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Diagnosis of Invasive Candidiasis in Neutropenic Children with Cancer by Determination of D-Arabinitol/L-Arabinitol Ratios in Urine

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Determination of D-arabinitol/L-arabinitol ratios (referred to as D/L-arabinitol ratios) in urine as a tool for the diagnosis of invasive candidiasis was investigated in a prospective study comprising 100 children with cancer. The analyses were made by gas chromatography. Positive D/L-arabinitol ratios were found for 10 of 10 children with confirmed invasive candidiasis, 12 of 23 patients undergoing empiric antifungal chemotherapy, and 4 of 67 children not receiving antifungal treatment. D/L-Arabinitol ratios were positive 3 to 31 days (median, 12 days) before the first culture-positive blood sample was drawn or empiric therapy was initiated. The regular monitoring of D/L-arabinitol ratios in urine holds great promise as a sensitive method for diagnosing invasive candidiasis in immunocompromised children with cancer. Moreover, it may be possible to use an early rise in D/L-arabinitol ratios as a basis for the institution of antifungal chemotherapy and as a means of avoiding unnecessary treatment with potentially toxic antifungal agents.

Invasive candidiasis is becoming increasingly common due to the growing number of immunocompromised hosts. An early and accurate diagnosis is of importance for improving survival resulting from the institution of antifungal chemotherapy (2, 15) and decreasing the unnecessary use of toxic antifungal agents such as amphotericin B. Unfortunately, currently available methods are not sufficiently sensitive and specific for diagnosing invasive candidiasis (11, 19). Therefore, empiric antifungal chemotherapy has been advocated for persistently febrile granulocytopenic patients not responding to broad-spectrum antibiotic therapy (21). Although such empiric therapy has been shown to decrease the frequency, morbidity, and mortality of invasive fungal infection (21), inevitably, it also leads to a potentially hazardous and extremely costly overtreatment of some patients.

D-Arabinitol is a major metabolite of most *Candida* species, and both D-arabinitol and L-arabinitol are present in normal serum and urine. In an earlier study (9), we developed a gas chromatographic method to determine the relative amounts of D-arabinitol and L-arabinitol (referred to as the D/L-arabinitol ratio) in urine. Elevated urine D/L-arabinitol ratios have previously been found in a small number of patients with invasive candidiasis (9, 16). Here, we report the results of a prospective study of pediatric oncology patients designed to determine the value of monitoring D/L-arabinitol ratios in urine for the early diagnosis of invasive candidiasis.

MATERIALS AND METHODS

Patients. From March 1992 through October 1995, 100 children (age range, 1 to 17 years; mean age, 9 years) were prospectively studied at the Department of Pediatrics, Division of Oncology, Lund University Hospital. All children were considered to be at high risk for invasive candidiasis. Their malignant diagnoses were acute leukemia for 47% of the patients, lymphomas for 13% of the patients, and Wilms' tumor for 14% of the patients; the remaining patients had various solid tumors. All patients had central venous catheters and were receiving cytotoxic chemotherapy. Broad-spectrum antibiotic therapy was instituted when patients were febrile and granulocytopenic. All hospitalized patients were given nystatin orally. During periods of hospitalization, the aim was to collect urine samples at least twice weekly. The children who were too young to deliver urine samples spontaneously and those who delivered only one sample were excluded from the study. In all, 1,076 urine samples were collected.

A febrile (>38.3°C), neutropenic (blood neutrophil counts, $<0.5 \times 10^9$/liter) patient not responding to broad-spectrum antibiotic treatment was defined as having invasive candidiasis when blood cultures were positive for *Candida* and/or when *Candida* species were cultured or proven histopathologically in tissue samples from normally sterile locations. Invasive candidiasis was clinically suspected when a febrile, neutropenic patient did not respond to antibiotic treatment, and in such cases, antifungal chemotherapy was empirically instituted even when blood cultures were negative for *Candida*. Patients were defined as having bacteremia when they responded to antibiotic treatment and blood cultures were positive for bacteria but negative for *Candida*. Patients were also evaluated during nonneutropenic periods, when all blood cultures were negative for *Candida* and bacteria and no antifungal treatment was being given.

