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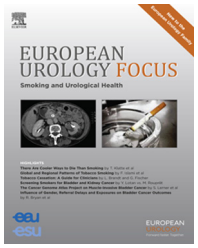

The Grey Zone

Non-molecular Methods to Detect Bacteriuria Prior to Urological Interventions: A Diagnostic Accuracy Systematic Review

Gernot Bonkat [a,*], *Olivier Braissant* [a,b], *Tomasso Cai* [c], *Bela Köves* [d], *Truls E. Bjerklund Johansen* [e], *Robert Pickard* [f], *Rajan Veeratterapillay* [f]

[a] *alta uro AG, Merian Iselin Klinik, Center of Biomechanics & Calorimetry (COB), University Basel, Basel, Switzerland;* [b] *Merian Iselin Klinik, Center of Biomechanics & Calorimetry (COB), University Basel, Basel, Switzerland;* [c] *Department of Urology, Santa Chiara, Reg. Hospital, Trento, Italy;* [d] *Department of Urology, South-Pest Teaching Hospital, Budapest, Hungary;* [e] *Department of Urology, Oslo University Hospital, Oslo, Norway;* [f] *Department of Urology, Newcastle University, Newcastle, UK*

Exclusion of bacteriuria is mandatory prior to invasive urological interventions [1]. The current diagnostic gold standard is urine culture (UC). However, UC has a typical time delay of 24–48 h between sample acquisition, pathogen identification, and delivery of antimicrobial susceptibility testing results. Furthermore, up to 80% of samples will not yield any microbial growth, resulting in high routine laboratory workload and costs. Therefore, faster and convenient diagnostic techniques are needed. Numerous methods have been investigated. However, the diagnostic accuracy of these techniques compared with the reference standard (UC) appears uncertain. The aim of this systematic review was to analyze the diagnostic accuracy of alternative diagnostic methods for the diagnosis of bacteriuria. PubMed, Embase, Medline, and Cochrane literature databases were electronically searched to identify clinical trials and meta-analyses describing diagnostic accuracy of alternative index tests compared with UC. Two reviewers screened a total of 3033 titles independently. Following the initial search, we widened the inclusion criteria to include all populations and not only patients scheduled for urological surgery as no studies were available for these patients. Out of these, 210 studies were selected for full text retrieval. Two reviewers performed independent scrutiny of these papers according to the QUADAS checklist [2]. Resolution of disagreement by a third reviewer and discussion resulted in the selection of 18 (Supplementary Table 1) single-arm cohort studies incorporating assessment of diagnostic accuracy of different index tests (ie, reagent strip [dipstick] urinalysis, automated microscopy, and dipslide testing) using UC as the reference standard. As urine-flow cytometry is a technique commonly used in this context, this method is discussed in this review as well. The study protocol for this review was published before data extraction [3].

Sixteen studies assessed dipstick urine analysis (Supplementary Table 1). A variety of threshold criteria for a positive test were used. Common findings indicating a positive test were nitrite positive only, leucocyte esterase positive only, at least one of nitrite or leucocyte esterase positive, and both nitrite and leucocyte esterase positive. The values for sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) are summarized in Figure 1 and Supplementary Figure 1. Use of both nitrite and leucocyte esterase being positive tended to give the lowest sensitivity, highest specificity, and reduced variation between studies. Criteria of having a single positive test only gave either poor sensitivity (nitrite only) or poor specificity (leucocyte esterase only) compared with other criteria. The criterion that resulted in the best overall diagnostic accuracy was when the test was considered positive if at least one of nitrite and leucocyte esterase were detected. However, the low sensitivity limits clinical applicability in the setting of assessment of bacteriuria prior to urological surgery. Additionally, high urinary protein or glucose levels should be taken into account when interpreting such results as their high levels might influence the biochemical reaction on the dipsticks. Studies have shown that including these confounders in the assessment of a

* Corresponding author.
E-mail address: bonkat@alta-uro.com (G. Bonkat).

