Nuclear medicine imaging of vertebral infections

Lazzeri, Elena

Chapter 7

Clinical Impact of SPECT/CT with ^{111}In-Biotin on the Management of Patients with Suspected Vertebral Osteomyelitis

Elena Lazzeri[1], Paola Erba[1], Marzio Perri[1], Roberta Doria[2], Carlo Tascini[2] and Giuliano Mariani[1]

([1]) Regional Center of Nuclear Medicine, University of Pisa Medical School, Pisa, Italy;
([2]) Division of Infective and Tropical Diseases, University Hospital of Pisa, Pisa, Italy

Submitted Clin Nucl Med 2009

ABSTRACT

Purpose: Early identification and localization of spine infection is necessary for the planning the most adequate therapy. We comparatively assessed the diagnostic and localization performance of ^{111}In-Biotin SPECT/CT *versus* planar and SPECT imaging in patients with suspected spine infection. **Methods**: 72 consecutive patients underwent SPET/CT and planar imaging 2-4 hours *post* i.v. injection of ^{111}In-Biotin. Final diagnosis was based on bacterial cultures and/or clinical/imaging follow-up for at least one year. The diagnostic and localization performance of ^{111}In-Biotin scintigraphy was evaluated by separately reading planar, SPECT alone, and SPECT/CT imaging. **Results**: ^{111}In-Biotin SPECT/CT and SPECT showed similar sensitivity (93.5% *versus* 92.1%) and identical specificity (92.3%), both higher than those achieved by planar imaging alone (80.4% sensitivity and 69.2% specificity), although with different degrees of statistical significance. In 13 out of the 46 patients with confirmed spine infection SPECT/CT provided additional diagnostic information (implying some change in therapy planning with definite clinical advantage over SPECT alone), by correctly depicting the infection as involving the bone only, or both bone and soft tissue; furthermore, in 3 additional cases it allowed to rule out true spine infection, by identifying infection to involve the para-vertebral soft tissues only. **Conclusions**: SPECT/CT enhances the clinical impact of ^{111}In-Biotin scintigraphy on clinical management of patients, allowing to localize the exact site of infection, therefore to select the most adequate therapy.

Key words: vertebral osteomyelitis, soft tissue infection, ^{111}In-Biotin scintigraphy, SPECT/CT imaging.

INTRODUCTION

Vertebral osteomyelitis (also defined as spondilodiscitis, SD) can be either primary (haematogenous) or secondary (direct bacterial contamination due to open-wound trauma, spine surgery, or other invasive medical procedures). A multidisciplinary approach is crucial to establish prompt diagnosis and to select proper therapy, because diagnosis is often delayed by poor specificity of symptoms. Delay of appropriate therapy can lead to irreversible neurological impairment and even to death [1-3].

Back pain is the most frequent symptom of SD, followed by fever (usually low-grade), anorexia, spinal tenderness and rigidity [1-6]. Neurological signs are present in only 15% of the patients, while blood chemistry abnormalities include high C-reactive protein levels; erythrocyte sedimentation rate and white blood cell count can vary, depending on the grade and type of SD [7-9]. The lumbar-sacral tract of the spine is the most frequent site of vertebral infection (45%) followed by the dorsal

(35%), and cervical tract (20%) [1]. Predisposing conditions include drug addiction, prior implantation of vascular devices including valve prosthesis [2-5], prior severe infection at other sites, and systemic metabolic diseases such as diabetes.

Suspicion of spine infection raised on clinical ground must be confirmed or ruled out by diagnostic imaging, including both radiologic and radionuclide procedures: Computed Tomography (CT), Magnetic Resonance Imaging (MRI), ^{99m}Tc-MDP bone scintigraphy combined with ^{67}Ga-citrate scintigraphy, ^{67}Ga-citrate SPECT, and Positron Emission Tomography (PET) with [^{18}F]FDG [10]. MRI is currently the modality of choice in patients with suspected spinal infection [11,12], especially in patients with primary SD. Nevertheless, post-surgical structural changes can hamper correct interpretation of MRI, and the diagnostic role of MRI is questioned during patients' follow-up and disease monitoring [1,13-17]. Although CT-guided biopsy with bacterial culture has 100% diagnostic specificity, its sensitivity ranges between 58%–91% [1,18-19]; this invasive procedure is therefore not routinely employed. On the other hand, few diagnostic algorithms and/or practical guidelines for imaging are available for secondary SD and for patients' follow-up after therapy [10,20].

