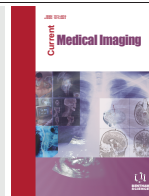


## Spine Infections: The Role of Fluorodeoxyglucose Positron Emission Tomography (FDG PET) in the Context of the Actual Diagnosis Guideline



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**Abstract:** Spondylodiscitis is an infectious process that requires numerous health care professionals to be clearly diagnosed and eventually successfully treated. It implies a variety of microbiological agents and conditions; during the diagnostic workup, it is difficult to correctly identify them, and the clinician has to rapidly choose the correct treatment to avoid permanent injuries to the patient. In this context, we conducted a review to better understand the most suitable use of Positron Emission Tomography with 18-Fluoro-deoxy-glucose (FDG PET) in a patient suspected of spondylodiscitis, based on current guidelines and literature. We wanted to review the role of FDG PET in the spondylodiscitis diagnosis and follow up in the context of the current guidelines.

**Keywords:** Spondylodiscitis, FDG PET, MR, diagnosis guideline, osteomyelitis, spine.

### 1. INTRODUCTION

Spondylodiscitis is an infectious process that involves the intervertebral discs and the adjacent vertebrae. In adults, an initial involvement of the vertebra, followed by a secondary disc infection, is more frequent. The infection may extend to the epidural space or the paravertebral space.

It is relatively uncommon as a pathology, accounting for 2-7% of all cases of osteomyelitis [1]. In industrialised nations, incidence is 1 case for every 100,000-250,000 inhabitants [2].

Males are more commonly affected than females, with a ratio of 3:2. All age groups can be affected, with an incidence peak from age 40 to 60 and another peak in teenage years [1].

The patient's age, state of health, immune status, and the etiological agent all influence the clinical-radiological presentation and the evolution of the infectious process.

The pathogenic agent can reach the spinal column through the blood from another site of infection or through direct inoculation during diagnostic-invasive procedures on the spine.

The most common vertebral site is in the lumbar region, followed by the thoracic and cervical regions, and as a rare occurrence in the sacral area [3].

The infection may be bacterial, fungal, or occasionally parasitic. The most frequently isolated etiological agents are *S. aureus* and *M. tuberculosis*.

Pyogenic infections mainly affect the lumbar vertebrae, while tubercular infections most frequently affect the thoracic or thoracolumbar vertebrae.

The main risk factors are diabetes mellitus, rheumatoid arthritis, concurrent infections, multi-system traumas, previous surgery, alcoholism, chronic hepatitis, chronic kidney failure, organ transplants, congenital and acquired immunosuppressed conditions (HIV), prolonged steroid therapy, chemotherapy, the use of urinary or central venous catheters and substance abuse.

At the onset of the pathology, it is underestimated by both the patient and healthcare professionals, as it shows specific symptoms and evolves slowly. These factors lead to a delay in diagnosis, which often leads to a serious evolution of the clinical situation, to the point of spinal deformity or severe neurological impairment.

Diagnosis requires a careful investigation of medical history, clinical evaluation, observation of the inflammation index (CRP, ESR, fibrinogen), and diagnostics using images, including MRI, X-ray, CT, and nuclear medicine [4].

Most authors maintain that surgery is essential in the event of: pharmacological therapy failure, neurological impairment, vertebral biomechanical instability, and severe deformity due to the collapse of vertebrae [5].

Prognosis is connected to the extent of the infection and the patient's general characteristics. In most cases, a clinical

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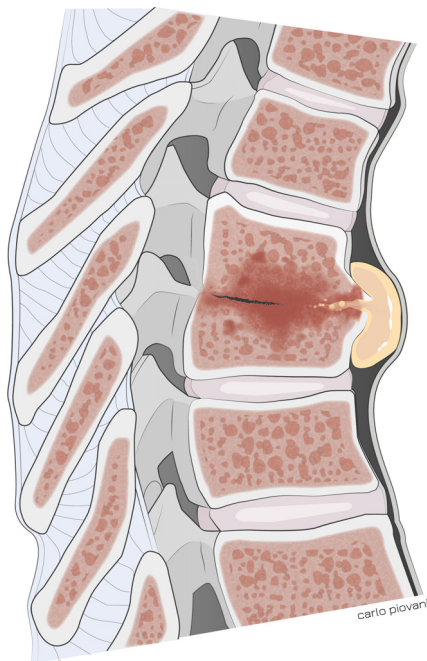
and radiological improvement can be seen in the space of 9-24 months from the onset of the disease.

Despite the arrival of new techniques, the problems of managing to achieve an early diagnosis that differentiates between spondylodiscitis and degenerative, neoplastic, and inflammatory pathologies of the spine remain. FDG PET CT has a role in this field.

### 1.1. Definition

Spinal infections include a broad scope of clinical-pathological entities. They are described in the literature in different ways. Therefore a clear, simple terminology is required. From a clinical pathological viewpoint, we can define spondylitis as the process that involves the vertebrae themselves, while discitis is when the discs and the adjacent vertebral spaces are affected. Lastly, spondylodiscitis is an infection that affects the intervertebral discs and the adjacent vertebrae.

From an etiological point of view, on the other hand, the infections can be pyogenic and granulomatous. Epidural abscesses and perivertebral soft tissue abscesses are inside-spinal canals and outside-spine sites of pus, which may be the only sign of infection. However, they are more commonly associated with spondylitis/spondylodiscitis (Fig. 1).



**Fig. (1).** Sagittal cut representation of the anatomical consequences of a thoracic spondylodiscitis. (A higher resolution / colour version of this figure is available in the electronic copy of the article).

### 1.2. Pathogenesis

Pyogenic infections tend to mainly involve the anterior elements of the spinal column, while the involvement of the posterior arch, although rare, implies a tubercular etiology.

The way in which a microorganism enters the spine may be haematogenic (otherwise known as “spontaneous”) or non-haematogenic, as in the cases of iatrogenic forms, with direct inoculation during diagnostic procedures or invasive spinal therapy. The most common causes of the haematogenic forms are other sites of infection: urinary infections, lung infections, dental infections, skin infections, endocarditis, or direct inoculation due to intravenous abuse of narcotics [6, 7].

Post-surgical forms occur, on the other hand, from direct inoculation into the intervertebral space, with an early involvement of the disc, followed by the spread to the adjacent vertebra. Iatrogenic spondylodiscitis occurs in 1-3% of adults.

Delayed diagnosis is a frequent occurrence: the pain is attributed to a normal post-surgery recovery. The MRI is difficult to interpret due to the intense, post-procedural swelling of tissues. In most cases, infection pain persists after surgery just with movement at first, but subsequently also when resting.

Early diagnosis and, even more so, identification of the etiological agent allows the correct treatment to be established in order to avoid complications (functional problems including an incapacity to return to daily activities; spinal instability and consequent pain and deformity, with the need for surgery; chronic and/or widespread infection).

With tubercular infection, spinal involvement is secondary to a diffusion of the mycobacteria through the bloodstream (miliary) or lymphatic system starting from the lungs or the genitourinary system. In this case, vertebral osteomyelitis may extend anteriorly with a paravertebral abscess, sometimes as far as the psoas or groin, or posteriorly with an epidural abscess.

The dura mater is an infection-resistant barrier: meningitis and myelitis are, in fact, exceptional complications during cases of spondylodiscitis.