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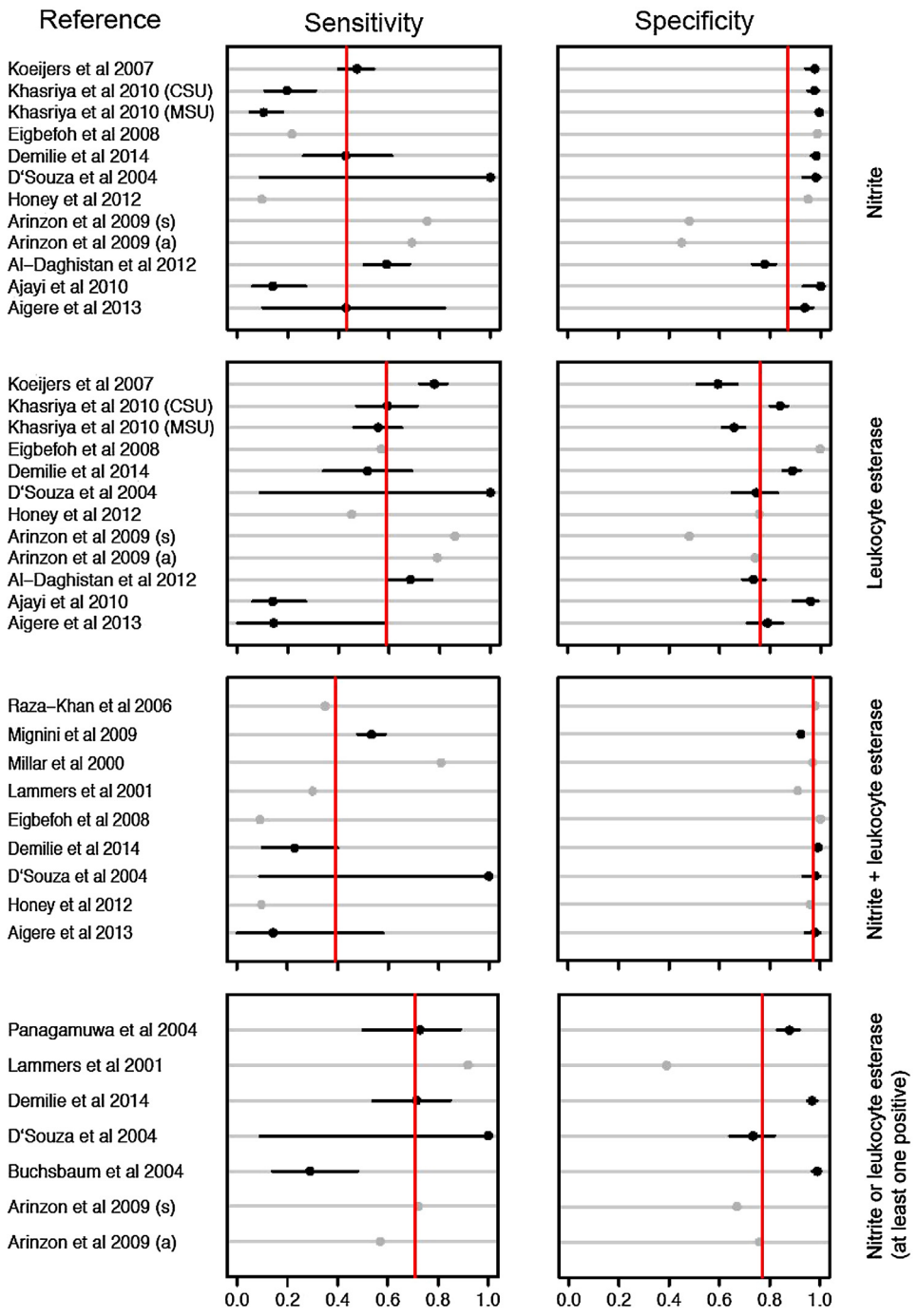

Fig. 1 – Forest plot showing the differences in sensitivity and specificity observed between studies focusing on dipsticks as well as between criteria used to consider the dipstick positive for bacteriuria. Black dots and lines are values recalculated from the raw data found in papers with their respective confidence intervals. Grey dots are values recovered from the papers in which raw data were not provided. Vertical red line indicate the average of the specificity and sensitivity for a specific criterion.

positive for bacteriuria dipstick result did not improve diagnostic accuracy [4].

