Candida growth in urine cultures: a contemporary analysis of species and antifungal susceptibility profiles

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Summary

Background: Recent publications suggest the distribution of Candida species causing candiduria may vary geographically, which has implications for the continued efficacy of antifungal therapy and emerging resistance.

Aim: To investigate the incidence of Candiduria at a university hospital in the UK. Further, to assess the distribution of species and the accompanying antifungal susceptibility profile, in order to monitor the clinical utility of current antifungal treatment guidelines for candiduria so that patients receive the best possible outcomes from the most up to date care.

Design: Retrospective audit.

Methods: From 1st January 2005 to 31st October 2014, we retrospectively reviewed 37,538 positive urine cultures recorded in a computerized laboratory results database. Identification and susceptibility testing was performed using the VITEK® 2 fungal susceptibility card (bioMérieux, Marcy d’Etoile, France).

Results: In total, 96 cultures were positive for Candida species, of which 69 (72%) were C.albicans, which translates to a prevalence of 2.6 per 1000 positive urine cultures. Candiduria was more common in younger patients, males and catheterized females. We report 94 and 73% of isolates of C.albicans and other non-C.albicans Candida species were susceptible to fluconazole. All isolates were susceptible to amphotericin B.

Conclusions: Our results add weight to the evidence supporting current European and North American guidelines recommending fluconazole or amphotericin B for treatment of candiduria, if antifungal treatment is clinically indicated.
Introduction
The presence of Candida species in the urine, or candiduria, is typically asymptomatic.1 Candiduria is rare in healthy patients but is more common in hospitalized patients and especially those in intensive care.2 In critically ill patients, candiduria may be predictive of increased mortality.3

Compared to bacterial urinary tract infection (UTI), fungal UTIs are relatively uncommon and so the corresponding susceptibility profile is not as well characterized. Fungal urinary colonization or infection is most commonly due to Candida species.4,5 Non-Candida albicans Candida species, which are associated with antifungal resistance, may be increasing in incidence in some geographic regions.6–8

Given that the incidence of Candida species causing UTI and candiduria may be increasing3 and that resistance to antifungals is of increasing concern,9,10 it is important that the antifungal susceptibility profile of Candida species causing candiduria is monitored. This is in order to ensure that current clinical guidelines for antifungal treatment of candiduria are based upon an up to date antifungal susceptibility profile for their optimal clinical utility to ensure the best possible outcomes for patients.

Our study presents contemporary European data regarding the incidence of candiduria, the distribution of species and the accompanying antifungal susceptibility profile which may be used to monitor the efficacy of current antifungal treatment guidelines for candiduria.

Materials and methods

Ethics approval
Our study was deemed surveillance by the Health Research Authority and as such formal ethical review or National Health Service Research and Development approval was waived.

Patient population
The computerized laboratory results database (MediTech) at Addenbrooke’s Hospital in Cambridge, UK, was searched for urinary isolates of all Candida species for the period 1st Jan 2005 to 31st October 2014. Testing and speciation for Candida was only performed on isolates from sterile site samples and for patients where Candida infection was considered clinically significant by the treating physician. Based on experience at our institution, we estimate that there were around 50 further positive Candida cultures deemed not clinically relevant and hence antibiotic sensitivity and speciation were not performed. These were not in our database and do not form part of our study’s sample. Urine samples received from outside our institution (including community isolates) were excluded from the analysis.

Culture criteria for inclusion
Urine was processed by calibrated loop sampling on to chromogenic clear media (Oxoid Ltd, Basingstoke, UK). A positive culture was defined as $10^5$ CFU/ml except for samples from children and pregnant women where a cut-off value of $10^3$ CFU/ml was used. Identification and susceptibility testing was performed using an automated commercial system (VITEK®️ 2 , bioMérieux, Marcy d’Etoile, France) and reported for amphotericin B, caspofungin, itraconazole, fluconazole, fluconazole and voriconazole. Isolates that were difficult to identify locally were sent to the National Mycology reference laboratory, Bristol for further analysis and confirmation of susceptibility.