Paravertebral epidural abscesses may also form without the presence of spondylodiscitis, secondary to haematogenic diffusion, traumas with superinfection of the haematoma, or iatrogenic procedures.

### 1.3. Etiology

A pyogenic infection can be distinguished from a granulomatous infection based on the type of immune response.

Several studies have shown the *Staphylococcus Aureus* as the most commonly involved microorganism in pyogenic infections (60%) and, to a lesser extent *Staphylococcus epidermidis*, group A or B *Streptococcus*, *Enterococcus*, *Streptococcus viridans*<sup>1</sup>. *Haemophilus influenzae* is more frequent in children and group B *Streptococcus* in infants. In recent years, *Kingella kingae* has frequently been isolated in children [8].

One-third of infections are caused by Gram-negative bacteria: *E. coli*, *Pseudomonas aeruginosa*, *Klebsiella*, *Serratia*, *Proteus*, and *Salmonella* [9].

*Escherichia coli* is found frequently in patients with recurring urinary tract infections, while *Pseudomonas* or *Serratia* are more frequent among drug addicts and iatrogenic forms.

The diagnosis of a pyogenic infection must be taken into consideration in any patient who arrives with lumbar or cervical pain, especially if with concomitant fever, weight loss, and high inflammation index [1].

An acute presentation with worsening pain, fever, general malaise, and weight loss is a rare occurrence; the subacute and chronic form occurs with vague symptoms, at times with thoracic, abdominal, or hip pain that may be masking lumbar pain [10]. Mortality associated with pyogenic spondylodiscitis is possible, especially in weak, elderly subjects.

The main etiological agent in granulomatous infections is *Mycobacterium tuberculosis*, followed by *Brucella species* and rarely by *atypical mycobacteria*. The most commonly affected vertebral area is thoracic [11] and thoracolumbar, followed by lumbar, cervical, or sacral. Several vertebral levels are often affected and skip lesions are found in more than 4% of cases. The epidemiology of the tubercular forms is linked to the increase in immunosuppressed conditions and secondarily to immigration from countries with high endemics.

The prevalence of tuberculosis is closely linked to HIV infection; the presence of one accelerates the development of the other. A tubercular infection has similar pathogenesis and presentation to the pyogenic form, but the path is more subtle; symptoms may be present for 3-18 months prior to diagnosis. The patient suffers progressive lumbar pain, sometimes associated with muscle spasms and rigidity. Fever appears in less than 40% of cases. High fevers, weight loss, night sweats, malaise, anorexia are rare symptoms. Neurological symptoms are found in 40% of cases [10].

*Brucella* is responsible for anthroponosis that mainly affects those who consume non-pasteurised milk or who come into contact with infected meat (butchers, veterinary surgeons). Bone involvement occurs in 2-70% of cases, with the spine being affected in 2-30%, mainly in the lumbar region. Men over the age of 50 are the most commonly affected [12]. Diagnosis is difficult as the clinical manifestations are not characteristic: pain, fever, malaise may occur at the onset or maybe present subclinically with asthenia and weakness. The Wright reaction test, which is diagnostic with a titre higher than 1:160, is used to search for specific antibodies.

Osteomyelitis caused by anaerobic bacteria is extremely rare (0.8%) [2]. They are found in particular in post-surgical forms. The most commonly isolated microorganism is *Propionibacterium acnes*, rarely *Bacteroides fragilis*, *Prevotella spp.*, and *Fusobacterium species*. If the infection originates from an extra-spinal focus, the most common sources are infections of the ear-nose-throat system, maxillofacial area, and dental infections.

Fungal infections may occur in immunocompromised patients due to opportunistic fungi such as *Candida*, *Aspergillus*, and *Cryptococcus*. Organ transplant patients have been found to be particularly susceptible. Pathogenic fungi such as *Blastomyces dermatitis*, *Coccidioides immitis*, and *Histoplasma capsulatum* may cause infections in patients who are not immunosuppressed.

Parasitic infections (*Echinococcosis*, *Onchocerciasis*, *Toxoplasmosis*, *Toxocariasis*) are much more frequent in developing countries [12].

## 1.4. Patient Evaluation

### 1.4.1. Medical History

In the event of spontaneous haematogenic infections, the primary infection site must be quickly identified: genitourinary, lung, skin, dental, or post-surgery infections.

Predisposing factors in elderly patients are often the presence of associated pathologies (diabetes, tumours), a higher frequency of surgical procedures, and a higher predisposition to asymptomatic urinary infections. In young patients, the incidence is especially linked to the increase in substance abuse and endocarditis.

In children, discitis occurs as an infection *ex novo*. The disc is vascularised and permits bacterial diffusion to the area. Spinal infections in children are rarer than in adults and account for 2-4% of paediatric osteomyelitis. The average age for the onset is approximately 3-5 years of age, even though it can also occur in infants and adolescents [13].

### 1.4.2. Clinical Evaluation and Physical Examination

In 80-90% of cases, the most frequent symptom found is pain; it may have been present for months or years to various degrees and is usually aggravated by movement and partly alleviated by rest. The most frequent sign is the intensification of pain on palpation or percussion of the affected vertebral region. One-third of patients have a fever.

Other aspecific symptoms, although less frequent, are weight loss, night sweats, general malaise, and asthenia.

Symptoms in paediatric spondylodiscitis are lumbar pain, sometimes radiating to the legs, paravertebral muscle spasms, stiffness, refusal to walk or sit down. The child may or may not have a fever, or it may only be slight. Spondylodiscitis in children tends to resolve spontaneously without treatment, and in more than 40% of cases, culture tests are negative. However, in some cases, kyphotisation of the moving segment may be severe and require suitable brace treatment.

In cases of spondylodiscitis affecting the cervical region, muscles may be contracted with rigidity, stiff neck, and if the patient is suffering from dysphagia and breathing difficulties, the development of a retropharyngeal abscess should always be suspected [1].

Symptoms of the formation of epidural abscesses is similar to that of osteomyelitis, but they differ in: more rapid de-

velopment of neurological symptoms, more common presence of fever, and signs of meningeal irritation. From the moment a situation of neurological symptoms appears, it tends to progress until a procedure is carried out to decompress the nervous structures: this is a surgical urgency.

A delay in diagnosis is extremely frequent as the symptoms are often insidious, vague, and aspecific. The patient underestimates the problem for a long time, and the doctor may not suspect it, thus falling afoul to diagnostic errors. Several scientific studies report a period of 2-6 months between the onset of symptoms and diagnosis<sup>1</sup>. Spondylodiscitis should be suspected in patients with spinal pain in order to perform a correct diagnostic-therapeutic approach and to prevent neurological complications and deformities that are often invalidating.

## 1.5. Diagnosis

### 1.5.1. Laboratory

During inflammation, the C-Reactive Protein (CRP) and Erythrocyte Sedimentation Rate (ESR) are often high, while the leukocyte count is often normal or only slightly raised.

The ESR is high in 70-97% of children with vertebral osteomyelitis, while in adults, it is 50 mm/h higher in 67%. It is, however, not specific, as it is found to be out of range in all inflammatory conditions and various pathologies. The CRP seems like a more sensitive, specific value, but like the other indicators, it cannot differentiate between granulomatous infections and pyogenic infections or neoplastic tumours.

