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Dissertation Abstract

Urinary Tract Infections in Danish Emergency Departments: Characteristics and diagnostic values of urine analysis and novel inflammatory markers

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Introduction

Urinary tract infections (UTIs) are a common reason for emergency department visits. In Denmark, over 15,000 patients are admitted annually due to UTIs. Diagnosis of UTIs is challenging, particularly in the elderly, due to the heterogeneity of symptoms and severity.

Due to the need for fast and accurate diagnosis in early goal-directed treatment of infected patients in the emergency department, urine dipstick analysis (UDA) has been utilised, given its short turnaround time. Urine flow cytometry (UFC) applies flow cytometry to urine, staining bacteria and white blood cells with fluorescent markers, illuminating them with a laser, and recording the scattered light. Improvements in technology have reduced the size of the analyser to the point that it potentially can be used as a point-of-care analysis with a short turnaround time.

Procalcitonin (PCT) is a precursor of calcitonin that is typically only found inside cells and gets converted into calcitonin. However, in case of an infection, the production of PCT is stimulated in all cells, leading to the release of uncleaved PCT into the bloodstream.

Soluble urokinase plasminogen activator receptor (suPAR) is the leftovers of the cleavage of the urokinase-type plasminogen activator receptor in activated immune cells. It is a possible new biomarker of infection.

C-reactive protein (CRP) and white blood cell count in the blood are commonly used as inflammatory markers to indicate if a patient is infected. However, they lack specificity and can give false negatives, especially for CRP, which can have a delayed increase. Consequently, there is a need for better inflammatory markers to improve diagnosis and antibiotic prescription in the emergency department.

Aims and objectives

The thesis aims to describe the characteristics and symptoms of patients admitted to the emergency department with UTIs and identify factors associated with UTIs. Additionally, the thesis aims to determine models and cut-offs for evaluating the diagnostic precision of UFC and UDA in ruling out positive urine culture and diagnosing UTI. Lastly, the thesis will determine cut-offs and assess the diagnostic precision of PCT and suPAR in diagnosing and grading the severity of UTIs and ruling out bacteriemia.

HVAD VED VI?

Tidligere studier af den diagnostiske værdi af urin- og blodanalyser til diagnostik af urinvejsinfektioner (UVI) er baseret på UVI definitioner, der ikke er klinisk relevante eller brugbare i akutmodtagelser og har vist sparsom diagnostisk værdi.

Fact box (in Danish)

Methods

The thesis is based on data collected as part of the Improved Diagnostics of Infectious Diseases in Emergency Departments (INDEED) trial, which is a multifaceted study aiming to evaluate new diagnostic tools and working methods that support a prompt and accurate diagnosis to prevent unnecessary antibiotic prescription. It is a pragmatic multicenter trial including adult patients admitted with suspicion of infection to the emergency departments of three hospitals in Southern Denmark. Exclusion criteria were if participation would delay lifesaving treatment, prior admission (>24 hours) within the last 14 days before admission, verified COVID-19 within 14 days before admission, pregnant patients or severe immunodeficiency. We recorded the suspected infectious focus, interviewed patients about symptoms and medical history, and collected data on vital signs, comorbidities, clinician's findings, and laboratory results from the medical records. A urine sample was sent for urine culture and analysed with UFC and UDA, and additional blood was taken to be analysed for PCT and suPAR. An expert panel retrospectively evaluated the medical records of each patient to determine their final diagnosis.

Study I was an exploratory cross-sectional study with prospective data collection to identify factors associated with UTIs and a cohort study to describe the outcomes of patients admitted with a UTI. We utilised descriptive statistics to summarise characteristics. Uni- and multivariate logistic regression models identified associated factors. Adjusted Cox regression and zero-inflated negative binomial logistic regression models were used to evaluate outcomes.

Study II was a type 1 diagnostic accuracy trial with prospective data collection to determine optimal cut-offs and the diagnostic precision of UFC and UDA for detecting bacteriuria and diagnosing UTIs. The index tests were UFC and UDA, and the reference tests were urine cultures and expert panel diagnosis. We used uni- and multivariate regression and area under the receiving operating characteristics curve (AUROC) to identify optimal models and cut-offs.

