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MAJOR ARTICLE

Percutaneous Bone Biopsy for Diabetic Foot Osteomyelitis: A Systematic Review and Meta-Analysis

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Background. Diabetes is the leading cause of lower extremity nontraumatic amputation globally, and diabetic foot osteomyelitis (DFO) is usually the terminal event before limb loss. Although guidelines recommend percutaneous bone biopsy (PBB) for microbiological diagnosis of DFO in several common scenarios, it is unclear how frequently PBBs yield positive cultures and whether they cause harm or improve outcomes.

Methods. We searched the PubMed, EMBASE, and Cochrane Trials databases for articles in any language published up to December 31, 2019, reporting the frequency of culture-positive PBBs. We calculated the pooled proportion of culture-positive PBBs using a random-effects meta-analysis model and reported on PBB-related adverse events, DFO outcomes, and antibiotic adjustment based on PBB culture results where available.

Results. Among 861 articles, 11 studies met inclusion criteria and included 780 patients with 837 PBBs. Mean age ranged between 56.6 and 71.0 years old. The proportion of males ranged from 62% to 86%. All studies were longitudinal observational cohorts, and 10 were from Europe. The range of culture-positive PBBs was 56%–99%, and the pooled proportion of PBBs with a positive culture was 84% (95% confidence interval, 73%–91%). There was heterogeneity between studies and no consistency in definitions used to define adverse events. Impact of PBB on DFO outcomes or antibiotic management were seldom reported.

Conclusions. This meta-analysis suggests PBBs have a high yield of culture-positive results. However, this is an understudied topic, especially in low- and middle-income countries, and the current literature provides very limited data regarding procedure safety and impact on clinical outcomes or antibiotic management.

Keywords: diabetic foot infection; diabetic foot osteomyelitis; percutanous bone biopsy.

Diabetes is the leading cause of lower extremity amputations globally, and diabetic foot osteomyelitis (DFO) is usually the terminal event before limb loss [1, 2]. Diabetic foot osteomyelitis generally occurs by contiguous spread from an infected diabetic foot ulcer that typically originates from repeated microtrauma due to a combination of foot deformities, peripheral neuropathy, and/or peripheral artery disease [1]. Diabetic foot ulcers are common, with estimates of lifetime prevalence ranging from 15% to 34% among people living with diabetes, and over half of all ulcers will become infected [1]. Diabetic foot osteomyelitis is present in more than 20% of patients with a diabetic foot ulcer infection, and more than 80% of patients with DFO will undergo an amputation [3, 4]. Improving DFO diagnosis and treatment is needed to increase limb salvage rates.

Antibiotics are the cornerstone of DFO management among patients treated without complete resection of infected bone (amputation) [5–7]. Identifying the bacteria causing DFO is needed to allow for the selection of the narrowest spectrum and least toxic antibiotics. Several studies have shown poor correlation between cultures obtained by soft tissue and bone sampling, suggesting that soft tissue samples are inadequate to guide DFO-related antibiotic therapy [8–10]. Thus, it is recommended that clinicians obtain bone specimens for microbiological analysis by percutaneous bone biopsy (PBB) for patients who are not undergoing surgery in several common scenarios (Supplemental Table 1) [5–7, 11].

Despite recommendations by several societal guidelines and international consensus meetings, PBBs are seldom performed [5–7, 11–13]. This may be because clinicians perceive few PBBs result in a positive culture, concerns of procedure-related harms, and/or lack of technical capability in many

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centers. The main goal of this study is to report on the microbiological yield of PBBs among patients with DFO (ie, proportion that are culture-positive). In addition, we sought to describe the bacterial species recovered by PBB and report on aggregated procedure-related adverse events, DFO outcomes, and antibiotic regimen adjustment according to PBB culture results.

METHODS

Search Strategy and Study Selection

We followed the PRISMA guidelines for systematic reviews and meta-analysis (checklist in the Supplemental File) [14]. We searched PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials on February 12, 2019, to identify articles published from database inception through December 31, 2018. We used the search terms "diabetic foot" AND "osteomyelitis" AND "biopsy" or "needle" or "aspiration" or "laboratory" as well as other related terms (see Supplemental File for details). There were no restrictions placed on the language of publication. The search was updated on January 29, 2020, to identify subsequent articles released during the 2019 calendar year.

We reviewed references listed in original articles included in this review, published reviews, and societal guidelines. We excluded case series with <5 subjects. Randomized clinical trials and observational studies were included. Conference abstracts were eligible for inclusion. Our primary objective was to determine the rate of culture-positive PBBs. Thus, we only included studies that reported the number of patients with DFO undergoing PBB (ie, the denominator) and not just the number of patients with DFO and culture-positive PBBs (ie, the numerator).

