Nuclear Medicine imaging of vertebral infections
Lazzeri, Elena
Chapter 8

Osteomyelitis: clinical update for practical guidelines

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\textsuperscript{*}In memory of Professor Vincenzo Consoli–March 2006

Abstract  Bone infections represent a diagnostic or therapeutic challenge for the infectivologist, orthopaedic surgeon, radiologist and nuclear medicine physician. Staphylococcus aureus is the major bacterium responsible for bone infections although Mycobacterium tuberculosis is emerging as an infectious agent in Italy because of immigration from Africa and Asia. Osteomyelitis requires long and expensive antibiotic treatment, including rifampicin administered parenterally for several weeks and the use of antimicrobial-impregnated cement in prosthesis substitution. Sometimes it is necessary to carry out surgical debridement of a necrotic bone or the consolidation of compromised bones and joint prosthesis implants. Radiographs and bone cultures are mainstays for the diagnosis of bone infections but are often useless in the lengthy management of these patients. Diagnosis of skeletal infections still includes conventional radiography but magnetic resonance imaging is essential in haematogenous and spinal infections. Bone scans are still useful in acute osteomyelitis whereas scintigraphy using labelled white blood cells is preferred in infections of peripheral bone segments or joint prosthesis. In the axial skeleton a combination of an agent for detecting inflammation (\(^{67}\text{Ga}\) citrate) and a metabolic agent (\(^{99m}\text{Tc}\)-methylene diphosphonate) enables an infection and an area of increased metabolic activity to be distinguished. \([^{18}\text{F}]\)Fluorodeoxyglucose positron emission tomography, where available, has a significant impact in the study of infections using radionuclides: high-resolution tomographic images represent an effective alternative to gallium in the assessment of inflammation of spine lesions but a comparison with morphological examinations (computed tomography or magnetic resonance imaging) is essential.

Keywords: osteomyelitis, spondylodiskitis, prosthesis-related infections, radionuclide imaging, antibiotics, antitubercular, arthroplasty, replacement

Introduction

Bone is normally highly resistant to infection, which can occur after large inoculums, trauma or in the presence of metal hardware or in the case of immunocompromised hosts. Infection associated with prosthetic joints is typically caused by microorganisms growing in bio film into organized communities. Bio film protects bacteria from antimicrobial agents and host immune responses. Staphylococcus aureus is the major cause of bone infections: microorganisms adhere to bone and to devices surgically implanted by expressing bone matrix receptors and a phenotypic resistance to antimicrobial treatment [1]. Column infections in Italy as a consequence of immigration from Africa and Asia. Early and specific treatment of osteomyelitis,
before extensive bone destruction or necrosis, produces the best results. The identification of the causative microorganisms is essential for specific antibiotic treatment but evidence from swabs of ulcers or fistulae is often misleading. Infections of joint prostheses, where biofilm microorganisms are involved, should be treated with a combination of antibiotics, which must include rifampicin. Surgery is usually unnecessary in acute haematogenous osteomyelitis and in diskitis but a combined antimicrobial and surgical approach should be common after injury with an open fracture or in infections associated with joint prostheses. Surgical treatments include debridement with retention of the prosthesis, or two-stage exchange with reimplantation of the new prosthesis delayed for a variable period of time. The use of antimicrobial-impregnated cement is suggested to correct length and allows partial joint mobility. The diagnosis of skeletal infections includes a variety of imaging methods, but conventional radiography is still necessary at presentation of acute osteomyelitis. It is of less importance during follow-up or in secondary and chronic infections. Ultrasonography and computed tomography (CT) are very useful for guiding needle biopsies in closed infections of either soft tissues or bones. CT and magnetic resonance imaging (MRI) have excellent resolution and can reveal oedema and any periosteal reaction or soft-tissue involvement: MRI is the preferred diagnostic imaging method for spinal osteomyelitis, but is not suitable for all patients and has certain limitations in the presence of metallic implants [2]. Nuclear medicine imaging procedures to evaluate osteomyelitis include three-phase bone scans, the use of leukocytes (white blood cells, WBCs) labelled with either $^{99m}$Tc-hexamethylpropylene amine oxime ($^{99m}$Tc-HMPAO) or $^{111}$In-oxime, and the use of $^{18}$F-fluoro-2-deoxy-D-glucose ($^{18}$F-FDG) positron emission tomography (PET) and $^{67}$Ga citrate [3–5]. The three-phase bone scan is the test of choice in evaluating acute osteomyelitis and doubtful diskitis but the specificity of this method falls in secondary osteomyelitis. The finding of increased metabolic activity in osteomyelitis is indistinguishable from post-traumatic injury or following surgery or cancer. WBCs accumulate at sites of infection and in bone marrow. The combination of the $^{111}$In-oxime WBC scan with a $^{99m}$Tc-sulfur colloid bone marrow scan is considered the ‘gold standard’ method for the study of infections of hip prostheses but can be also helpful in the study of peripheral bone segments. Three-phase $^{99m}$Tc-HMPAO WBC scintigraphy is widely used in Italy as a helpful alternative to the combined method of WBC/sulfur colloid: a WBC scan is less sensitive for imaging those bones where red marrow is present (i.e., the axial skeleton and spine). In these cases, by combining $^{67}$Ga citrate and bone scintigraphy it is possible to distinguish the activity of secondary vertebral osteomyelitis from other causes of increased bone metabolism. $^{18}$F-FDG PET, where available, has a significant impact in the radionuclide study of infections: the high-resolution tomographic images
represent an effective alternative to gallium in the assessment of inflammation of spinal lesions but a comparison with morphological examinations (CT or MRI) is essential.

The pathophysiology of osteomyelitis

Osteomyelitis is an inflammatory suppurative process of the bone marrow in which both the endosteum and periosteum participate actively whereas the trabeculae and Haversian system participate passively with necrosis and osteolysis. Bone is a tissue that is resistant to bacterial colonization and, in effect, to cause a bone infection, other negative events must occur such as traumas, the presence of foreign bodies, prostheses or an inoculation of aggressive bacteria or other bacteria that generally have characteristics that inherently favour implants; characteristics of adherence, for example [6].

Classification of osteomyelitis

The classification by Waldvogel et al. [7] is rather old, but still topical, and is based on the genesis of osteomyelitis (haematogenous or secondary) and on the modality of onset. Acute haematogenous osteomyelitis symptoms last no more than 10 days. The chronic form is by far the more frequent and includes all the remaining cases (Table 1). The classification by Cierny et al. [8] is more recent and relevant as it proposes the anatomical and histological subdivision of osteomyelitis (medullary, superficial, located or diffused) and introduces the important concept of host immunocompetence, which is highly relevant regarding the onset and diffusion of infections (Table 2).