An increased CRP is an early indicator of infection, but, more so, the return to normal values indicates that the process has been resolved.

It returns to normal in approximately 14 days following surgery, therefore in less time than the ESR.

Blood cultures must be carried out at the peak of fever, but positive results are only found in a relatively low percentage (20-30%) [14].

Urinary culture tests can also be carried out as routine to exclude the presence of a remote infection site.

### 1.5.2. Imaging

(Please refer to the next chapter for more information on this topic)

### 1.5.3. Biopsy

Etiological diagnosis accuracy depends on biopsy. In more cases, these are carried out using a CT-guided fine-needle aspiration. This procedure is now routine on the lumbar or thoracic region, while for the cervical region, it must be evaluated and entrusted to expert hands. Many authors suggest open biopsy procedures if, when there is a high clinical or radiological suspicion of spondylodiscitis, it is not possible to obtain a suitable tissue sample or isolate the pathogenic agent [15]. The biopsy provides for a morphological,

microscopic, and cultural examination, for a certain identification of the etiological agent, and to differentiate the diagnosis from neoplastic tumours (it is important to also carry out microbiological tests as well as histological tests). It is essential to establish a correct antibiotic treatment when used together with an evaluation of pharmacological sensitivity.

A CT-guided percutaneous biopsy allows the etiological agent to be isolated in 20-90% of cases [10, 14, 16]. Considering the high percentage of failures but also the fundamental importance of an etiological diagnosis, it is important to repeat the procedure even three times if necessary. To increase the success percentage, perform a large-core needle (8G) biopsy and not a FNAB (Fine needle aspiration biopsy).

The inability to identify the pathogenic agent does not necessarily exclude the fact that there has been an infection, nor does it mean that antibiotic therapy chosen empirically will not be successful in these patients.

The only absolute contraindication of the CT-guided needle biopsy is the severe alteration of coagulation processes.

Special attention must be paid in the case of suspected Echinococcus infection: the needle biopsy may cause an anaphylactic shock.

## 1.6. Treatment

Treatment aims to eradicate the infection, prevent or reduce neurological impairment and deformities, control the pain and restore mobility.

### 1.6.1. Antimicrobial Therapy

Optimal therapeutic management of pyogenic vertebral osteomyelitis is based upon a targeted antimicrobial treatment, with no necessity of surgery in the majority of cases.

Most patients affected by native vertebral osteomyelitis show no neurological symptoms and no signs of sepsis; in these cases, international guidelines suggest focusing on microbiological diagnosis, holding antimicrobial treatment [17].

Conversely, in the case of sepsis, progressive neurological deficits, or the absence of a microbiological diagnosis (despite adequate and invasive procedures), an adequate empirical antimicrobial therapy should be promptly started. The choice of empiric antimicrobials should cover the most common etiological agents (such as *Staphylococcus* spp, *Streptococcus* spp, and Gram-negative bacilli) using agents with a favourable PK-PD (pharmacokinetic/pharmacodynamic modeling) in terms of bone penetration, activity in biofilm. No randomized trial provides definitive evidence of the superiority of an agent over the other, therefore the choice must be individualized on each patient characteristics, risk factors and local antimicrobial resistance epidemiology.

Antimicrobial treatment duration is also a matter of debate. In past years most experts agreed on a standard treatment duration of at least 12 weeks, given the limited antibiotic penetration into the bone and the need for several weeks

for the bone to revascularize. However, some small retrospective cohorts started suggesting that a shorter antibiotic course may be equally effective in some special populations [18, 19].

In 2015 Bernard *et al.* published a multicenter, open-label, non-inferiority randomized controlled trial demonstrating no difference in cure rates between patients with microbiologically proven pyogenic vertebral osteomyelitis treated with a 6-week targeted antibiotic treatment *vs.* a 12 weeks course [20]. Nevertheless, in this study, non-inferiority of a 6-weeks treatment was not achieved in some subgroups where a longer treatment length may be considered: age >75 years, immunosuppression or diabetes, endocarditis, and presence of neurological signs. Some limitations of this study include the low incidence of spinal abscesses (only 19%) and the low incidence of MRSA (only 5.5%).

Park *et al.* suggested that patients affected by a microbiologically proven vertebral osteomyelitis with at least one risk factor for recurrence (MRSA etiology, undrained paravertebral abscess, and end-stage renal disease) should be treated for  $\geq 8$  weeks. In the absence of these risk factors, the likelihood of relapse in patients treated for < 8 weeks was low [21].

In this scenario, no standard treatment schedule can be proposed. However, therapy should be individualized again on patient's risk factors, on radiologic findings (abscess, *etc.*), on etiology, and considering clinical and laboratory follow-up (normalization of signs, symptoms, and inflammatory markers) [22].

Given the poor antibiotic penetration into bone tissue, most experts suggest treating vertebral osteomyelitis with a parenteral course of antimicrobial therapy in order to achieve the best PK/PD. However, prolonged parenteral treatment for bone infections implies management difficulties, the major costs, and especially adverse events related to parenteral infusion.

Oral antimicrobials with excellent bioavailability, including fluoroquinolones, rifampin, linezolid, tetracyclines, and cotrimoxazole allow an early switch to the oral route without compromising efficacy [20, 23, 24].

The best evidence supporting oral treatment for bone infection is provided by OVIVA trial, showing that oral antibiotics were non-inferior to intravenous antibiotic therapy for complex orthopedic infections [25].

IDSA guidelines published in 2015 underline the efficacy of early switch from parenteral to highly bioavailable oral antibiotics. Nevertheless, they do not define patients who may benefit from a parenteral to oral conversion nor the optimal timing for the switch [17].

Finally, no trial has investigated so far the efficacy and safety of an entirely oral treatment for some subgroups of patients affected by vertebral osteomyelitis.

Medical therapy efficacy is evaluated based on clinical improvement (reduced pain and fever, restored mobility), radiological improvement, and inflammation index improvement.

If CRP is not helpful, repeated FDG PET scan SUV comparison can be extremely useful in the evaluation of therapy efficacy and patient response.

Therapy is said to have failed if, after 1 month of treatment for pyogenic infections, or 3 months for tubercular infections, the symptoms persist or worsen, if the ESR and CRP remain high, or if the radiological images show persisting infection.

### 1.6.2. Orthopaedic Treatment

The objectives of non-invasive treatment are:

- To achieve “no mechanical stress/stability” of the area affected by the infection, to allow healing;
- To avoid the onset of spinal deformity (kyphosis-scoliosis).

For this purpose, in addition to bed rest, several types of supports, busts, and plaster casts are used that the patient must wear until recovered. This type of treatment is especially effective in paediatric spondylodiscitis, also preventing possible kyphosis.

These containing devices differ depending on the spinal region that needs immobilising.

### 1.6.3. Surgery

Indications for surgery consist of: neurological impairment, spinal instability or deformity, failure of medical therapy, need for cultural isolation, abscess drainage.

Surgery aims to remove the infected tissue (*debridement*), decompress the nervous structure, and maintain a correct alignment of the spinal.

Surgery is resorted to if there is no improvement after 2-3 weeks of intravenous antibiotics if pain persists, the radiological picture deteriorates, or if there is a development of mechanical instability or progressive deformity.

