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Urinary Candidiasis: A Prospective Study in Hospital Patients

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Summary. In a prospective study of 29 hospital inpatients with candiduria, yeasts were frequently isolated from the urine in the absence of symptoms and no serious deep fungal infection occurred. The prevalence of diabetes mellitus and urinary catheterisation was significantly increased in this group compared to the general hospital population. There was a high incidence of yeast species other than *Candida albicans* in the urine, non-*albicans* species constituting 39% compared with 18% from other sites ($p < 0.01$).

Key words: Candiduria, Non-*albicans* Candida, Diabetes mellitus, Catheterisation.

Introduction

Candiduria is not an infrequent finding on routine culture among hospital patients, but its significance is uncertain. We have therefore carried out a prospective study to determine the prevalence and natural history of candiduria, to identify risk factors and to assess its significance and the need for treatment.

Patients and Methods

For a nine-months period hospital inpatients were admitted to the study who had a significant growth (greater than 10^4 organisms per ml) [4] of yeasts on routine urine culture and in whom progress could be followed for at least one week. We excluded those patients with leukaemia and bone marrow transplant recipients. An initial questionnaire was completed for each patient including records of urinary symptoms, antibiotic use, and conditions thought to predispose to candiduria: diabetes mellitus, immunosuppression (either neutropenia of $<1.5 \times 10^9$ neutrophils/l [1], steroid use (more than 10 mg/day of prednisolone or equivalent) or other causes (azathioprine, radiotherapy), the presence of a urinary catheter, and use of broad spectrum antibiotics or antibiotic combinations [5].

Patients were assessed weekly, and the presence of urinary symptoms, fever or leucocytosis, and antibiotic treatment was noted. Weekly urine specimens from each patient were examined, and the isolation of yeasts and bacteria from urine was recorded, as was the isolation of yeasts from any other site. Patients were observed until discharge from hospital or death, or until no urinary yeasts had been found for three successive weeks. Yeasts isolated from urine were considered to be causing infection if there were symptoms typical of cystitis or a urinary leucocytosis of 3+ or more, in the absence of significant bacterial growth.

Yeast-like organisms seen on direct microscopy of urine were quantitated by streaking a 0.004 ml loopful of urine across a Sabouraud's dextrose agar plate and either estimating the extent of confluent growth after overnight incubation at 37 °C or, with small numbers, counting the number of colonies. Leucocyte numbers were graded semiquantitatively on microscopy on a scale of "1+" to "4+". Yeast isolates which on incubation for three hours in horse serum at 37 °C produced germination tubes were classified as *Candida albicans*. Yeasts which produced no germ tubes were further identified using the API auxanogram method [2].

The Phoenix system on the hospital's CTL Mod 1 computer [7] was used to analyse the urine microbiology reports over the preceding eight months. Data were obtained on the total number of inpatient urine cultures performed, the frequency of significant bacteriuria and candiduria, and the incidence and type of yeast isolates from non-urinary sites. The incidence of diabetes mellitus was determined from hospital discharge records, and the estimated incidence of urinary catheterisation by spot surveys of wards.

The hospital has a leukaemia and bone marrow transplantation unit, and results from this unit were analysed separately. Patients from these units were excluded from the prospective study to enable results to be drawn of more general application than to this very atypical group.

Statistical significance of the findings was assessed using Student's paired t-test in all cases.

Results

Twenty-nine patients were admitted to the study. Their clinical details are summarised in Table 1. The mean age was 68 years (range 20 to 93 years): nine were male. Twelve patients had a fever of 38 °C or more at entry to the study,

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Table 1. Clinical details of study patients