Data Abstraction and Study Quality Assessment

Titles, abstracts, and full texts were screened by a single reviewer. We extracted data into standardized forms. Given that there is no gold standard for DFO, we did not calculate the sensitivity and specificity of PBBs [15]. Instead, we report the proportion of PBB obtained from patients with suspected DFO that were culture-positive. We defined a culture-positive PBB as any positive bacterial culture not classified as a contaminant by the study authors. Other variables that may have affected the PBB bacterial culture yield and/or procedure related-adverse events were extracted, including microbiological laboratory procedures (transport media, incubating time), criteria to classify a positive culture as a contaminant, biopsy route (through the ulcer vs through intact skin), needle type and size, biopsy method (bedside vs image-guided), severity of diabetic foot infection, presence of peripheral artery disease (PAD), anatomical site biopsied (forefoot vs mid- and hindfoot, phalanges vs metatarsals), and prebiopsy antibiotics (within the previous 2 weeks before the PBB). Included studies were reviewed for procedure-related adverse events. Despite limitations, soft tissue sampling through superficial ulcer swab or soft tissue biopsy is often used to guide antibiotic therapy for DFO. Thus, we also extracted data on concordance between PBB and soft tissue samples when available. Samples were classified as "identical" when all bacterial species cultured by bone and soft tissue samples were the same. Samples were classified as concordant for a single bacterial species (eg, *Staphylococcus aureus*) when both samples were culture-positive or culture-negative for that species. Finally, we reviewed included studies for DFO outcomes and antibiotic regimen adjustments based on PBB culture results.

We assessed the quality of included studies using an adapted QUADAS (Quality Assessment of Diagnostic Accuracy Studies)-2 tool (Supplemental File) [16]. Two domains were assessed: (1) patient selection and (2) PBB and microbiological laboratory methods. The risk for bias regarding patient selection was determined by enrollment of consecutive patients without inappropriate exclusions. Patient selection applicability to our study question was based on selection of patients for PBB based on clinical and radiological criteria that are routine practice (eg, probe-to-bone and x-ray). Regarding PBB and microbiological laboratory methods, risk of bias was determined based on whether and how authors reported on the microbiology laboratory criteria used to define contaminants (eg, coagulase-negative *Staphylococci*). Applicability was determined based on use of standard PBB and microbiological laboratory methods because our goal was to describe yield of PBB in routine practice. The quality domains were scored in relation to our main outcome (PBB microbiology yield), not our secondary outcomes (procedure-related adverse events, DFO outcomes, and antibiotic regimen adjustments).

Statistical Analysis

Analyses were performed with the meta package (version 4.10-0) [17] using R version 3.6.2. We calculated the pooled proportion of culture-positive PBBs using a random intercept logistic regression model via the metaprop function. We used a random-effects model because between-study patient populations and PBB techniques were heterogeneous. Forest plots with 95% confidence intervals (CIs) were built. The I^2 statistic was used to assess between study heterogeneity with *P* values based on the Q-statistic. Funnel plots were built to assess for publication bias.

Senneville et al [9] and Aslangul et al [18] included some patients that had >1 PBB, and results from both biopsies were included in the meta-analysis. Couturier et al [19] performed 2 PBBs per patient: 1 through intact skin and 1 through an ulcer. To minimize the number of duplicate patients, we excluded the results from biopsies performed through an ulcer from our primary meta-analysis and retained the results for biopsies performed through intact skin because this is the approach usually recommended by guidelines. We performed 2 subanalysis: one stratifying studies by PBB approach (through intact skin vs through an ulcer) and another stratifying studies by inclusion

or exclusion of patients who received antibiotics ≤2 weeks before the PBB.

RESULTS

Study and Patient Characteristics

Eight hundred sixty-one unique titles were screened, and 11 studies met inclusion criteria, including 2 conference abstracts (Figure 1) [8–10, 18–25]. Ten studies had longitudinal observational study design, and 1 study did not report design (Supplemental Table 2). Ten studies were conducted in Europe, 9 were conducted in France, and 3 were by the same first author (Table 1). The author confirmed that there was no overlap between patients included in these 3 studies. Among included studies, the median sample size was 71 patients (range 26–144). Studies generally selected patients for PBB using well established clinical and radiological criteria for DFO [9, 26] (see Supplemental Table 3 for included studies' patient inclusion and exclusion criteria).

Ten studies reported patients' age, and the mean age ranged from 56.6 to 71.0 years old. Five studies reported patients' gender, and the proportion of males ranged from 62% to 86%. No consistent definition of PAD was used across studies. Four studies excluded patients with advanced PAD (Supplemental Table 3). Six studies reported PAD prevalence among included patients (range 18%–61%), but no study reported PBB results or safety stratified by presence of PAD.

Five studies reported diabetic foot infection severity scores, but none reported PBB results or safety stratified by infection severity. Three different infection severity scores were used, and no more than 2 studies used the same system. Regarding use of antibiotics before PBB, 4 studies excluded patients that received antibiotics ≤2 weeks before the PBB, and it was unclear whether patients received antibiotics ≤2 weeks before the PBB in 4 other studies. Three studies included patients that received antibiotics ≤2 weeks before the PBB. The proportion of patients receiving antibiotics ≤2 weeks before the PBB ranged between 32% and 53% in these studies. No study reported antibiotic class, spectrum, or route before the PBB.

