

Evaluation of Technetium-99m Ciprofloxacin (Infecton) in the Imaging of Infection

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Abstract

Introduction: The aim of this study was to evaluate the usefulness of technetium-99m (Tc-99m) ciprofloxacin in imaging inflammation/infection. The ciprofloxacin for labelling, as a kit, was obtained from St Bartholomew's Hospital in London. **Materials and Methods:** Patients were injected intravenously with Tc-99m ciprofloxacin and imaging was done at 10 minutes, 4 hours and 24 hours if necessary. Tomographic images (SPECT) were obtained in a few patients. Ninety-six patients were studied using Tc-99m ciprofloxacin. Forty-eight patients had bone scans and 22 had Tc-99m IgG scans. Eight patients were imaged using Tc-99m HMPAO labelled white blood cell, and bacteriological culture results were available in 24 patients. Organisms cultured included *Acinetobacter baumannii*, *Streptococcus*, *Staphylococcus aureus*, *Pseudomonas*, *Klebsiella*, *Blastococcidia*, *Methicillin-resistant S. aureus*, *Salmonella* and *Candida*. **Results:** Findings were evaluated against microbiology, alternative imaging modalities and clinical outcome. There were 47 true positives, 33 true negatives, 5 false positives and 11 false negatives, giving a sensitivity of 81% and specificity of 87%. The positive and negative predictive values were 90% and 75%, respectively. There were no side effects and the scan was particularly useful in the evaluation of painful joint prosthesis to exclude infection. Repeat studies on 8 patients given antibiotics over a long period were very useful in deciding on termination of the antibiotic treatment.

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Introduction

Over the past 10 years we have used various radiopharmaceuticals (RPCs) for imaging of inflammation and infection. These include gallium-67 citrate and the technetium-99m labelled nanocolloids, immunoglobulin (IgG), antigranulocyte antibodies (AGAB) and HMPAO-labelled leukocytes. The major mechanism of uptake of the RPC is increased capillary permeability which precedes leukocyte migration, and is a characteristic of both inflammation and infection. Hence, there is non-specific uptake of tracer at the focus of inflammation/infection. Gallium-67 has receptor-binding to lactoferrin. Labelled white cells have chemotactic activation and AGAB may show more specific uptake as labelled antibodies against granulocyte antigens.

There is no single RPC that is suitable for all clinical situations. To some extent, the biodistribution and radiation exposure influence the choice of which RPC is used, as uptake in liver, spleen, kidneys, bowel, bone marrow or

blood may confuse the interpretation of results.

A frequent difficulty with these RPCs is also the relative lack of specificity (other than labelled leukocytes) in distinguishing aseptic inflammation from infection. Hence, technetium-99m ciprofloxacin (Infecton) which binds to the DNA-gyrase of living bacteria was considered a promising agent to localise infection as opposed to inflammation. As part of a multicentre study co-ordinated by the International Atomic Energy Agency (IAEA), we evaluated this RPC in a study of patients with suspected infection.

Materials and Methods

Ninety-six patients with suspected infection were referred by the attending clinicians for infection imaging, and were entered into the study. Informed consent was obtained from all patients and the study was approved by the local ethics committee. Scanning was performed with Tc-99m ciprofloxacin (Infecton) and in addition, Tc-99m IgG

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scans were done in 22 cases, usually within an interval of 3 days. A bone scan was performed in 48 patients. The Infecton kit was obtained from St Bartholomew's Hospital in London with funding from the IAEA, and radiopharmaceutical preparation and injection was done using an established protocol. Technetium-99m IgG was prepared in-house, as described previously.¹ The technetium-99m dose was 400 MBq for both scans.

No adverse reactions occurred following intravenous administration of Infecton.

Following injection, scans were performed at 10 minutes (blood pool), 4 hours, and 24 hours if considered necessary. Images were acquired on ADAC Vertex gamma camera with high resolution collimators. Some patients, especially those suspected of malignant otitis externa, had SPECT scans of the skull, which were repeated at two-month intervals until no abnormality was noted on the scan. Twenty-two patients had an IgG scan, 8 patients were imaged using Tc-99m HMPAO labelled white blood cell. Infection was proven microbiologically in 24 patients.