Study			Reason for admission	Diabetes mellitus	Immunosuppression			Urinary catheter	A/biotics[b]	Clearance of c'uria[c]	Survival of pt.
No.	Age	Sex			Steroids	N'penia[a]	Other				
1	69	f	Acute renal failure	No	No	No	No	Yes	5	Yes	Yes
2	52	m	Renal transplant	No	Yes	No	Yes	Yes	1	No	Yes
3	73	f	Pyonephrosis	No	No	No	No	Yes	2	Yes	Yes
4	73	m	Panproctocolectomy	No	No	No	No	Yes	7	No	No
5	62	m	Bladder tumour	No	No	No	No	Yes	2	No	No
6	59	m	Renal transplant	No	Yes	No	Yes	No	1	Yes	Yes
7		f	Hepatojejunostomy	Yes	No	No	No	Yes	4		No
8	77	m	Hip fracture	No	No	No	No	Yes	2	No	
9	77	f	Femoral fracture	No	No	No	No	No	1		Yes
10	37	f	Investign. of nausea	No	No	No	No	No	0	Yes	Yes
11	20	f	Drug abuse, pregnant	No	No	No	No	No	0		Yes
12	65	f	Alcoholic, hepatitis	Yes	No	No	No	No	0		Yes
13	89	f	Osteomyelitis	No	No	No	No	No	0	Yes	Yes
14	70	f	Pneumococcal meningitis, Hodgkin's disease	No	No	No	Yes	Yes	1	Yes	Yes
15	86	f	Cerebral haemorrhage	Yes	No	No	No	Yes	0		Yes
16	71	f	Carcinomatosis	No	Yes	No	No	Yes	1		Yes
17	93	m	Confusion	No	No	No	No	No	1	Yes	No
18	69	f	Myelofibrosis	No	No	Yes	No	Yes	4	No	No
19	79	f	Cholelithiasis	No	No	No	No	Yes	2	Yes	Yes
20	88	m	Total hip replacement	No	No	No	No	Yes	3	Yes	Yes
21	88	f	Femoral fracture	No	No	No	No	No	4	Yes	No
22	68	f	Osteomyelitis	Yes	No	No	No	Yes	4	Yes	No
23	81	f	Perforated peptic ulcer	No	No	No	No	Yes	2	Yes	Yes
24	65	f	Femoral fracture	No	No	No	No	Yes	1	Yes	Yes
25	72	f	Confusion	No	No	No	No	No	0	Yes	Yes
26	64	m	Multiple sclerosis	No	No	No	No	Yes	2	No	Yes
27	20	f	Aplastic anaemia, pregnant	No	No	Yes	No	No	6	No	Yes
28	62	m	Varicose ulcers	No	No	No	No	Yes	2	Yes	Yes
29	69	f	Renal transplant	No	Yes	No	Yes	No	6	No	No

[a] N'penia: neutropenia (neutrophils $<1.5 \times 10^9$/l). Pt. 18, $1.0 - 0.8 \times 10^9$/l; Pt. 27, $1.3 - 0.7 \times 10^9$/l. Other immunosuppression: azathioprine for renal transplant, 3; radiotherapy for Hodgkin's disease, 1

[b] A/biotics: Number of different antibiotics given within 2 weeks before entry or during study period

[c] Clearance: Absence of candiduria for three weeks

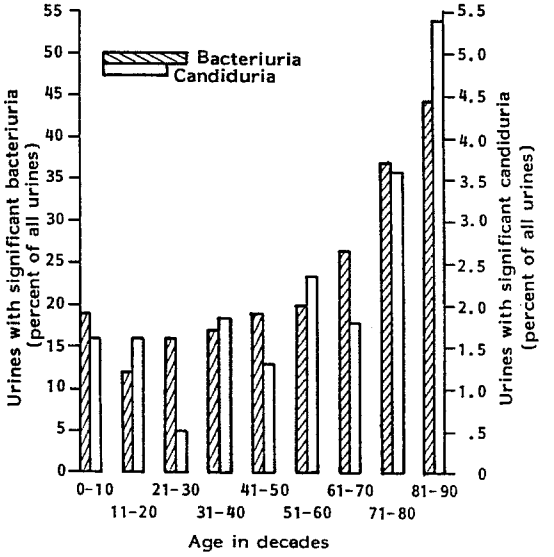

Fig. 1. Incidence of bacteriuria and candiduria in different age groups (non-haematology patients). (4,644 specimens; overall bacteriuria incidence 23%, candiduria incidence 2%. Yeasts 8% of all urine isolates)

