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Distinguishing asymptomatic bacteriuria from urinary tract infection in the elderly – the use of urine levels of heparin-binding protein and interleukin-6

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ABSTRACT

Asymptomatic bacteriuria (ABU) is highly prevalent among elderly patients. It can be difficult to distinguish ABU from symptomatic urinary tract infection (UTI) in this population, which leads to unnecessary antibiotic treatment. Urinary heparin-binding protein (U-HBP) and urinary interleukin-6 (U-IL-6) have previously been studied as diagnostic markers for UTI. In this study, biomarkers were measured in the urine of 134 nursing home residents. The prevalence of ABU in this population, excluding patients with urinary catheter, was 32.8%. Levels of U-HBP and IL-6 were significantly lower among residents with ABU when compared to 49 patients with verified UTI. When previously defined cut-off limits were used, U-HBP had a high negative predictive value for UTI (93%), however, the specificity for differentiating patients with UTI and ABU was low. Discriminatory values were better for U-IL-6 with a sensitivity of 80% and specificity of 82% for the differentiation between the subgroup of pyelonephritis and ABU.

1. Introduction

Asymptomatic bacteriuria (ABU) is defined as presence of bacteriuria in a patient without symptoms or signs referable to urinary tract infection (UTI). It is a common condition with a prevalence of >20% among healthy women >80 years of age and of up to 50% among elderly persons residing in nursing homes (Nicolle, 1993, 1997). Current consensus guidelines suggest that ABU should not be treated with antibiotics except in a limited number of patients, such as pregnant women and patients undergoing urologic procedures (Nicolle et al., 2005). In the elderly population with ABU, it has been shown that antibiotics do not affect the morbidity or the mortality. Instead, antibiotic treatment of ABU may cause adverse effects and contributes to the spread of resistant organisms (Abrutyn 1994, Nicolle LE, 1987; Ouslander et al., 1995). In case of a positive urine culture, pyuria, or a positive nitrite test, present guidelines require clinical signs or symptoms of UTI for the initiation of antibiotic treatment (McGeer, 1991; Warren et al., 1999). However, in clinical practice symptoms can be difficult to interpret in the elderly patient who may have cognitive impairment or less pronounced inflammatory reaction. The discrepancy between guidelines and clinical reality was recently demonstrated in two large studies in which over a third of patients with ABU were treated with antibiotics, contrary to guideline recommendations (Lin et al., 2012; Rotjanapan et al., 2011).

The neutrophil-derived heparin-binding protein (HBP) is stored in secretory and azurophilic granulae and is rapidly mobilized upon activation of neutrophils (Tapper et al., 2002). Among several functions the protein acts as a chemo-attractant and an activator of monocytes (Linder et al., 2010b). Clinical investigations have demonstrated the release of HBP in various infectious diseases (Linder 2009, Linder 2011, Linder 2010). Recently, increased levels of HBP in the urine (U-HBP) during UTI have been reported in three separate studies (Kjölvmark 2014, Kjölvmark 2012, Lertdumrongluk 2015). U-HBP was a good diagnostic marker for the detection of UTI, superior to U-interleukin-6 (IL-6), another biomarker candidate. The proinflammatory cytokine IL-6 is produced by uroepithelial cells upon stimulation with bacteria (Hedges et al., 1991), and several studies have demonstrated elevated urine levels during clinical infection (Hedges et al., 1992; Rodriguez et al., 2008).

Pyuria is present with ABU in 90% of elderly institutionalized patients (Nicolle, 1997), and thus, not sufficient for differentiating UTI from ABU. The aim of the present study was to investigate if the release of HBP is decreased from neutrophils residing in the urinary tract during ABU as compared to symptomatic infection. Measurement of urinary IL-6 (U-IL-6) has previously been used to discriminate between ABU and UTI (Rodhe et al., 2009), and was used as a comparative analysis.

Abbreviations: (HBP), Heparin-binding protein; (IL-6), Interleukin-6.

