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Clinical significance and antimicrobial susceptibility of emerging uropathogens Aerococcus urinae, Aerococcus sanguinicola and Actinotignum schaalii: a multicentre prospective study

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Background: *Aerococcus urinae* (Au), *Aerococcus sanguinicola* (As) and *Actinotignum schaalii* (Asc) have been for a long time considered as contaminants or misidentified by conventional identification methods. Since the introduction of the MALDI-TOF mass spectrometry and optimized culture conditions, their pathogenic role has been undoubtedly demonstrated, especially in urinary tract infections (UTIs). Because they have been poorly studied so far, the aim of this multicentric prospective study was to investigate clinical significance and antimicrobial susceptibility profiles of these emerging uropathogens.

Material/methods: Over a one-year period, all urine samples positive for Au, As or Asc were prospectively included from 12 French institutions. Clinical data were collected and bacterial identification was done by MALDI-TOF mass spectrometry (Microflex, Bruker Daltonics) or by 16S rRNA gene sequencing. MICs of the following antibiotics were determined by the broth microdilution method using Mueller-Hinton supplemented with lysed horse blood (5%) and β-NAD (20 mg/L) at 35°C for 48h in 5% CO_2 (Au/As) or anaerobic atmosphere (Asc): ampicillin, cefotaxime, cefixime, mecillinam, gentamicin, vancomycin, norfloxacin, ofloxacin, ciprofloxacin, levofloxacin, nitrofurantoin, fosfomycin and cotrimoxazole. When possible, clinical interpretation was performed according to EUCAST breakpoints recommended for viridans group streptococci (Au/As) or anaerobes (Asc).

Results: A total of 261 patients with non-redundant isolates were included, representing approximatively 0.3% of all positive urine samples during the study period. The most prevalent species found was Au (n=164, 63%), followed by Asc (n=64, 24%) and As (n=33, 13%). The mean age of patients was 75 years (range, 1-102 years), with a sex ratio F/M at 1.75, regardless of the species. Different underlying comorbidities were noted, such as advanced age (>65 years) (84%), urological disease (32%), immunodeficiency (28%), hypertensive disease (25%), malignancies (19%) and diabetes mellitus (14%). The clinical case was considered as an UTI for 119 patients (46%) including 79 cystitis (66%), 25 pyelonephritis (21%) and 15 prostatitis (13%). All strains were susceptible to amoxicillin (MICs $\leq$1 mg/L) and vancomycin (MICs $\leq$1 mg/L). Most of the strains appeared susceptible to cefotaxime (MIC_{90} $\leq$2 mg/L) and nitrofurantoin (MIC_{90} $\leq$32 mg/L) whereas they usually exhibited elevated MICs for fluoroquinolones (MIC_{50} $\geq$1 mg/L). The in vitro activity (MIC_{50}) of cefixime, mecillinam, cotrimoxazole and fosfomycin significantly differs between the species: 4/16/1/32 mg/L, 32/16/16/64 mg/L and 2/2/32/32 mg/L for Au, As and Asc, respectively. A majority of patients (61%) were appropriately treated with a β-lactam.

Conclusions: This first multicentric prospective study confirms the clinical significance of Au, As and Asc as uropathogens. Even though the prevalence of UTIs remains quite low (0.3%), microbiologists and clinicians should be aware about these emerging uropathogens, especially in the elderly, in patients with underlying urological diseases or in case of treatment failure with antibiotics classically used for UTI. A therapy with β-lactams is recommended.