



Ten Versus Five Polymorphonuclear Leukocytes as Threshold in Frozen Section Tests for Periprosthetic Infection: A Meta-Analysis

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ARTICLE INFO

Article history:

Received 12 July 2012

Accepted 18 October 2012

Keywords:

frozen section tests

periprosthetic infections

diagnosis

polymorphonuclear leukocyte

specificity

ABSTRACT

We objectively appraised available evidence regarding the threshold for the number of polymorphonuclear leukocytes required in frozen section tests used to diagnose periprosthetic infection. Pooled summary estimates for sensitivity, specificity, positive likelihood ratio, negative likelihood ratio and diagnostic odds ratio (OR) were compared for ten and five polymorphonuclear leukocytes per high power field as the threshold. The total cohort included 1011 patients and the rate of infection was 19.2%. Although there was no difference in sensitivity or diagnostic OR, specificity was significantly higher for ten than for five polymorphonuclear leukocytes per high power field ($p = 0.007$). In sum, a threshold of 10 polymorphonuclear leukocytes is better for diagnosing periprosthetic infections.

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Diagnosing periprosthetic infections for joint revision is difficult, with no consensus yet reached on the optimal approach. Although culturing preoperative aspirates from the joints was recommended as part of a two-stage revision protocol [1–5], the results were reported to be unstable [6]. Other criteria include erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) concentration and cell counts, but these tests are not definitive because other diseases can affect the results [7–9].

Based on results showing that infiltration by polymorphonuclear leukocytes occurred only during acute infection [10,11], frozen sections have been utilized to diagnose periprosthetic infection during revision surgery. Although many studies over the past 40 years have confirmed that this method can distinguish infectious from non-infectious loosening [12–18], the testing threshold remains unclear. Five polymorphonuclear leukocytes per high power field were considered the standard threshold, until its sensitivity in 107 patients was shown to be lower than previously reported, suggesting that over-reliance on this technique in a revision setting should be avoided [19]. Although a threshold of ten polymorphonuclear leukocytes per high power field has been proposed [11,20–23], it has been assessed in a limited number of patients, with variable

results among studies. Recently, Tsaras et al. reported a meta-analysis about ten and five polymorphonuclear leukocytes as the threshold. However, they failed to use sensitivity/specificity as the indexes and only found an obscure relationship between these two groups [24].

We performed a sub-group meta-analysis of the results of frozen section tests, comparing the accuracy of five and ten polymorphonuclear leukocytes per high power field as the threshold. We systematically analyzed all studies on frozen sections from 1973 [18] to date (July 2012).

Material and Methods

This study conformed to the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analysis) statement, without republication of the review protocol [25,26].

Two authors independently searched the literature to identify all available articles, published between January 1972 and July 2012, using frozen section tests to assay for periprosthetic infection. If the test threshold was not clearly described in the article, the authors were contacted for details. Articles were included in this review if (1) they utilized intraoperative frozen tests for periprosthetic infection; (2) the threshold was five or ten polymorphonuclear leukocytes per high power field (400×); (3) they utilized intraoperative cultures as the gold standard in testing for periprosthetic infection; and (4) the articles were published in peer reviewed journals.

The Conflict of Interest statement associated with this article can be found at <http://dx.doi.org/10.1016/j.arth.2012.10.015>.

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Online databases, including the Cochrane library, PubMed, OVID MEDLINE, EMBASE, Web of Science and Scopus, were searched using terms such as “frozen section”, “infection”, “sensitivity and specificity” and related terms (Supplementary Table 1). Articles in all languages were included, but articles containing previously published data were excluded.

Each article's quality was assessed independently by three authors, using a blinded review technique, in which information on the article's author and institution was withheld. Rather, assessments relied on the use of the 14 quality items of the QUADAS tool to calculate reliability and validity [27]. The quality score was calculated by assigning 1 point for each item fulfilled, 0.5 points for unclear items, and 0 points if the item was not fulfilled. A score <11 indicated poor quality, whereas a score ≥ 11 indicated good quality. Conflicts were resolved by discussion among the authors [28].

Study characteristics assessed included details about study design, patients, index test, and reference standard; 2×2 count data were extracted.

The risk of publication bias was assessed by a funnel plot and bivariate meta-regression of the diagnostic odds ratio in log scale (LOR). The regression slope of LOR versus $ESS^{-1/2}$ was tested for positivity with a significance level set at $p < 0.10$. LOR was defined as $\text{logit}(\text{sensitivity}) + \text{logit}(\text{specificity})$, and ESS was defined as $4 \times RP \times RN / (RP + RN)$, where RP = positive reference tests and RN = negative reference tests [29].