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2. Methods

2.1. Study population and clinical evaluations

All 484 residents living in seven different nursing homes in Helsingborg, Sweden, were screened for enrollment in the study. After an initial evaluation together with the staff at the nursing homes, 321 persons were considered inappropriate for participation (Fig. 1). The exclusion criteria were cognitive impairment or dementia (n = 296), inability to provide urine samples (n = 12), antibiotic treatment some time during the seven days preceding the inclusion (n = 3), or absence/not available at the time of inclusion (n = 10). In addition, 18 patients declined participation in the study. This left 145 residents that were enrolled in the study between February and April 2013. All participants answered standard questions on present symptoms of UTI and urinary incontinence. Supplementary information on medical history was obtained from medical records. Urine samples were collected from 127 participants as midstream samples. The urine bladder incubation time was registered, and varied from about 10 minutes to more than 4 hours. In addition, urine samples from 18 residents with indwelling catheters were collected in a sterile syringe by puncturing the disinfected catheter after clamping the catheter for 0.5–1 hour. Women without an indwelling urine catheter and who had a first positive urine culture were sampled a second time. Based on the results of the urine culture or presence of indwelling catheter, subjects were divided into three different groups:

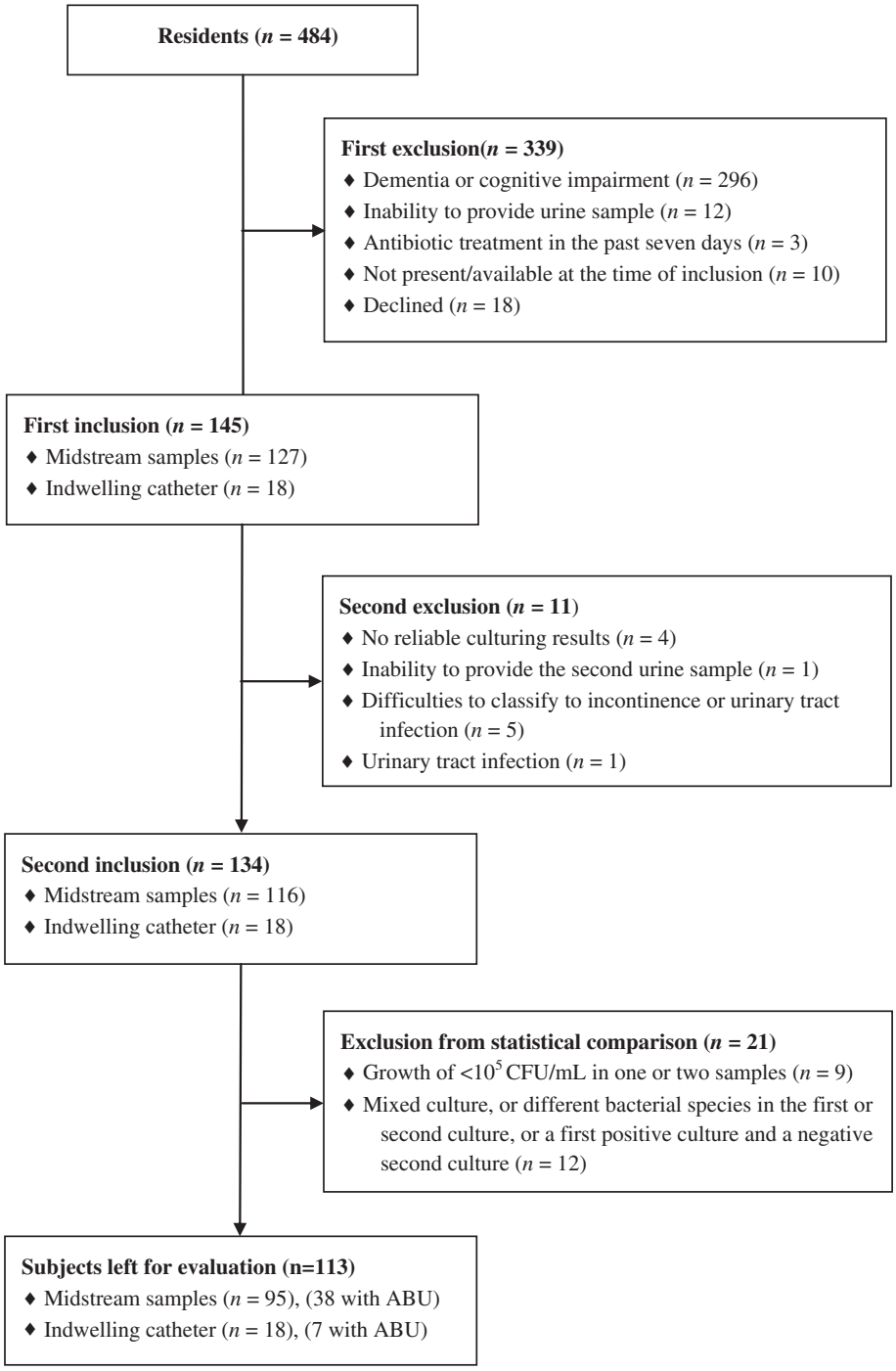

Fig. 1. Flow chart of study participants in the nursing home cohort.