Prior studies have shown the high diagnostic accuracy of ^{111}In-Biotin scintigraphy in patients with spinal infections [21-24]. In this regard, the recent introduction of hybrid SPECT/CT systems has provided the opportunity to enrich purely functional images characterized by relatively low anatomic definition (such as those obtained with planar and tomographic ^{111}In-Biotin scintigraphy) with the correlation to anatomical landmarks for better localizing the foci of abnormal uptake. In this study we explored the added clinical value of SPECT/CT with ^{111}In-Biotin to detect vertebral osteomyelitis and to identify possible involvement of the adjacent paravertebral soft tissues in a large series of consecutive patients in a relatively early stage of disease.

MATERIALS AND METHODS

Patients

Between April 2005 and April 2007, we evaluated 106 consecutive patients with suspected vertebral osteomyelits. The study protocol was approved by our Institutional Review Board, and informed consent was obtained from all patients.

Inclusion criteria were: (a) age >18 years, (b) no pregnancy or lactation, (c) suspicion of vertebral infection on the basis of clinical presentation (presence of at least back pain and fever, or back pain and positive blood culture), routine blood chemistry (erythrocyte sedimentation rate, C-reactive protein, white blood cell count, etc.) and radiological findings suggesting vertebral osteomyelitis. Detailed clinical history was obtained in all cases. All the patients gave their written informed consent prior to inclusion. All patients underwent physical examination, conventional x-ray as well as ^{111}In-Biotin scintigraphy within 40 days after the onset of clinical signs or

symptoms. Bacterial culture (from samples obtained by CT-guided biopsy or during open surgery), histopathologic analysis, and/or clinical/imaging follow-up for at least one year were used as standard of reference for final diagnosis. SD was confirmed in case of positive bacterial growth on biopsy/intraoperative sampling or in case of typical/specific positive findings at clinical, laboratory and scintigraphic imaging (^{99m}Tc-MDP bone scan and/or ^{67}Ga-citrate scan), with partial/complete response to antibiotic therapy and normalization of imaging abnormalities after at least 3 months of therapy. Negative clinical/imaging signs and laboratory findings after 6 months without antibiotic therapy, as well as negative surgical findings or culture, permitted to rule out the diagnosis of spinal infection. Thirty-four patients were excluded from the study because no adequate follow-up data were available. The remaining 72 patients formed therefore our study group, which was further divided into two subgroups, respectively with suspected haematogenous infection (n=44) and with suspected post-surgical infection (n=28) The main clinical data and site of suspected SD of the study population are summarized in Table 1. A total of 46 patients also underwent MRI, 7 patients underwent CT imaging, and 15 underwent both MR and CT imaging.

Table 1 – Main clinical features of the study population.

Mean age (yr)	57.7 ± 14.3
Median, and range	56, 31–86
Men/Women	29/43
Prior spinal surgery	28
Suspected site:	
lumbar	46
thoracic	11
L5–S1	8
cervical	5
multiple levels	2
Antibiotic therapy	18

Radiopharmaceutical

Diethylene-triamine-penta-acetic acid (DTPA)-conjugated biotin [Ω-bis(biocytinamide)], purchased from Sigma (St. Louis, MO, USA), was diluted in sterile acetate buffer 0.05 M, pH 5.5. Aliquots containing 500 µg/ml of DTPA-Biotin were then prepared and stored at 4℃ for subsequent labeling with Indium-111. Just prior to administration, a 500 µg DTPA-Biotin aliquot and ^{111}In-chloride (111 MBq in about 1 mL) were mixed at room temperature for 15 minutes, and labeling efficiency was assessed by ascending chromatography [22-23]; labeling efficiency was always $\geq$98%.