The Centres for Disease Control and Prevention (CDC) criteria² were used to decide on whether patients were deemed to have infections, and these were categorised as not infected, definite infection and probable infection. A patient was considered to have definite infection if the CDC criteria were met. A diagnosis of probable infection was made if the CDC criteria were not met but the patient was treated as infected by the clinician. For the study criteria, if the infection is probable by CDC criteria, the Infecton scan is interpreted as true positive if positive, but false negative if negative.

Results

Infecton scans were performed in 96 adult patients. Most patients were in the 40 to 70 years age group.

The results are summarised in Tables I to III, and are presented under (1) all patients imaged, (2) osteomyelitis and (3) pneumonia.

Of the total of 96 patients, 8 had repeat studies over a period of 6 to months to assess their response to antibiotic treatment. These patients had malignant otitis externa with bone involvement.

The overall sensitivity and specificity for the studies on these 96 patients were 81% and 87% respectively, with positive and negative predictive values of 90% and 75%, respectively. The sensitivity and negative predictive values are better when considering only osteomyelitis (sensitivity 89%, specificity 79%, positive predictive value 89%, negative predictive value 79%), while in patients with pneumonia, there was good specificity (100%) and positive predictive value (100%), but reduced sensitivity (75%) and negative predictive value (67%).

TABLE I: ALL PATIENTS IMAGED

	Infecton (Technetium-99m ciprofloxacin)		Total
	Positive	Negative	
CDC criteria			
Definite/probable infection	47 (TP)	11 (FN)	58
CDC criteria not infected	5 (FP)	33 (TN)	38
Total	52	44	96

CDC: Centres for Disease Control and Prevention; FN: false negative; FP: false positive; TN: true negative; TP: true positive

TABLE II: OSTEOMYELITIS (41 PATIENTS IMAGED)

	Infecton (Technetium-99m ciprofloxacin)		Total
	Positive	Negative	
CDC criteria			
Definite/probable infection	24 (TP)	3 (FN)	27
CDC criteria not infected	3 (FP)	11 (TN)	14
Total	27	14	41

CDC: Centres for Disease Control and Prevention; FN: false negative; FP: false positive; TN: true negative; TP: true positive

TABLE III: PNEUMONIA (12 PATIENTS IMAGED)

	Infecton (Technetium-99m ciprofloxacin)		Total
	Positive	Negative	
CDC criteria			
Definite/probable infection	6 (TP)	2 (FN)	8
CDC criteria not infected	0 (FP)	4 (TN)	4
Total	6	6	12

CDC: Centres for Disease Control and Prevention; FN: false negative; FP: false positive; TN: true negative; TP: true positive

In the 8 patients with MRSA infections, 6 were true positive and 1 was false negative. One patient had a negative scan after treatment, a true negative.

Discussion

There are many nuclear medicine methods to localise sites of inflammation/infection with varying degrees of accuracy. Most of the currently available radio-pharmaceuticals localise in both inflammation and infection. Hence, it would be useful to have bacterial-specific imaging agents, such as Tc-99m-Fab' fragment directed against *Pneumocystis carinii* or labelled antibiotics such as Tc-99m ciprofloxacin to locate sites of infection. The Tc-99m HMPAO labelled leukocytes only indicate leukocyte infiltration, and not necessarily bacterial infection. The