For patients with confirmed or suspected candidiasis, blood for culture was always drawn at the time of urine collection. Additional blood cultures were also performed once or twice daily for many of these patients. On the other hand, during nonneutropenic periods without clinical suspicion of fungal infection, the twice-weekly urine sampling was not always accompanied by blood culturing.

For comparison, single urine samples from 56 healthy nonhospitalized children (age range, 1 to 15 years; mean age, 5 years) were also studied.

Samples. The urine samples were divided into 1-ml aliquots and were then stored at −20°C before analysis for D/L-arabinitol ratios (see below). A biphasic blood culture system (Septi-Check; Roche Products, Skärholmen, Sweden) was used to culture bacteria and fungi. For detection of fungi, blood was cultured aerobically for 5 days at 37°C, followed by 9 days at 30°C; the cultures were inspected daily for turbidity and were also shaken twice daily. Tissue samples were cultured on Sabouraud agar and on agar with 4% horse erythrocytes for 7 days at 30°C. Typing of the *Candida* organisms to the species level was done by testing for production of chlamydospores and fermentation of glucose, galactose, saccharose, maltose, lactose, and trehalose on rice agar (10).

D/L-Arabinitol analysis. Urine samples were filtered (0.45-μm-pore-size cellulose acetate filters; Schleicher & Schuell, Dassel, Germany), and a 5- to 15-μl portion of the filtrate was dried under a stream of nitrogen. Trifluoroacetic anhydride and hexane (200 μl each) were added, and the preparations were heated at 80°C for 10 min and again dried. Thereafter, hexane (200 to 500 μl) was added, and a 1- to 3-μl aliquot was used to obtain D/L-arabinitol ratios by gas chromatography. As described previously (9), the method has an interassay coefficient of variation of 7.7%. The total time for handling and analysis of each sample was less than 1 h.

Study design. Samples were coded and were then submitted to the laboratory and analyzed in blind batches. The results were not available to the pediatricians treating the patients to ensure that the initiation of antifungal therapy would be based solely on clinical observations and the results of blood or tissue cultures and histopathology. The following was recorded for each patient: cytotoxic and radiological therapy, antimicrobial therapy and prophylaxis, microbiological results, and neutropenic and febrile events. Student's two-tailed *t* test was used to make comparisons between the D/L-arabinitol ratios for different groups. The study was approved by the Ethics Committee at the Medical Faculty, University of Lund.

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TABLE 1. Peak D/L-arabinitol ratios for febrile, neutropenic children with cancer and confirmed invasive candidiasis

Patient no.	Primary disease	Species	Peak D/L-arabinitol ratio	Time interval (days) between positive D/L-arabinitol ratio and positive blood culture	No. of positive samples/no. of all samples[a]	Diagnosis based on:	Patient status
1	ALL[b]	*C. albicans*	30	NA[c]	3/24	3 blood cultures	Dead
2	NHL[d]	*C. albicans*	30	8	7/24	7 blood cultures	Dead
3	AML[e]	*C. albicans*	7.4	16	5/22	2 blood cultures, histopathology	Alive
4	ALL	*C. parapsilosis*	5.8	NA	2/12	7 blood cultures	Alive
5	ALL	*C. parapsilosis*	6.7	21	2/3	2 blood cultures, histopathology, pre- and postmortem culture	Dead
6	ALL	*C. albicans*	10.4	4	4/16	2 blood cultures	Alive
7	ALL	*C. parapsilosis*	30	3	3/18	2 blood cultures	Alive
8	Aplastic anemia	*C. tropicalis*	30	NA	5/13	17 blood cultures	Alive
9	T-cell leukemia	*C. albicans*	30	9	5/12	2 blood cultures, postmortem cultures	Dead
10	ALL	*C. glabrata*/*C. albicans*	5.1	3	2/2	2 blood cultures, postmortem cultures	Dead

[a] Number of positive urine samples/total number of urine samples.
[b] ALL, acute lymphatic leukemia.
[c] NA, no adequately timed samples available.
[d] NHL, non-Hodgkin's lymphoma.
[e] AML, acute myeloid leukemia.