Scintigraphic imaging

Scintigraphy was performed with a hybrid SPECT/CT dual-head gamma camera (Infinia Hawkeye, GE Healthcare, Milwaukee, WI, USA). Medium-energy collimators and 20% energy windows centered around the 173 keV and 247 keV energy peaks of ^{111}In were employed for imaging. In all patients planar and SPECT/CT images of the site of suspected infection were acquired 2-4 hours after i.v. injection of the radiopharmaceutical. Anterior and posterior planar images (matrix 128×128 pixels, with an 1.33 electronic zoom factor) were acquired for 500.000 counts each; the kidneys and bladder (sites of physiologic excretion) were shielded when included in the imaging field of view. SPECT images were obtained in a step-and-shoot mode, employing 3° angular steps with a range of 180° per gamma camera head and a 30-second acquisition per step. The image matrix was 256×256 pixels, and images were reconstructed as 4.42-mm-thick sections by using an iterative algorithm. CT images were simultaneously acquired (matrix of 256x256, slice step 10 mm, 2.5 mA, 140 KV), to correct for tissue attenuation and to generate fused images (SPECT/CT). The patients suspected to have haematogenous infection underwent also total-body scan.

Image interpretation

Separate planar, SPECT and SPECT/CT images were interpreted jointly and in consensus by two experienced nuclear medicine physicians (E.L. and P.A.E.) who were unaware of the final diagnosis and of the results of other imaging modalities. Image analysis was performed in three separate reading sessions. Only planar images were reviewed initially, and classified as positive if ^{111}In-Biotin uptake was present at the site of suspected vertebral infection and negative if no ^{111}In-Biotin uptake was detected. In the second reading session SPECT images (in transaxial, coronal and sagittal planes, and as maximum intensity projection) were reviewed directly on a workstation using Xeleris software (eNtegra 2.5202, GE Healthcare, Waukesha, WI, USA). The images were classified as positive or negative according to the presence of ^{111}In-Biotin uptake in the spine. Fusion imaging was subsequently evaluated (third reading session), and the SPECT/CT findings were compared with

the findings obtained with SPECT alone and with planar imaging alone. SPECT/CT was considered contributory when it provided data that could not be obtained from the assessment of planar and SPECT images concerning not only the presence of infection but its precise location (bone involvement only or extension to the adjacent paravertebral soft tissues).

Statistical Analysis

Data were expressed as mean values ± standard deviation, and/or confidence intervals whenever appropriate. The number of cases in which SPECT/CT changed scintigraphic interpretation with respect to the presence or exact location of infection was recorded and used for comparing the diagnostic performances of planar, SPECT and SPECT/CT imaging, respectively. ^{111}In-Biotin planar, SPECT and SPECT/CT sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy for detection of spinal infection were calculated and compared using the McNemar's test. Statistical analyses were performed using SPSS 14.0 (SPSS, Chicago, IL, USA). Two-tailed *P* values of 0.05 or less were considered to be statistically significant.

RESULTS

Spinal infection was confirmed in 46/72 patients (63.9%) by means of either positive tissue cultures from bioptic/surgical samples (n=26), or positive clinical, laboratory and imaging follow-up data (n=20). Out of the 26 cases with positive bacterial culture, the infectious agent was identified in 23 cases, *Staphylococcus aureus* being the predominant germ (n=14) (see Figure 1 *for St. aureus* infection involving only the soft tissues) followed by *Mycobacterium tuberculosis* (n=5), *Streptococcus* (n=2), *Aspergillus* (n=1), and *Propionibacterium acnes* (n=1). The specific strain was not identified in the remaining 3 cases with positive bacterial growth. The 26 patients who did not have spine infection had either compression fracture (n=6), degenerative disease (n=5), malignancies (n=5), or disk hernia (n=3). Less common conditions included pleuro-pulmonary infection and vasculitis (1 patient each). No clear pathologies were definitely identified in the remaining 5 patients.