Study III was also a type 1 diagnostic accuracy trial with prospective data collection. This study aimed to determine the optimal cut-off values and diagnostic precision of PCT, suPAR and CRP for diagnosing and grading the severity of UTIs and ruling out bacteremia. The index tests were PCT, suPAR and CRP, while the reference tests were blood culture, expert diagnosis and severity grading. We utilised univariate logistic regression and

AUROC to establish optimal models and cut-offs. We then determined the diagnostic precision for each model and cut-off.

Results

We assessed 2197 patients for eligibility and included 966 (44.0%). Of these, 200 (20.7%) had a UTI.

Study I found that UDA for leukocyte esterase is the best-associated factor with UTI, with an odds ratio up to 21.4 (95%CI 10.6-43.4), followed by dysuria (OR 7.8 95%CI 4.9-12.4), new urine retention (OR 6.4 95%CI 3.8-10.6) and incontinence (OR 4.5 95%CI 2.8-7.1), palpatory flank or suprapubic tenderness (OR 4.3 95%CI 2.6-7.1), presence of an indwelling catheter (OR 4.6 95%CI 2.8-7.6) and UDA for nitrite (OR 4.0 95%CI 2.6-6.2). We found no significant differences in outcomes.

Study II found that UFC can rule bacteriuria out safely using bacterial (cut-off 7/µl) or white blood cell (cut-off 3.2/µl) count, but only in 10.9% of patients (model AUROC 0.83, sensitivity 98.6% and NPV 94.6%). UDA cannot safely be used to rule out bacteriuria with the optimal model using leucocytes (cut-off +1) or nitrite (cut-off positive) (model AUROC 0.78 sensitivity 74.5% and NPV 79.2%). In contrast, both UFC and UDA performed well in ruling out UTI. Using only white blood cell count (cut-off 15/µl) UTI could safely be ruled out in 38.8% of the patients (model AUROC 0.86, sensitivity, 94.9% and NPV 97.0%), while UDA using leucocytes (cut-off +1) or nitrite (cut-off positive) could rule out UTI in 52.8% though with a slightly higher false negative rate (model AUROC 0.81, sensitivity 86.2% and NPV 93.9%). Neither test could diagnose UTIs in clinically relevant numbers, even with cut-offs optimised for specificity.

Study III found acceptable discrimination of PCT and CRP for diagnosing UTIs in patients suspected of UTI with matching AUROCs of 0.72. However, sensitivity analyses showed that these results were driven by sensitivity to infections in general and not UTIs. For grading severity of UTI, PCT had an adequate AUROC of 0.71 but a poor NPV of 54.5% in our high prevalence population, while CRP had both a poor AUROC of 0.68 and a poor NPV of 50.0%. However, we found that PCT performed well in ruling out bacteremia in patients suspected of UTI with an AUROC of 0.81 and an NPV of 96.3% in our population using a cut-off of 0.15 µg/L. suPAR performed poorly with all three reference tests. The AUROCs for diagnosing and grading the severity of UTIs were not significantly different from 0.5. Although the AUROC for bacteremia (0.69) was significantly different from 0.5, it could only rule out bacteremia in 16.3% of patients, and of these, 7.1% were false positive.

HVAD TILFØJER AFHANDLINGEN?

- Med en klinisk diagnose stillet af et ekspertpanel fandt vi, at urinstix og urinflowcytometri kun har en brugbar negativ prædiktiv værdi for UVI. Procalcitonin og C-reaktivt protein har ikke specificitet for UVIer og ikke kan bruges til diagnostik af disse, om end Procalcitonin sikkert kan bruges til at udelukke bakteriæmi.
- En blank urinstix eller negativ urinflowcytometri udelukker med god sikkerhed UVI i akutmodtagelsen og en procalcitonin under 0,15 µg/L kan bruges til at udelukke bakteriæmi, hos patienter med mistænkt UVI.

Fact box (in Danish)

Discussion

UDA leucocytes and nitrite, symptoms of UTI, suprapubic or flank tenderness and the presence of an indwelling catheter are the strongest associated factors to UTI in patients admitted with suspicion of infection. Urine analysis performed poorly in ruling out bacteriuria, but both UFC and UDA can safely rule out UTIs in patients suspected of infection. Neither PCT nor CRP can be used as a diagnostic test for UTIs. However, in patients suspected of UTI in the ED, PCT may be a safe and accurate test to rule out bacteremia, allowing clinicians to prescribe more targeted antibiotics or oral antibiotics and, in some cases, discharge earlier. Our results indicate that suPAR has minimal diagnostic value in UTI patients in the ED.

Conflict of interest

The author declares that they have no conflicts of interest.

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