Percutaneous Bone Biopsy Characteristics

Six studies only obtained PBBs through intact skin and 3 studies only obtained PBBs through an ulcer (Table 1). Biopsy approach was unclear in one study. All studies used conventional microbiological culture methods, and no study used nonculture-based microbiological techniques such as polymerase chain reaction. Other PBB characteristics and methods are described in Supplemental Tables 3 and 4. Few studies reported needle size (n = 6), bone sample transport media (n = 5), or culture incubation time (n = 4).

Proportion of Positive Percutaneous Bone Biopsies

On average across all studies, the proportion of culture-positive PBBs ranged from 56% to 99%. After removing the biopsies

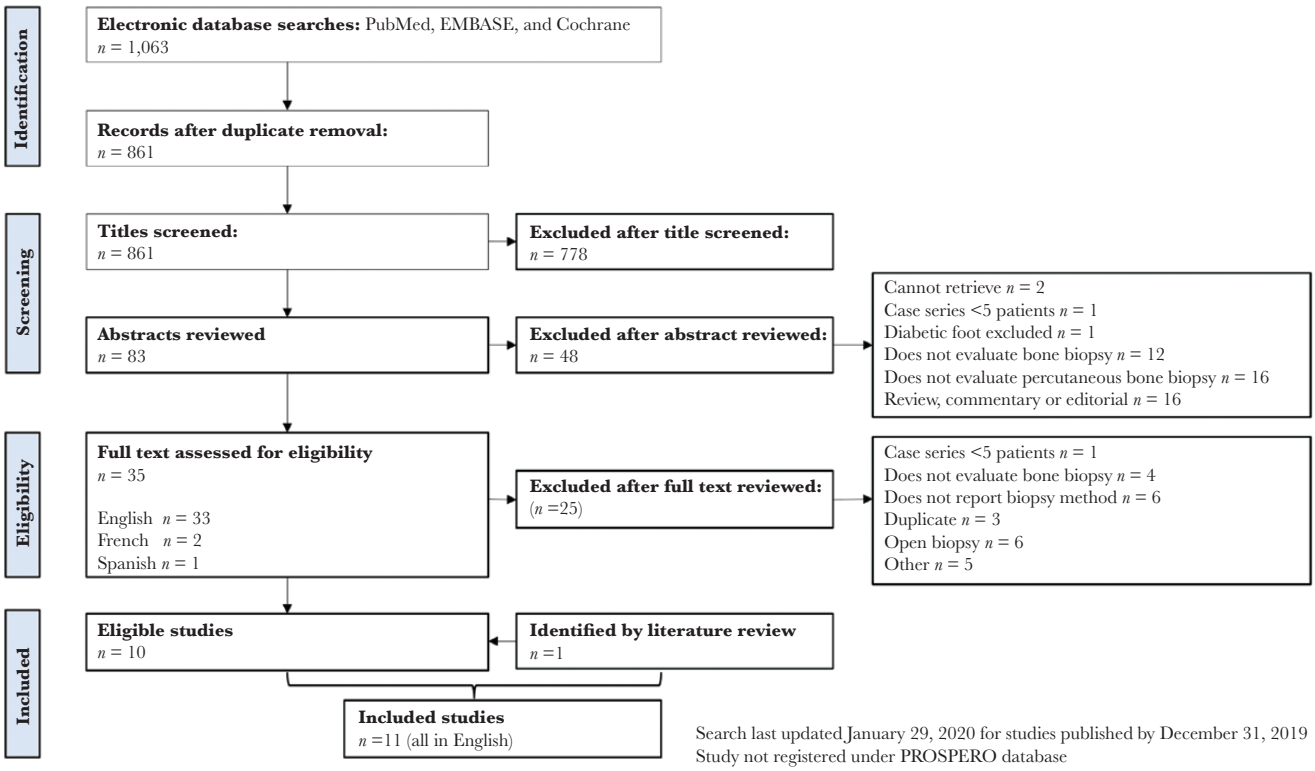


Figure 1. PRISMA flow diagram.