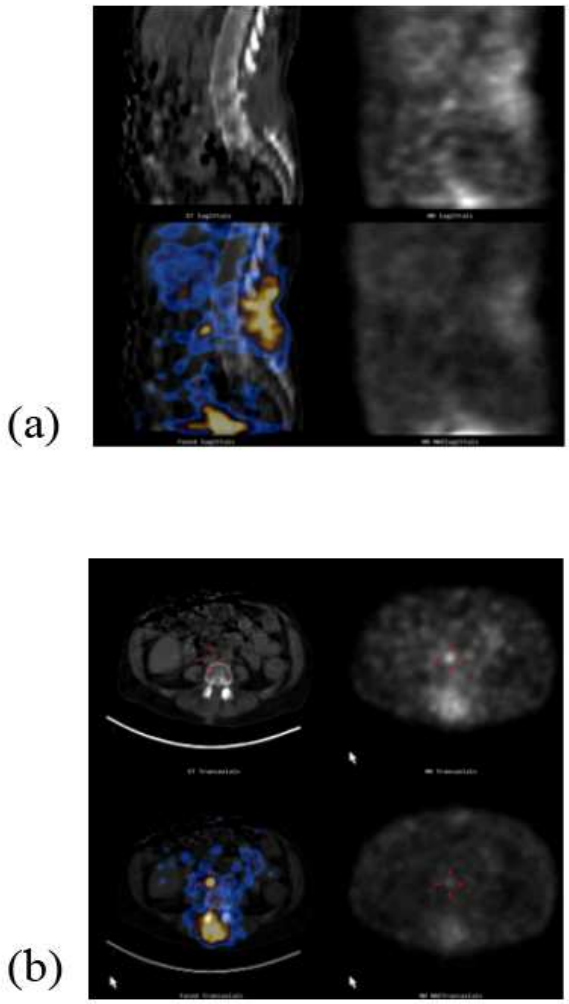

Fig. 1 Patient with *St. aureus* post-surgical infection involving the posterior soft tissues adjacent to the L3-L5 lumbar tract, with ^{111}In-Biotin accumulation at the site of infection and in the corresponding abdominal lymph node, without bone involvement. (**a**): sagittal SPECT, CT, and fused sections. (**b**): transaxial SPECT, CT, and fused sections

^{111}In-Biotin SPECT/CT was positive in 45/72 (multiple foci of infection being detected in 2 cases) and negative in 27/72 patients. The diagnostic performance parameters of planar, SPECT and SPECT-CT ^{111}In-Biotin scintigraphy in terms of sensitivity,

specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy for detecting vertebral infection are reported in Table 2.

Table 2 – Comparative diagnostic performance parameters of planar imaging, SPECT imaging, and SPECT/CT fusion imaging, respectively (PPV = positive predictive value; NPV = negative predictive value; N.S. = not significant, with P>0.05).

	Planar	SPECT	SPECT/CT	SPECT *vs* Planar (P)	SPECT/CT *vs* Planar (P)	SPECT/CT *vs* SPECT (P)
Sensitivity, %	80.8 *(38/46)*	92.1 *(41/46)*	93.5 *(43/46)*	N.S.	0.0313	N.S
Specificity, %	68 *(17/26)*	92.3 *(24/26)*	92.3 *(24/26)*	0.0313	0.0313	N.S.
Accuracy, %	76.4 *(55/72)*	90.3 *(65/72)*	93.0 *(67/72)*	0.0020	0.0005	N.S
PPV, %	82.6 *(38/46)*	95.3 *(41/43)*	95.5 *(43/45)*	N.S.	0.0313	N.S.
NPV, %	65.3 *(17/26)*	82.7 *(24/29)*	88.8 *(24/27)*	0.0313	0.0313	N.S.

SPECT performed significantly better than planar imaging as regards specificity, overall accuracy and negative predictive value (but not for sensitivity and positive predictive value), while all the diagnostic performance parameters of SPECT/CT were significantly better than those of planar imaging. Nevertheless, there was no statistically significant difference in the diagnostic performances of SPECT/CT *versus* those of SPECT alone (see Table 2), although SPECT/CT resulted in more accurate localization of the site of infection in 16/45 cases (35.5%), e.g., by detecting infection involving also the adjacent soft-tissues in addition to spine infection. Furthermore, in 3 of such 16 cases hybrid imaging clearly localized ^{111}In-Biotin uptake in the paravertebral soft-tissues only, thus excluding true bone infection; these 3 patients had had recent spine surgery, and SPECT/CT correctly identified post-operative infection limited to the surgical wound. Overall, SPECT and SPECT/CT imaging reduced both false-positive and false-negative results of planar imaging alone. In particular, 8 false-positive results of planar imaging were reduced to 2 with either SPECT or SPECT/CT, while the 9 false-negative findings of planar imaging were reduced to 5 and to 3, respectively with SPECT and with SPECT/CT. In the latter instance, SPECT/CT correctly reclassified as positive for spinal infection two cases with mild tracer uptake in the anterior portion of the vertebral body that had been misinterpreted as vascular blood pool both on planar imaging and on SPECT imaging. Incorrect SPECT/CT findings included two false-positive and three

false-negative results. The false-positive cases included one patient with Wegener's granulomatosis (Figure 2) and one patient with aseptic vertebral phlogosis, both confirmed by bone biopsy. The SPECT/CT false-negative findings included two patients with non-pyogenic spinal infection (*Mycobacterium tubercolosis*) (Figure 3) and one patient with meticillin-sensitive *Staphylococcus aureus* infection.