Surgical drainage is the preferred treatment for epidural abscesses, together with intravenous antibiotic therapy.

Early surgical decompression brings about a rapid improvement of the neurological situations, reduces kyphotic deformities, and lends stability through bone fusion, which should always be sought if compromised by the pre-surgical infection or by decompressive surgery.

After years of debate about the suitability and possible risk of using metal instruments to treat an acute infection, it would seem that there is no longer any doubt about the primary need to stabilise the infected segment of the spine and about the safety of implants (naturally after ample surgical cleaning and washing). It seems that titanium is safer than steel: the latter, in fact, allows a pseudocapsular coating to form, which is the ideal site for bacterial replication, while titanium, which is more porous, allows soft tissues to integrate and does not hinder antibiotic actions, even on the metallic surface. Several articles have recently been published that confirm the safety of titanium cages used to reconstruct the anterior column in cases of spinal infection [26].

## 1.7. Prognosis

In most cases, medical treatment provides a clinical, radiological solution to the infection in a period of 9-12 months. The relapse rate is 0-4% after correct treatment [27].

Delayed complications may sometimes occur (kyphosis, neurological impairment), especially in the period when the infection has been controlled. However, the infected tissue has not yet been replaced by newly formed bone.

Long-term complications depend on the patient's general and immune state, the delay in reaching a diagnosis, and the degree of neurological compromise at the time of diagnosis.

Some of the risk factors of long-term disability are the presence of neurological impairment at diagnosis, a period longer than 8 weeks between the onset of symptoms and diagnosis, and the concurrent presence of a debilitating chronic pathology [28].

## 2. STATE OF THE ART: TRADITIONAL IMAGING IN SPINAL INFECTIONS

### 2.1. Introduction

The gold standard in the radiographic diagnosis of any inflammatory disease, including infections, is the Magnetic Resonance, which represents the most sensitive radiographic modality in detecting vertebral osteomyelitis and epidural abscess (An, 2006). CT could be contemplated in those cases when MRI is not available. Conventional radiographs can demonstrate advanced diseases, but additional imaging would be required to assess the extent of disease and the presence of complications (epidural or paraspinal abscess). Radionuclide scanning may be useful if MRI is contraindicated or not enough to clarify the diagnosis (claustrophobia/presence of implantable devices that are incompatible with MR / differential diagnosis with other spinal inflammations) [17].

A biopsy is still warranted to confirm clinical and/or radiographic suspicion of vertebral infection and establish a microbiologic or histologic diagnosis. A biopsy can be achieved with an open procedure or as a needle biopsy under CT guidance.

### 2.2. Magnetic Resonance Imaging

MRI is the most reliable method to diagnose spinal infections [29] due to its elevated sensitivity (96%) and high specificity (94%), and ability to offer radiological high-quality details on paraspinal tissues and epidural space [30].

Decreased T1 bone/disc signal intensity, decreased definition of the endplate definition, and increased T2 bone/disc signal intensity constitute clear signs of spondylodiskitis. Intravenous contrast administration would show signs of infection as well as the T2 weighted sequences. Therefore, justification of the ever so rare possibility of an allergic reaction has to be considered. The contrast would offer additional information in those cases where a paraspinal abscess or phlegmon is suspected (ring enhancement of paraspinal abscesses

formation and homogeneous enhancement of paraspinal phlegmons). The extension in the paraspinal tissues is more common in tuberculosis and less common in bacterial infection.

Infection-related MRI findings could be appreciated as early as 2 weeks from the onset of symptoms [31].

False negatives have been reported in patients with epidural abscess and meningitis, and false positives are possible in case of bone infarction or fracture [32].

One of the pitfalls of the MR investigation is the lack of differentiation between malignancy, fracture, and infection, particularly in those rare cases when the disc is spared [33].

In fact, despite remaining the radiological gold standard, the MR cannot offer a specific pathognomonic finding that dependably discriminates between spinal infection and possible neoplasm [30].

### 2.3. Computed Tomography Imaging

CT signs of vertebral infection are shown earlier than they become appreciable on plain radiographs. However, it may take 3 to 6 weeks after the onset of symptoms for bony destruction to become evident, which would result in a delay in diagnosis [34, 35].

Although it shows well-detailed bony sequestra and involucra, the results from computed tomography show early structural changes with poor definition and have a high false-negative rate for epidural abscesses [29].

This makes the CT investigation a less suitable tool for the diagnosis of spinal infections. Nevertheless, CT is commonly used in CT-guided biopsy and for instrumentation procedural planning [36].

### 2.4. Conventional Radiography

Despite its low specificity (59%) and low value in detecting early irregularities of the vertebral endplates and/or intervertebral disc height changes, a number of literature studies still report that plain and flexion/extension X-ray should be performed in every baseline evaluation. This is likely related to the fact that a possible instability during follow-up can be detected reliably by flexion/extension films [30].

Most of the time, plain films are normal in the early phases of spinal infection and only become positive when there is obvious dysmorphism of the vertebral bodies, which might not be appreciable for 3 or more weeks after the onset of symptoms [37, 38].

Isolated infections to a single vertebral body are rare, but mimic vertebral compression fracture on X-ray [39, 40].

### 2.5. Conventional Radionuclide Scanning

Radionuclide scanning is a valid alternative to MR (when this is contraindicated) or a useful adjunct to diagnosis when radiographic changes on plain films or CT scans are absent or equivocal and the suspicion for infection is high [41].

In one prospective study including 32 patients with suspected vertebral infection, MRI performed better in detecting epidural/spinal abscess, and 18-fluorodeoxyglucose (FDG) positron emission tomography (PET) scanning was more useful for metastatic infection [42].

<sup>18</sup>F-FDG-PET/CT scanning is highly sensitive. The specificity is also reasonably high but may be decreased by tumors, degenerative spinal diseases, and spinal implants [43] (see the following chapter for FDG PET/CT).

Gallium imaging is both sensitive and specific for vertebral osteomyelitis, showing vivid uptake in two adjacent vertebrae with loss of the intervening disc. In a study recruiting 41 patients with suspected vertebral osteomyelitis, increased gallium uptake was detected in 100% of patients with positive biopsy results [44].

Three-phase bone scintigraphy using labeled technetium is a relatively sensitive and specific test. However, it may produce false positives in patients with noninfectious injuries such as fracture and false negatives in early infections or concomitant bone infarction.

Labeled leukocyte scans are not useful for the diagnosis of vertebral osteomyelitis [43].

### 3. FDG PET/CT IMAGING

#### 3.1. Materials and Methods

We searched English publications in PubMed and PubMed Central with publication date from 2000 to July 2020 with a first search string ((PET) OR (Positron emission tomography)) AND ((Discitis) OR (Spondylodiscitis) OR (spondylodiscitis) OR (espondilodiscite) OR (spondylodiskitis)) which yielded on PubMed Central 383 papers and on PubMed 90 papers and a second search string with terms “spine” [MeSH Terms] AND “infections” [MeSH Terms] AND (“positron-emission tomography” [MeSH Terms] OR “positron-emission” [All Fields] AND “tomography” [All Fields] OR “positron-emission tomography” [All Fields] OR “positron” [All Fields] AND “emission” [All Fields] AND “tomography” [All Fields] OR “positron emission tomography” [All Fields] OR PET-FDG [All Fields]) which yielded 22 papers on PubMed Central and 60 paper on PubMed. After checking for duplicates, our search yielded for a total of 213 papers.