*Table 1 Classification of osteomyelitis according to Waldvogel et al. [7] (modified)*

<table>
<thead>
<tr>
<th>Classification of Osteomyelitis</th>
<th>Characteristics</th>
</tr>
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<tbody>
<tr>
<td>Haematogenous osteomyelitis</td>
<td></td>
</tr>
<tr>
<td>Secondary</td>
<td></td>
</tr>
<tr>
<td>Infection next to focal point</td>
<td></td>
</tr>
<tr>
<td>With vascular impairment</td>
<td></td>
</tr>
<tr>
<td>Without vascular impairment</td>
<td></td>
</tr>
<tr>
<td>Acute</td>
<td></td>
</tr>
<tr>
<td>Suppuration and oedema, venous congestion and small vessel thrombosis</td>
<td></td>
</tr>
<tr>
<td>Vascularization is compromised if nearby soft tissue becomes involved</td>
<td></td>
</tr>
<tr>
<td>If haemat. and periosteal flow rates are reduced, large areas of dead or isolated tissue form</td>
<td></td>
</tr>
<tr>
<td>Chronic</td>
<td></td>
</tr>
<tr>
<td>A knot of necrotic bone tissue or scar tissue surrounded by ischaemic soft tissue</td>
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</table>

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Table 2 Classification of osteomyelitis according to Cierry et al. [8]

<table>
<thead>
<tr>
<th>Anatomical type</th>
<th>Physiological class</th>
<th>Clinical stage</th>
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<tbody>
<tr>
<td>I Medullary osteomyelitis</td>
<td>A-Host Good immune system and delivery</td>
<td>Type + class Stage IV BS osteomyelitis = a diffuse lesion in a systemically compromised host</td>
</tr>
<tr>
<td>II Superficial osteomyelitis</td>
<td>B-Host Compromised locally (BL) or systemically (BS)</td>
<td></td>
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<tr>
<td>III Localized osteomyelitis</td>
<td>C-Host Requires suppressive or no treatment; minimal disability; treatment worse than disease; not a surgical candidate</td>
<td></td>
</tr>
<tr>
<td>IV Diffuse osteomyelitis</td>
<td>Example</td>
<td></td>
</tr>
</tbody>
</table>

BL: local host compromised; BS: sistemic host compromised.

Haematogenous osteomyelitis
Haematogenous osteomyelitis affects children in 85% of all cases and it often originates from unknown primary foci (nasopharynx) via direct inoculation but can also be contiguous. The most affected group varies from 2 to 5 years of age and the elective location is the lower limbs (femur 27%, tibia 22%). The incidence of osteomyelitis is between 1:1000 and 1:20 000 and mortality reached 50% in the pre-antibiotic era. Nowadays, mortality through osteomyelitis is almost zero. The primary focus is not found in 70% of cases and even when present, may be far from clear. It can be from a simple boil, an infected ulcer, a urinary tract infection or other soft-tissue focal infection. In adults, the infection locations are often in the vertebrae. S. aureus is the most frequent microorganism but in the 2–3 year age group, streptococci such as Haemophilus influenzae can predominate. In haematogenous osteomyelitis, Gram-negative microorganisms (Escherichia coli, Klebsiella, Salmonella and Proteus) are found, and in some immunocompromised patients (e.g., drug addicts) Pseudomonas aeruginosa and, occasionally, Candida aspergillus [9,10].

Secondary osteomyelitis
Secondary osteomyelitis includes post-traumatic osteomyelitis after compound fractures involving a mass of bacteria, the nature of which depends on the environment in which contamination occurred. Post-operative osteomyelitis partly includes the above for open-fracture reduction but also other operations on bones such as the cranium, vertebral column and sternum, and for prosthesis implants and ozone therapy.

**Contiguous osteomyelitis**

Contiguous osteomyelitis includes, besides the classical diabetic foot, osteomyelitis of the heel following unrecognized traumas (puncture and scratch injuries) and osteomyelitis of the jaw following radiotherapy for neoplasms of the head and the neck. S. aureus is the most frequent microorganism of postsurgical osteomyelitis and it is multi-resistant to antibiotics: in Italy, the global incidence of methicillin-resistant staphylococci exceeds the 50% of the isolated bacteria. Nevertheless, the surgical prophylaxis guidelines still foresee the use of cephalozolin, which is not effective over two of these infections. It should therefore be necessary for each hospital to assess its own incidence of methicillin-resistant infections, using glycopeptides in surgical prophylaxis only when the incidence of these microorganisms exceeds 50%. Hence, the indiscriminate use of teicoplanin and vancomycin can be avoided.

**Periprosthetic osteomyelitis**

Periprosthetic osteomyelitis is the new osteomyelitis. Nowadays, the elderly insist on more mobility and an ever-increasing number of prostheses are being fitted; at present there are more than 600 000 in the USA (Table 3). Postoperative infections of prosthetic joints have decreased from 5.9% (± 1.8) in the 1970s to 1.2 (± 0.5) since 2000 [11]. In Italy, between 45 000 and 50 000 prosthetic hip joints and between 9000 and 10 000 knees are fitted each year. Although the incidence of hip prosthesis infections in 1999 was approximately 1.5% per year for new implants, this incidence tripled in reimplantation cases even if the re-implant was not required for a previous infection of the prosthesis. We can therefore estimate that 10–15 significant infections will develop in each 100 prosthetic operations over a 10-year period, which is the average life span of a prosthesis. The orthopaedic surgeon’s worst enemy is still S. aureus, even if other clinically significant bacteria such as P. aeruginosa and S. epidermidis appear [12,13]. The early forms of periprosthetic osteomyelitis develop in the first month, while the delayed form arises in the first year following surgery and the late form can arise many months or years after the initial event. The symptoms are pain, fever, oedema and fistula. Table 4 gives a classification of prosthesis infections. In precocious prosthetic hip infections, infection tends to set in within a month of surgery and stems from bacterial activity during surgery, or in the immediate postoperative period, around the operation site,
then develops in the periprosthetic soft tissues with little involvement of the bone
prosthesis interface. This means that the infection is located within the surgical
access area and to identify it we can use a method that thoroughly studies soft
tissues. If diagnosed early, these infections have a good prognosis and save the use
of another implant. In delayed or late infections that have occurred from 2 to 15
months after an operation, the rejection of, or reaction to, a foreign body (the
prosthesis) can offer an excellent point of attack for bacteria that lodge in the body.
During the course of 1 day, there can be episodes of bacteraemia in the blood which
are easily overcome by healthy subjects. In patients with prosthesis, however, if the
bacteraemia is severe, perhaps because the patient has a dental abscess or a
chronic urinary tract infection, osteomyelitis develops on the prosthesis. This is also
due to the presence of a reactive phenomenon to the use of polyethylene in
prostheses. This results in a subsequent reaction with the appearance of periprosthetic osteolysis or of less vascularized centres and the possible occurrence
of circulating bacterial colonies. In this infection, the seat is typically the
prosthesis/bone interface, with the soft tissue involved secondarily. In this case, the
diagnostic approach must be to use a method that allows this to be carefully studied.
Prognosis in these cases is rather poor and the nuclear physician and radiologist
must therefore be fully aware of the patient’s clinical background and have all the
relevant laboratory data [14–16].