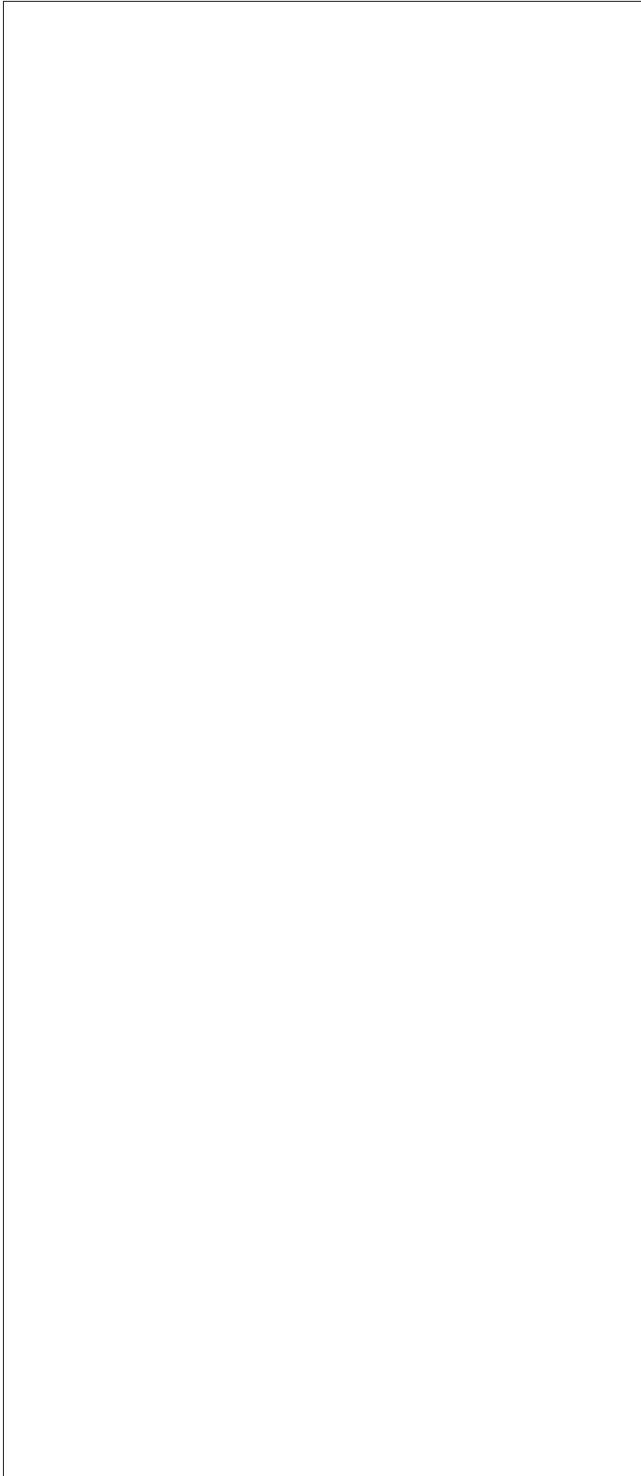


Fig. 1. Immunocompromised patient presenting with L4/L5 vertebral osteomyelitis and associated psoas abscess. (a) Bone scan shows mildly increased tracer activity at L4 & L5 (small black arrows) which is non-specific. (b) Labelled leukocyte scan showing a cold area at L5 (arrow head) and increased uptake at the L4/L5 disc space (thick black arrow) best seen anteriorly, indicating marrow replacement at L5 and the presence of infective process at the L4/L5 disc space. (c) Tc-99m Infected scan shows increased uptake at L4 and L5 (white arrow), correctly localising the site of infection.