We included clinical trials, case reports, case series, and retrospective cohort studies in English in which there was evidence or the suspect of a spine infection. It was carried out at least one PET/CT with F18-FDG exam during their clinical course.

We included 36 papers between 2001 and august 2020 in our literature review.

In this paper, we will focus on the use of the PET/CT in the clinical setting of spine infections, its use for diagnosis in combination with other radiological imaging, its possible use in differential diagnosis from infectious and non-infectious diseases, and its clinical advantages in treatment fol-

low up. We will also glance at the future perspective of PET/CT and their use in the clinical course of spine infections.

#### 3.2. Principles of PET Imaging

PET (positron emission tomography) is an imaging technique that is suited to estimate *in vivo* and non-invasively the metabolism, function, or receptorial expression of body tissues and organs. A PET/CT scanner consists of a combination of a PET scanner and a CT scanner with the facility to fuse the PET image series (metabolic or receptorial study) with the CT image series (anatomical study): this allows accurate localization of any pathological PET finding with great detail. The CT component is also essential for providing an attenuation map to enhance the contrast resolution of the PET images. Several different PET tracers can be injected but the most widely employed, especially in the field of infective – inflammatory diseases, is <sup>18</sup>F-FDG (<sup>18</sup>F-Fluoro-deoxy-glucose). This tracer is a glucose analog, binding into cells with increased glucose consumption, which is the case of, for example, osteomyelitis or spondylo-diskitis [45, 46].

Technically, a small amount of tracer is injected intravenously after asking the patient to fast for at least 6 hours. This period of fasting is mandatory as postprandial circulating insulin diverts the tracer to muscles and, therefore, significantly reduces the amount available tracer for uptake into pathological sites. In this situation, sensitivity for small lesions may be decreased. For the same reason, it is not recommended to inject insulin in a diabetic patient before the procedure. After the administration of <sup>18</sup>F-FDG, the patient is asked to relax for approximately one hour. This period is needed to allow an adequate and stable (steady-state) accumulation of <sup>18</sup>F-FDG in normal and dysmetabolic tissues as well as to allow a sufficient renal excretion of unbound tracer, reducing the background signal [47].

Then, the patient is positioned supine (however, any preferred decubitus is allowed) under the tomograph, and PET images are recorded. They are subsequently reconstructed and corrected for attenuation with a corresponding CT attenuation map, acquired in a low-dose modality and, generally, non-contrast-enhanced. The scan usually encompasses the whole body. A complete scan takes approximately 15-25 minutes to be completed, but this is variable depending on the patient’s height and the scanner sensitivity.

A final PET/CT image can be read in a multiplanar modality with an axial, sagittal, and coronal cut.

In adults, <sup>18</sup>F-FDG uptake can be quantified using the maximum Standardized Uptake Value (SUV), which is an index of tracer uptake within the lesion: the higher the SUV max, the higher the glucose consumption. Hypermetabolic pathological processes are typically areas of malignancies and inflammations, which can be detected with high sensitivity. One interesting aspect of PET is that SUV max changes rapidly after the administration of one specific antineoplastic or anti-inflammatory therapy, making PET an optimal tool

not only for diagnosis but also for therapy assessment, both early after onset or at the end of treatment [48].

It is of great importance to remind that some tissues normally present a high FDG concentration. Some of them have a natural high glucose consumption, such as the brain or the myocardium (except for cases undergoing the scan after prolonged fasting). Other tissues contribute to eliminating the unbound tracer: kidneys, ureters, and urinary bladder. Other tissues have natural and unrestrainable motility, such as the bowel and the stomach. These areas can be less accurately studied.

The spine and bones in general, on the contrary, are optimal sites to evaluate with FDG PET/CT since the physiological background is really reduced.

### 3.3. FDG PET/CT in the Context of Imaging Assessment of Spine Infection

Diagnosis of spinal infection has always been an issue; in the last years, many authors tried to answer the unsolved questions in the diagnostic work-up of patients with clinical suspects of spondylodiscitis.

Through the years, few guidelines have been published: the Infectious Diseases Society of America (IDSA) guidelines, published in 2015, guide diagnosis and treatment of native vertebral osteomyelitis, without addressing secondary spondylodiscitis, such as post-surgical SD [17], and they also take into limited consideration radiologic and nuclear medicine techniques for the assessment of spine infection.

In 2011 Gasbarrini *et al.* [49] drew up a guideline from a multidisciplinary management project (SIMP); through a multidisciplinary work panel, they prospectively collected data on spine infection applying a previously elaborated flow chart [50]. In the SIMP flow-chart are included both MRI and FDG-PET/CT, where PET increases the diagnostic accuracy of MR, especially when it was impossible to distinguish between severe degenerative process (negative at FDG-PET/CT) and infective processes [49, 51, 52].

In 2019 a wider consensus and flow chart were composed by a joint EANM/ESNR and ESCMID-document for the diagnosis of spine infection in adults [53], taking into account the different imaging modalities available. The authors analysed a variety of aspects about the difficulty of getting through the diagnosis of SD.

MRI is the most sensitive, specific, and accurate imaging modality for SD diagnosis. This is correlated to the high contrast resolution, direct multiplanar imaging capability, high sensitivity for soft tissue and bone marrow abnormalities, the absence of ionising radiation, which makes MRI the reference standard for imaging of spinal infections also in the postoperative setting, whereas it is usually not indicated inpatient follow-up, as MRI findings can worsen despite clinical improvement [54, 55].

Although MRI is the most often used imaging technique in diagnosing SD, it has few disadvantages (metal devices implantation after back- surgery, degenerative changes, such

as Modic 1 type change, no morphological changes in first 2-4 weeks of infection) [55-57]; Few authors have discussed the possibility to overcome these problems by the use of an FDG- PET/CT scan to increase the sensibility and specificity of the diagnosis [58].

### 3.4. Advantages of PET/CT in Comparison to MRI

The urge to get through the diagnosis of SD with functional imaging has been known since the early 2000s [59].

In these last 5 to 10 years, both retrospective and prospective studies have been published about the possible use of FDG PET/CT where MRI is inconclusive or could lead to a misleading result.

In a prospective study, Stumpe *et al.* [58] demonstrated that FDG PET/CT is a specific imaging modality to differentiate between Modic changes, in particular, Modic I and infection. In their study, FDG accumulation was absent at all disk levels with the degenerative disease diagnosed on MR images [58]. These findings induced greater cohort studies.

Gratz *et al.* [60] showed that FDG- PET/CT is superior to MRI in those cases of postoperative infection of the operative site in the presence of metal clips because functional imaging is not affected by metal artefacts. In their study, FDG-PET/CT was the only imaging procedure to elucidate the extension of the infection. The only indeterminate case they had was due to a case of a recent vertebral fracture; it is well known that increased bone remodelling can lead to false-positive results. FDG -PET/CT was superior to all the other diagnostic imaging modality such as <sup>67</sup>Gallium-citrate [60].

