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Quantitative Urine Cultures Do Not Reliably Detect Renal Candidiasis in Rabbits

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The significance of quantitative urine cultures in patients at risk for hematogenous disseminated candidiasis is controversial. While various concentrations of *Candida* spp. in urine have been suggested as critical cutoff points in the diagnosis of renal candidiasis, other investigators consider quantitative cultures less critical in diagnosing upper tract infections. To determine the significance of quantitative urine cultures in renal candidiasis, we studied serial quantitative urinary cultures of *Candida albicans* in a rabbit model of hematogenous infection. Of 197 urine samples from 34 infected animals, 144 were culture positive, with a sensitivity of 73.1% for urine cultures and a lower limit of detection of 10 CFU/ml. The yield of urine cultures varied according to severity and duration of infection. The mean renal and urinary concentrations of *C. albicans* from rabbits with subacute candidiasis differed significantly from those from rabbits with acute candidiasis ($P = 0.013$ and $P \leq 0.001$, respectively). During the first 4 days of subacute renal candidiasis, more than one-half of all urine cultures were negative for *C. albicans*. Only 12 (8.1%) of 148 urine cultures in animals with subacute renal candidiasis had concentrations of $>10^3$ CFU/ml, 2.7% had concentrations of $>10^4$ CFU/ml, and none were $\geq 10^5$ CFU/ml. By comparison, all urine cultures from the animals with lethal acute renal candidiasis had higher concentrations of *C. albicans* and were positive throughout the course of infection. Urinary concentrations of *C. albicans* were not predictive of the amount of *Candida* in the kidney ($r \leq 0.49$) and did not correlate with survival ($r = 0.0232$). However, the renal concentration of *C. albicans* (in CFU/gram) inversely correlated with the duration of survival (in days) of rabbits with renal candidiasis ($r = 0.76$; $P < 0.001$). These findings indicate that a negative urine culture in rabbits does not preclude the presence of renal candidiasis. The interpretation of a urine culture positive at any concentration, on the other hand, must involve an analysis of the risk factors for renal candidiasis, for any urinary concentration of *C. albicans* may reflect kidney infection.

Urinary tract infections due to *Candida albicans* are increasingly being described in a variety of clinical situations (4, 7, 10, 13, 26, 35), particularly in intensive care units (ICUs) (9, 31). In many instances, these infections represent local bladder infection or colonization related to the presence of indwelling bladder catheters. Other cases, however, may reflect a population of immunocompromised patients with occult infection in the kidneys. Distinguishing between renal candidiasis and *Candida* cystitis in this population of patients carries important therapeutic and prognostic implications.

The isolation of *C. albicans* from blood in these settings is often considered synonymous with deep-tissue candidiasis, particularly renal infection (4, 11, 12). By comparison, the significance of positive urine cultures remains controversial. Whether positive urine cultures for *Candida* spp. represent renal candidiasis and whether quantitative urine cultures can distinguish between upper and lower urinary tract infections is not known. Published clinical reviews on candiduria (7, 15, 19, 43) propose various levels of colony counts per milliliter of urine as critical cutoff points for renal infection. These studies are limited by the lack of tissue-confirmed cases, the variable clinical settings studied, and the methodology of urine sampling.

In order to understand the utility and significance of quantitative colony counts in hematogenous renal candidiasis, we studied quantitative urine cultures for *C. albicans* in a rabbit model of this infection. Rabbits received various inoculum sizes of *C. albicans* intravenously (i.v.) in order to stimulate varying degrees of severity of infection. We then compared the urinary concentrations of *Candida* to quantitative cultures of kidney tissue and histopathologic evidence of renal candidiasis. These studies provide an experimental foundation for understanding the significance of quantitative urine cultures for *C. albicans* as a marker for renal candidiasis.

MATERIALS AND METHODS

Animals. Female New Zealand White rabbits (Hazleton, Rockville, Md.), weighing 2 to 3 kg, were used in all experiments. Silastic central venous catheters were inserted into all rabbits, as previously described (42). Forty-four rabbits were studied in these experiments. All animals were individually housed and provided with food and water ad libitum in accordance with National Institutes of Health (NIH) guidelines for animal care and American Association of Laboratory Animal Care criteria (8).