Table 1. Study Characteristics and Results

Study (Country)	Number of Patients	Infection Severity	Prebiopsy Antibiotics	Biopsy Approach	Number of PBBs	Number (%) of Culture-Positive PBBs
Senneville et al [9] (France)	88	Wagner's[a] Grade 3 80% Grade 4 20%	None 4 weeks before the PBB	≥2 cm from ulcer; less for toe biopsy Dorsal approach for plantar ulcers	93	81 (87)
Senneville et al [20] (France)	26	NR	Some patients received antibiotics 4 weeks before the PBB[b]	≥2 cm from ulcer; less for toe biopsy Dorsal approach for plantar ulcers	26	22 (85)
Senneville et al [10] (France)	31	NR	None 2 weeks before the PBB	≥2 cm from ulcer; less for toe biopsy Dorsal approach for plantar ulcers	31	21 (68)
Elamurugan et al [8] (India)	144	Wagner's Grade 3 60.4% Grady 4 ~20%	57% received antibiotics before PBB. Timing, duration, route, and spectrum NR.	PBB through apparently normal skin	144	134 (93)
Lesens et al [21] (France)	80	NR	53% received antibiotics ≤2 weeks before PBB. Route, duration, and spectrum NR.	Through the ulcer	80	78 (97)
Aslangul et al [18] (France)	40	NR	None 2 weeks before the PBB	Through "intact uninfected skin"; aspiration of bone marrow	43	24 (56)
Navratil et al [22] (Czech Republic)	35	NR	NR	Through the ulcer	35	23 (66)
Ducloux et al [23] (France)	71	Armstrong wound grade used. Some with A and C grades, which are reserved for patients without infections[a]	None 2 weeks before the PBB	≥2 cm from ulcer	71	50 (70)
Letertre-Gibert et al [24] (France)	76	UT staging system Grade 3 stage B 70% Grade 3 stage D 30%	32% received antibiotics <1 week before PBB. Timing, duration, route, and spectrum NR.	Through the ulcer	76	75 (99)
Féron et al [25] (France)	146	NR	NR	Not reported	146	99 (67)[c]
Couturier et al [19][d] (France)	43	UT staging system[e] Grade 3 stage B 32 (70%) Grady 3 stage D 14 (30%)	42% received antibiotics ≤2 weeks before PBB. Route, duration, and spectrum NR.	All patients had 1 biopsy through intact skin (1 cm from the ulcer) and 1 through the wound	46 through intact skin 46 through the wound	38 (83) 45 (98)

Abbreviations: NR, not reported; PAD, peripheral artery disease; PBB, percutaneous bone biopsy; UT, University of Texas.

[a]Among culture-positive PBBs.

[b]Authors report antibiotic use 4 weeks before presentation among patients that did and did not undergo PBB 12 (24%). Proportion among those that underwent PBB not reported.

[c]Authors report separately results of blinded biopsy at bedside (62 [64%] positive) and by fluoroscopy or surgeon (37 [77%] positive).

[d]All patients in this study had paired PBB through intact skin and through the wound.

[e]Authors present severity score for each ulcer biopsied.

through an ulcer from Couturier et al [19], the sample size for the meta-analysis was 791 PBBs. The pooled proportion of culture-positive PBBs was 84% (95% CI, 73%–91%) (Figure 2). Between-study heterogeneity was high ($I^2 = 91\%$, $P < .01$) and the funnel plot was highly asymmetric. Two studies exhibited a large proportion of culture-positive PBBs, and we performed a sensitivity excluding these studies. After excluding these studies, the pooled proportion of culture-positive PBBs was 77% (95% CI, 68%–85%). Between-study heterogeneity ($I^2 = 82\%$, $P < .01$) funnel plot asymmetry was decreased.

Among 7 studies that performed PBBs through intact skin (n = 454 PBBs), the proportion of culture-positive PBBs ranged from 56% to 93%, and the pooled proportion was 80% (95% CI, 69%–88%) (Figure 3). Among 4 studies that performed PBBs through an ulcer (n = 237 PBBs), the proportion of culture-positive PBBs ranged from 66% to 99% and the pooled proportion was 96% (95% CI, 81%–99%).

Among the 4 studies that excluded patients that received antibiotics ≤2 weeks before the PBB (n = 238 PBBs), the proportion of culture-positive PBBs ranged from 56% to 87% and the pooled proportion was 72% (95% CI, 59%–83%). All of these studies performed the PBB through intact skin. Three studies included patients that received antibiotics ≤2 weeks before the PBB, including the