In 2003 De winter *et al.* prospectively investigated the value of FDG- PET/CT in patients suspected of having spinal infection after earlier surgery of the spine. In this study, FDG-PET/CT showed an overall sensitivity, specificity, and accuracy of 100%, 81%, and 86%, respectively. In the group without metal implants, false-positive occurred only in the first 6 months after surgery, and in the group with metallic implants, false positive were not confined to recently operated patients [61]; this could mean a possible instability of material which is causative of mimicking infection through a foreign body reaction [61].

As we already mentioned, FDG- PET/CT, as stated by Othori *et al.* [51], is a trustworthy imaging modality to differentiate between Modic changes type I (segmental hypermobility) and initial stadium of infectious SD; even though they suggest and strengthen the results previously reached by Stumpe *et al.* [58] they also suggest that FDG- PET/CT should not be used alone to diagnose infectious SD but in addition to other imaging modality as support in infectious SD diagnosis, where it is unclear by other imaging modality if it's common Modic change or spinal infection.

In 2013 Hungenbach *et al.* [62] retrospectively examined a total of 42 FDG- PET/CT with the indication to find active infectious foci suspected to be SD in a patient who was previously operated on of spine surgery and /or had aspecific findings. This study showed how a qualitative



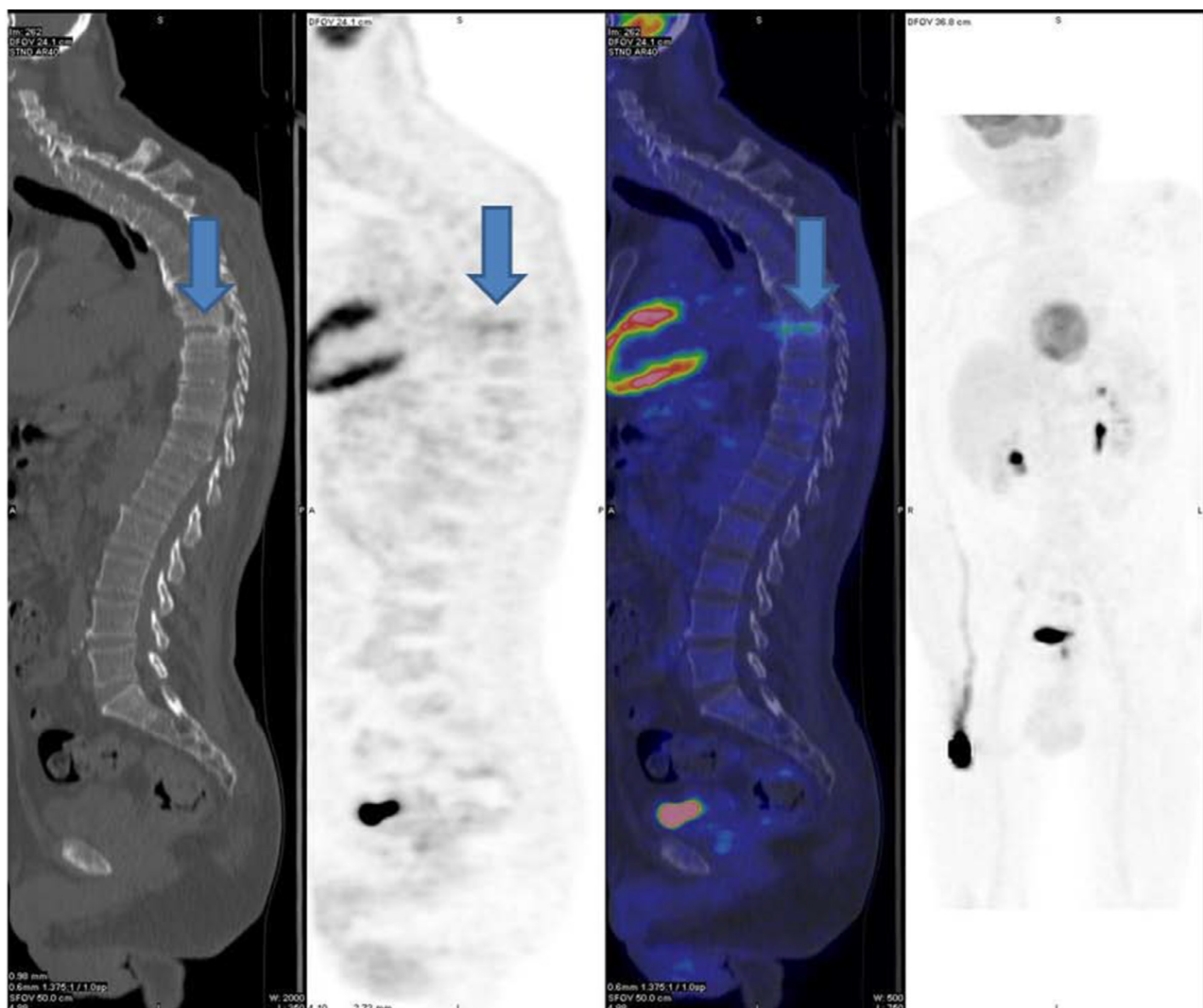
analysis with a differentiation of the pattern up-take in scores can differentiate the uptake pattern from aspecific until clear spondylodiscitis.

Score 0: Normal findings and physiological  $^{18}\text{F}$ -FDG distribution. Score 1: Slightly elevated uptake above physiological bone marrow uptake in the intervertebral or paravertebral region. Score 2: Clearly elevated uptake above physiological bone marrow uptake of a linear or disciform pattern in the intervertebral space (Fig. 2). Score 3: Clearly elevated uptake above physiological bone marrow uptake of a linear or disciform pattern in the intervertebral space and involvement of ground or cover plate or both plates of the adjacent vertebrae (Fig. 3). Score 4: Clearly elevated uptake above physiological bone marrow uptake of a linear or disciform pattern in the intervertebral space and involvement of