RESULTS

The D/L-arabinitol ratios (mean ± standard deviation) for the 56 healthy nonhospitalized children were 2.0 ± 0.6, and for the 95 children with cancer, the ratios were 2.5 ± 0.7 ($P < 0.01$) during nonneutropenic periods. The latter group was used to define the upper cutoff limit (mean ratio + 3 standard deviations, corresponding to a value of 4.6), and values of >4.6 were considered positive.

Ten patients with long-standing fever and neutropenia were diagnosed with invasive candidiasis on the basis of blood cultures, tissue cultures, and/or histopathology, and all these patients had positive peak D/L-arabinitol results (Table 1; Fig. 1, group A). By using multiple blood cultures, *C. albicans* was isolated from five patients, *C. parapsilosis* was isolated from three patients, *C. tropicalis* was isolated from one patient, and *C. glabrata* was isolated from one patient. For the last patient, postmortem tissue cultures were also positive for *C. albicans*. Urine samples were available from 7 of 10 patients before blood cultures were positive and showed increased D/L-arabinitol ratios 3, 3, 4, 8, 9, 16, and 21 days, respectively, before the first culture-positive blood sample was drawn. The time course of the D/L-arabinitol ratios in one of these patients is presented in Fig. 2. Five patients died from invasive candidiasis, and in four of these patients the D/L-arabinitol ratio was positive 3, 8, 9, and 21 days, respectively, before the first culture-positive blood sample was drawn (Table 1).

Antifungal chemotherapy (amphotericin B or fluconazole) was instituted empirically (due to a lack of response after 3 to 5 days of broad-spectrum antibiotic treatment) for 23 neutropenic and febrile patients with blood cultures negative for *Candida* and bacteria. Twelve children had positive peak D/L-arabinitol ratio results (Table 2; Fig. 1, group B). Ten of 12

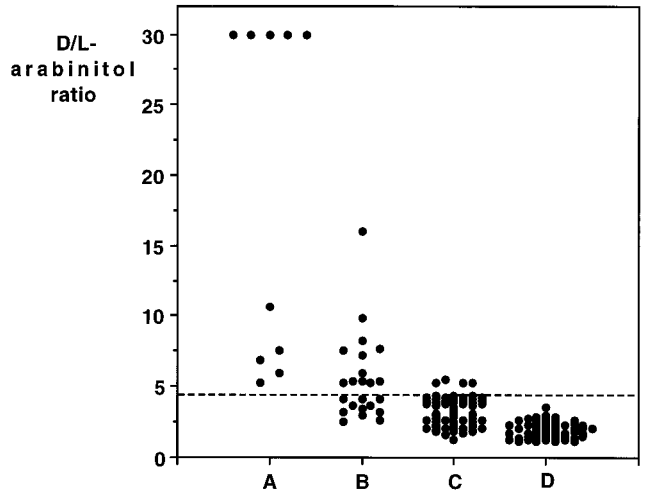

FIG. 1. Peak D/L-arabinitol ratios obtained for the following: patients with confirmed invasive candidiasis (group A; $n = 10$), patients receiving empiric antifungal treatment (group B; $n = 23$), patients not undergoing antifungal treatment or showing evidence of invasive candidiasis (group C; $n = 67$), and single samples from healthy nonhospitalized children (group D; $n = 56$). The broken line at the value of 4.6 corresponds to the upper cutoff limit.

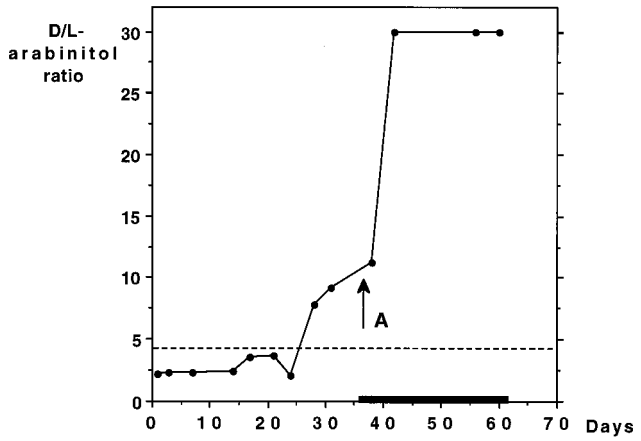

FIG. 2. D/L-Arabinitol ratios for patient 2 (Table 1) with confirmed invasive candidiasis. A, the time at which the first blood sample, culture positive for *C. albicans*, was drawn. Amphotericin B was given from day 36 to day 62, when the patient died (horizontal black bar). The broken line at the value of 4.6 corresponds to the upper cutoff limit.

