Clinical Infectious Diseases
REVIEW ARTICLE

Diagnostic Accuracy of Probe to Bone to Detect Osteomyelitis in the Diabetic Foot: A Systematic Review

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(See the Editorial Commentary by Senneville on pages 949–50.)

The probe-to-bone (PTB) test is a commonly used clinical test for osteomyelitis (OM), but its utility has been questioned in clinical settings where the prevalence of OM is low. This article aims to systematically review the accuracy of the PTB test to diagnose diabetic foot OM. We searched Ovid Medline and Scopus databases for studies using the keywords "probe to bone," "osteomyelitis," and "diabetic foot" from 1946 to May 2015. We summarized characteristics of the included studies and pooled the accuracy numbers using a bivariate random-effects model. Seven studies met our inclusion criteria. Pooled sensitivity and specificity for the PTB test was 0.87 (95% confidence interval [CI], .75–.93) and 0.83 (95% CI, .65–.93), respectively. We conclude that the PTB test can accurately rule in diabetic foot OM in the high-risk patients and rule out OM in low-risk patients.

Keywords. osteomyelitis; probe to bone; diabetic foot; meta-analysis; accuracy.

The lifetime incidence of foot ulcers among patients with diabetes mellitus is estimated to be as high as 25% [1]. Diabetic foot infection (DFI) may occur in up to 60% of patients with diabetic foot ulcers (DFUs) and can complicate the treatment course of the ulcer, increase the time to heal, and increase the risk of amputation [2–4]. Infection starts at the level of the DFU, but can spread contiguously up to the level of the bone. Most DFIs in the ambulatory setting can be treated with local wound care and oral antibiotics, but moderate to severe infections require surgery and parenteral antibiotics. Thus, it is imperative for the clinician to differentiate between soft tissue infection and osteomyelitis (OM) because the management and prognosis of the 2 disease processes are significantly different. Therefore, when a DFU is present and there is suspicion of infection, the patient should undergo a probe-to-bone (PTB) test and a plain radiograph [5].

Although bone histopathology and culture are the criterion standards for diagnosing OM, resources or expertise to perform bone biopsy are unavailable in many settings [6]. Therefore, clinicians often use surrogate diagnostic markers to differentiate OM from soft tissue infection. A commonly used clinical test for OM is the PTB test. The basis behind the PTB test is that if a probe can reach bone, so can bacteria. This is consistent with the etiology of diabetic foot OM; bacteria reach bone via contiguous spread from adjacent soft tissue. The PTB test is performed by inserting a sterile, metal surgical probe into the ulcer and is positive if a hard, gritty surface is felt inside. For large wounds, this may require gentle exploration of the wound with the probe. Since it was first reported in 1995, there have been varying reports regarding the accuracy of the test [7–9]. In particular, the applicability of the test has been questioned in clinic settings, where the pretest probability of OM is low [9]. Prior literature reviews of the PTB test were small [10, 11]. The aim of this study is to find an estimate for the sensitivity and specificity of the PTB test, and to determine at what pretest probability is the PTB test useful to diagnose OM.

METHODS

Search Strategy and Study Selection

We performed an Ovid Medline and Scopus search with the input "probe to bone and OM and diabetic foot" as keywords for all study types written in English from 1946 through May 2015. A bibliographic review was also performed for any additional articles. A single author (K. L.) selected studies for 2-author review if it (1) stated the sensitivity and specificity of the PTB test, (2) focused solely on DFIs, and (3) used bone histopathology or bone culture as a reference standard. We excluded case reports, meta-analyses, and literature and systematic reviews. Each selected article was randomly assigned to 2 authors (either K. L., T. N., J. L. F., S. A. V. v. A.) for review. If disagreements between the 2 authors emerged in either the data extraction or the quality assessment, results were finalized through consensus.

Data Extraction

Two authors independently extracted information from each article using a standardized collection form. Collected data

Received 25 February 2016; accepted 3 June 2016; published online 1 July 2016.

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Clinical Infectious Diseases® 2016;63(7):944–8

DOI: 10.1093/cid/ciw445

included first author, publication year, sample size, study design, inclusion and exclusion criteria, reference standard(s) used, clinical setting, and reported contingency tables.