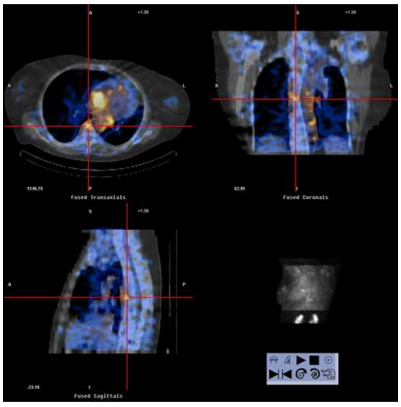

Fig. 2 Patient with Wegener's granulomatosis. Transaxial, coronal, and sagittal fused SPECT/CT sections showing mild ^{111}In-Biotin uptake in dorsal vertebra (false-positive finding)

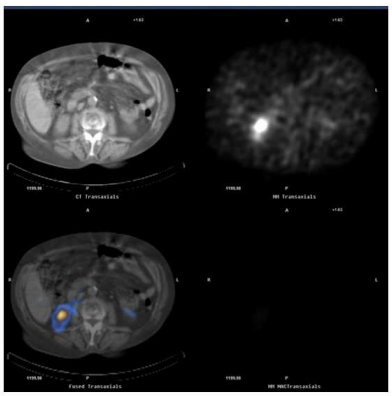

Fig. 3 Patient with *Mycobacterium tuberculosis* infection of the L3 body. Transaxial CT, SPECT and fused sections showing no obvious ^{111}In-Biotin accumulation at the infection site (false-negative result)

DISCUSSION

Although radiological imaging, particularly MR, represents the method of choice for the diagnosis of haematogenous vertebral infection, such procedures suffer from some limitations especially in the differential diagnosis between SD and other conditions such as degenerative disease or myeloma-chordoma [14-16]. Furthermore, the diagnostic accuracy of radiological imaging is reduced in patients with secondary SD, because of the difficulty in discriminating infection from reactive postoperative changes. Moreover, since MR cannot always discriminate between sterile inflammation and bacterial infection [13,15], its usefulness for the follow-up of patients undergoing treatment is controversial. Although radionuclide imaging with, e.g., ^{99m}Tc-MDP, ^{67}Ga-citrate or [^{18}F]FDG is highly sensitive in patients with suspected vertebral osteomyelitis, its specificity varies widely [25-31]. On the other hand, nuclear medicine procedures offer the advantage of whole body acquisition during a single imaging session, thus making possible the detection of unknown sites of infection either in the spine and/or in other organs. Among other radionuclide approaches explored, ^{99m}Tc-ciprofloxacin (a radiolabelled antibiotic) [32,33] has demonstrated high specificity for osteomyelitis, not confirmed however in the specific setting of secondary spine infections [34]. Most of the above limitations to radionuclide imaging for detecting spine infections have been overcome by ^{111}In-Biotin scintigraphy, which has shown high accuracy in detecting spine infection [24]. The mechanism of ^{111}In-Biotin accumulation at the infection sites has been linked to the fact that bacterial Acetyl-coA carboxylase, involved in the synthesis of fatty acids, is biotin dependent and many bacteria utilize biotin as their growth factor [35].

The results of the present study indicate that the high diagnostic performance of ^{111}In-Biotin scintigraphy may be further improved by the combined SPECT/CT acquisition. In fact, the diagnostic accuracy of ^{111}In-Biotin SPECT/CT observed in our study (93%) is higher than the values observed with either planar scintigraphy or SPECT as stand-alone examinations (76.3% and 90.3%, respectively).