Table 3. Incidence of device-associated infections in the United States

<table>
<thead>
<tr>
<th>Device</th>
<th>Usage/year</th>
<th>Infection risk (%)</th>
</tr>
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<tbody>
<tr>
<td>Joint prostheses</td>
<td>600,000</td>
<td>1–3</td>
</tr>
<tr>
<td>Fracture fixators</td>
<td>2 million</td>
<td>5–10</td>
</tr>
<tr>
<td>Dental implants</td>
<td>1 million</td>
<td>5–10</td>
</tr>
</tbody>
</table>
Table 4. Classification of prosthesis infections

<table>
<thead>
<tr>
<th>Onset of infection</th>
<th>Infecting organism</th>
</tr>
</thead>
</table>
| Preoccous (<1 month) | *Staphylococcus aureus*  
*Staphylococcus coagulase-negative*  
*Aerobic Gram-negative bacteria* |
| Delayed (2–12 months) | *Staphylococcus coagulase-negative*  
*Skin bacteria (S. epidermidis)* |
| Late (>12 months) | *Staphylococcus aureus* (methicillin-resistant)  
*Staphylococcus coagulase-negative*  
*Skin bacteria (S. epidermidis)*  
*Anaerobes*  
*Streptococcus species*  
*Escherichia coli* |

Infections of the vertebral column

Infections of the vertebral column are haematogenous infections but primarily strike adults over 50 years of age. Drug addicts are an exception and are particularly exposed to infections of the vertebral column just like diabetics and dialysis patients. The infections present as spondylitis or vertebral osteomyelitis, diskitis and secondary diskitis where the infection shows an effect either by itself or in association with adjacent vertebrae and intervertebral disks. Diskitis is a specific or non-specific bacterial infectious process (very occasionally mycotic) of two or more adjoining vertebrae and of the respective intervertebral disk. The infection sometimes spreads to the surrounding soft tissue. Backwards extension of the infection can result in an epidural or subdural abscess or in meningitis, whereas forward and/or lateral extension can result in para vertebral, retropharyngeal, mediastinal or retroperitoneal abscesses [6,17,18]. Infections of the vertebral column can be divided into spontaneous and iatrogenic forms, these last due to invasive manoeuvres or to surgical interventions. The spontaneous forms, which are supported by an arterial haematogenous dissemination in almost all cases, are unspecific bacterial or mycotic and they represent the 2–4% of all vertebral osteomyelitis. The source of infection can be presented both from venous inoculation and from different kinds of sources (e.g., genitourinary apparatus, cutaneous or subcutaneous, respiratory, dental) or from vascular devices. In 24–37% of cases, the source of infection remains unknown. The most susceptible vertebrae are the lumbar (45%), followed by the dorsal, above all the inferior, (35%) and the cervical (20%). A greater incidence of the cervical forms has been noticed among the drug addicts. *S. aureus* is the most frequently isolated agent (55–85% of cases), followed by coagulasenegative staphylococci, enterobacteria (Salmonella
spp, E. coli, Klebsiella spp, Serratia spp), P. aeruginosa (frequent among drug addicts) and Candida (among drug addicts and in infections of vascular devices) [19,20].

Spontaneous specific diskitis
Spontaneous specific diskitis is represented by vertebral tuberculosis or Pott’s disease supported by a haematogenous dissemination originating from the lung or from other lymph nodes or from genitourinary infections, often within disseminated tuberculosis. Vertebral infections are increasing, especially among immigrants from Romania, India, Sri Lanka and Africa, as well as in patients over 80 years of age who have compromised immune systems. The tubercular infection begins from the anterior part of the vertebral body and usually involves the subcondral region, spreading then to the cortical region and to the adjacent disk. It can result in vertebral abscesses involving the ileopsoas muscles. The classic symptomatology of spontaneous specific diskitis is represented by ‘back pain’ with accentuation of the painful symptomatology in the passage from the clino to the orthostatic position and from the seated to the erect position. Because of the insidious symptomatology, whose progress can last weeks or months, the moment of the diagnosis it is often delayed (it may be between 3 weeks and 3 months). The fever, usually around 37.5°C, is present in 50% of patients. Laboratory data show a modest leukocytosis in 50% of subjects while erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are usually increased [19,21].

Iatrogenic diskitis
Iatrogenic diskitis follows direct inoculation of microorganisms after spinal anaesthesia, chemonucleolysis and local infiltrations with analgesic purpose. Above all, it follows surgical interventions for slipped disk, spondylolysis and spondylolisthesis. Also, in such cases, staphylococci play the principal aetiological role, with the prevalence of coagulase-negative strains. The painful symptomatology, similar to that in spontaneous diskitis, involves the site of the intervention and can sometimes be associated with subcutaneous infections noticeable during physical examination. The onset of the painful symptomatology can vary from a few days to 2–3 months from the invasive or surgical manoeuvre. The fever is not constant, while an increase of ESR and CRP is typical, with or without variations in granulocytes [22].

Assessment of the disease
Symptoms of osteomyelitis
The symptoms of osteomyelitis are variable: in the typical form, fever, pain, motor limitations and local inflammation or septicaemia, are found, as is usual among infectious diseases. A bone infection leads to tissue destruction, which can result in the functional loss of the involved bone and the surrounding soft tissues [23].
Results of laboratory tests (CRP, ESR, neutrophilia) are used in the diagnosis of the infection, but a precise diagnosis and effective therapy cannot be formulated unless the microorganism is isolated and the culture examined [6,7,17,18]. Onset of infection is variable: a thick inoculation of virulent bacteria generates an acute infection but a thick contamination in a guest immunocompetent patient produces a faint infection. In these cases, the appearance is delayed, even after years: there are often fewer virulent bacteria but with adhesive abilities. A third possibility is that there is a low intra-operating contamination, with low virulence of the organism, and it can be easy to maintain under controlled conditions. Possibly, it also exists in a haematogenous manner, it is not frequent and is a consequence of oral, endoscopic or urinary surgical interventions. The infection should be prevented by effective antibiotic prophylaxis before the intervention.