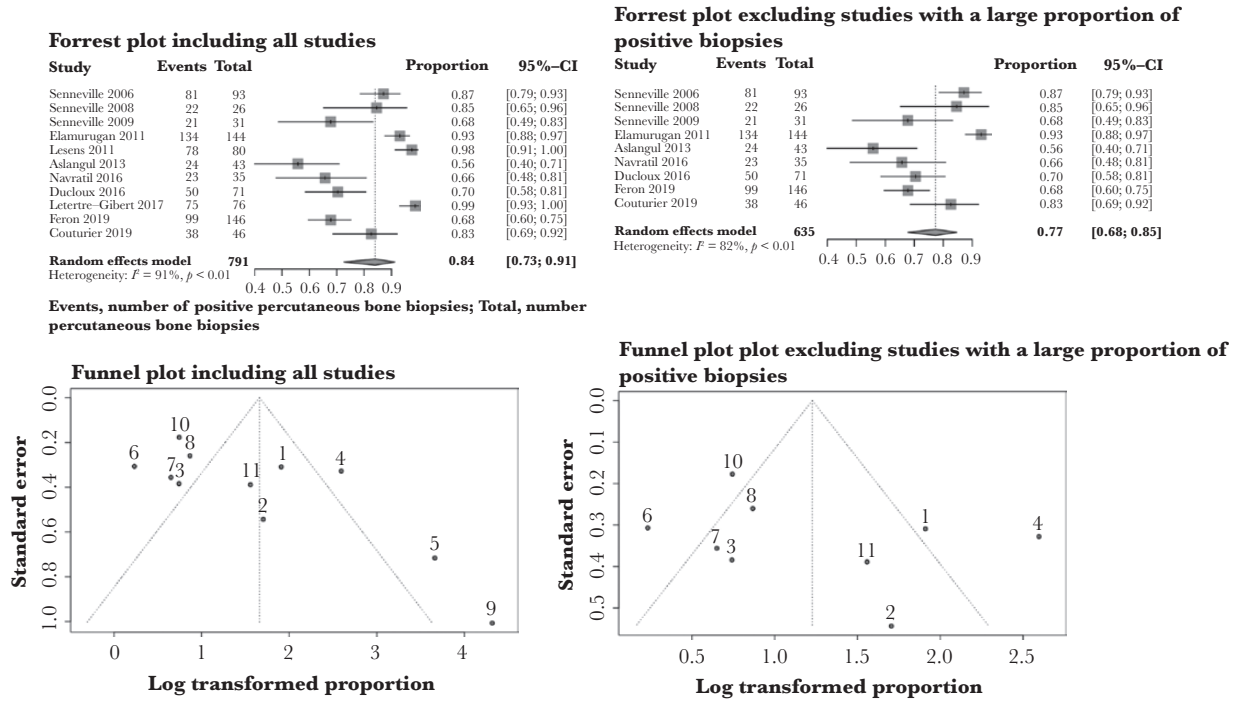


Figure 2. Meta-analysis of the proportion of culture-positive percutaneous bone biopsies. CI, confidence interval.

Couturier et al [19] study in which patients had 2 PBBs: 1 through intact skin and 1 through an ulcer. After removing the biopsies through an ulcer from Couturier et al [19], the proportion of culture-positive PBBs ranged from 83% to 99%. In this subset (n = 202 PBBs), the pooled proportion of positive PBBs was 96% (95% CI, 84%–99%). The 2 studies other than Couturier et al [19] performed the PBB through an ulcer.

Bias and Applicability Assessment

Regarding patient selection, we classified 5 of the 11 studies as low risk of bias. We could not assess risk of bias in 5 studies (Supplemental Table 5). One study excluded patients with ≤12 months of follow-up and therefore was classified as high risk of bias. We determined that patient selection in 8 studies were applicable to our review question. There were concerns regarding applicability in 2 studies: 1 that only included patients

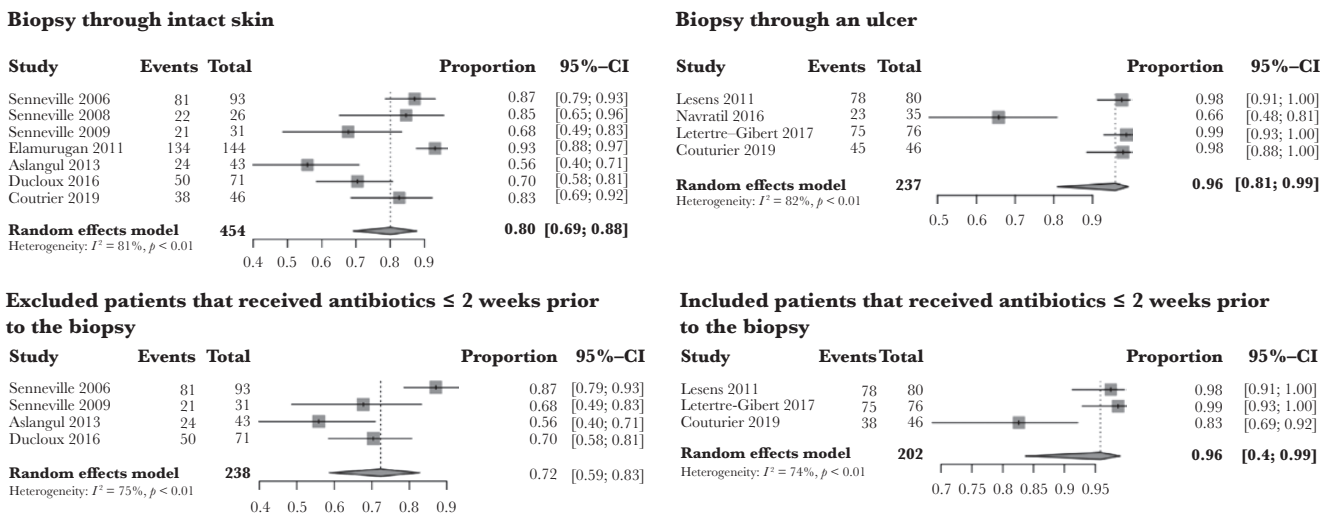


Figure 3. Meta-analysis of the proportion of culture-positive percutaneous bone biopsies stratified by biopsy approach and antibiotic use before biopsy. CI, confidence interval.

that had a blood culture collected after the PBB, and 1 that only included patients with very high pretest probability of DFO and used PBB just for microbiological confirmation. We could not assess applicability in one study.