^{111}In-Biotin SPECT/CT allowed the correct diagnosis of spine infection in 43/46 affected patients, or 93.5% of the cases. The false-negative cases included two cases of infection from *Mycobacterium tuberculosis*. Such observation, which is consistent with our previous findings in a different population of patients [24], is probably explained by the slow replication rate (with consequent lower utilization of biotin) of this microorganism *versus* other bacteria. The third false-negative ^{111}In-Biotin scan was observed in a patient with spine infection from meticillin-sensitive *Staphylococcus aureus* after long-term antibiotic therapy. Such therapy might have caused reduction of the microrganism load (although without definite cure of the infection) with subsequent reduction of tracer incorporation. The 24/26 true-negative results included 5 patients with bone metastasis, none of them exhibiting any uptake

of ^{111}In-Biotin at the suspected site of infection. On the other hand, there were two false-positive results, observed in a patient with Wegener granulomatosis and in a patient with aspetic phlogosis of a vertebral body, respectively (both confirmed by CT-guided biopsy). In both such conditions nonspecific ^{111}In-Biotin accumulation might have occurred because of local changes of vascular permeability. When comparing planar with SPECT images, the former showed a higher proportion of false-positive results (8 *versus* 2), due to poor identification of physiological or patho-physiological areas of tracer uptake in, e.g., the ureters (n=3), heart wall (n=1), pleural region (n=1), lymph-nodes (n=2) or vertebral crush (n=1). Planar imaging also yielded more false-negative cases than SPECT imaging (9 *versus* 5), most likely linked to small size of the areas with abnormal ^{111}In-Biotin uptake at the infection site. There were two discordant findings between planar imaging and SPECT (both being true-positive) concerning localization of the infection; in both cases SPECT demonstrated that infection was not confined to bone (as planar imaging would indicate) but rather involved also the adjacent soft tissues. The better imaging performance of SPECT was further improved when adding image fusion analysis (SPECT/CT), concerning especially the false-negative cases and the true-positive cases with soft tissues involvement of infection. In fact, although both SPECT alone and SPECT/CT reduced the false-positive findings on planar imaging in the same manner (from 8 to 2), SPECT/CT reduced the false negative findings on planar imaging from 9 to 3 (compared with 9 to 5 for SPECT alone). In particular, in 6 cases SPECT/CT correctly identified ^{111}In-Biotin accumulation as due to physiologic uptake/excretion sites (that had been mistaken as infectious foci by planar imaging) and in 3 cases planar imaging failed to detect abnormal uptake due to infection because of small size of the infection within the affected vertebral body (located anteriorly). Overall there were 18 discordant findings between planar and SPECT/CT imaging, mainly concerning the site and extension of the infectious foci. In all these patients, bone involvement was evident already in the planar images, but SPECT/TC identified as separate entities the following conditions: sole bone involvement (n=1), sole soft tissue involvement (n=3), and the concomitant infection both bone and soft tissues (n=14). Identifying the true site of infection in the vertebral and/or paravertebral region is a crucial factor for selecting the therapeutic strategy most appropriate according to the actual extension of infection. In fact, drainage of the abscess is performed and specific antibiotics are used if infection is limited to the paravertebral soft tissues, while other antibiotics are reserved when bone infection is present [36]. Although the specific antibiotic is selected on the basis of resistance testing, different classes of antibiotics are usually employed according to the site of infection [37]. It should also be noted that early and correct localization of infection is important for prognostic purposes, as the infection limnited

to the para-vertebral soft tissue only has better outcome than true bone infection [37,38].

Finally, although SPECT and SPECT/CT showed concordant true positive results in 41 patients, in 18 of such cases the two imaging modalities defined however different burdens of infection (bone and/or soft tissue infection correctly identified by SPECT/CT *versus* bone infection only identified by SPECT). Furthermore, SPECT/CT corrected two false-negative SPECT scans, in which a small amount of activity, found in the anterior region of vertebral body, had been misinterpreted as vascular blood pool on the SPECT images alone. In this regard, the contribution of hybrid imaging (SPECT/CT) is crucial for correctly identifying the site of uptake of ^{111}In-Biotin, which does not accumulate in normal bone and/or bone marrow and therefore does not provide unequivocally identifiable anatomic landmarks as topographic reference.