Radiological investigation

In the initial phases of the haematogenous osteomyelitis, we find a medullar inflammation characterized by the hyperaemia, the oedema, the leukocytes infiltration and the purulent transformation. In this phase the radiological diagnosis is limited because there are no definite signs of infection in the first 2 weeks after onset. There are some specific signs such as soft-tissue oedema and the disappearance of the fascial levels, which are easily found by nuclear medicine techniques and MRI [24,25]. The abscess of Brodie is a unique focal infection, with chronic evolution, generally located at the proximal metaphysis of the tibia or femur. X-rays show an oval osteolytic area that is better seen by MRI with spin-echo T2-weighted sequences and a heterogeneous signal hyperintensity. The stir sequences of the MRI provoke the suppression of the fat, and they confirm the presence of oedema and the involvement of the soft tissues [26,27]. The infection can spread to the cortical with lifting of the periosteum and interruption of the vascular support. X-ray examination shows osteopenia and a worm-hole aspect of the bone with a meaningful re-absorption up to the osteolysis. The consequence is bone death, which can lead to alterations such as swelling of the surrounding skeletal soft tissues, periostitis, endosteitis and the disappearance of the medullar canal up to the lamellar osteonecrosis and thickened bone. In the following phase, sequestration with clear demarcation of necrotic bone from healthy bone can be seen; this is due to the phenomenon of osteoclastic demolition. After the sequestrum, a chronic process is followed with the overproduction of bone and therefore a demarcation from the surrounding bone. Conventional X-rays show osteolytic areas of infection delimited by a diffusely and heterogeneously thickened bone. The MRI spin-echo T1-weighted sequences demonstrate sequestration of bone and the activity of the infection. If a patient receives gadolinium, the MRI shows hyperaemia, definite
expression of the process activity [28–30]. The CT shows very well the partly corpuscular swelling of the soft tissues around bones and joints.

Radionuclide imaging

Radionuclide imaging is usually employed after the radiological investigations, in the diagnosis of haematogenous osteomyelitis and of soft-tissue infections. The three-phase bone scan with 99mTc-disphosphonates shows an increase of bone perfusion and of the surrounding soft tissues in the dynamic and blood pool images. In delayed images bone uptake appears blurred in the boundaries of healthy bone, and can easily be distinguished from cellulites in which the involvement also includes soft tissues. However, the efficacy of a three-phase bone scan decreases in follow-up or after antibiotic or surgical treatment because the modifications of bone metabolism, and the normalization of scintigraphic images, are very slow. An increased uptake of labelled diphosphonates can persist for months or years after recovery of a bone fracture or after osteomyelitis. In paediatric patients the water content and perfusion supply of bone are increased in comparison with adults. So, septic bone necrosis is not rare and can result in cold areas on methylene diphosphonate bone scintigraphy (Fig. 1). Haematogenous osteomyelitis can involve more bones, which is the reason why a whole body bone scan is essential in these cases. The diagnosis of bone infections becomes difficult in cases of recently implanted prostheses, in delays of consolidation of exposed fractures and after repeated surgical or therapeutic interventions. The principal problem in osteomyelitis remains the search for infections in a bone with altered structure caused by re-absorption or new apposition processes where there is a loss of specificity of bone scintigraphy, CT and MRI. Radiological methods are also limited by the presence of synthesis materials or by implants or prostheses that provoke important artefacts in both CT and MRI scans. In these contexts the most reliable investigation for verifying the presence of bone infection remains scintigraphy with labelled leucocytes. In this technique, either WBCs or pure granulocytes labelled with either 111In-oxime or 99mTc-HMPAO can be used: the choice of cell or radiolabel is not critical. The most important factor influencing the accuracy of this examination is the time required to follow the diapedesis of the granulocytes, prolonging the examination to at least 24 h. In this way it is possible to observe labelled granulocytes migrating from the blood to the soft tissues and concentrating around the prostheses, in the cavities, in fistulas, and, sometimes, in the regional lymph nodes [4,7,16–18]. Moreover, the scintigraphic accuracy of labelled leucocytes is modified by the presence of the red marrow in bones involved in osteomyelitis. In haematogenous osteomyelitis of the axial skeleton or of the proximal appendicular skeleton 30–75% of cold areas are found with WBC scintigraphy. These are areas where there is zero or very low blood flow and are the equivalent of sequestered
bone on X-ray examinations. In these cases scintigraphy with leucocytes (or even monoclonal antibodies) labelled in vitro, is useless in assessing the activity of inflammation because cold areas can persist indefinitely, maintaining this situation for years. In young patients the bone marrow is extended in all the skeleton segments up to the distal appendicular ones. Therefore, in paediatric age groups we have, more or less, the same limitations in the use of labelled WBCs that we have in the axial skeleton of adults and labelled WBCs in vitro (or monoclonal antibodies) are often useless. Unspecific radiopharmaceuticals for detecting inflammation, such as $^{67}$Ga or $^{18}$F-FDG, with an uptake proportional to the vascular permeability or to metabolic activity, should be preferred in secondary bone infections of axial skeleton. In these cases the scintigraphy is ordered only for assessing whether the infection is still active or not after therapeutic approaches (e.g., surgery, antibiotics).

Fig. 1 Bone scan in a right foot osteomyelitis in a 6-year-old child. The cold area corresponding to the navicolar bone of the right foot is expressing septic necrosis