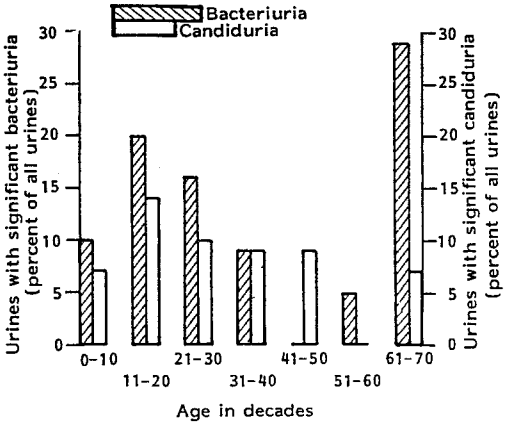

Fig. 2. Incidence of bacteriuria and candiduria in different age groups (haematology patients). Note: ten-fold right-hand scale difference from Fig. 1. (181 specimens; overall bacteriuria incidence 10%, candiduria incidence 11%. Yeasts 53% of all urine isolates)

but only two (patients 10 and 21) had symptoms of a urinary tract infection (U.T.I.) at any time. One of these two (patient 10) had a concomitant bacterial U.T.I. Six other patients met the criteria for a yeast U.T.I. with 3+ or more pus cells, and in two the infection resolved without antifungal treatment. Yeasts were isolated from the remaining four throughout the study period. Pyuria was an inconstant feature of candiduria, varying from large numbers of white cells to none. There was no correlation with symptoms or with profusion of organisms.

Twenty-four patients (83%) had at least one and seven (24%) had two or more factors which might predispose to fungal infection (Table 1). Nineteen patients (68%) had received antibiotics in the two weeks before entry, 13 having had two or more different agents. Six received no antibiotics throughout the study period. Eighteen patients (62%) had urinary catheters on entry to the study, while in a random survey on three occasions of patients in the hospital, 27 of 241, 14 of 207, and 23 of 197 patients were catheterised, an overall prevalence of 10%. Four of the study patients had diabetes (14%) while of 17,663 patients discharged or dying during one year (1981), 299 (1.7%) were recorded as having diabetes mellitus. The increased frequency in the study patients of urinary catheterisation and of diabetes mellitus was highly significant ($p < 0.001$).

Candiduria persisted throughout the study period in eight of 23 patients, but none was thought clinically to have had a systemic fungal infection and only two patients received any form of antifungal treatment. Patient 18, who was given intravesical amphotericin B, was a 69-year-old woman with myelofibrosis and neutropenia who died three days after being admitted to the study. Patient 27, a 20-year-old pregnant woman with aplastic anaemia, received oral nystatin as part of her gut decontamination regimen (framycetin, colistin and nystatin: "FRACON"). From patient 1, a 69-year-old woman with acute renal failure, a yeast indistinguishable from the urinary isolate was obtained from blood cultures on two occasions. No antifungal treatment was given. Blood cultures taken six days later were sterile, and candiduria disappeared after two weeks.

The deaths of all eight patients who died during the study period was attributed to causes other than fungal infection. Autopsies were performed on two of these; there was no evidence of renal or deep mycosis.

Candida albicans was isolated from the urine of seventeen patients (61%); 5 (18%) had *C. glabrata (Torulopsis glabrata)*, 2 had *C. parapsilosis*, while 4 patients were infected with an otherwise unidentified germ-tube negative yeast. In one patient, the infecting species was unknown. In all, 11 patients (39%) had species other than *C. albicans*. A computer search of 127 reports of candiduria over the previous 12 months found non-*albicans* species in 40 (32%), while for 517 previous non-urinary strains, non-*albicans* species were isolated in 94 (18%). This difference is significant ($p < 0.01$), and is maintained when isolates from vaginal and vulval swabs (16% non-*albicans*) are compared with those from urine.

