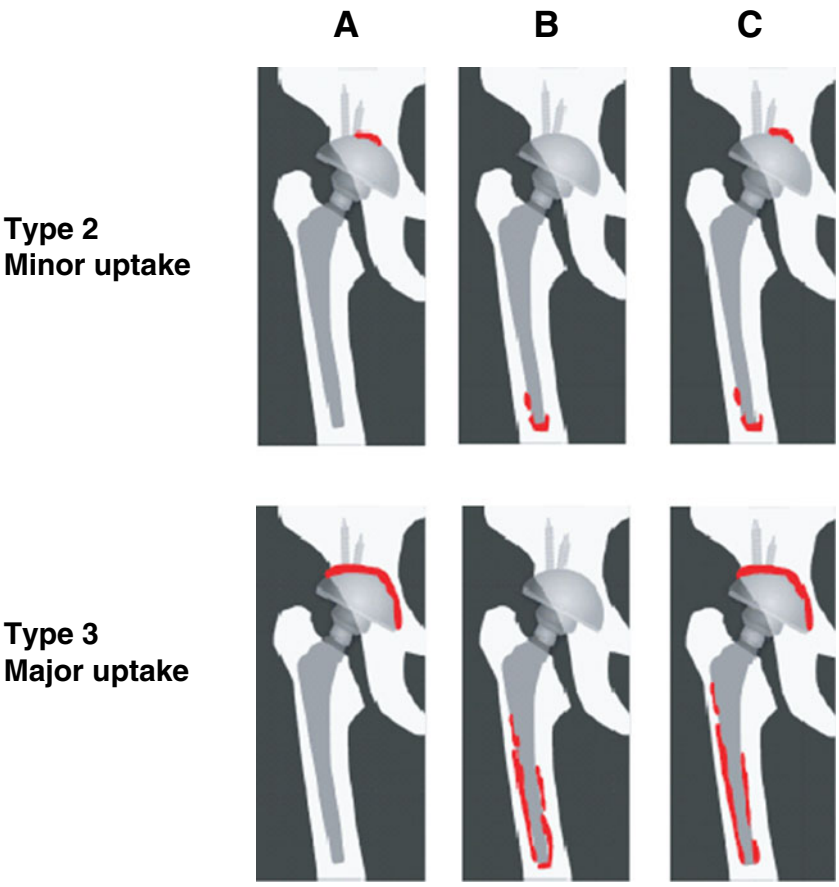

Fig. 15 Qualitative analysis of Fluoride uptake according to the classification system of Kobayashi et al demonstrate several patterns differentiating PJI (type 3, major uptake) from aseptic loosening (type 2, minor uptake), and normal findings (type 1, no uptake, not shown), in patients scanned with an interval of 1 year after hip arthroplasty; subtypes are defined as follows: (*A*) uptake localized on the cup side; (*B*) uptake localized on the stem side; (*C*) uptake localized on both the cup and stem sides (adapted with permission from [124])

infection instead of trafficking white blood cells, such as expressed in osteomyelitis [126–128].

Finally, there are numerous other PET radiotracers under development that may have applications in inflammatory disorders, such as [^{11}C]choline and [^{18}F]fluorothymidine (FLT) PET, which are currently used as markers of cellular proliferation.

Summary

Over the past 20 years, radionuclide imaging has improved the accuracy of the diagnosis of PJI [30]. Sequential bone/gallium scintigraphy, the first generation of scintigraphic imaging techniques introduced for this purpose, has been replaced by combined leucocyte/bone marrow scintigraphy [2]. Despite an accuracy of about 90%, the technique is expensive, time consuming, labour intensive, not widely available and potentially hazardous [80]. Unfortunately, data on FDG PET are rather inconsistent and suggest no additional benefit to conventional nuclear medicine modalities, e.g. combined leucocyte/bone marrow scintigraphy, for the diagnosis of PJIs [129]. Although hybrid imaging is entering the field of PJI imaging, today data are however still limited and further studies are needed to verify if this new modality may really become clinically relevant in the near future [130]. Finally, in order to replace combined leucocyte/bone marrow imaging for the differentiation between aseptic and septic prosthetic loosening, agents that can differentiate infection from aseptic inflammation must be developed [131].

Take home messages: PJI imaging

Introduction

- Infection imaging became widespread in 1971 with the introduction of ^{67}Ga-citrate, despite the significant limitations of this agent
- Development of radiolabelled leucocytes with ^{111}In or ^{99m}Tc improves infection imaging compared with ^{67}Ga, but these agents also localize to inflammatory regions, despite the cumbersome ‘in vitro’ labelling technique
- A multitude of techniques have been tried to improve PJI imaging, meeting with limited success

Established imaging agents for PJI: enhanced methods

- ^{99m}Tc or ^{111}In LS/BS: high negative predictive value, but limited specificity in discerning PJI from aseptic loosening
- ^{99m}Tc or ^{111}In LS/BMS: high accuracy in diagnosing PJI, but contemporary bone marrow imaging adds to the complexity of the study, and sulphur colloid is not widely available in Europe (alternative agent is nanocolloid)
- Serial phase ^{99m}Tc LS imaging: 1-h LS image as a surrogate marker for bone marrow image has the potential to replace sulphur colloid scan (if validated in larger homogeneous trials)
- Antigranulocyte antibody and fragment scintigraphy: high negative predictive value, but limited specificity in discerning PJI from aseptic loosening; can be improved by serial time point imaging and/or adding nanocolloid

Investigational agents for PJI

- Since the late 1980s a wide variety of diagnostic agents have been tried in an attempt to improve infection imaging, such as:
  - Colloids/HIGs/liposomes: no translation into clinical practice—not commercially available
  - Chemotactic peptides: LTB_4 lack of human studies
  - Cytokines: IL-8 first study in infection is promising, but not commercially available
  - Ciprofloxacin and/or quinolone family: sensitive technique for the inflamed prosthesis, but limited specificity in discerning PJI from aseptic loosening
  - Biotin: first studies in infections are promising, but the value of this agent in PJI is not known
  - Ubiquicidin: data on the role of this agent for diagnosing PJI in humans are encouraging, but still very limited
  - Bacteriophage: no studies in humans are available
  - Thymidine kinase: pilot study of musculoskeletal bacterial infection in humans is very promising, but the value of this agent in PJI is not known
- For more than two decades, several authors have promoted PET as an optimal PJI imaging modality
  - ^{18}F-FDG: pooled average sensitivity and specificity are 84%, more accurate for hip than for knee prostheses; lack of consensus on FDG uptake patterns specific for PJI
  - ^{18}F-FDG-labelled WBCs: comparable results to in vitro leucocyte scintigraphy, cumbersome ‘in vitro’ labelling technique
  - ^{68}Ga: experimental data are promising, but the value of this agent in PJI is not known
  - ^{64}Cu-labelled WBCs: experimental data are promising, but human studies are lacking
  - ^{18}F-Fluoride: fluoride uptake pattern allowed discerning PJI from aseptic loosening, has to be further validated

Hybrid imaging modalities: new bright future!

- Since the late 1990s SPECT/CT and PET/CT have been developed
  - Those superb dual-imaging modalities are very promising for imaging the failed prosthetic implant, especially in combination with the current and future diagnostic agents
- But superiority above single-imaging modality has still to been proven in further trials

Future perspective

- Future work must concentrate on the development of a truly infection-specific imaging agent that works well with the improved SPECT/CT and PET/CT devices

Conflicts of interest None.

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