**Prosthetic joints**
Orthopaedic surgeons and clinicians must identify the position and extent of infection when dealing with prosthetic joints. Furthermore, they have to provide accurate information on the prosthesis, taking into account patient history, the clinical possibility of infection, X-ray images, and laboratory data. Most importantly, they must identify the kind of prosthesis with which they are working. Cemented prostheses are custom-made because the cement hardens within 20 min and gives immediate mechanical stability to the prosthesis. However, as the cement hardens it
produces an exothermic reaction, which may bring about an endosteal necrosis that affects vascular flow in the bone–cement interface. The polyethylene waste product that builds up over time because of wear and tear of the cotyloid cavity may lead to osteolysis near the cement of the prosthesis showing a characteristic accumulation of labelled diphosphonate. Non-cemented prostheses, on the other hand, inevitably bring about a reshaping of adjacent tissues that may either erode the bone or cause new bony deposits. This reshaping depends on the material used in the prosthesis, on its design, its primary anchoring, and on whether the prosthesis is coated with osteo-inductive materials. Chrome–cobalt molybdenum alloys, once commonly used, are very rigid, and produce significant reshaping of the bone, which induces a considerable necrosis in bone tissue due to the accumulation of deposits of both bone and metal. For this reason, titanium alloys are now being used, as they are less rigid and produce fewer deposits and less bone necrosis [31]. Design and primary anchoring are equally important. The so-called distal press-fit involves long prostheses while proximal press-fit and distal filling have completely different osteo-metabolic characteristics. Another key factor is the potential presence of an osteo-inductive coating. The purity and porosity of this coating have an impact on the extent of reshaping that takes place around the prosthesis, and consequently on the degree of diphosphonate uptake at bone scintigraphy. Traditional X-ray reveals specific details of the bone–prosthesis interface but it is of little help if the infection is in soft tissue. Characteristic signs are small and unclear, and conventional X-rays often give negative results. In soft-tissue infection, ultrasonography will provide highly detailed information; for example, in identifying whether an abscess is relative to vascular and nerve bundles. This is essential to plan access, intervention and debridement. If this infection is extensive, it can spread to the abdomen or the pelvis. The limits of the technique are that, in the early phase, it fails to distinguish post-surgical haematoma from septic haematoma, which may affect soft tissues [32]. CT and MRI are excellent techniques but, when dealing with infections near prostheses, lose some of their effectiveness because the quality of the resulting images is severely affected by the presence of the metal hardware. CT can provide information about the movement of the prosthesis, but fails to distinguish between mechanical and infectious loosening. However, CT can play a role if used with WBC scintigraphy, which allows a morphological examination of their location and accumulation. Likewise, CT–PET can reveal the morphology of $^{18}$F-FDG accumulation. By using CT, the surgeon can obtain important information on the extent to which an infection has spread through muscular tissues, while CT fistulography is useful if abdominal tissue is involved. CT allows the biopsy to be guided to the location of infection and an antibiogram, which is essential for curing the infection with specific antibiotics, to be obtained. With infections in hip
prostheses, a three-phase bone scan shows an increase in early perfusion and a
delayed metabolic accumulation of diphosphonate all around the prosthesis,
marking out its contour. The specificity of bone scintigraphy in hip prostheses ranges
from 50 to 70% according to case specific circumstances [33] because the bone
scan signal requires months if not years before returning to normality even if the
clinical problem has been resolved. In the case of simple instability, on the other
hand, there is no early increase in perfusion while the delayed accumulation of
diphosphonate is typically concentrated in the load-bearing points at the top of the
acetabulum, in the minor and major trochanter and at the top of the prosthesis stem.
A three-phase bone scan has a sensitivity of about 85% in hip prostheses infection
[34]. In knee prostheses, the role of three-phase bone scintigraphy is less definite
and it is more difficult to differentiate a case of movement from a case of infection
[35]. Scintigraphy with WBCs or granulocytes labelled with $^{111}$In-oxime [36] or with
$^{99m}$Tc-HMPAO [37] is the most accurate method for studying bone infections.
Leukocytes accumulate by diapedesis in musculoskeletal infections, attracted by
chemotaxis, thus the type of white-cell accumulation changes over time. Successive
scintigraphies will reveal these movements and migration of labelled cells within the
tissues leads to a progressive concentration in the fistula or spaces near the
prostheses, in joints, and sometimes in local lymph nodes (Fig. 2). White-cell
distribution in the body, however, sharply limits clinical use of WBC scintigraphy. For
example, the study of infections of the dorsolumbar area and of the lower ribs is
difficult because labelled white cells tend to concentrate in the liver and spleen with
higher resulting activity of the overlapping abdominal and thoracic wall. Furthermore,
in 30–75% of cases of infection in the axial skeleton and nearby areas, cold areas
are observed with WBC scintigraphy linked to the low flow of cells within the
inflamed bone tissue [38,39]. This is equivalent to radiological sequestra, which
increase with the duration of the infection, and with repeated antibiotic treatment.
In the same way, granulomatous chronic infections (i.e., tubercular osteomyelitis, or
mycosis) are characterized by a low percentage of granulocytes and are hardly
revealed using labelled WBCs or pure granulocytes [40,41]. Antibiotics and
immunosuppressants can reduce the accumulation of white cells because these
drugs reduce the diapedesis of granulocytes by reducing the concentration of
cytokines in tissues. Their inhibitory action is proportional to the duration and
efficacy of antibiotic therapy as well as to the bacterial population causing the
infection. Pyogenics, such as S. aureus, bring about the highest white-cell
accumulation but the intensity of uptake is also more susceptible to the antibiotic
effect. Patients suffering from acute infections should not suspend antibiotic
treatment, however, as this would worsen their clinical state. In these cases,
scintigraphy should be carried out as soon as possible after the onset of symptoms.
In patients with chronic infection or undergoing long-term antibiotic treatment, scintigraphy should be delayed until at least 2 weeks after the end of therapy. In this way, it is possible to determine accurately whether therapy has been successful or if the infective foci remain. In adults with prosthetic joints and post-traumatic infections, surgical intervention may bring about a peripheral displacement of the bone marrow towards surrounding spaces, which may then be mistakenly interpreted as septic. To avoid this inconvenience, Palestro et al. [42] suggested comparing $^{111}$In-leukocyte scintigraphy with a bone marrow scan (with $^{99m}$Tc-sulfur colloids). The discrepancy between the two scintigraphic images (leukocytes greater than colloids) very accurately identifies the presence of infection. As an alternative, repeating scintigraphic observations at 1, 4 and 20 h after the re-injection of cells makes it possible to distinguish the invariant accumulation with time (that is, bone marrow) from progressively rising accumulation in osteomyelitis. Comparing the three images, it may be possible to follow the path taken by the white-cell diapedesis from the location of the infection to the fistulas or other periprosthetic spaces [43]. The two methods have equivalent sensitivity at around 95% for peripheral bone tissue with a specificity of 97% [44]. The same figures are lower for axial skeleton and in chronic infections [45].

**Fig. 2** Infection of a left-hip prosthesis. Three-phase $^{99m}$Tc-HMPAO white blood cell (WBC) scintigraphy shows increased activity of labelled WBCs in soft tissues of the left thigh in the first images (1 h after i.v. injection), which significantly increases in the images after 4 and 10 h. The path to the hip prosthesis is also well demonstrated.

*Management of patients with osteomyelitis*
A multidisciplinary and structured approach to the management of bone infections is important. Antibiotic therapy must rest on the identification of the pathogen. This allows an accurate antibiogram, which will pinpoint the group of antibiotics to be used in the treatment. Among these, we are then able to choose the antibiotic that can best penetrate bone tissue and which has low toxicity. Staphylococcus is enemy number one. Rifampicin, macrolides and teicoplanin have excellent diffusion profiles, thus whenever possible this group of antibiotics should be favoured. On the other hand, we know that teicoplanin has a good degree of coverage for methicillin-resistant S. aureus and of vancomycin-resistant Enterococcus, although vancomycin is associated with a higher risk of relapse when compared to teicoplanin. As for quinolones, the paired quinolone–rifampicin has an excellent pharmacokinetic profile and therefore can be a useful combination in treating some forms of staphylococci [46,47].