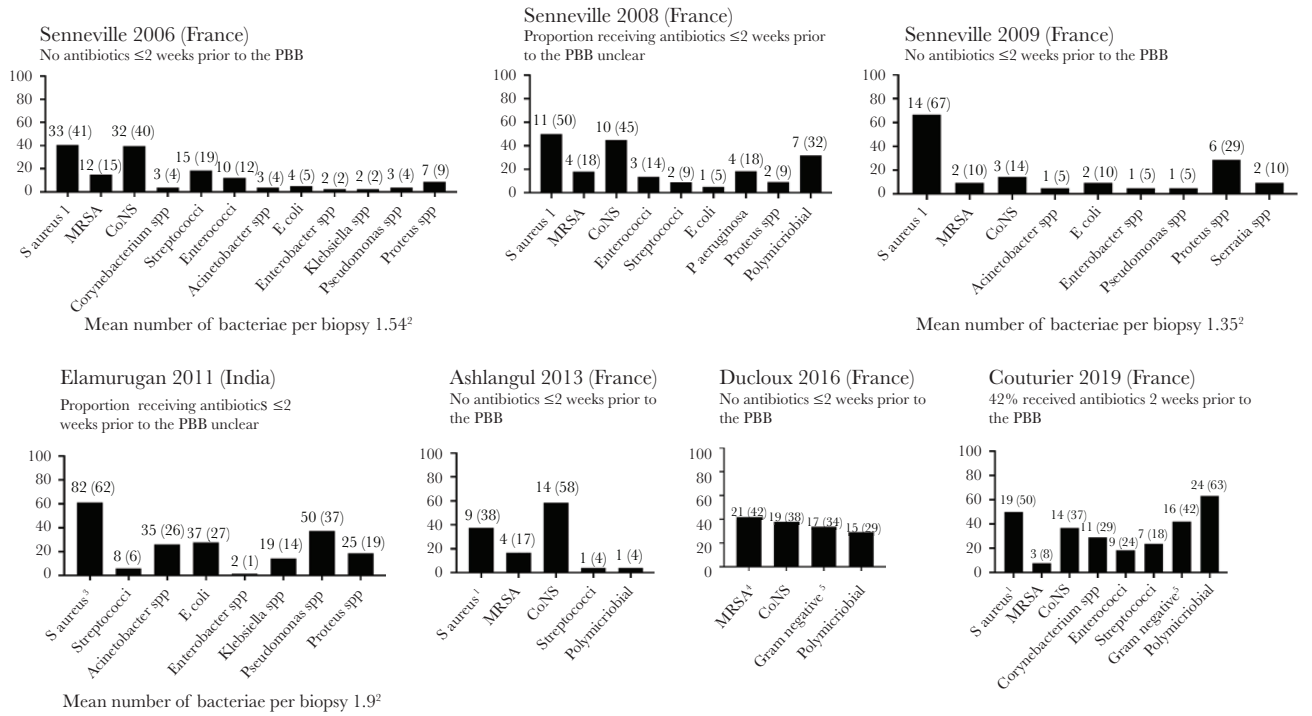
Regarding PBB and microbiological laboratory methods, one study provided a description of criteria to determine whether a positive culture resulted from contamination and was deemed low risk for bias (Supplemental Table 4). All other studies did not provide description of criteria for contaminants and/or description of PBB technique, and we could not determine risk of bias. Ten studies used conventional PBB and microbiological methods and therefore were applicable to our study question. One study used bone marrow aspiration guided by single-photon emission computed tomography ([SPECT]/CT), which is not standard of care and therefore less applicable to our study question.

Bacterial Species Cultured by Percutaneous Bone Biopsy

Nine studies described some or all the bacterial species recovered by PBBs. See Figure 4 for microbiology of PBBs obtained through intact skin and Supplemental Figure 1 for microbiology of PBBs obtained through an ulcer. In all of these studies, *S aureus* was the most common pathogen (range 38%–67% of culture-positive biopsies). Five studies reported the presence or absence of *Pseudomonas* spp, which were present in 4% to 37% of culture-positive PBBs (4 studies were conducted in France and 1 in India). The highest proportion of culture-positive PBBs for *Pseudomonas* spp occurred in the study conducted in India in which 57% of patients received antibiotics at some point before the PBB. In this same study, *Acinetobacter* spp was found in 26% of culture-positive PBBs. Five studies reported the proportion with polymicrobial culture growth, which were present in 4% to 76% of culture-positive PBBs. Bacterial species sometimes considered contaminants were grown frequently among studies that reported the presence or absence of *Corynebacterium* spp (range 9.7%–17.8%) and/or coagulase-negative *Staphylococci* (range 26.8%–38.9%) (Supplemental Figure 2). See Supplemental Figure 3 for the distribution of bacterial species cultured by PBB stratified by antibiotic use ≤2 weeks before the biopsy.