Study Quality Assessment

We performed a quality assessment using the QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies) tool [12]. The QUADAS-2 tool is a set of 14 questions that evaluate the risk of bias in a study's patient selection, index test, reference standard, and patient flow.

Statistical Analysis

Individual study sensitivity, specificity, diagnostic odds ratio, positive predictive value, and negative predictive value were calculated directly from the study's 2×2 contingency table. The Wilson score interval was used to calculate individual study confidence intervals (CIs). The Wilson score interval assumes an underlying normal distribution, but does not assume that the sample mean equals the population mean. It has been shown that the Wilson score interval performs better than the Wald interval when estimating proportions near 0 or 1, and when sample size is low [13]. Correlation between prevalence of OM in the study population and clinical setting with PTB was calculated using the Pearson correlation coefficient. The calculations for pooled sensitivity, specificity, and odds ratio were carried out in SAS using the MetaDas macro, which pools data using a bivariate random-effects model [14, 15]. Prevalence was added to the base model as a covariate. Pooled positive and negative predictive values were calculated by directly summing studies' patient data.

RESULTS

Search Results and Study Characteristics

The initial query resulted in 14 results from Ovid Medline, 23 abstracts in Scopus, and 1 from a bibliographic review (Figure 1). 29 articles were excluded: 12 were duplicates, 10 were reviews, and 7 articles did not fit our inclusion criteria. Of the 9 articles that made it to the 2-author review, 7 were included in the present study. One article was excluded because it did not specify the number of patients who received the PTB test and the other did not use bone biopsy as a reference standard.

Characteristics of the studies are shown in Table 1. Six studies were prospective cohort studies and one was a retrospective case series [16]. A total of 1017 patients (1022 ulcers) were enrolled across the 7 studies with a range of 58–338 patients. The inclusion and exclusion criteria differed slightly between all included studies. Two studies enrolled all patients hospitalized for DFI [17, 18]. One enrolled patients with a DFI that failed to heal in 4 weeks, had exposed bone, or was located over a bony prominence [7]; one included all patients presenting with DFI [16]; one included all patients with a DFU [8]; one enrolled clinic patients with signs of DFI, normal radiograph, and scheduled for surgery [19]; and one enrolled patients with a DFU and signs of infection or a DFI that was persistent despite antibiotic use or prior surgery [20]. The clinical suspicion of foot infection was defined in 3 studies using Infectious Diseases Society of America guidelines, which define DFI by the presence of purulent secretions or $\geq$2 of the following signs: redness, warmth, swelling or induration, and pain or tenderness [6–8, 20]. Two studies excluded patients with prior or scheduled surgery [18, 20]. Three excluded patients with ischemic ulcers [17, 19, 20]. One study excluded patients with chronic OM as determined by radiography [19]. One study excluded patients on systemic antibiotics at the time of PTB test [16]. Ulcer characteristics, complications of diabetes, time to biopsy, and follow-up times were seldom reported. Grayson et al and Lavery et al reported follow up times of 27 and 21 months, respectively [8, 18]. Grayson et al also reported time to biopsy and found that the accuracy of PTB decreases as the time between index test and biopsy increases [18]. Specifically, the average time to biopsy in those with a true-positive PTB test was 8 days vs 31 days in those with a false-negative PTB [18]. All studies used a blunt metal probe to perform the PTB test except one that used Halsted mosquito forceps [17]. Findings on magnetic resonance imaging (MRI) [7], bone histopathology [7, 17–20], and bone culture [8, 16, 17] were the reference standards used among the studies. Six studies used bone biopsy as the sole method to confirm OM [8, 16–20]. The remaining study used bone culture for 35% of the patients and MRI for the rest [7]. Aragon-Sanchez et al, Grayson et al, Morales Lozano et al, and Zaiton et al used histology as a reference standard, but only Aragon-Sanchez et al, Grayson et al, and Morales Lozano et al included the histologic criteria used to define OM [17–20]. The histologic criterion used was the presence of an inflammatory infiltrate and bone necrosis to identify OM. Zaiton et al also included the presence of cortical erosion [19], while Grayson et al and Morales Lozano et al included the presence of reactive bone formation [18, 20]. Lavery et al, Malone et al, and Aragon-Sanchez et al used bone culture as a reference standard [8, 16, 17].