Automated microscopy of urine sediment following centrifugation aims to use electronic analysis of a digital picture for specific particle recognition. It should not be confused with flow cytometry, which although also based on optical detection, does not generate a digital image. The selected studies used the same system (SediMax; A. Menarini Diagnostics, Florence, Italy). In a first study [5], the sensitivity, specificity, PPV, and NPV for bacteriuria compared with culture were 98.3%, 59.0%, 34.9%, and 99.4%, respectively. The following thresholds were used to define positive samples: white blood cells (WBC) > 4/HPF (=18 cells/μl), bacteria > 10/HPF (44 elements/μl). However, as demonstrated earlier by Lammers et al [6], the threshold chosen for bacteria, WBC, and red blood cells can greatly influence the

sensitivity, specificity, PPV, and NPV. However, combination with dipstick might reveal a better option to increase the specificity. Conceptually, automated microscopy remains an attractive alternative compared with flow cytometry as it simultaneously performs both detection and identification of particles without the need to check identification by conventional microscopy. Indeed, approximately 40–70% of flow cytometry flagged samples require further processing by microscopy.

Dipslides consist of a plastic layer on both sides of which two or more different microbiological growth media are applied. For dipslides, CLED agar and MacConkey agar are typically used. However, Uriselect3 and EMB are also used, rendering comparison of the diagnostic accuracy of different types of dipslides difficult. We found two studies on dipslide technology [7,8] with conflicting results. In a study [7] using a two-media dipslide (Uricult, Orion, Espoo, Finland), sensitivity, specificity, PPV, and NPV above 98% was reported; however, contaminated samples were excluded. The other study [8] used a three-media dipslide (Uricult trio, Orion, Espoo, Finland) and showed sensitivity of 80%, specificity of 53%, PPV 36%, and NPV 89%. Overall, dipslide technology seems to have the potential to rule out bacteriuria. However, further studies are required to critically evaluate the results using different dipslides with other combinations of culture media.

Flow cytometry is a laser-based technology used for cell counting. The sample under study is passed through a liquid stream to a set of lasers that illuminate individual particles. Although 40 papers investigating flow-cytometry were found, no studies met our inclusion criteria. A recent meta-analysis acknowledged the poor quality of available studies [9]. With respect to various cut-offs chosen, sensitivity values ranging from 53% to 97% for detection of bacteriuria and sensitivity of 73% to 99% for detection of WBC were described. The specificity values ranged from 36% to 99% and from 42% to 92% for bacteria and WBC, respectively. With such a variation of sensitivity and specificity, routine use of this technique to rule out bacteriuria cannot be recommended.

Overall, considering the lack of solid evidences supporting the use of alternative techniques, UC still has to be considered as the gold standard to rule out bacteriuria at concentrations currently considered to be clinically relevant. Urologists should, therefore, ensure that UC results are available prior to urological procedures where the presence of bacteria might affect the outcome or influences perioperative care.

Conflicts of interest: The conflict of interest statements of all members of the EAU Urological Infections Guideline Panel can be found at http://uroweb.org/guideline/urological-infections/?type=panel. Béla Köves has received a fellowship/travel grant from the EAU and was in receipt of honoraria or consultation fees from the Ferring Nocturia Advisory Board. Gernot Bonkat, Robert Pickard, Tommaso Cai, and Rajan Veeratterapillay do not have any conflicts of interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.euf.2018.03.004.

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