Concordance Rates Between Percutaneous Bone Biopsy and Other Specimens

Three studies reported the proportion of PBBs and wound swabs with identical culture results, which varied from 2.8% to



Horizontal axis, percentage of culture-positive biopsies in which the bacteria was grown
number (%) for each bacteria on top of the bars

Abbreviations: PBB, percutaneous bone biopsy; MRSA, methicillin-resistant *S. aureus*; CoNS, coagulase-negative *Staphylococci*

1-Including MRSA
2-Proportion with polymicrobial growth not reported
3-Methicillin-susceptiblity not reported
4-Proportion with methicillin-sensitive *S. aureus* not reported
5-Individual gram-negative species not reported; this is the sum of all gram-negatives

Figure 4. Distribution of bacteria isolated by percutaneous bone biopsy among studies performing biopsy through intact skin.

17.4% (Supplemental Table 6). In these studies, *S aureus* was the bacteria with the highest proportion of concordant results (42.8% to 82.3%). One study compared culture results between PBBs obtained through intact skin to those obtained through an ulcer. The proportion of positive PBBs obtained through intact skin was lower compared with those obtained through the ulcer (83% and 98%, respectively, $P < .01$) and 42% had identical results. One study collected post-PBB blood cultures and 12 of 80 (15.8%) were positive. Bacterial species cultured in the blood were also isolated by PBB in 11 (92%). Data on concordance between soft biopsy by needle puncture are in Supplemental Table 6.

Percutaneous Bone Biopsy Safety

No study provided a clear definition of PBB-related adverse events. Six studies did not mention whether adverse events occurred, and 4 studies reported no PBB-related adverse events (Supplemental Table 7). One study reported that 2 (4%) patients had minor adverse events.

Diabetic Foot Osteomyelitis Outcomes and Antibiotic Regimen Adjustments

Two studies reported DFO outcomes and antibiotic regimen adjustments after PBB (Supplemental Tables 8 and 9). One study performed PBBs in 26 patients and 22 were culture-positive, 19 of which had antibiotic regimen adjustment based on PBB results. Seventeen patients initiated antibiotics after PBB results were available. Among 5 patients started on an empiric regimen, 2 had antibiotics adjusted based on PBB results. Diabetic foot osteomyelitis outcomes of the 22 culture-positive PBB patients were compared with antibiotic-treated patients with culture-negative PBB (n = 4) or those who had antibiotic regimen based on ulcer swab alone (n = 24). Twelve-month amputation-free survival was 82% among PBB culture-positive patients and 50% among PBB culture-negative/no PBB patients (adjusted odds ratio 4.78 [95% CI, 1.0–22.7]). One study (n = 50) used SPECT/CT to determine need for a PBB. Patients with a negative SPECT/CT (n = 13) or positive SPECT/CT and culture-negative PBB (n = 16) did not receive antibiotics. No patients with negative SPECT/CT and most (15 of 16) patients with positive SPECT/CT and culture-negative PBB had signs of DFO 1 year later. All SPECT/CT and PBB positive patients (n = 24) received antibiotic regimens that were based on PBB culture results, and 19 (79%) had ulcer healing or improvement defined as ≥50% reduction in ulcer size. Six studies did not report DFO outcomes and antibiotic regimen adjustment, and 3 studies reported DFO outcomes but not antibiotic regimen adjustment.

DISCUSSION

We performed a systematic literature search without date or language restrictions and found scarce literature regarding PBB culture yield in suspected cases of DFO. The limited available literature was especially surprising considering that a diabetes-related amputation occurs every 30 seconds globally [27], most amputations are preceded by DFO [1], and PBBs are recommended by guidelines in several common scenarios [5–7]. The proportion of culture-positive PBBs in our meta-analysis was high (84%), suggesting that the perception of PBBs being low yield may be incorrect. Even after excluding studies with the highest rate of PBBs with a positive culture, the proportion of culture-positive PBBs was 77%. We noted no major differences in yield with different routes of PBB and found that defining and reporting adverse events, DFO outcomes, and antibiotic adjustment was too inconsistent to be useful. Altogether, this meta-analysis suggests that PBBs are a useful and underutilized tool for the microbiological diagnosis of DFO. For comparison, image-guided biopsy for native vertebral osteomyelitis is widely used and appear to have a similar proportion of culture-positive results (36%-91%) to PBB for DFO [28].

Although we found a high rate of culture-positive PBBs, the clinical implications of this finding are unknown. Among included studies, only Senneville et al [20] compared DFO outcomes stratified by use of antibiotic regimen guided by PBB culture results. Although use of antibiotic regimens guided by PBB was associated with increased odds ratio of amputation-free survival, the study had a small sample size (n = 50) and large CIs (95% CI, 1.0–22.7) [20]. Another included study reported DFO outcomes among patients with positive nuclear scan (SPECT/CT) but culture-negative PBB, and most (15 of 16) had no signs of DFO 12 months later.