Aetiological therapy
Aetiological therapy cannot do without rifampicin, which has an optimal intercellular concentration, a very good sensitivity profile for methicillin-resistant staphylococci and when used with teicoplanin offers significant clinical advantages that have been demonstrated both in the laboratory and in practice [48]. Among new drugs, linezolid inhibits bacterial protein synthesis and is very effective on methicillin-resistant staphylococci and on vancomycin-resistant Enterococcus. Linezolid is also easily absorbed which is a great advantage when associated with 100% bioavailability and has excellent bone penetration. For the time being, however, there are no agreed protocols for the use of this antibiotic in osteomyelitis [49,50]. Quinupristin–dalfopristin is sometimes used. This antibiotic also blocks protein synthesis, spreads easily amongst macrophages, and has a good tissue distribution. However, its use in osteomyelitis is advisable only in particularly selected cases [51,52].

Empirical therapy
Empirical therapy has to be resorted to when it is impossible to isolate the root of the infection. In this case local epidemiological factors must be taken into account, together with determining whether the infection has been contracted in hospital or elsewhere. Infected contracted outside hospitals are usually from methicillin-sensitive staphylococci, and are frequently polymicrobial infections with the presence of Gram-negative bacteria. In these cases, the clinician should start with an amino penicillin associated with a beta-lactamase inhibitor, on the following antimicrobial associations: rifampicin + quinolone, oxacillin or teicoplanin or clindamycin + ceftriaxon or cezepime or quinolone [53]. Hospitalcontracted infections, on the other hand, have a high probability of being derived from methicillin-resistant staphylococci, which should be dealt with through a glycopeptide, particularly teicoplanin, together with rifampicin, possibly associated
with antibiotics active on Gram-negatives [14,54]. The antibiotics should preferably be administered parenterally for several weeks. This raises the problems of cost, patient cooperation, and morbidity. Most patients will have to remain in hospital because it is not always possible to identify an antibiotic that can be administered parenterally at home, given that dosages are seldom intended for individual home use. Oral therapy has been considered but we do not yet have enough data. For the time being, oral therapy is indicated only in children. Furthermore, oral therapy can only be used with patients whose compliance is certain. Treatment duration is not standardized at present. In any event, it must be based on the type of infection. For instance, haematogenous infections must be dealt with by determining whether bone sequestration is occurring and whether debridement is necessary. Depending on the specific case, therapy for 4–6 weeks may be enough or it may prove necessary to increase it to 6 weeks or longer [55,56]. Often osteomyelitis fails to improve because bacteria have the ability to resist to antibiotics. S. epidermidis sticks to the prosthesis and is enclosed in the biofilm: a polymeric matrix acts as a protective mantle to impede phagocytosis and the delivery of the antibiotic [57,58]. The reduced growth of biofilm bacteria is responsible for their resistance to many antibiotics that are only active in this phase. Rifampicin acts on the biofilm and must therefore always be used with other antibiotics when a prosthesis infection is present. Failure to use rifampicin within a month or a few weeks of treatment will allow infection to start again.

**Treatment of prosthesis infections**

Antibiograms in prosthesis infections should be performed, mixing the materials that replicate the impact of the prosthesis itself. For example, ofloxacin affects the Gram-positives of a fluid culture but adding some polystyrene beads to the broth better simulates real conditions. In this case, antibiograms change completely and bio film producing bacteria develop. It follows that the duration of the antibiotic treatment is not standardized. It has to be defined according to infection type: in haematogenous infection, it is necessary to check for bone sequestration. If debridement is called for, therapy for 4–6 weeks can be enough or it may prove necessary to prolong therapy for 6 weeks or more [19]. The causes of pain in hip prostheses can be mechanical or ‘biological’. Mechanical causes are load bearing, excessive periprosthetic re-absorption, possible sinking following the original placement, fractures (macro or micro) in the femur near or under the prosthesis. Biological causes are reactions to polyethylene deposits (in cases of antiseptic movements) and infection (in the case of septic movement). In cases of infection, a two-stage intervention must be accompanied by medical therapy of up to 6 weeks, comprising collecting biotic samples and examining cultures in the removal stage and resorting to antibiograms to fine-tune the antibiotic. In the case of prosthesis infection, different surgical
interventions are possible: from simple debridement, to one-stage or two-stage intervention, to outright removal. Different interventions will, of course, demand different therapies. In one-stage interventions, antibiotic therapy must be particularly long, at least 4 weeks before the intervention and up to 16 weeks afterwards. Note that, especially in this type of intervention, resorting to empirical therapy will be simpler than the more rigorous aetiological approach. Therapies lasting less than 4 weeks have been shown to carry a high risk of re-infection; thus, they should be continued for at least 6 weeks. While it is difficult to be certain that the bone has healed, combining clinical, radiological and biochemical information (such as carefully monitored CRP follow-up) can definitely be of assistance. As for CRP data, it is well to keep in mind that recurrent inflammation episodes may over-ride all other considerations.

Use of antibiotic-loaded acrylic cement
In 1970, Buchholz and Engelbrecht [59] introduced antibiotic-loaded acrylic cement to the treatment of prosthesis infections, a technique that has since been used frequently. Simply put, its advantages are higher concentrations of antibiotic in the soft tissues and in the bone than would be possible by alternative delivery methods, low serum concentration and, consequently, lower toxicity. In our opinion, the technique has benefited from the well-known suggestion, in 1988, by Wilde and Ruth [60] of a space block and multiple stage treatment. The space block has a double advantage: mechanical and biological. The first is in preventing joint head fusion, while maintaining the correct length of muscular structures and reducing post-surgery blood pooling. The second is in assisting the disinfection of localized septic points and maintaining high local concentrations of antibiotic. In addition, the two-stage technique allows for a repeat of surgical cleaning and the use of un-anchored prostheses. The most important problem remains the choice of dosage of the antibiotic associated with the cement. Bactericidal tests performed on various stocks of pathogenic agents have shown the absolute ineffectiveness of some antibiotics. Our conclusion is that for S. aureus and S. epidermidis and Pseudomonas, the most effective bactericide was a combination of vancomycin and imipenem cilastatin, most likely because their actions were mutually reinforced to the greater porosity of the cement, which leads to a greater release of the antibiotic. Furthermore, two-stage procedures offer better control of the infection because they give the opportunity of introducing a prosthesis without cement, while the onstage intervention forces the use of a cemented prosthesis [61,62]. This treatment requires cooperation between epidemiologists, microbiologists and nuclear physicians. Its high cost may discourage hospital administrations and private nursing homes, however [63].

Diagnosis of patients with suspected osteomyelitis
Clinical examination of the patient always allows the detection of functional impairment and laboratory tests can provide bone infection data. Conventional X-ray is the first imaging procedure in the diagnostic flow chart of osteomyelitis: if the results are positive, this is sufficient to begin the appropriate therapy.