In conclusion, the results of the present study demonstrate that ^{111}In-Biotin SPECT/CT is an efficient and reproducible imaging modality for the detection of vertebral osteomyelitis, able to differentiate bone infection from soft tissues infection. ^{111}In-Biotin SPECT/CT allows, in particular, to choose the adequate therapy in patients with spine infection, as different regimens of antibiotic therapy are employed if there is only bone infection, or combined bone and soft tissues involvement, or infection of soft tissues only. Finally, ^{111}In-Biotin SPECT/CT can also provide prognostic information, as each of the three different clinical settings mentioned above is characterized by varying clinical outcomes. The procedure is safe, easy to perform and does not entail long-time acquisition.

Since local uptake of ^{111}In-Biotin is most likely due to the presence of bacteria with high proliferative rate, this scintigraphic approach might find an important role in the diagnosis of spine infections. Furthermore, it might be of extreme usefulness during the follow-up of antibiotic therapy.

References

1. Chen HC, Tzaan WC, Lui TN. Spinal epidural abscesses: a retrospective analysis of clinical manifestations, sources of infection, and outcomes. Chang Gung Med J. 2004;27:351-358.
2. McHenry MC, Easley KA, Locker GA. Vertebral osteomyelitis: long-term outcome for 253 patients from 7 Cleveland-area hospitals. Clin Infect Dis. 2002;34:1342-1350.
3. Carragee EJ. Pyogenic vertebral osteomyelitis. J Bone Joint Surg Am. 1997;79:874-880.
4. Tyrrell PN, Cassar-Pullicino VN, Mc Call IW. Spinal infection. Eur Radiol. 1999;9:1066-1077.
5. Mader JT, Calhoun J. Osteomyelitis. In: Mandell GL, Bennett JE, Dolin R, eds. Principles and Practice of Infectious Diseases. Vol. 1. Churchill Livingstone, 2000:1182-1196.
6. Honan M, White GW, Eisenberg GM. Spontaneous infectious discitis in adults. Am J Med. 1996;100:85-89.
7. Perry M. Erytrocyte sedimentation rate and C reactive protein in the assessment of suspected bone infection-are they reliable indices? J R Coll Surg Edinb 1996;41:116-118.
8. Carragee EJ, Kim D, van der Vlugt T, Vittum D. The clinical use of erythrocyte sedimentation rate in pyogenic vertebral osteomyelitis. Spine. 1997;22:2089-2093.
9. Perronne C, Saba J, Behloul Z, et al. Pyogenic and tuberculous spondylodiskitis (vertebral osteomyelitis) in 80 adult patients. Clin Infect Dis. 1994;19:746-750.
10. Gemmel F, Dumarey N, Palestro CJ. Radionuclide imaging of spinal infections. Eur J Nucl Med Mol Imaging. 2006;33:1226-1237.
11. Van Goethem JW, Parizel PM, van den Hauwe L, Van de Kelft E, Verlooy J, De Schepper AM. The value of MRI in the diagnosis of postoperative spondylodiscitis. Neuroradiology. 2000;42:580-585.
12. Longo M, Granata F, Ricciardi K, Gaeta M, Blandino A. Contrast-enhanced MR imaging with fat suppression in adult-onset septic spondylodiscitis. Eur Radiol. 2003;13:626-637.
13. Grane P, Josephsson A, Seferlis A, Tullberg T. Septic and aseptic post-operative discitis in the lumbar spine: evaluation by MR imaging. Acta Radiol. 1998;39:108-115.
14. Wolansky LJ, Heary RF, Patterson T et el. Pseudosparing of the endplate: a potential pitfall in using MR imaging to diagnose infectious spondylitis. AJR. 1999;172:777-780.
15. Enzmann DR. Infection and inflammation. In: Enzmann DR, DeLaPaz RL, Rubin JB, eds. Magnetic Resonance of the Spine. St. Louis: Mosby, 1990:260-300.
16. Balériaux DL, Neugroschl C. Spinal and spinal cord infection. Eur Radiol. 2004;14:E72-E83.