Statistical Analysis

Results were analyzed using Review Manager 5 (The Nordic Cochrane Centre, The Cochrane Collaboration, 2011) and Meta-Disc 1.4 (Department of Public Health & Epidemiology, University of Birmingham, UK) [30,31]. Pooled summary estimates for sensitivity, specificity, positive likelihood ratio, negative likelihood ratio and diagnostic OR were calculated by Meta-Disc, while forest plots and ROC figures were determined using Review Manager 5.

Between-study heterogeneity was assessed using *I*-squared statistics [31]. A bivariate random effects model was used, with subgroup analyses utilized to compare the two thresholds [32]. A *p* value <0.05 was considered as statistically significant.

Results

Search Results

A total of 2442 articles on total hip arthroplasty were reviewed. Of these, 2408 articles were excluded based on reviewing information in the title and/or abstract. The remaining 34 studies were examined in detail by reading their full texts. Of these, 22 articles were excluded for not using one of the thresholds being examined (Fig. 1). The remaining 12 articles were included; of these, seven used a threshold of five polymorphonuclear leukocytes per high power field (400×) [15,33–38], two used a threshold of ten polymorphonuclear

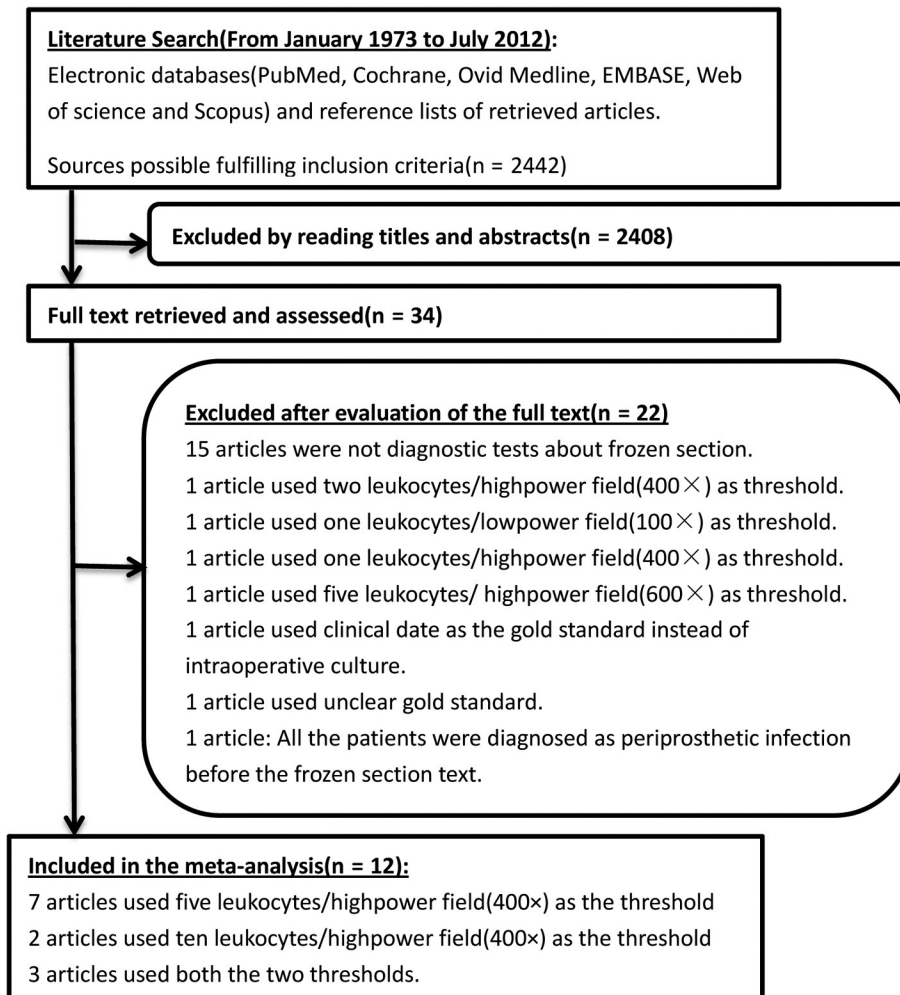


Fig. 1. Flow diagram of articles included in the meta-analysis.

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