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Short Communication

Funguria. Nitroxoline an Option for the Treatment of Fluconazole Resistant Fungal Species, for Example *Trichosporon spp.*

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Introduction

Bacteria are the most common causes of urinary tract infections; among them uropathogenic strains of *Escherichia coli* are the most frequent ones. Fungi are also found in microbiologic cultures of urines and indeed not seldomly. Generally, yeasts especially ascomycetic ones predominate; moulds are only occasionally detected. Risk factors for funguria are vesicular catheters, obstruction, hospitalisation, particularly in intensive care units, diabetes, old age and prior treatment with antibiotics [1-3]. Unfortunately, only few antimycotics achieve sufficient concentrations in the urinary tract. Hence, therapy of funguria is sometimes difficult. This holds especially true for infections with fungi moderately or even resistant to certain antimycotics, such as the basidiomycetic *Trichosporon spp*., in particular *Trichosporon asahii*.

The role of nitroxoline, in fact an antibiotic, for the treatment of funguria is largely underestimated, although this drug is generally active against most yeasts [4].

Laboratory results

Urine specimens send to the laboratory Limbach, Heidelberg/ Germany in 2023 were cultured according to the recommendations of the AWMF guideline [5]. The differentiation was done by MALDI-TOF (Bruker, Bremen/Germany).

The majority of fungal isolates from urine were found in specimens from hospitalized patients afflicted obviously with certain risk factors (table 1). The species *Candida albicans* was isolated most frequently followed by *Candida glabrata*. Other species were definitely less common (table 1). *Candida auris* was not detected in this survey. *Trichosporon asahii*, a basidiomycetic yeast, was found in 3 hospitalized patients.

species	hospitals	medical practices	dialysis centers
total	2 060 100%	443 100%	133 100%
C. albicans	1 243 60%	226 51%	60 45%
C. glabrata	398 19%	101 23%	19 14%
C. tropicalis	144 7%	17 4%	12 13%
C. krusei	110 5%	36 8%	18 14%
C. parapsilosis	63 3%	21 5%	8 6%
C. lusitaniae	16 1%	4 1%	5 4%
C. dubliniensis	16 1%	8 2%	1 1%
Saccharomyces	42 20%	15 4%	9 7%
annotation: among the various yeasts also 3 isolates of Trichosporon asahii were detected namely in hospitalized patients.			

Table 1: Yeasts isolated from urinary cultures in 2023 submitted by different senders (Laboratory Limbach Heidelberg).

T. asahii is susceptible in vitro to nitroxoline, since in an agar diffusion test the diameter of the inhibition zone was > 17mm (figure 1).

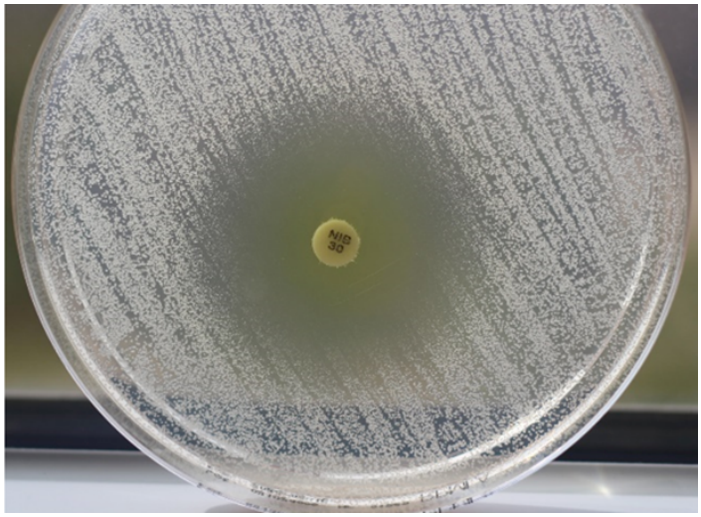

Figure 1: In vitro activity of nitroxoline against Trichosporon asahii (agar diffusion test).

Discussion

Yeasts were found often in urine specimens especially from hospitalized patients (table 1). By far the most prevalent yeast species in this series was *C. albicans*, amongst various other species (table 1). Principally, still other species such as *C. auris* also can be present [8]. The yeast *T. asahii* as well as other species can be isolated occasionally in urine [Table 1; 4, 6-16]. Obviously, patients with chronic kidney diseases are particularly susceptible for those fungi [17]. Elderly people [6,13,15] as well as diabetic persons [7,9,13] are also at risk. One has to keep particularly in mind nosocomial cases [17].

Not each funguria needs imperatively antimycotic treatment, since patients are often asymptomatic [18]. This holds especially true for the presence of *Saccharomyces spp*., which will indicate a mere colonization (table 1). Indeed, often an overtreatment can be observed [19,20]. On the other hand funguria in patients with severe underlying diseases, for example patients in an intensive care unit or with anomalies of the urinary tract or with medical devices in the urinary tract such as indwelling catheters, may require an antimycotic therapy, because otherwise the risk of a threatening fungemia may emerge. In cases of fungal urinary infections requiring antimycotic therapy usually fluconazole is applied according to expert opinions [4].

Nevertheless, the rising frequency of fluconazole-resistant *C. albicans* represents a growing obstacle for successful treatment [21]. In addition, there are species found in urines such as *Candida glabrata*, *Candida krusei* (Pichia kudriavzevii), *Candida parapsilosis* (table1) and *Candida auris* which tend to be a priori resistant to fluconazole [8,21-23] as well as to other antimycotics. Furthermore, absolutely fluconazole resistant strains of otherwise susceptible yeasts arise steadily [11]. *T. asahii* strains, are, in general, moderately susceptible to fluconazole [14,15] but resistant strains also exist [11]. Hence, it can be anticipated that the common fluconazole therapy will not be effective for certain urinary infetions. While voriconazole and posaconaole can be used for therapy of systemic infections with these yeasts [14,15], these drugs fail in case of a urinary infections, because these azoles are preferentially eliminated via the bile tract and only minimal amounts are excreted unmodified into the urinary tract (product information). *T. asahii* is, however, inherently susceptible to nitroxoline (figure 1) an antibiotic approved for the treatment of urinary tract infections at least in certain countries [24] and indicated even in infections with multidrug resistant E. coli [25]. Indeed, an effective therapy of *T. asahii* in urine is required occasionally, since *T. asahii* possesses indeed a lot of virulence factors so that funguria can finally cause fungemia [17]. Hence, for the treatment of funguria with fluconazole resistant or moderately susceptible yeasts – among them *T. asahii* - nitroxoline, an antibiotic achieving high urinary concentrations [4] represents a suitable alternative. By the way nitroxoline can be used even in case that a susceptibility testing is not feasible, since it is reliably effective against practically all medically relevant yeasts [4] even *C. auris* [8].

Furthermore, indwelling catheters can be colonized by yeast biofilms, where azoles including fluconazole are inactive [26], whereas nitroxoline is principally active against microorganisms in biofilms [27].

Summary

Yeasts are present in urine rather frequently; therapy is, however, not indicated in every case, since in most instances colonization remains asymptomatic. In case that an antimycotic therapy is stringent, usually flucanzole is used. But one has to foresee the presence of fluconazole resistant species; in addition, fluconazole is not active against pathogens in biofilms. Although funguria by fluconazole resistant *T. asahii* is rather rare this yeast species is difficult to treat with conventional antimycotics. Nitroxoline, which is eliminated principally via the urinary tract and effective against most yeasts even in biofilms, would be the drug of choice, if treatment is indicated, i.e. in case that risk factors for dissimination exist.

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