Critical Review Form
Diagnostic Test

Correlation of imaging techniques to histopathology in patients with diabetic foot syndrome and clinical suspicion of chronic osteomyelitis, *Diabetes Care* 1999; 22: 294-299

<u>Objective:</u> To define "the role of high-resolution ultrasound in the diagnosis of chronic osteomyelitis in the diabetic foot in comparison with MRI, bone scintigraphy (BS), and plain film radiography (PFR) as competitive methods and histopathology as the reference standard ." (p. 294)

<u>Methods:</u> Patients with World Health Organization (WHO) defined type-2 diabetes presenting over an unspecified time period to the surgery or internal medicine outpatient clinics at the University of Tübingen (Germany) were eligible. An additional eligibility requirement was that a minor amputation for foot-problems had to be planned, but "the interdisciplinary decision for minor amputation was made by the diabetologist and the surgeon without knowing the results of the different imaging procedures". (p. 294). Eligible patents also had to have foot lesions equal to or greater than <u>Wagner grade 2</u> (defined below at bottom) and impaired wound healing "despite pathogenesis-adapted therapy" for over 4-weeks.

Investigators assessed the following confounding variables: diabetic neuropathy (using a 10-g Semmes-Weinstein monofilament 128-Hz tuning fork pathologic = ≤ 4 out of 8 and diminished ankle jerks). Peripheral vascular disease using history, physical exam, duplex sonography and transcutaneous oxygen tension using a radiometer), wound or specimen cultures, WBC, C-reactive protein, and HbA_{1c} drawn two days before surgery.

High resolution ultrasound was obtained using AU4 Idea equipment with a 7.5 to 10.0 MHz and 10.0 to 13.0 MHz linear array transducer with a maximal axial resolution of 0.12 cm and a penetration depth of 1.0 – 4.5 cm using B-mode scanning. Scans were taken in cross-sectional and longitudinal views with patient in the supine position. Sonographic criteria for the diagnosis of osteomyelitis had been previously described (<u>Steiner 1992</u>, <u>Howard 1993</u>) and included "an echoless zone with a distance of > 2mm adjacent to the cortex of the bone morphologically reflecting an elevation of the periosteum, histopathologically confirmed as subperiosteal abscess". (p. 295) Optional criteria included direct connection of the echoless zone with the surface of the skin reflecting fistula formation.

Three-phase bone scintigraphy was performed after intravenous injection of 740 MBq 99m Technetium using a gamma-camera equipped with a low-energy high resolution collimator. Dynamic perfusion images with 3-seconds per frame were

acquired over 1-minute followed by static blood-pool images with 300 kilocounts in plantar and lateral projection. Static images were obtained 3 hours after injection. No bone scan definition of osteomyelitis is provided.

MRI was performed on a Siemens Vision 1.5T after immobilizing the foot with cotton and a blanket. After gadolinium injection, dynamic imaging was obtained using a T1-weighted flash sequence. Ostomyelitis was defined by high signal intensity on short tau inversion recovery images with an adjacent inflammatory soft-tissue mass or ulcer.

Plain film imaging was obtained in 2-views and no criteria for interpreting them as osteomyelitis are provided. The criterion standard for osteomyelitis was bone marrow purulent or chronic inflammation with or without fibrosis. The *a priori* power calculations were not referenced and did not provide pre-study estimates of sensitivity, specificity or osteomyelitis prevalence required to compute sample sizes for diagnostic studies, but suggested a need for 38 patients to identify sensitivity estimates within 17% ranges. Sensitivity, specificity, positive and negative predictive values were reported at 95% CI's.

Guide		Comments
I.	**Are the results valid?**	
A.	**Did clinicians face diagnostic uncertainty?**	Yes. "Results of all imaging techniques and the histopathological result were read independently by two different, experienced observers who were blinded for the results of the other noninvasive imaging methods and the result of the histopathology". (p. 276)
B.	**Was there a blind comparison with an independent gold standard applied similarly to the treatment group and to the control group? (Confirmation Bias)**	Yes. Inclusion criteria ensured that all subjects had a biopsy specimen obtained and as noted above the pathologists were blinded to other imaging and clinical data.
C.	**Did the results of the test being evaluated influence the decision to perform the gold standard? (Ascertainment Bias)**	By design, all eligible subjects had to have been referred by somebody for amputation of a suspicious foot lesion in a type-2 diabetic. Although ascertainment bias by this design since test results did not influence amputation decision, a selection bias may have been present. For example, did diabetics with foot wound lacking leukocytosis, elevated CRP or neuropathy never get referred for amputation yet suffer from chronic osteomyelitis nonetheless?
II.	**What are the results?**	