Computer analysis of urine microbiology results over the same period found 4,825 reports, of which 181 were from haematology patients and were handled separately. For the non-haematology patients both bacteriuria and candiduria increased in parallel with increasing age. The proportion of all U.T.I. due to yeasts remained nearly constant at about 8% at all ages (Fig. 1). For haematology patients, the incidence of candiduria as a cause of U.T.I. was significantly higher – 53% for all age groups (Fig. 2) ($p < 0.001$).

Discussion

In this prospective study of 29 consecutive hospital inpatients, candiduria was found to be a benign, usually self-limiting event which rarely required specific treatment. A

surprising, and perhaps related, observation was the significant increase in the frequency with which non-*albicans* species of Candida were found in the urine.

The overall incidence of candiduria during the study period was 2.0%, with yeasts representing 8% of all urinary isolates (Fig. 1). These figures are a little lower than other reported series. Vejlsgaard et al. [12] in a study of 1,989 pregnant women found yeasts in urine in 8.5%, and noted no correlation with symptoms of U.T.I. or with other clinical observations. In a series of 954 hospital patients, Umenai and Ishida [11] found an incidence of candiduria of 6.5% but saw no clear relationship between the finding and disseminated candidiasis, although both these studies used less defined criteria for candiduria. While commenting that "Candida in the urine ... is a potentially lethal pathogen", Wise, Goldberg and Kozinn [13] note that "7–8% of all urine specimens submitted for culture are positive for Candida" and "not all of these cultures represent a serious problem". Despite the fact that our series included many "high-risk" patients (and indeed confirmed the association with predisposing factors such as diabetes mellitus and urianry catheterisation), none of our patients developed deep fungal infection, and the single episode of candidaemia appeared to have been only transient.

In a group of 23 critically ill patients with *Candida* spp. isolated from any site, Neumann and Rakower [6] found a mortality of 52%, in contrast to 21 similar patients without candida whose mortality was only 19%. The mortality in our patients was 28%, and no deaths were attributed clinically to candidosis, although in seven patients, four of whom died, yeasts were isolated from multiple sites. Clearly widespread colonisation may develop in very ill patients for a number of reasons, and indeed on occasion may proceed to deep-seated or systemic infection, particularly in an immunocompromised host. Wise et al. [13] suggested that elevated serum candida precipitins are predictive of disseminated disease and an indication for treatment, but the interpretation of candida antibody tests can be difficult [8].

Significant candiduria as defined by Goldberg et al. [4] occurred in most patients without other clinical or laboratory evidence of infection. Recently, Stark and Maki [10] suggested that low level candiduria (less than 10^5 organisms per millilitre) frequently progressed to heavier colonisation in catheterised patients and would be a valid index of infection in this situation. We did not see such progression to symptomatic infection in this smaller series, eighteen of whom were catheterised.

The incidence of candiduria caused by species other than *C. albicans* was surprisingly high. *Candida glabrata* was the most common of the non-*albicans* species isolated, and *C. parapsilosis* was obtained from two patients. A similar proportion (33%) of non-*albicans* yeasts was found by Sandford et al. [9] in the urine of 89 granulocytopenic patients. They also found a high incidence (28%) of *C. tropicalis*, which was not present in our series. The frequent occurrence of non-*albicans* yeasts was confirmed by a computer search of yeasts isolated in the microbiology laboratory during the preceding year. The explanation for this higher proportion in urines is unclear, but may be related either to the specific growth conditions in the urinary tract or to the inherent pathogenicity of the organisms. *C. albicans* is regarded as the most pathogenic species of the genus [3] and the relatively benign outcome of candiduria that we have described may thus be a reflection of the decreased pathogenicity of the non-*albicans* strains. Alternatively, factors such as increased creatinine concentration or low pH may favour these species, and studies aimed at investigating this are planned.

Candiduria occurs frequently in hospital patients, particularly among those who are old or who have impaired host defences for any reason. The urine is more often colonised by non-*albicans* yeast species than are other sites. Very often candiduria does not require specific anti-fungal treatment, remaining asymptomatic or resolving spontaneously. Systemic spread is uncommon.

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