We decided to exclude patients aged <16 years as paediatric populations have separate treatment guidelines to adult populations. We excluded samples of heavy mixed growth, defined as $3$ organisms, as this likely represented a contaminated sample. Unusual specimen types such as a nephrostomy, ileal conduit, extraprostatic secretion, suprapubic aspirate or a bag specimens were also excluded as they each represent distinct clinical scenarios. We also excluded samples if they were ordered less than 30 days after a previous sample (unless a different organism was isolated) as this would skew our data by analysing the same infection multiple times.

Statistical analysis
Data management and analysis was performed using Stata SE v.12.0 (Statacorp, College Station, TX). To assess the influence of the risk factors, sex, catheterization and age, on the incidence of candiduria versus bacterial infection/colonization, we fitted a multivariable logistic regression with all these variables entered simultaneously with all interaction terms between them also present. Candiduria was set as the outcome and the balance of the positive tests in our entire cohort as the comparison outcome. For the purposes of assessing effect modification, age was dichotomized at 65 years. There was a significant interaction ($P < 0.05$) present between sex and catheterization hence the final multivariable model includes these as four separate, stratified categories along with age as a continuous variable scaled to ten years for ease of interpretation.

Results
We initially identified 49 864 positive urine cultures. Exclusion criteria were applied as follows: 873 heavy mixed growth, 2198 missing age, gender or antibiotic/antifungal susceptibility, 3094 aged <16 years, 693 unsuitable specimen type and 5469 samples repeated within 30 days. This left 37 537 positive urine cultures remaining.

Of these, 96 were Candida species from 92 individual patients. The majority (69) were C. albicans. Five other species were isolated: 11 C. glabrata, 6 C. tropicalis, 4 C. parapsilosis and 1 each of C. lusitaniae and C. inconspicua. Four species were not identified or not reported. This corresponded to an incidence of Candida species of 2.6 per 1000 positive cultures.

The distribution of risk factors differed between patients with candiduria and the rest of the cohort. Candiduria patients were more likely to be younger with a median age 5 years younger than those with a bacterial infection. Additionally there was preponderance of males (45.8 vs. 30.8%) and of catheterized specimens (35.4 vs. 21.3%) in patients with the fungal infection.

The effect of a urine specimen drawn from a catheterized patient on the risk of candiduria versus bacterial infection differed according to the sex of the patient (Table 1). For a female patient, being catheterized conferred a risk greater than 3.6 times the odds of a non-catheterized patient. This was not the case for male patients as the increased odds were only ~4% higher and this difference is far from conventional statistical significance ($P = 0.89$). Younger age was an independent predictor of candiduria infection, with every ten year increase in age decreasing the odds of a fungal UTI versus bacterial UTI by 12% ($P = 0.008$).

Susceptibility of different Candida species to antifungal agents: amphotericin B, fluconazole, voriconazole, itraconazole, and...
flucytosine and caspofungin are presented in Table 2. We found isolates of C. albicans over 90% susceptible to the most common antifungal agents with 100% susceptibility to itraconazole, amphotericin B and caspofungin. These latter two agents were shown to be 100% effective for the other candida species.

About 94 and 73% of C. albicans and non-C. albicans Candida species, respectively, were susceptible to fluconazole.

Only 6 of the 11 isolates of C. glabrata were susceptible to fluconazole and all were resistant to itraconazole.

All isolates of Candida species were susceptible to amphotericin B. Only 27% of non-C. albicans Candida species were susceptible to itraconazole and 75% were susceptible to voriconazole.

Table 3 shows the susceptibility of C. albicans and non-C. albicans Candida species to fluconazole and amphotericin B reported in selected studies from different geographical regions.

**Discussion**

Multiple treatment guidelines recommend fluconazole as the first-line antifungal agent for candiduria, symptomatic cystitis and pyelonephritis primarily due to efficacy against C. albicans and high urine concentrations when administered orally. In cases where antifungal resistance or infection from non-C. albicans Candida species is suspected guidelines recommend consideration of amphotericin B or flucytosine, perhaps in combination. Our key message is that the contemporary antifungal susceptibility data we have presented in this article supports ongoing use of these clinical guidelines.