Haematogenous osteomyelitis
In haematogenous osteomyelitis, a three-phase bone scan can provide a result within 24-48 h after the onset of osteomyelitis symptoms and can be used very profitably in radiologically negative cases or for whole-body studies because haematogenous osteomyelitis is often multifocal. In children and adolescents, pain is the main symptom of osteomyelitis, accompanied by other joint diseases such as arthritis, aseptic necrosis or epiphysiolysis of the hip, which can be quickly identified and distinguished from osteomyelitis by using bone scintigraphy. Finding cold areas on the scintigraphic image of a septic necrosis that complicates haematogenous osteomyelitis is more common in children due to their higher bone water content [64]. The interpretation of conventional radiological results becomes complicated where there are prosthetic joints and secondary or post-traumatic osteomyelitis, or where there has been bone re-modelling, previous operations and the presence of synthesis materials or metal support devices. Nevertheless, such tests are carried out to assess the bone condition. If there are any doubts about the Xray results, CT and MRI provide a more detailed morphological study and offer the orthopaedic surgeon a guide regarding surgical drainage of abscesses or the debridement of necrotic bone. The presence of synthesis materials, however, hinders or limits the detection of persistent infection by CT or MRI imaging. In these cases, where a surgical approach is difficult, it is necessary to establish whether the secondary osteomyelitis is truly cured or whether it is merely present following consolidation surgery. Scintigraphy with WBCs, in association with the appropriate suspension of antibiotic therapy, is the most accurate way of determining the persistence of an infection [65].

Post-traumatic infections
In our experience, post-traumatic infections are studied with laboratory tests and conventional radiography. If the results of these tests all suggest infection, medical therapy is initiated, guided by a culture test and an antibiogram and possibly by pulsed magnetic therapy especially in the presence of late consolidation or a pseudoarthrosis (Fig. 3). An alternative is to begin antibiotic medication followed by surgery, a clinical follow-up, radiography and scintigraphy with radiolabelled leucocytes to assess recovery. If the conventional radiography produces doubtful or negative results, and there are positive clinical and laboratory indications of inflammation, we carry out scintigraphy with radiolabelled leucocytes, which may give positive, doubtful or negative results. If positive, the next step is to prescribe
antibiotic therapy for 2–4 months and pulsed magnetic therapy or surgery. In the event of a doubtful positive result with scintigraphy, antibiotics are prescribed along with magnetic field therapy and a subsequent clinical and radiological follow-up after 4 weeks. This is followed by scintigraphy with labelled leucocytes after 2 weeks of suspension of the antibiotic therapy. If the results of WBC scintigraphy are negative, the antibiotics can be restarted to consolidate the results and the clinical and radiological follow-up can take place after 4 weeks followed by labelled-leucocyte scintigraphy at 2 months.

Fig. 3. Diagnostic flow chart of peripheral post-traumatic and secondary bone infections

Infections of prosthetic joints
With infections of prosthetic joints, however, a different approach is required for hip and knee. As the knee is closer to the surface and more easily reached it allows a quicker arthrocentesis and thus the possibility to obtain a specific diagnosis and implement a targeted therapy regime. In these cases, in addition, we need to know
the extent of the infection and degree of activity but in the event of a painful prosthesis, the first thing to be done is to obtain conventional X-rays and carry out laboratory tests (Fig. 4). If the results of these examinations are negative but the prosthesis is still causing pain, we order a three-phase bone scan. If the scan results are normal in all three phases, we begin aetiological therapy and observation regarding pain and inflammation. If the bone scan results are positive in all three phases (perfusion, blood pool and metabolic phase) and there is bone remodelling, but the laboratory tests are negative for infection, we institute a regimen of medication and physiotherapy along with pulsed magnetic therapy and subsequent follow-up with radiography and a three-phase bone scan. On the other hand, if the initial laboratory tests (ESR or C-reactive protein) and radiological examinations are positive for an infection, we order WBC scintigraphy. If the result of scintigraphy is negative for infection, we implement physiotherapy with pulsed magnetic therapy, or consider re-implanting the prosthesis, although this is not an easy clinical decision to make. If the scintigraphy results are positive, we have the opportunity to conduct antibiotic therapy followed by radiography then radiological and labelled leucocytes scintigraphic checks (Fig. 5). If the results of WBC scintigraphy are negative, physiotherapy is again the option. If the results remain positive, we prefer explanting the prosthesis and put in the antibiotic-impregnated cement spacer along with systemic administration of antibiotics for 4–6 weeks. Only when the follow-up with labelled WBCs has become negative do we proceed with the re-implantation of the joint prosthesis. There is a third possibility: that of the doubtful positive of the radiographic images and the laboratory tests. In this case, we prefer to carry out WBC scintigraphy, which is a better determinant. If this is negative, we return to medical therapy and physiotherapy. If it is positive we proceed to antibiotic therapy or even removal of the joint prosthesis, depending upon the case.
Fig. 4 Diagnostic flow chart of the diagnosis of suspected infection in painful joints prosthesis