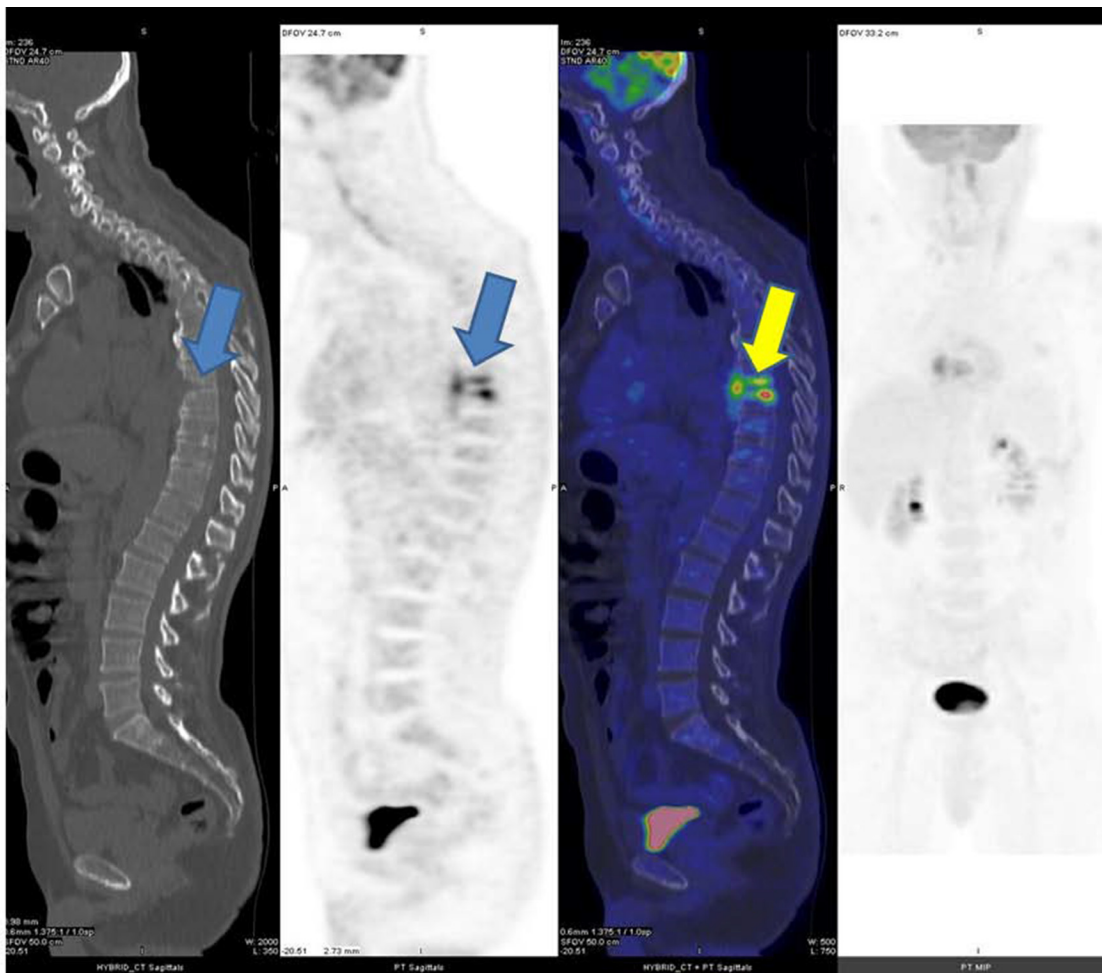
ground or cover plate or both plates of the adjacent vertebrae + surrounding soft-tissue abscess [62].

It has been shown that the detection of spondylodiscitis using FDG uptake pattern had a sensitivity of 86% and a specificity of 95%. The only false-positive result came from a patient who had recent sintering of a vertebral body, and three false-negative results were found to be in patients with a chronic low infection level and with a blood glucose level of 18.9 mmol/L, which affected the FDG uptake in tissues.

This study showed how FDG uptake pattern in an FDG PET-CT scan is of easy and immediate use to distinguish those cases in which conventional imaging results are inconclusive [62] and how the additional functional imaging can help in the workup of the diagnosis of a difficult and rare disease as it is SD.



**Fig. (2).** FDG PET/CT scans of a patient with clearly elevated uptake above physiological bone marrow uptake of a linear or disciform pattern in the intervertebral space (Fig. 2 is a sagittal cut, Fig. 2 bis is an axial cut). (A higher resolution / colour version of this figure is available in the electronic copy of the article).



**Fig. (3).** FDG PET/CT scans of a patient with clearly elevated uptake above physiological bone marrow uptake of a linear or disciform pattern in the intervertebral space and involvement of ground or cover plate or both plates of the adjacent vertebrae Fig. (3) is a sagittal cut, (Fig. 3) bis is an axial cut). (A higher resolution / colour version of this figure is available in the electronic copy of the article).

Lately, few authors [42, 63-66], both with retrospective and prospective studies, have examined the diagnostic value of  $^{18}\text{F}$ -fluorodeoxyglucose (FDG-PET/CT and MRI in diagnosing SD and its complications (*i.e.*, epidural and paraspinal abscesses). They concluded that the two techniques are both necessary in diagnosing vertebral osteomyelitis SD and could be considered complementary or a valid alternative to MRI [64]. FDG-PET/CT is a robust diagnostic tool to diagnose postoperative hardware related spinal infections [65], and the advantages of an FDG- PET/CT are the larger field of view (FOV), allowing diagnosis of regional abscesses that can be missed on MRI [42, 67] and the visualization of metastatic infection especially in patients with bacteremia, and the possibility to avoid metal implant artifacts [42].

### 3.5. Differential Diagnosis with Functional Imaging

Getting through the diagnosis of SD is a complex issue that requires many professionals. FDG-PET/CT is a valid alternative to clear doubts when MRI is inconclusive or misleading [42, 67].

As stated above, FDG PET/CT has a specificity of 95% [42, 62] modality to differentiate from Modic I changes and an infective/inflammatory disease in the suspect of SD.

FDG-PET/CT is also useful to differentiate from acute osteoporotic fracture and other causes of back pain [68]. It has been shown that an acute osteoporotic fracture does not have any FDG uptake, and it can be expected that FDG-PET/CT allows the differentiation of osteoporotic vertebral fractures from pathological fractures due to malignancy or inflammatory disease, such as SD. It has to be reminded that FDG is not tumour or infective specific [69, 70], and it could help in the identification of the right site for biopsy [71, 72]. It has to be mentioned that FDG uptake was found in inflammatory and rheumatologic diseases [73, 74], such as aseptic spondylodiscitis in a patient with HLA-B27 positive patient [74]. We always have to remember that FDG is not specific for the presence of microorganism, but the presence of our immune system reaction to external offences and increased metabolism cells, such as tumoral ones.

Before an FDG PET-CT examination, the nuclear physician needs a clear clinical query and an exact clinical history of the patient with his previous oncological and rheumatologic diseases well declared in order to be as specific as possible for the clinician in his diagnosis work-up.

### 3.6. Different SUV uptake for Different Bacteria

What is missing from all the guidelines we found is whether FDA-PET/CT can give a suggestion on which bacteria takes part in the infectious process. There is truly little evidence about this topic. In an *in vitro* experiment [75], the authors tried to investigate whether or not the bacteria metabolism contributes to the FDG uptake; they found that bacterial pathogens, both Gram-positive and Gram-negative, may contribute to the signal observed in FDG PET/CT imaging and that infecting bacteria potentially contributes to the overall signal detected by PET imaging of bacterial infections. To the extent of our knowledge, it is the inflammatory status of the infected tissue that impact the SUV total signal [76], and this means that things get complicated in an *in vivo* clinical setting, where the total SUV will be different for individual patients' immune system response and the acute/chronic infection is an extremely hard issue to analyse in the clinical setting.

The FDG uptake of the infection may be extremely variable: from a subtle/moderate uptake in the capsule of a *Mycobacterium TB* cold abscess and low in the centre, due to its necrotic nature [77], to an avid FDG uptake [52]. Some authors stated that FDG PET/CT might help in the differential diagnosis through the analysis of SUV, especially in distinguishing a tuberculosis infection from a pyogenic one [52, 78].

Lee *et al.* [52] analysed 22 consecutive patients suspected of having SD by the clinical and radiological suspect. After a biopsy of the infected site, 11 of them were diagnosed with pyogenic SD and the remaining 11 with tuberculous SD. With their study, they wanted to find a statistical significance difference between the SUVmax, SUVmean in dual time point imaging FDG-PET/CT to differentiate between a pyogenic SD and a tuberculous SD. They found that there is no significant statistical difference for dual-time point imaging and SUVmean to differentiate from a pyogenic or a tuberculous SD, but the SUVmax value has a significant statistical difference in order to differentiate between them.