All 7 studies were included for pooling of sensitivity and specificity (Table 2). Pooled sensitivity and specificity for the PTB test were 0.87 (95% CI, .75–.93) and 0.83 (CI, .65–.93), respectively. The correlation coefficient between prevalence and sensitivity was 0.53, and the coefficient for specificity was −0.41 (both not significant). When added as a covariate to the model, an increase in sensitivity and decrease in specificity was observed with increasing prevalence. The model did not converge when clinical setting was added as a covariate.

Quality Assessment

With regard to the timing and consistent use of bone histology or culture as a reference standard, 4 studies had a high risk of bias [7–9, 17, 18], and 3 studies had an unclear risk of bias [16, 19, 20]. Four studies had an unclear risk of bias due to the conduct and interpretation of the reference standard as they did not mention blinding of the index test in the interpretation

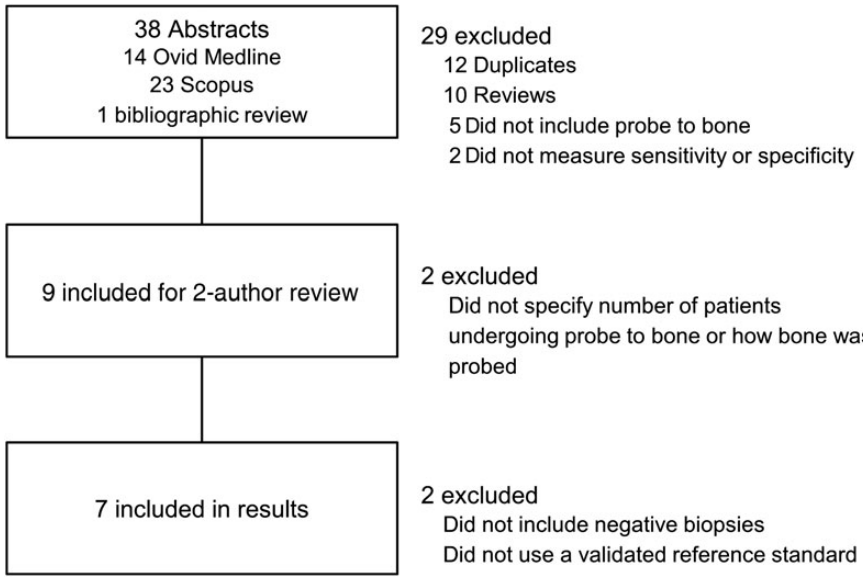

Figure 1. Study selection.

of the gold standard [17–20]. Of the studies that had a high risk of selection bias, Mutluoglu et al used the results of PTB as part of their criteria to evaluate for suspected DFI [7]. Zaiton et al only selected patients already scheduled for surgical management, and the impact of the PTB test in the decision process was not discussed [19]. Malone et al performed a retrospective case series and only selected patients with a positive biopsy [16].

Three studies had 100% biopsy rates [16, 19, 20]. Four studies included patients for whom bone culture or histology was not used as a reference standard [7, 8, 17, 18]. These studies were included because they still used bone samples to confirm OM in high-risk patients. Samples were not procured from low-risk patients. Specifically, the decision to procure a bone sample was made by a positive PTB test or plain radiograph [17]; a positive PTB test, exposed bone after debridement, or bone available after resection for tissue ischemia [18]; and suspected bone infection based on clinical examination and imaging studies [8]. One study did not explain how the decision to biopsy was made [7].