Fig. 5 Example of a woman with infection of a left-knee prosthesis. (a) $^{99m}$Tc-MDP scintigraphy on September 3rd 2002. The blood pool images show an increased perfusion in the tissues surrounding the knee prosthesis. The delayed images show that the uptake of MDP prevails in the tibial epiphysis and in patella. (b) $^{99m}$Tc-HMPAO WBC scintigraphy on September 18th 2002 shows a significant increase of labelled WBCs both in femur and tibia periprosthetic bone, in surrounding soft tissues and in the articular cavity. (c) $^{99m}$Tc-HMPAO WBC scintigraphy check-up on December 5th 2002 after removal of the infected prosthesis, implant of antimicrobial-impregnated cement and 6 weeks of antibiotic therapy.
Vertebral osteomyelitis
In diagnosing vertebral osteomyelitis, a series of haematocchemical assessments must be carried out, including indices of inflammation, culture tests on biological liquids and instrumental examinations, including biopsies. Early diagnosis is the key to resolving septic spondylodiskitis as it can prevent the onset of permanent neurological deficits and the formation of vertebral deformities. MRI is, without doubt, the most important and most sensitive tool and allows the formulation of a differential diagnosis with degenerative and metastatic processes as it supplies data on the anatomy and the extension of the infectious process in haematogenous spondylodiskitis. In the study of post-operative spondylodiskitis, the sensitivity and specificity of radiological methods suffer a substantial loss due to the presence of scar tissue and/or post-operative reactions. From the diagnostic point of view, biopsies are very important examinations in identifying pathogenic agents and can be affected by the transpedicular or disk routes or by open surgery. This procedure can produce negative results in 30–50% of cases, however, and is therefore not particularly useful in diagnosing spondylodiskitis, which in 90% of cases is postoperative, with bones that have been altered by non-specific re-modelling and is thus difficult to diagnose using radiological methods. In traditional diagnostic algorithms (Fig. 6), scintigraphy with $^{99m}$Tc-hydroxymethylene diphosphonate ($^{99m}$Tc-HDP) and $^{67}$Ga citrate are often mentioned. Both methods use tracers that accumulate in inflamed areas and are highly sensitive. Nowadays, even if this use has not been fully referred to in diagnostic algorithms, nuclear medicine makes great use of this technique in diagnosing post operative spondylodiskitis. The radiopharmaceuticals to be used in a case of suspected spondylodiskitis are, amongst those available in all the centres, $^{99m}$Tc-HDP, $^{111}$In- and $^{99m}$Tc-labelled WBCs, immunoscintigraphy with monoclonal antibodies and $^{67}$Ga citrate.
Others still in the experimental stage include $^{111}\text{In}$-biotin and $^{99m}\text{Tc}$-ciprofloxacin (Fig. 7). In descending order of accuracy of scintigraphic tracers, the data from the study of spondylodiskitis is as follows: $^{18}\text{F}$-FDG (90%) (Fig. 8), $^{67}\text{Ga}$ citrate (88.50%), antigranulocyte antibodies (88.5%) and labelled WBCs (65.5–80%). The data regarding accuracy with experimental markers is $^{111}\text{In}$-biotin (95.2%) and $^{99m}\text{Tc}$-ciprofloxacin (81.5%) [66–72]. This demonstrates therefore that the radiopharmaceuticals to be used in cases of suspected spondylodiskitis are $^{99m}\text{Tc}$-HDP and $^{67}\text{Ga}$ citrate, which are available in all the centres, $^{18}\text{F}$-FDG is available in selected centres and $^{111}\text{In}$-biotin and $^{99m}\text{Tc}$-ciprofloxacin where possible (Fig. 9).
Fig 7. Lumbar diskitis in a 65-year-old woman. 99mTc-MDP, 99mTc-HMPAO WBC scintigraphy and 99mTc-Infecton were used in the study. In the upper row the images of the lumbar spine are reported as spot views, while in the lower row, the images are the corresponding coronal SPECT views for each tracer. There is a typical linear hot spot in the space between L5-S1 vertebral bodies in the bone scan images which corresponds to a cold area in the WBC scan. The Infecton images show a focal uptake in the spine without involvement of soft tissues.

Fig. 8 (a) $^{99m}$Tc-MDP bone scan and a $^{67}$Ga scan of a diskitis of the whole lumbar column treated by antibiotics and surgical stabilization of multiple vertebral bodies. In comparison with
the normal uptake of the dorsal column increased uptake of $^{99m}$Tc-MDP and decreased uptake of $^{67}$Ga by the lumbar spine was found. In our experience such result is unusual. (b) Fusion of the lumbar SPECT with $^{67}$Ga and $^{18}$F-FDG PET of the same patient 2 weeks later. Uptake of $^{18}$F-FDG in two linear areas located at the second (filled arrow) and fourth (unfilled arrow) intervertebral space of lumbar spine. The uptake of gallium is limited to the fourth space.

Fig 9 Diagnostic flow chart of infective diskitis with experimental nuclear imaging procedures

Scintigraphy with inflammation tracers must be used as a complementary examination to current radiological methods (CT or MRI) where haematogenous diskitis is suspected. It may be chosen, however, as the primary investigative tool in
cases of suspected post-operative diskitis and its follow-up. Scintigraphy with inflammation markers must always be ordered where there is suspected post-operative diskitis or diskitis of another type, where there are doubtful or negative CT and/or MRI results in the event of positive results from a bone scan. In vertebral osteomyelitis the use of a specific therapy against the agent demonstrated in cultures of blood or in biopsy is preferable. More frequently, the antibiotic treatment is empirical and this may be justified in primitive diskitis without tubercular marks or in iatrogenic infections in which S. aureus is the most common aetiological agent. If there is no clinical improvement or significant reduction of inflammation indices, after at least 4–6 weeks of therapy against Staphylococcus aureus, it is necessary to repeat the antibiogram by a biopsy or by an open surgical incision. The therapeutic choice against Staphylococcus will be decided because of its methicillin resistance: we use oxacillin if the bacteria are methicillin-sensitive or teicoplanin if the bacteria are methicillin-resistant. The therapeutic treatment generally begins during hospitalization with an association of oxacillin–rifampicin or teicoplanin–rifampicin administered by intravenous injection for 4–6 weeks or in selected cases with oral therapy with linezolid to obtain a regression of clinical signs and normalization of laboratory tests. The treatment continues with oral administration of antibiotics, including amoxicillin–clavulanic acid, minocyclin, moxifloxacin in association with rifampicin. The treatment of diskitis by Gram-negative aetiology consists of the utilization of protected ureidopenicillin (pipercillin–tazobactam), carbepenems, third-generation cephalosporins, aztreonam with aminoglycosides for 4 weeks and then quinolones. The duration of therapy is based on clinical response, inflammation indices and diagnostic imaging. In our experience, we found full recovery from disease after 3–18 months of therapy. The diskitis of Candida aetiology is treated initially with amphotericin B liposomal or caspofungin i.v. with a switch to oral fluconazole or voriconazole for at least 6 months. Tubercular diskitis needs an association therapy with isoniazid, rifampicin, pyrazinamide and ethambutol at least for 2 months followed by isoniazid and rifampicin for the successive 7 months.

Conclusions
Osteomyelitis is an infection with multiple aspects but it is always difficult to treat because of the characteristics of the microorganisms involved (adherence to bone and prostheses or biofilm production). In fact, most bone infections are chronic or become chronic with complications as sequestra or bone destruction, which can require orthopaedic interventions for debridement or consolidation. The management of these patients is complicated and needs the cooperation of clinicians, orthopaedic specialists, radiologists and nuclear medicine physicians. The objective of the diagnosis of bone infections is to identify the agent in order to provide an aetiological antibiotic therapy. When this is not possible, it becomes necessary to assess if there
is an infection or a simple inflammation or reaction to bone injury. As a start, the diagnostic flow charts of osteomyelitis require physical examination, laboratory tests and then radiological imaging. Nuclear medicine plays an important role in the diagnosis of bone infections. A three phase bone scan is more advanced than other imaging modalities in haematogenous osteomyelitis. In the follow up or after surgical interventions on bones, the importance of nuclear medicine procedures increases. In prosthetic-joint infections or in peripheral fractures radionuclide studies with WBCs labelled with either $^{111}$In-oxime or $^{99m}$Tc-HMPAO are the primary imaging modality for determining if an infection is present and to differentiate it from a simple inflammation or other bone alterations. The tracers available for assessing the activity of a bone infection also include $^{67}$Ga and $^{18}$F-FDG which are essential in the assessment of persistence or activity of a secondary infection of the axial skeleton.
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