TABLE 2. Peak D/L-arabinitol ratios in febrile, neutropenic children with cancer, empirically treated for invasive candidiasis

Patient no.	Primary disease	Peak D/L-arabinitol ratio	Time interval (days) between positive D/L-arabinitol ratio and empiric treatment	No. of positive samples/no. of all samples[a]	Patient status	Postmortem culture and histopathology result
11	ALL[b]	3.2	NA[c]	0/21	Alive	
12	AML[d]	5.0	14	3/8	Alive	
13	Wilms' tumor	7.2	28	4/9	Alive	
14	Non-Hodgkin's lymphoma	7.7	NA	5/15	Alive	
15	Rhabdomyosarcoma	3.7	NA	0/11	Alive	
16	ALL	3.6	NA	0/36	Dead	Negative
17	ALL	8.2	12	9/29	Alive	
18	Megacaryocyteleukemia	4.5	NA	0/2	Alive	
19	Malignant Schwannoma	4.6	10	2/18	Dead	Negative
20	Rhabdomyosarcoma	2.6	NA	0/12	Dead	Negative
21	B-cell lymphoma	3.4	NA	0/17	Alive	
22	ALL	4.9	15	2/12	Alive	
23	ALL	16.0	NA	2/5	Dead	Not done
24	CML[e]	3.2	NA	0/17	Alive	
25	ALL	5.5	21	2/6	Alive	
26	B-cell lymphoma	4.1	NA	0/8	Alive	
27	B-cell lymphoma	4.3	NA	0/26	Dead	Not done
28	B-cell leukemia	3.6	NA	0/9	Alive	
29	AML	9.8	31	8/18	Alive	
30	Neuroblastoma	4.9	13	2/5	Alive	
31	AML	7.6	6	2/20	Dead	Negative
32	AML	4.9	10	4/16	Alive	
33	CML	2.5	NA	0/2	Alive	

[a] Number of positive urine samples/total number of urine samples.
[b] ALL, acute lymphatic leukemia.
[c] NA, no adequately timed samples available.
[d] AML, acute myeloid leukemia.
[e] CML, chronic myeloid leukemia.

children showed positive D/L-arabinitol ratios 6, 10, 10, 12, 13, 14, 15, 21, 28, and 31 days, respectively, before empiric antifungal chemotherapy was instituted, and Fig. 3 presents the ratios over time for one of these patients. Six patients died; four of them died during or shortly after the institution of antifungal chemotherapy.

The remaining 67 patients received no antifungal treatment, and the mean of their D/L-arabinitol ratios, determined by using each patient's peak value, was 3.2 ± 1.1 (Fig. 1, group C). Four patients had peak values above the cutoff limit, but for all of these patients the values later returned to normal. Four patients died due to their malignancies, and none of these had a positive D/L-arabinitol ratio.

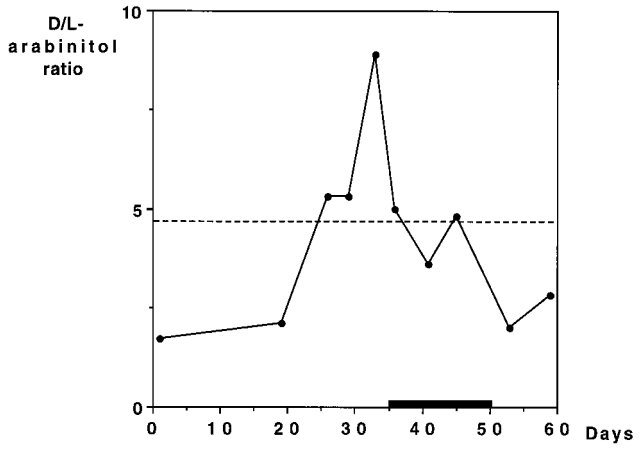

FIG. 3. D/L-Arabinitol ratios for patient 17 (Table 2), who was receiving empiric antifungal therapy. Amphotericin B was given from day 35 to day 50 (horizontal black bar). The broken line at the value of 4.6 corresponds to the upper cutoff limit.