C. albicans is thought to be intrinsically susceptible to all antifungal drug classes and resistance must be acquired. Our results indicate that C. albicans is largely susceptible to all antifungal agents tested as shown in Table 2 and is consistent with other studies as shown in Table 3.

Some isolates of C. glabrata are thought to be intrinsically resistant to fluconazole and itraconazole. This is supported by our results. A high level of susceptibility with amphotericin B, voriconazole, and caspofungin was observed, which again agrees with the literature. Since non-C. albicans candida species, particular C. glabrata may not be susceptible to fluconazole, amphotericin B may be recommended as first line for these cases. A mechanism for overall increasing antifungal resistance may be the increase in the prevalence of this intrinsically resistant species and could reflect the increasing use of azole prophylaxis in clinical practice.

C. tropicalis has been reported as the most prevalent Candida species in some regions. Our susceptibility data closely agrees with other publications. However, one author reports 66–80% susceptibility for amphotericin B, fluconazole and voriconazole. These differences may indicate systematic differences in acquired resistance between the geographically separated C. tropicalis populations.

In terms of the distribution of Candida species, our results are consistent with those previously reported in Europe and North America. The proportion of Candida species are known to vary by geographic region. Recent studies from Turkey, Brazil and India recorded C. tropicalis prevalence as much higher than those reported in older studies Europe and North America. Geographical variation, particular increasing incidence of C. glabrata, has implications for antifungal therapy as it suggests fluconazole may be less effective in some regions. Our continued observation of a high proportion of C. albicans is reassuring as the reverse would increase concerns regarding antifungal resistance.

Increasing age, female gender and catheterization have previously been identified as risk factors for candiduria which...
differ from our results (Table 1). In contrast to those studies, we calculated risk factors for candiduria relative to a positive bacterial urine culture, which we feel is more relevant to the clinical perspective. Other risk factors not considered in our study include diabetes mellitus, increased length of stay, prior antibiotic use, urological abnormality and instrumentation.2,6,23,24

Our study suffers from the inherited limitations of its retrospective nature such as the lack of clinical data to correlate with pathology results as the samples could be from symptomatic or asymptomatic patients. As our study included isolates from across a 10-year period, the protocol for which antifungal agents were tested on each organism varied somewhat. Finally, our results are from a single tertiary centre and therefore may not apply to other district general hospitals.

Despite our focus on antifungal therapy it is important to remember that risk factor modification is a key element in treating candiduria. Removal of precipitating factors such as urinary catheters and unnecessary antibiotic therapy is critical as is improving glycaemic control in diabetic patients.5 These may resolve asymptomatic candiduria in up to 47% of cases without resorting to antifungal therapy.2,6

Conclusion

Candidiasis is uncommon and appears more often in males and catheterized females. C. albicans was the species most frequently identified. Our results provide contemporary insight into the antifungal susceptibility profile of Candida species causing candiduria and provide additional evidence for continued application of current European and North American guidelines recommending fluconazole and amphotericin B as first and second line agents, respectively.

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Conflict of interest: None declared.

References

12. Singla N, Gulati N, Kaithna N, Chander J. Candida colonization in urine samples of ICU patients: determination of

Table 3. Incidence and antifungal susceptibility profile of selected studies

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<th>Reference</th>
<th>N (All Candida species)</th>
<th>N (C. Albicans)</th>
<th>Setting</th>
<th>Country</th>
<th>Prevalence (%)</th>
<th>% Susceptible Fluconazole (C. Albicans)</th>
<th>% Susceptible Fluconazole (non-C. Albicans Candida species)</th>
<th>% Susceptible Amphotericin B (C. Albicans)</th>
<th>% Susceptible Amphotericin B (non-C. Albicans Candida species)</th>
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<td>This study</td>
<td>96</td>
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<td>All positive urine cultures</td>
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<td>Ragini et al.7</td>
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<td>8</td>
<td>All positive urine cultures</td>
<td>India</td>
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<td>Yashavanth et al.3</td>
<td>66</td>
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<td>267a</td>
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aIncludes isolates from both blood and urine.
bAntifungal susceptibility testing performed on very few samples.

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