Organism and inoculation. *C. albicans* NIH 86-21b, a well-characterized isolate from a patient with autopsy-proven disseminated candidiasis, was utilized for all experiments. Organisms from stock isolates stored in skim milk at −70°C were streaked onto Sabouraud glucose agar (SGA) plates and incubated at 37°C for 24 h. Four to five well-isolated colonies were then inoculated into 50 ml of Emmon's modified Sabouraud broth (pH = 7) and incubated at 37°C for 16 h on a shaking incubator at 80 rpm. The *Candida* suspension was then centrifuged at $4,500 \times g$ for 10 min, and the pellet was resuspended in sterile normal saline after serial washing. After quantitation in a hemacytometer, the inoculum was diluted to the desired concentration of blastoconidia in a 5-ml volume of saline per rabbit. The inoculum size was confirmed by plating serial dilutions onto SGA check plates.

Thirty-four rabbits each i.v. received a single inoculum, ranging from 10^5 to 10^8 blastoconidia of *C. albicans* depending on the dosage group, in order to simulate

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TABLE 1. Yields of urine cultures and concentrations of *C. albicans* in 17 rabbits with subacute renal candidiasis[a]

Day of infection	No. of samples	% Positive cultures[b]	% Positive urine samples at *C. albicans* concn[c] of:					Survival (%)[d]
			10^1	10^2	10^3	10^4	10^5	
1	11	27.3	33.3	66.6				100
2	14	50	85.7	14.3				100
3	17	41.1	75	25				100
4	10	40	50	50				100
5	10	60	50	50				100
6	10	80	25	75				100
7	10	90	44	56				100
8	10	80	37.5	37.5	25			100
9	10	90	44.4	44.4	11.1			100
10	10	50	20	60		20		100
11	10	60	83.3	16.7				100
12	9	89	75	12.5	12.5			94.1
13	9	78	57.1	28.6		14.3		94.1
14	8	50		25	75			82

[a] *C. albicans* blastoconidia (10^5 to 10^6 CFU) were administered i.v. to each rabbit.

[b] Percentage of urine specimens positive by culture for *C. albicans*/all specimens obtained per day of infection.

[c] Percentage of positive cultures with different concentrations of *C. albicans* per milliliter of urine.

[d] Percentage of surviving rabbits/infected rabbits.

the different levels of severity of renal candidiasis in patients with this infection. Inocula of 10^5 and 10^6 blastoconidia established a pattern of subacute renal candidiasis ($n = 17$), while inocula of 10^7 and 10^8 blastoconidia established a pattern of acute renal candidiasis ($n = 17$). Ten noninfected rabbits served as controls. Urine specimens were serially collected during the course of the infection over 2 weeks. Rabbits were terminally euthanized by i.v. pentobarbital (500 mg/kg of body weight) at the end of 2 weeks or sooner if warranted by NIH guidelines (8).

Urine collection. Urine was collected daily following inoculation. Sterile normal saline was administered i.v. over a 10- to 20-min period, followed by i.v. furosemide (0.5 mg/kg) to facilitate the scheduled collection of urine specimens. Thirty minutes later, light anesthesia, consisting of 0.1 to 0.2 ml of a mixture of 2 ml of ketamine (100 mg/ml; Fort Dodge Laboratories, Inc., Fort Dodge, Iowa) and 1 ml of xylazine (20 mg/ml; Mobay Corporation, Shawnee, Kans.), was given i.v. for light sedation as well as to facilitate relaxation of urinary sphincters. Voided urine, obtained by gentle suprapubic compression, was collected onto sterile petri dishes and immediately transferred to 15-ml conical tubes.

Direct urinalysis and quantitative cultures. After careful vortexing, each sample of urine was cultured immediately by streaking 0.1 ml of the serial 10-fold saline dilutions of urine onto pairs of SGA plates supplemented with chloramphenicol (16 μg/ml) and gentamicin (8 μg/ml). Plates were incubated aerobically at 37°C for 24 h. The detection level for quantitative cultures used in this study was 10 CFU/ml, represented by a single colony of *C. albicans* on a plate. Dipsticks (Bili-Labstix; Miles Inc., Diagnostics Division, Elkhart, Ind.) were used to assay pH, leukocytes, blood, nitrites, ketones, protein, and bilirubin. All urine samples were examined microscopically for the presence of blastoconidia and pseudohyphae. A sagittal section of kidney was prepared postmortem for quantitative cultures of tissue homogenates as previously described (41).