Senneville et al [29] reported outcomes among patients with suspected DFO and a culture-negative PBB and therefore were excluded from the meta-analysis. In this cohort, 10 of 41 (24%) with a culture-negative PBB developed DFO during the 2-year follow-up. Although limited, these data suggest that PPBs may allow for meaningful adjustments in antibiotic therapy, including withholding antibiotics when cultures are negative.

Most guidelines recommend performing the PBB through intact skin to reduce culture contamination [5–7]. Nonetheless, because of technical issues and safety concerns, PBBs are commonly performed through an ulcer. As expected, we found a higher pooled proportion of culture-positive PBBs among studies performing biopsy through the ulcer versus intact skin in our meta-analysis; however, there were insufficient data to compare safety between these 2 approaches. A recent meta-analysis including percutaneous and open bone biopsy for patients with various forms of osteomyelitis concluded that recent antibiotic use had no impact on the rate of culture-positive bone biopsies [30]. In our study, the pooled proportion of culture-positive PBBs was higher among studies that included patients with recent antibiotic use. These findings should be interpreted with great caution. First, most studies including patients with recent antibiotic use performed PBBs through an ulcer. Second, no study reported the proportion of positive PBBs stratified by

antibiotic use, and therefore the higher positivity rates could reflect study characteristics other than antibiotic use. Finally, no study reported antibiotic route, spectrum, or duration before the PBB. Given that patients with DFO often have concomitant soft tissue infections requiring immediate treatment, it is not always possible to withhold antibiotics. A sequential approach of antibiotic therapy for the soft tissue infection, followed by an antibiotic-free period, followed by a bone biopsy to guide DFO therapy led to a 68% DFO remission rate in a small single-center study [31]. Further studies describing this approach are needed. In addition, PBBs are generally recommended when patients are failing antibiotic therapy. Thus, future studies should report results stratified by recent antibiotic use in addition to detailed antibiotic characteristics and culture results.

As expected, *S aureus* was the most common bacteria recovered by PBB among included studies. However, bacteria other than *S aureus* were common among culture-positive PBBs, highlighting the importance of pursuing DFO microbiological diagnosis. It is well known that organisms commonly described as "skin flora" and usually considered contaminants by microbiology laboratories such as coagulase-negative *Staphylococci* and *Cornybacterium* spp are often found in bone cultures from patients with DFO. The prevalence of coagulase-negative *Staphylococci*-positive cultures was up to 58% among included studies. To better understand the prevalence and role of these bacteria in DFO, it is important for studies to provide a clear definition of contaminants; however, only 1 of the included studies provided this description. The prevalence of *Pseudomonas* spp was generally low, except for the one study in India where these bacteria were present in 37% of culture-positive biopsies. This finding is in line with the notion that there is a higher prevalence of *Pseudomonas* spp and other Gram-negatives in diabetic foot ulcers occurring among those residing in humid climates. Given the local environmental effect on DFO microbiology, increasing the geographic diversity of studies reporting PBB results would be beneficial.

Our review uncovered limitations in the PBB literature. First, studies seldom reported important technical aspects such as needle type and size and sample transport media. A better description of procedure techniques could facilitate implementation in centers currently not performing PBBs. Second, only 5 studies reported infection severity scores, and no more than 2 studies used the same system. This lack of standardization hampers our ability to compare studies. The diabetic foot research community would benefit from using a single infection severity score, such as the International Working Group on the Diabetic Foot system, which is also endorsed by the Infectious Diseases Society of America [6, 7]. Reporting of technical aspects, detailed reports of prior antibiotic use, and use of a single infection severity score system would allow better understanding of the large between-study heterogeneity. Third, there is little data regarding the impact of PBB on DFO outcomes or antibiotic stewardship. This may be especially important in countries with high rates of diabetes and antimicrobial resistance (eg, India). Fourth, the PBB literature does not reflect the global epidemic of diabetes given that almost all reports are from France [2]. Finally, all studies used conventional culture methods. A study of DFO samples obtained by percutaneous and open approaches showed higher positivity rates by 16S ribosomal ribonucleic acid assay compared with conventional cultures, suggesting that this and other nonconventional microbiology techniques should be explored for DFO [32]. This meta-analysis also has limitations. We could not include studies that reported on yield of PBB for various forms of osteomyelitis when data for DFO were not reported separately, and this lead to the exclusion of some studies in which image-guided PBB had low yield (<35%) [33–35]. In addition, we did not compare the yield, safety, and outcomes between percutaneous and open bone biopsy.

CONCLUSIONS

In summary, we report the first meta-analysis of PBBs for DFO and found high rates of culture-positive PBBs among included studies. We uncovered several limitations of this literature and suggest several measures to improve our understanding of this diagnostic method. If proven to be a safe and reliable diagnostic tool, PBBs could be of great benefit for patients with DFO because they could help establish a microbiological diagnosis and thus allow clinicians to use the narrowest spectrum antibiotics possible.

Supplementary Data

Supplementary materials are available at Open Forum Infectious Diseases online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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Potential conflicts of interest. All authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

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