A. **What likelihood ratios were associated with the range of possible test results?**

- Only 19 patients were enrolled and only 16 had bone scans including only five with 3-phrase and tagged WBC scan. 14 had osteomyelitis (prevalence = 74%).
- All 14 osteomyelitis patients had wounds graded worse than Wagner grade 2. Foot lesions had been present for an average of 40 weeks in osteomyelitis vs. 31 weeks in non-osteomyelitis.
- Most lesions were on the plaster surface of the first metatarsal (68%).
- CRP (5 mg/dL vs. 0.9 mg/dL p = 0.02) levels were significantly elevated in osteomyelitis patients but not WBC (8.4 vs. 7.2, p = 0.13) or TcP_{02} (51.8 vs. 56.4, p = 0.55).
- Infections were polymicrobial (S. aureus 43%. S. epidmeridis 30%, P. aeruginosa 29%, E. faeclis 14%).
- The imaging studies yielded the following estimates for diagnostic accuracy †(Table 3, p. 297)

Imaging Study	Sensitivity (95% CI)	Specificity (95% CI)	LR^+ (95% CI)	LR^- (95% CI)
X-ray	69 (38 – 90)	80 (28 – 99)	N/A	N/A
US	86 (73 – 91)	80 (44 – 96)	4.3 (13 – 22)	0.18 (0.09 – 0.62)
BS*	83 (52 – 98)	75 (19 – 99)	N/A	N/A
MRI	100 (75 – 100)	80 (48 – 80)	5 (17 – 5)	0 (0 – 0.24)

*Bone scan results as reported are illogical. For example, from five osteo-negatives how does one get a 75% specificity?

†Investigators do not provide enough detail to re-calculate sen/spec/LR's for bone scan or x-ray. The values for US and MRI were derived from the following 2x2 tables and differ from what the authors report.

US	Osteo +	Osteo -
+	12	1
-	2	4

MRI	Osteo +	Osteo -
+	14	1
-	0	4

III.	**How can I apply the results to patient care?**	
A.	**Will the reproducibility of the test result and its interpretation be satisfactory in my clinical setting?**	Uncertain since the authors provide no quantitative estimates of reproducibility. Who performed the sonography and how much experience had they previously had? Who read the plan films, bone scans, and MRI's and what was their expertise? What was the Kappa for "normal/abnormal" for x-rays, bone scans, US, or MRI?
B.	**Are the results applicable to the patients in my practice?**	No, these are not ED patients and they had chronic osteomyelitis.
C.	**Will the results change my management strategy?**	Yes, recognizing that Wagner Grade >2 diabetic foot ulcers refractory to ≥ 4-weeks of antimicrobial therapy have high prevalence (74%) of histopathologically confirmed osteomyelitis and that x-rays alone will miss 31%. Based upon this study MRI is the superior study to rule-out the diagnosis of osteomyelitis with a negative –LR < 0.01.
D.	**Will patients be better off as a result of the test?**	Probably. The investigators do not provide any formal diagnostic algorithm or cost-benefit hypotheses, but they do provide the following costs for each imaging modality. <u>Imaging Test</u> — <u>Mean Price ($US) 1999</u> US — 21 X-ray — 27 MRI — 244 BS+ WBC scan — 667 Given these raw costs, one would need to contemplate several other variables in constructing a cost-benefit analysis: • How accurate are these tests in other settings (other departments and other institutions)? • How reproducible are test interpretations across a spectrum of experienced readers? • What are the patient-oriented outcomes of interest?

		• What are the risks of false-negative and false-positive imaging results? Without understanding these parameters one cannot opine a reasonable guess about whether patients would benefit from this manuscript.

Limitations

1) **Insufficient description of methods. Over what period of time were patients recruited? Who recruited them and how were they recruited? How many patients were approached but disqualified? Who performed the scans, how was their "experience" quantified, and what was the reproducibility (Kappa) of their interpretation?**

2) **No methods reported for sample-size calculation and under-powered for their *a priori* assumptions anyway.**

3) **Incorrect reporting of diagnostic accuracy based upon text description of overall results. Also, no reporting of LR's and insufficient detail to verify the reported sen/spec/LR's for x-ray and bone scan. In general, reporting individual tests 2x2 tables is preferable to vague reports of sensitivity and specificity when the denominator is not consistent.**

4) **Potential selection and spectrum bias with limited external validity for emergency medicine.**

Bottom Line

Poor quality diagnostic accuracy manuscript of select medicine/surgery patients with chronic antimicrobial-refractory diabetic foot ulcers suggesting that MRI is superior to high resolution US or 3-phase bone scan or x-rays to rule-in or rule-out the diagnosis of chronic osteomyelitis. MRI should be the first line imaging modality to exclude osteomyelitis after x-ray (which are used because of low-cost, high availability, and their utility to diagnose fractures or foreign bodies), but future cost-effectiveness research is needed to better define whether the MRI ought to occur in the ED or later in the hospital course.

Wagner Grading Scale

- Grade 0 = no open lesions; may have evidence of healed lesions or deformities
- Grade 1 = superficial ulcer
- Grade 2 = deeper ulcer to tendon, bone, or joint capsule
- Grade 3 = deeper tissues involved, with abscess, osteomyelitis, or tendinitis
- Grade 4 = localized gangrene of toe or forefoot
- Grade 5 = gangrene of foot