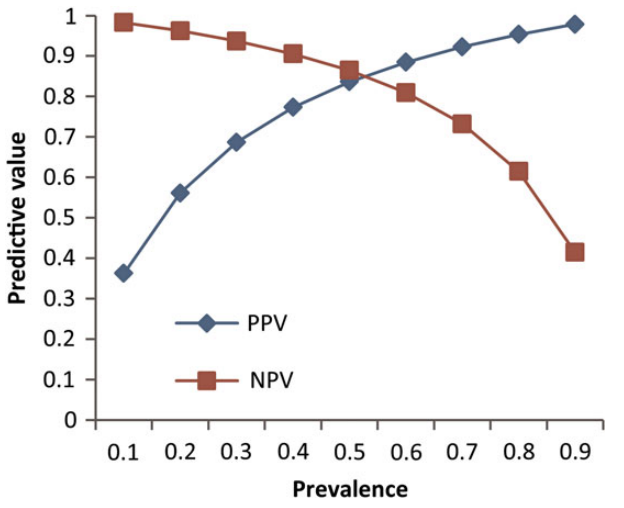

Figure 2. Calculated positive and negative predictive values given pooled sensitivity and specificity. An increase in prevalence results in a decrease in negative predictive value (NPV), but an increase in positive predictive value (PPV). The opposite occurs with decreasing prevalence.

DISCUSSION

Current International Working Group on the Diabetic Foot guidelines recommend using the PTB test to diagnose OM in high-risk patients with DFI and to rule out OM in those with a low risk of DFI [5]. Our results support this recommendation. The positive predictive value of the PTB test crosses 90% at a pretest probability of 60%, and the negative predictive value is >95% at pretest probability below 20%. Therefore, in a hospital setting with high-risk patients, the PTB can be used to confirm OM, whereas in a low-risk setting, such as a primary care clinic, the PTB test can be used to rule out OM.

It is unknown which factors decrease the accuracy of the PTB test. Lavery et al's study had the lowest positive predictive value of all the studies, but it included all ulcers regardless of etiology and had the lowest prevalence of OM [8]. The studies that excluded ulcers of ischemic etiology had the highest positive predictive values, but prevalence of OM was >70% in all of those studies [17, 19, 20]. Malone et al's study had the lowest negative predictive value. Although this study had patients with a high baseline risk of OM, prevalence of 78%, and used bone culture as the reference standard, which may be prone to false positives, this number is still lower than expected [16]. It is unclear what

Table 1. Key Characteristics of Included Studies

First Author, Year	Patients No.	Inclusion	Exclusion	Setting	Design	Reference Standard	Percentage With Biopsy
Aragon-Sanchez, 2011 [17]	338	DFI	Limb ischemia	Inpatient	Prospective cohort	Bone histology or bone culture	74 (n = 256)
Grayson, 1995 [18]	75	DFI	No ulcer, recent foot surgery	Inpatient	Prospective cohort	Bone histology	70 (n = 53)
Lavery, 2007 [8]	247	DFU	No ulcer	Both	Prospective cohort	Bone culture	12 (n = 30)
Morales Lozano, 2010 [20]	132	DFI	Limb ischemia, scheduled for unrelated surgery	Outpatient	Prospective cohort	Bone histology	100
Malone, 2013 [16] (unpublished data)	58	DFI	Systemic antibiotics at enrollment	Both	Retrospective case series	Bone culture	100
Mutluoglu, 2012 [7]	65	DFI	Not stated	Both	Prospective cohort	MRI or bone histology	35 (n = 17)
Zaiton, 2014 [19]	102	DFI	Chronic osteomyelitis, limb ischemia	Both	Prospective cohort	Bone histology	100

Abbreviations: DFI, diabetic foot infection; DFU, diabetic foot ulcer; MRI, magnetic resonance imaging.

else may have contributed to this result. Although not observed in the present study, pretest probability may not only affect positive and negative predictive values, but also the sensitivity and specificity (Figure 2) [21]. In a theoretical and experimental model, prevalence was shown to influence sensitivity and specificity of tests with subjective thresholds [22, 23]. A relationship between prevalence and sensitivity and specificity may have been masked by differences in patient selection; prevalence of peripheral vascular disease; glycemic control; size, depth, and location of the ulcer; and time from PTB to biopsy [1, 18, 24, 25]. These variables were seldom reported in the included studies.

The reliability of the PTB test may vary with clinician experience and ulcer location. A small case series studied the interobserver reproducibility of the PTB test and found a moderate amount of interobserver agreement that was highly dependent on the qualifications of the professionals who performed the diagnostic test [26]. In a subsequent study, ulcers on the central metatarsals had the highest interobserver agreement, whereas those on the minor toes had the lowest; even among experienced physicians the κ score was 0.35 [24].