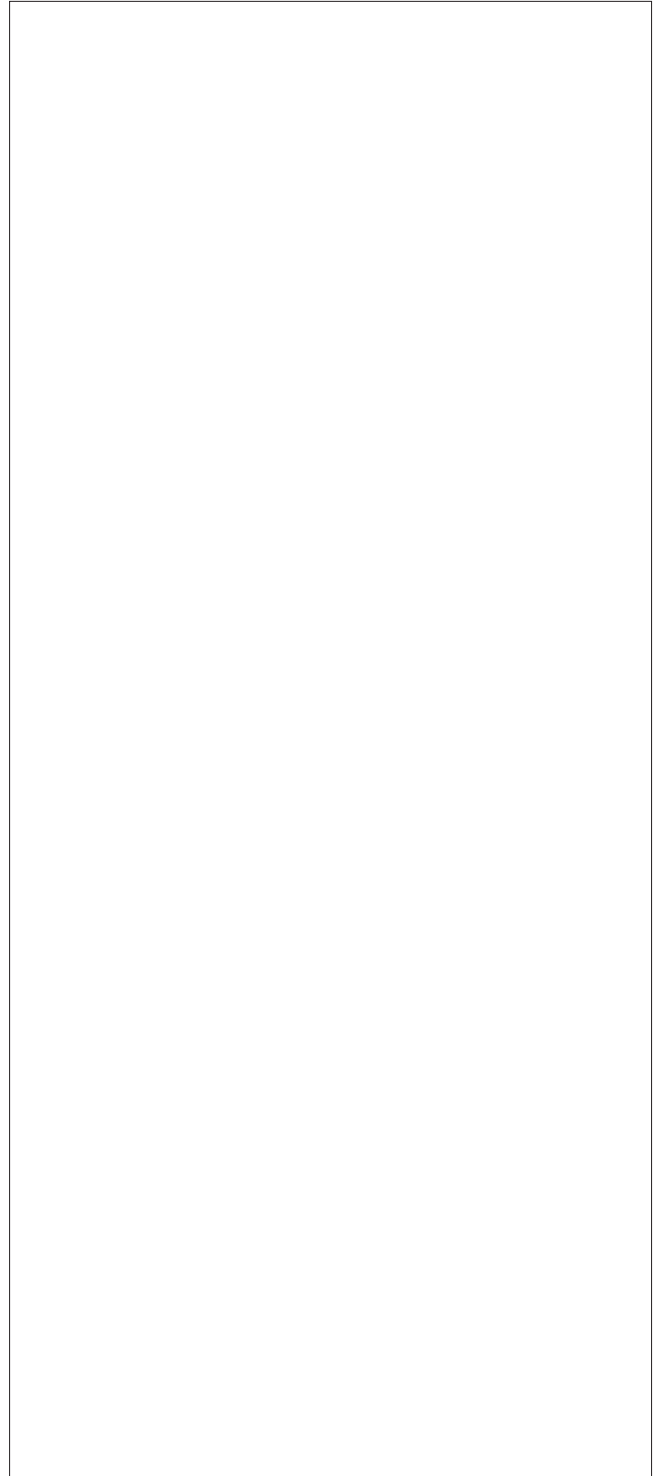


Fig. 2. MRSA osteomyelitis. Patient had right tibia/fibula fracture and internal fixation 1 year ago, now presenting with pain and erythema in the leg. (a) Bone scan shows intense tracer uptake at the junction of the middle and lower thirds of the right tibial shaft (arrow heads). In addition, a focus of moderately increased uptake is seen at the distal right tibia (small arrow). (b) Tc-99m Infected scan shows corresponding increased uptake at the junction of the mid and lower tibial shaft (thick arrow), correctly localising the site of infection. The lesion at the distal right tibia seen on bone scan, which is due to stress at previous fracture site, shows no significant uptake of Tc-99m Infected, correctly excluding infection.