Bassetti *et al.* [78], in their retrospective study with 30 patients (10 cases and 20 control), observed a significant difference between SUVmax in TBSD and control patients showing a cut-off value above 8, more often associated with TBSD disease compared to pyogenic spondylodiscitis.

In a most recent study [79], on the other hand, it has not been shown any significant difference between the two entities. Therefore they suggested that SUVmax values are inconclusive for differentiation between the two infection types.

All the studies enrolled a small number of subjects which results in a numerosity bias.

In the UDIPROVE study [72], it has been noticed that the SUVmean was higher for tubercular VO when compared with pyogenic spondylodiscitis.

The association of specific FDG-PET/CT features with tubercular, such as high SUV, has been reported but remains to be definitively determined.

What is known about SUV is that where it is the highest, it is a good target for biopsy [80].

### 3.7. Follow Up

The prompt evaluation of the antibiotic therapy response is very problematic for clinicians since inflammatory indexes may not currently be accurate enough, and standard imaging does not show acceptable sensitivity; a follow up with MRI would be worthless and even misleading, and it is not usually indicated in patients follow-up, as MRI findings can worsen despite clinical improvement [54, 55]. The definitive assessment of complete healing comes only months after completion of therapy. This extraordinarily long time is clinically unacceptable if therapy is unsuccessful. Conservative management aims to avoid major surgery, and it brings significant advantages in terms of reduced risks and high probability of cure. However, the mobilization of the patients comes months after diagnosis. This approach is mandatory because spine infections are recognized as strong predisposing factors to vertebral fractures, leading to deformity and, in the worst cases, paraplegia [81].

In order to overcome these difficulties, it has been investigated the value of FDG PET/CT examination in the therapeutic follow-up of the SD patients. Despite its relatively low specificity of radiopharmaceuticals available to study spine infection, radionuclide imaging is deeply recommended for assessing disease activity during follow-up after medical therapy [72, 80-84].

In 2009 Kim *et al.* [84] designed a prospective study in order to assess whether FDG PET/CT follow-up imaging after treatment in patients with spinal infection could provide useful prognostic information and determine the residual SI. The study proved that the application of quantitative indexes of FDG PET/CT to initial and follow-up images after treatment of SI express useful prognostic implications regarding residual or non-residual diseases; the SUVmax and SUVmean had optimal diagnostic efficacy for discriminating residual and non-residual SI.

These results were also confirmed by Nanni *et al.* [81]: according to their results, a decrease in SUVmax (evaluated before therapy and 2 to 4 weeks after the start of therapy) of at least 34% is highly predictive of a complete response, providing a sensitivity and specificity of 82%. Although no statistically significant difference was found between the global performance of delta-SUVmax and delta-C Reactive Protein in this preliminary study, delta-SUVmax supplied a higher sensitivity for the early identification of responders. This may have a strong influence on the clinical management of patients since CRP is known to be falsely negative from the start in a significant percentage of patients (approx-

mately 10% in our series). Their results show that FDG PET/CT may be used as a tool to assess the response to antibiotic therapy incredibly early in patients affected by haematogenous spondylodiscitis, especially in those with a non-diagnostic CRP test at diagnosis.

Riccio *et al.* [83], in their study, analysed the changes in SUVmax after antibiotic treatment, finding that it may be difficult to differentiate between residual uptake of inflamed intervertebral disc and residual infection, suggesting that, even though intervertebral discs are a-vascular, the infection may stimulate angiogenesis within them and the possibility to keep seeing vertebral uptake even after the infection is clinically resolved.

Russo *et al.* in 2019 described the UDIPROVE protocol [72], the management of vertebral osteomyelitis, together with the role of FDG-PET in diagnosis and FU of SD, over an eight-year period: they assessed that FDG-PET/CT together with CRP is associated with higher accuracy in the monitoring of the response to therapy and it can contribute to the early determination of the response to therapy.

Some most recent studies analysed the usefulness of FDG-PET/TC in antibiotic therapy monitoring treatment response; they executed an FDG-PET/TC scan after 2 and 3.6 months which showed an overall improvement in 82% of the cases, whereas MN monitoring showed no change or worsened appearance: they concluded that FDG-PET/TC is a valuable method to assess treatment response to therapy [82].

The SIMP flow chart revision, which aimed to standardize the diagnostic process and management of spinal tuberculosis, FDG-PET/CT was used in 90% of the cases during diagnosis. In 89.5% of the cases confirmed the diagnosis of spondylodiscitis through the increased SUVmax. They performed a PET/CT in 68% of their patients at the end of treatment (range between 9-22 months), which demonstrated that after treatment, there was the normalization of SUVmax in 70% of patients and a SUVmax reduction of the remaining 30% [80].

FDG-PET/CT is a useful technique in order to understand if there is an early response to antibiotic therapy [81] or if therapeutic approach should be changed.

### 3.8. Future Perspectives: PABA, Radiolabelled Antibiotics

One issue of FDG PET/CT is the aspecific nature of the signal derived from FDG uptake. In fact, FDG accumulates in the same way both in sterile inflammations and in areas of inflammation caused by a bacterial infection. Although this is not a heavy issue in the evaluation of spondylodiscitis with PET because there are only a few causes of aspecific FDG uptake in the spine, some authors hypostasized to create new tracers based on antibiotic molecules to increase specificity. So far, most of these tracers are labeled with  $^{99m}\text{Tc}$  for SPECT imaging. Some examples are  $^{99m}\text{Tc}$ -ciprofloxacin,  $^{99m}\text{Tc}$ -norfloxacin,  $^{99m}\text{Tc}$ -cephazolin,  $^{99m}\text{Tc}$ -ceftizoxime [85].

There are also some available PET tracers whose uptake is based on an increased bacterial-specific metabolism.  $^{11}\text{C}$ -Para-aminobenzoic acid (PABA) is a molecule that was demonstrated to accumulate in a broad class of bacteria, including Gram-positives, Gram-negatives (as well as *Pseudomonas* spp.), and *Mycobacterium tuberculosis* [86].  $^{11}\text{C}$ -rifampicin [87] and 2-deoxy-2-[ $^{18}\text{F}$ ]fluoroacetamido-D-glucopyranose ([ $^{18}\text{F}$ ] FAG) [88] have been synthesized and tested in animal settings with promising results.

Despite promising ideas and good preliminary results, these tracers are now too unripe to be considered for an eventual clinical application on a routine basis in a short time.

The gold standard for the diagnosis of spinal infectious diseases remains the MR investigation. Contrast MR has a limited role, it is not essential to diagnose the infection, but it can differentiate paraspinal abscesses and phlegmons.

Radionuclide scanning is a valid alternative when MR is contraindicated or a useful adjunct when radiographic changes on plain films or CT scans are absent or equivocal.

CT scan could be used when MR is not available or for biopsy or procedural planning.

FDG-PET/CT is a useful technique in order to understand if there is an early response to antibiotic therapy or it should be changed the therapeutic approach.

## CONCLUSION

A plain radiograph is useful to promptly detect concomitant or consequent instabilities but has a limited role and ideally would require further evaluation with MR or Radionuclide scanning to evaluate the extent of the disease.

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Not applicable.

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## CONFLICT OF INTEREST

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