On the basis of the results for patients in groups A and C, the sensitivity of the arabinitol test in diagnosing invasive candidiasis is 100% and the specificity is 94%, resulting in a positive predictive value of 71% and a negative predictive value of 100%. If it is assumed that all the empirically treated group B patients did have invasive candidiasis, positive and negative predictive values are both 85%.

Forty children were diagnosed with bacteremia. Of these patients, 19 had at least two blood cultures positive for gram-positive bacteria, 15 patients had blood cultures positive for gram-negative bacteria, and mixed infections were seen in 6 patients. The mean D/L-arabinitol ratio during bacteremia was 3.1 ± 0.9, and one patient had a positive value of 5.2, which, however, was recorded during a period of empiric antifungal chemotherapy. One patient died from streptococcal bacteremia and one died from a mixed infection (these two patients had previously received empiric antifungal chemotherapy; see above).

D/L-Arabinitol ratios were significantly higher during neutropenic periods when antifungal therapy was not given (3.0 ± 1.1) than during nonneutropenic periods (2.5 ± 0.7) ($P < 0.01$). Also, D/L-arabinitol ratios were significantly higher during periods of bacteremia (3.1 ± 0.9) than during nonneutropenic periods ($P < 0.01$).

In all, a total of 1,039 blood samples for culture were drawn during the study period. Forty-six cultures of blood from 10 patients were positive for *Candida* species, and 237 cultures of blood from 40 patients were positive for bacteria. The mean numbers of urine samples per patient delivered for D/L-ara-

binitol analysis were 15, 14, and 9 for groups A, B, and C, respectively.

DISCUSSION

This is the first prospective study on the diagnostic value of monitoring urine D/L-arabinitol ratios in immunocompromised patients at high risk of invasive candidiasis. All 10 patients with confirmed invasive candidiasis, based on multiple positive blood cultures alone (6 patients) or such cultures together with tissue biopsies or postmortem examination (4 patients), showed positive D/L-arabinitol ratios (Table 1; Fig. 1). Positive ratios were also found for 12 of 23 children who had negative blood cultures and who were being empirically treated with antifungal chemotherapy (Table 2; Fig. 1) and for 4 of 67 patients not receiving antifungal therapy. However, blood cultures are usually positive for only about 50% of patients with proven disseminated candidiasis, even when biphasic media or lysis-centrifugation is used (1, 14, 19). It is thus tempting to speculate that 12 of the 23 empirically treated patients with increased D/L-arabinitol ratios had unconfirmed invasive candidiasis. This study was not designed to monitor therapy by using D/L-arabinitol ratios, but the data presented for two patients (Fig. 2 and 3) indicate that the outcome of antifungal treatment correlates with changes in D/L-arabinitol ratios.

C. glabrata has not been shown to produce D-arabinitol when it is grown in vitro (9). The patient with both positive blood cultures for *C. glabrata* and increased D/L-arabinitol ratios probably had a mixed candidal infection, since all postmortem tissue cultures were positive for *C. albicans*. Considering subjects not included in the present study, we have also found elevated D/L-arabinitol ratios in two nonimmunocompromised patients with *C. glabrata* fungemia, but for these two patients no tissue cultures were performed (unpublished data).

During nonneutropenic periods, children with cancer had higher D/L-arabinitol ratios (2.5 ± 0.7) than healthy nonhospitalized children (2.0 ± 0.6) ($P < 0.01$). The ratios further increased (3.0 ± 1.1) during neutropenic periods without empiric antifungal chemotherapy. This could reflect an increased fungal load in these patients at risk for fungal infection, although fungal surveillance cultures were not included in our study, and all patients were given nystatin orally. D/L-Arabinitol ratios also increased (3.1 ± 0.9) during bacteremia, and it has previously been reported that bacteremia is a risk factor for fungal infection in patients with hematologic disorders (7). We do not believe, however, that bacteremia per se gives rise to increased D/L-arabinitol ratios in urine, since we have found normal D/L-arabinitol ratios in all of 25 adult nonimmunocompromised patients with bacteremia whom we studied (unpublished data).

