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Invited critical review

Systematic review and meta-analysis of flow cytometry in urinary tract infection screening

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ABSTRACT

Background: Automated urine sediment analysis of white blood cells (WBCs) and bacteria is a promising approach for urinary tract infections (UTIs) screening. However, available data on their screening efficacy is inconsistent.
Methods: English articles from Pubmed, EMBASE, and Web of Science published before December 1, 2012 were analyzed. The Quality Assessment for Studies of Diagnostic Accuracy (QUADAS) tool was used to evaluate the quality of eligible studies. Performance characteristics of WBCs and bacteria (sensitivity, specificity, and other measures of accuracy) were pooled and examined by random-effects models.
Results: Nineteen studies containing 22,305 samples were included. Pooled sensitivities were 0.87 (95% confidence interval [CI], 0.86–0.89) for WBCs and 0.92 (95% CI, 0.91–0.93) for bacteria. Corresponding pooled specificities were 0.67 (95% CI, 0.66–0.68) for WBCs and 0.60 (95% CI, 0.59–0.61) for bacteria. Areas under the summary receiver operating characteristics curves were 0.87 and 0.93 for WBCs and bacteria, respectively. The major limitation of eligible studies was that enrolled subjects were often not representative of clinical patient populations in which UTI would be suspected.
Conclusions: WBC and bacterial measurements by the UF-100 and UF-1000i are useful indicators in UTI screening; however, the performances of these systems should be rigorously evaluated by additional studies.

Contents

1. Introduction

Urinary tract infections (UTIs) are common in the general population and hospitalized patients [1]. A positive urine culture is the "gold standard" for UTI diagnosis [1]. Although urine culture has therapeutic implications, allowing both UTI diagnosis and antibiotic susceptibility

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testing, it is also associated with three intrinsic disadvantages. First, urine culture is laborious and requires special training to perform, which hampers its diagnostic use in community hospitals. Second, it is time-consuming and, especially in the event of sample contamination, can delay the diagnosis and treatment of suspected UTI patients. Third, since the sign or symptoms of UTI are not necessarily specific, many samples from suspected UTI patients ultimately test negative for bacteria, but still require time and resources to process and increases costs for clinical microbiology laboratories. Therefore, it is important to develop alternative screens for UTI that are easily performed, rapid, and economical.

Urine sediment analysis using microscopy to count the white blood cells (WBCs) is a promising approach to screen for UTI [2–4]. However, special training for laboratory staff is required for this method, and it is susceptible to observer variation. Urine flow cytometry systems, such as the Sysmex UF-100 and UF-1000i, have been developed to standardize urine sediment analysis. These automated analyzers rapidly quantify urine particles, including WBCs, bacteria, red blood cells, and casts. Previous studies have demonstrated that these systems have good precision with low interference, low carryover contamination, and are consistent with microscopic counting results [5–8]. These advantages make the UF-100 and UF-1000i promising screening platforms for UTI.

Among the analytics provided by the UF-100 and UF-1000i, WBC and bacterial contents were the most common indicators used in UTI screening. Numerous studies have assessed the UTI screening capabilities of the UF-100 and UF-1000i using WBC and bacterial detection, but the results have been inconsistent. Therefore, we performed a systematic review and meta-analysis to determine the overall UTI screening performance of the UF-100 and UF-1000i. The aim of the analysis was to address deficiencies in previous studies and better guide future ones.

2. Methods

2.1. Search strategy and study selection

Two researchers (Y.S. and Q.W.) independently searched for eligible studies published before December 1, 2012 on the electronic databases Medline (using Pubmed as the search engine), EMBASE, and Web of Science. Keywords used for the literature searches included: Urinary tract infection, UF-100, or UF-1000i. References cited by eligible journal and review articles were also examined and potentially included. There was no language restriction initially, but only articles published in English were used in the full-text review and final analysis.

The inclusion criteria for the meta-analysis were: 1) studies of the screening or diagnostic performance of the UF-100 or UF-1000i, 2) both sensitivity and specificity data were available to construct 2×2 tables, and 3) the total sample size was greater than 40 and the number of UTI patients was greater than 10 (i.e., because studies of small sample size could introduce bias). The exclusion criteria were: 1) studies conducted in animals, 2) duplicate studies, 3) conference abstracts and letters to editors because such publications lacked sufficient data for analysis. Eligible studies were independently identified by two reviewers (Y.S. and Q.W.) by using the criteria above.