To maximize both the reliability and accuracy of the PTB test, we recommend it to be only used for DFIs of neuropathic or neuroischemic or traumatic etiology. The clinician should use a blunt metal probe to gently explore the entire wound. If a metal probe is unavailable, Halsted mosquito forceps will suffice without an apparent decrease in accuracy [17]. Bone will feel rock-hard and there will be a grinding sensation when moving the probe over the surface. Always inspect the wound, and in the case of a seemingly positive test, check that there is no obvious intervening soft tissue between the probe and the bone. Other than removing an overlying eschar, it is important to perform the test prior to any debridement; the test cannot be used on ulcers that have recently been surgically debrided.

Clinicians have more than just PTB to diagnose diabetic foot OM. Other physical exam findings that have been reported to correlate with OM include wound depth, ulcer area, a "sausage" toe, and ulcer location [25, 27–30]. When physical examination findings are combined with results from plain radiographs, MRI, and serum inflammatory markers, both the accuracy and reliability of diagnosis increase [17, 31, 32]. Future prospective trials are needed to confirm which combinations of clinical, laboratory, and imaging findings are most suitable and cost effective.

Several limitations of our study affect the accuracy of our findings. The high likelihood of verification and selection bias in these studies may have led to an overestimation of the accuracy numbers. Three studies had 100% biopsy rates, but were

Table 2. Performance Characteristics of Studies Providing Sufficient Data to Allow Calculation

First Author, Year	Sensitivity (95% CI)	Specificity (95% CI)	PPV	NPV	DOR (95% CI)	Prevalence
Lavery, 2007 [8]	.87 (.71–.95)	.91 (.86–.94)	0.57	0.98	64 (4.5–900)	0.12
Mutluoglu, 2012 [7]	.67 (.51–.80)	.85 (.67–.94)	0.87	0.63	11 (.61–200)	0.60
Grayson, 1995 [18]	.66 (.52–.78)	.85 (.67–.94)	0.89	0.56	11 (.65–180)	0.66
Zaiton, 2014 [19]	.83 (.73–.90)	.77 (.58–.89)	0.92	0.59	16 (1.3–190)	0.75
Malone, 2013 [16] (unpublished data)	.87 (.74–.94)	.23 (.08–.50)	0.80	0.33	1.95 (.05–69)	0.78
Aragon-Sanchez, 2011 [17]	.94 (.90–.96)	.98 (.92–.99)	0.99	0.83	630 (21–19 000)	0.79
Morales Lozano, 2010 [20]	.98 (.93–.99)	.78 (.59–.90)	0.94	0.91	180 (3.9–8300)	0.80
Pooled values	.87 (.75–.93)	.83 (.65–.93)	0.91	0.84	32 (8.7–120)	0.59

Abbreviations: CI, confidence interval; DOR, diagnostic odds ratio; NPV, negative predictive value; PPV, positive predictive value.

complicated by problems with patient selection [16, 19, 20]. Moreover, there was heterogeneity in the reference standard used.

The findings from this meta-analysis show that the PTB test is an effective tool in the diagnosis of diabetic foot OM. The pooled sensitivity, specificity, and diagnostic odds ratio of 0.87, 0.83, and 32 (range, 1.95–630), respectively, for the PTB test are similar to reported values for MRI (0.90, 0.83, and 42 [33]) and the erythrocyte sedimentation rate (0.81 and 0.90 [34]). However, the evaluation of published studies is complicated by inconsistent use of operational definitions, patient selection, and reference standards. Although publication bias is a concern, there were too few studies to power an analysis for funnel plot asymmetry [35]. To understand the limitations of the PTB test, more data and more consistent reporting of comorbidities are needed to find factors that decrease the test's accuracy.

Notes

Acknowledgments. We thank Dr Matthew Malone for his contribution of his unpublished data.

Potential conflicts of interest. L. A. L. has served as a consultant for Aplion Medical Users, Harbor MedTech, Podometrics, and HyperMed; has received grant funding from Osiris, MacroCure, Integra, GlaxoSmith-Kline, KCI, and Cardinal; and is a member of the speaker's bureaus for Osiris, Integra, and Smith & Nephew. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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