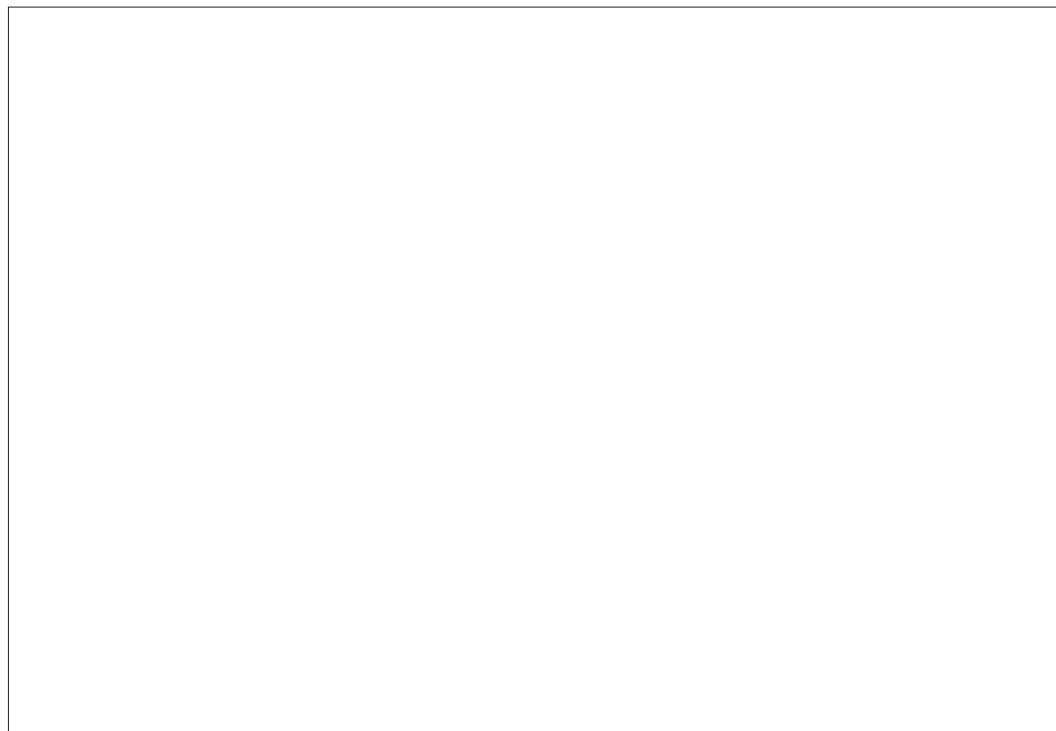


Fig. 3. Malignant otitis externa with osteomyelitis. Coronal SPECT images of the skull. (a) Bone scan shows focal increased uptake at the right petrous temporal bone (arrow head). (b) Tc-99m Infecton scan showing corresponding increased uptake at the site of osteomyelitis (black arrow). Serial scans were done to assess response to antibiotic therapy, which was discontinued when the scans converted to negative.

specificity of Tc-99m Infecton has been shown to be superior to radiolabelled leukocytes in the evaluation of bacterial infection.³

Gallium-67 entails high radiation exposure, is not routinely available in Singapore, and has unfavourable characteristics for gamma-camera imaging.^{4,5} With the use of Tc-99m labelled nanocolloids, the sensitivity ranges from 87% to 95% and specificity between 77% to 100%. The diagnostic accuracy is 87%.⁶ Radiolabelled white blood cell has been considered the gold standard for detection of inflammation and is useful in imaging abscesses, inflammatory bowel disease and prosthetic infections,⁷ but the procedure is laborious. Immunoscintigraphy with technetium-99m labelled antigranulocyte antibodies is simple, but reliable differentiation of inflammatory from infective lesions is not always possible since some of the antibody circulates as free immunoglobulin. Accuracy varies from site to site, but is high for appendicular skeletal infections.⁸ Using Tc-99m IgG, we have had good results in detecting inflammation, but could not reliably distinguish sterile and infected acute inflammation.^{1,9,10} Technetium-99m ciprofloxacin (Infecton) shows promise as a new diagnostic tool for specifically detecting sites of bacterial infection.^{11,12} This method is simple to use, compared to the labour-intensive leukocyte labelling.

In the present multicentre study co-ordinated by the IAEA, Tc-99m ciprofloxacin has been used to visualise

various sites of infections. Our study population has been mainly referrals from Orthopaedic Surgeons and Chest Physicians, with most of the indications for the imaging procedures being osteomyelitis (Fig. 1) and prosthesis infection, septic arthritis and pneumonia. The studies where bacterial culture has been available reveal a wide variety of causative organisms, including MRSA (Fig. 2). The 8 patients with malignant otitis externa and bone involvement had SPECT scans of skull. These were useful in localising the site and extent of infection (Fig. 3). This study was useful in that serial studies showed ongoing infection in most of these patients and antibiotics had to be given for up to 6 months before the scans converted to negatives.

There is no 'gold standard' for assessing the efficacy of Infecton imaging. We have used the CDC criteria for infection diagnosis, and categorised the infection status as not infected, definite infection and probable infection. In the interpretation of the Infecton scan, we have considered results of other imaging modalities and clinical course of the patient, especially when there is no microbiological data available.

Our results with Tc-99m ciprofloxacin are generally encouraging, with sensitivity, specificity, positive and negative predictive values comparable to that reported by Hall et al¹³ (sensitivity 70%, specificity 93%, positive predictive value 93%, negative predictive value 72%). The overall accuracy is 83% and for osteomyelitis,

85%. The better results are obtained for imaging of bone infections.

The limitation to the study is that not all patients have microbiological data; however, use of CDC criteria has helped in making a probable diagnosis of infection. Patients were reluctant to come for a number of scans, e.g. bone, IgG, Infecton and hence, it was not possible to study a larger number of patients with Tc-99m IgG for comparison.

Conclusion

Technetium-99m labelled ciprofloxacin is a safe, useful and accurate agent for imaging of infection, particularly in bones and at sites of prosthesis. Repeat scans over a period of time have clearly indicated ongoing infection or healed infection and emphasise the need to maintain patients on antibiotic treatment until the Infecton scan becomes negative.

For the future, it is possible that new agents such as technetium-99m labelled interleukins, chemotactic peptides that bind specifically to granulocytes, labelled liposomes and specific monoclonal antibodies to bacterial antigens will be available for infection/inflammation imaging.^{14,15}

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