2.2. Data extraction and quality assessment

Two reviewers (Y.S. and Q.W.) independently extracted data from eligible studies. The data included: the name of the first author, publication year, sample sources, reference standard for UTI, total sample size, and cutoffs used for screening. The sample sizes of positive and negative UTI tests, sensitivity, and specificity allowed the following variables to be calculated in each article and sorted into 2×2 tables: number of true positives (TPs), false positives (FPs), true negatives (TNs), and false negatives (FNs).

The Quality Assessment for Studies of Diagnostic Accuracy (QUADAS) tool was used to assess the quality of all included articles [9]. Items screened by QUADAS that could greatly influence the credibility of studies were listed and analyzed. Discrepancies in data extraction and quality assessment were resolved by a third reviewer (Z.H. or A.D.).

2.3. Statistical analyses

Sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), and diagnostic odds ratio (DOR) were pooled by a random-effect model [10]. Forest plots and summary receiver operation characteristics (sROC) curves showed the overall screening performance and heterogeneity among studies [11,12]. The χ^2 and inconsistency indices were used to detect potential heterogeneity [13]. Heterogeneity attributed to threshold effects was analyzed by the Spearman approach [14]. Analyses were performed with MetaDisc 1.4 software [14].

3. Results

3.1. Summary of included studies

Nineteen studies containing 22,305 samples were included in our study [5,6,15–31]. Ten studies used the UF-1000i for UTI screening [5,16,20,23,25–27,29,30] and 8 studies used the UF-100 [6,15,18,19,21,22,24,31]. All studies used urine culture as the reference standard, but the cutoffs were different. Tested samples in most studies were sent to laboratories for urine culture, but three studies collected samples from patients in nephrology and urology clinics [22] or from outpatients [6,30]. Table 1 summarizes the eligible studies. Eight studies evaluated UTI screening performance based on WBC data [6,15,17,21,23,29–31], 11 studies screened using bacterial data [6,15–17,20,21,23,25,29–31], and 6 studies used strategies that combined data from both [5,18,19,26,27] or the flags given by the UF-100 [22] to screen UTI.

Table 2 shows the design of the screening approaches and results for the eligible studies. The overall QUADAS scores of included studies were moderate, ranging from 3 to 8. Important study design parameters that influence the QUADAS score included: 1) inclusion/exclusion criteria based on symptoms or history; 2) dose testing and blinded data interpretation; 3) consecutive and random sample collection; and 4) reporting of unexplained results (Table 2). There were no clear symptoms or signs utilized as inclusion/exclusion criteria in eligible studies, and samples sent to clinical microbiology laboratories served as study cohorts. Additionally, included studies did not report whether testing and data analyses were performed in a blinded fashion. Two studies reported that measurements were randomly collected from urine samples sent for urine culture [5,30], and 6 studies consecutively analyzed samples sent for culture [17–19,22,23,29], but the remaining studies did not report how sampling was conducted. Periodic contamination is inevitable in urine culture, but only 7 studies reported the number of contaminated samples [16,20,21,25,26,29,31].

3.2. Screening performance

Next, we performed a meta-analysis to assess the capabilities of the UF-100 and UF-1000i to screen for UTI based on WBC and bacterial data. Six studies used only combined data from both WBC and bacteria (in parallel or series) [5,18,19,26,27] or only the flags given by the UF-100 [22] to screen UTI. It was impossible to construct these data into 2×2 tables for meta-analysis, and these studies were therefore excluded. The remaining 8 studies which evaluated UTI screening performance of WBC data [6,15,17,21,23,29–31] and 11 studies screened using bacterial data [6,15–17,20,21,23,25,29–31], were included. Fig. 1 shows the sensitivity and specificity results for WBC and bacteria in UTI screening. Table 3 shows the overall UTI screening performance of the UF-100 and UF-1000i according to the detection of WBCs and bacteria.