17. Wagner SC, Schweitzer ME, Morrison WB, Przybylski GJ, Parker L. Can imaging findings help differentiate spinal neuropathic arthropathy from disk space infection? Initial experience. Radiology. 2000;214:693-699.
18. Dullerud R, Nakstad PH. Side effects and complications of automated percutaneeous lumbar nucleotomy. Neuroadiology. 1997;39:282-285.
19. Felix SC, Mitchell JK. Diagnostic yield of CT-guided percutaneous aspiration procedures in suspected spontaneous infectious diskitis. Radiology. 2001;218:211-214.
20. Concia E, Prandini N, Massari L, et al. Osteomyelitis: clinical update for practical guidelines. Nucl Med Commun. 2006;27:645-660.
21. Rusckowski M, Paganelli G, Hnatowich DJ, et al. Imaging osteomyelitis with streptavidin and Indium-111-labelled biotin J Nucl Med. 1996;37:1655-1662.
22. Lazzeri E, Manca M, Molea N, et al. Clinical validation of the avidin/indium-111 biotin approach for imaging infection/inflammation in orthopaedic patients. Eur J Nucl Med. 1999;26:606-614.
23. Lazzeri E, Pauwels EK, Erba PA, et al. Clinical feasibility of two-step streptavidin/^{111}In-biotin scintigraphy in patients with suspected vertebral osteomyelitis. Eur J Nucl Med Mol Imaging. 2004;31:1505-1511.
24. Lazzeri E, Erba P, Perri M et al. Scintigraphic imaging of vertebral osteomyelitis with ^{111}In-Biotin. Spine. 2008;33:198-204.
25. Gratz S, Dorner J, Oestmann JW et al. ^{67}Ga-citrate and ^{99m}Tc-MDP for estimating the severity of vertebral osteomyelitis. Nucl Med Commun. 2000;21:111-120.
26. Love C, Patel M, Lonner BS, Tomas MB, Palestro CJ. Diagnosing spinal osteomyelitis: a comparison of bone and Ga-67 scintigraphy and magnetic resonance imaging. Clin Nucl Med. 2000;25 963-977.
27. Stumpe KD, Dazzi H, Schaffner A, von Schulthess GK. Infection imaging using whole-body FDG-PET. Eur J Nucl Med. 2000; 27: 822-832.
28. Schmitz A, Kalicke T, Willkomm P, Grunwald F, Kandyba J, Schmitz O. Use of fluorine-18 fluoro-2-deoxy-D-glucose positron emission tomography in assessing the process of tuberculous spondilitys. J Spinal Disord. 2000;13:541-544.
29. Gratz S, Dorner J, Fischer U, et al. ^{18}F-FDG hybrid PET in patients with suspected spondylitis. Eur J Nucl Med. 2002;29:516-524.
30. De Winter F, Gemmel F, Van De Wiele C, Poffijn B, Uyttendaele D, Dierckx R. 18-Fluorine fluorodeoxyglucose positron emission tomography for the diagnosis of infection in the postoperative spine. Spine. 2003;28:1314-1319.
31. Rosen RS, Fayad L, Wahl RL. Increased ^{18}F-FDG uptake in degenerative disease of the spine: characterization with ^{18}F-FDG PET/CT. J Nucl Med. 2006;47:1274-1280.
32. Sarda L, Cremieux AC, Lebellec Y, et al. Inability of ^{99m}Tc-ciprofloxacin scintigraphy to discriminate between septic and sterile osteoarticular diseases. J Nucl Med. 2003;44:920-926.
33. Larikka MJ, Ahonen AK, Niemela O et al. Comparison of ^{99m}Tc ciprofloxacin, ^{99m}Tc white blood cell and three-phase bone imaging in the diagnosis of hip

prosthesis infections: improved diagnostic accuracy with extended imaging time. Nucl Med Commun. 2002;23:655-661.
34. De Winter F, Gemmel F, Van Laere K et al. ^{99m}Tc-ciprofloxacin planar and tomographic imaging for the diagnosis of infection in the postoperative spine: experience in 48 patients Eur J Nucl Med Mol Imaging. 2004;31: 233-239.
35. Attwood PV. The structure and the mechanism of action of pyruvate carboxylase. Int J Biochem Cell Biol 1995;27:231-49.
36. Livorsi DJ, Daver NG, Atmar RL, Shelburne SA, White AC, Musher DM. outcomes of treatment for hematogenous Staphylococcus aureus vertebral osteomyelitis in the MRSA ERA. Journal of Infection 2008;57:128-131.
37. Reihsaus E, Waldbaur H, Seeling W. Spinal epidural abscess: a meta-analysis of 915 patients. Neurosurg Rev 2000;232:175-204
38. Priest DH, Peacock JE. Hematogenous vertebral osteomyelitis due to Staphylococcus aureus in the adult: clinical features and therapeutic outcomes. South Med J 2005;98:854-862.