Perhaps the most striking finding of this study is that D/L-arabinitol ratios often increased days to weeks before invasive candidiasis was suspected or confirmed through blood cultures or histopathology. Elevated D/L-arabinitol ratios were found 3 to 31 days (median, 12 days) before a culture-positive blood sample was first drawn from 7 of 10 children with confirmed invasive candidiasis and before empiric antifungal treatment was initiated for 10 of 12 children. The time gain achieved with D/L-arabinitol ratios was actually even greater considering the time needed for culture. It has previously been reported that the outcome for patients with invasive candidiasis depends largely on the early institution of antifungal therapy (2, 15).

Renal dysfunction influences the absolute levels of D-arabinitol in both serum and urine (18). The method of using D/L-arabinitol ratios, which was first suggested by Roboz et al. (18), has been found to overcome this problem, and, using negative chemical ionization mass spectrometry, Roboz and Katz (17) found increased D/L-arabinitol ratios in serum from 15 of 16 patients with confirmed candidiasis. The present study indicates that monitoring of D/L-arabinitol ratios in the urine of immunocompromised children with cancer is useful for diagnosing invasive candidiasis. A considerable advantage of our method is that the analysis can be performed on a standard gas chromatograph, which expands the diagnostic applicability of D/L-arabinitol ratio measurements. It should be emphasized that the method has not yet been evaluated prospectively with immunocompromised adults or multitrauma patients with *Candida* superinfections due to long-term broad-spectrum antibiotic treatment. Nevertheless, we have found increased D/L-arabinitol ratios in urine samples from several such patients (unpublished data).

Another approach to solving the problem of increased concentrations of D-arabinitol in the serum of patients with renal dysfunction is to determine the D-arabinitol/creatinine ratio. In a prospective study, Walsh et al. (22) found elevated D-arabinitol/creatinine ratios in 74% of cancer patients with verified candidemia and in 40% of patients with deep-tissue candidiasis without fungemia. Although they used another method to detect the in vivo production of D-arabinitol, the results of Walsh et al. (22) support our unpublished observations that increased D/L-arabinitol ratios in urine are seen also in adult cancer patients with invasive candidiasis.

A number of circulating candidal antigens, e.g., the cytoplasmic *Candida* enolase antigen, cell wall mannan, and heat-labile glycoprotein antigens (Cand-Tec), have also been used for diagnosis (5). Analysis of multiple serial serum samples may improve the sensitivity of *Candida* detection, since antigens are cleared rapidly from serum and/or immune complexes are formed. Walsh et al. (20) found a diagnostic sensitivity of 75% and a specificity of 96% in a prospective clinical trial by using multiple sampling and an assay for *Candida* enolase in serum. Studies on the detection of serum mannan have shown sensitivities from 0 to 65%, as reviewed by de Repentigny (5).

Antibody tests are often negative for immunocompromised patients, and it has been claimed that such tests are of more prognostic than diagnostic significance (11). Nevertheless, Deventer et al. (6) found anti-*Candida* enolase antibodies in 53% of a group of immunodeficient patients with invasive candidiasis, and Navarro et al. (12) reported a sensitivity of 89% when analyzing antibodies to cell wall-bound and cytoplasmic antigens. It should be pointed out, however, that neither of the cited reports presented any data regarding antibody kinetics during the course of infection. Newer techniques such as *Candida* DNA amplification have produced encouraging results in small studies, and sensitivities of between 60 and 79% for culture-positive clinical specimens have been achieved (3, 4, 8). Another approach involves a *Limulus* amoebocyte lysate assay for the detection of elevated levels of 1,3-β-D-glucan in plasma, which was found to have a sensitivity of 90% for patients with confirmed fungal infection (13). To date, however, neither of these two methods has been thoroughly evaluated in prospective clinical studies.

The lack of a "gold standard" for the diagnosis of invasive candidiasis complicates the evaluation of new diagnostic methods. However, the results of the present study indicate that elevated D/L-arabinitol ratios can be detected and used as a valuable predictor at an early stage of invasive candidiasis in children with cancer. Therefore, we suggest that, together with routine blood and tissue cultures, the D/L-arabinitol ratios for such patients should be monitored routinely, and for patients with increased ratios, antifungal chemotherapy should be instituted.

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