Histologic studies of kidneys. A sagittal section of the kidney submitted for histologic studies was fixed in 10% neutral buffered formalin, embedded in paraffin, sectioned, stained with periodic acid-Schiff stain, and examined by light microscopy. A diagnosis of renal candidiasis was based on histologic evidence of abscesses, revealing blastoconidia and/or pseudohyphae infiltrating the renal parenchyma, surrounded by inflammatory cells.

Validation of rabbit model of renal candidiasis. All study rabbits demonstrated histologic evidence of fungal infection with or without positive cultures in the kidneys, and all but one had urine cultures positive for *C. albicans*. Histologic criteria for assessing severity of renal involvement utilized a score of the number of low-power fields demonstrating fungal abscesses for every 100 low-power fields examined on a periodic acid-Schiff-stained section of the kidney. There was a direct relationship between the severity of renal candidiasis, the concentration of *C. albicans* in tissue, and the size of the inoculum administered. *Candida* lesions were more numerous in animals with acute renal candidiasis (10^7 to 10^8 CFU of inoculum) than in those with subacute renal candidiasis (10^5 to 10^6 CFU of inoculum). The concentration of *C. albicans* in tissue in rabbits with acute renal candidiasis was $3.0 \times 10^8 \pm 2.6 \times 10^8$ CFU/g of kidney, and that in rabbits with subacute renal candidiasis was $7.9 \times 10^5 \pm 7.8 \times 10^5$ CFU/g of kidney ($P = 0.013$). Acute renal candidiasis was characterized by the development of azotemia and early mortality in the study animals, whereas animals with subacute renal candidiasis did not develop azotemia and survived into the 2nd week of infection. The one study animal with urine cultures negative for *Candida* received 10^5 CFU of *C. albicans*, was found to have a *C. albicans* concentration of 7.4×10^3 CFU/g in the kidney, and succumbed to *Clostridium spiriforme* colitis. None of 10 control rabbits had either histologic evidence of or urine cultures positive for *Candida* spp.

Statistical analysis. Differences between means were determined by Kruskal-Wallis nonparametric analysis of variance and adjusted by Dunn's multiple-comparisons test. Results were expressed as means ± standard errors of the means (SEM). Correlations between groups were determined by using Spearman rank correlation coefficients. Overall sensitivity, specificity, positive predictive value, and negative predictive value were determined by a two-by-two analysis, where sensitivity = $a/(a + c)$, specificity = $d/(b + d)$, positive predictive value = $a/(a + b)$, and negative predictive value = $d/(c + d)$.

RESULTS

Yield of quantitative urine cultures. One hundred ninety-seven urine samples were collected from all study animals over the course of infection; of these, 148 (75%) were from animals with subacute renal candidiasis (Table 1) and 49 (25%) were from animals with acute renal candidiasis (Table 2). All 112 urine samples from the 10 control animals without renal candidiasis were negative for *C. albicans*, whereas 144 of the 197 study samples were positive for *C. albicans*, with a sensitivity of 73.1%, a specificity of 100%, a positive predictive value of 100%, and a negative predictive value of 69% for quantitative urine cultures detecting at least 10 CFU/ml of urine in this model of renal candidiasis. The yield or apparent sensitivity of quantitative urine cultures, however, varied according to the severity and duration of infection.

Tables 1 and 2 show the relationship among patterns of renal candidiasis (acute and subacute), the percent yield of daily urine cultures, and the concentration (in CFU/milliliter) of *C. albicans* in quantitative urine cultures for rabbits with renal candidiasis. During the first 4 days of subacute renal candidiasis, only 25 to 50% of urine cultures were positive for *C. albicans*. The maximum yield of urine cultures was seen on days 7 to 9 and was followed by a decline, such that only half of the urine specimens were positive at day 14. Among the positive urine specimens, the urinary concentrations of *C. albicans* re-

TABLE 2. Yields of urine cultures and concentrations of *C. albicans* in 17 rabbits with acute renal candidiasis[a]

Day of infection	No. of samples	% Positive cultures[b]	% Positive urine samples at *C. albicans* concn[c] of:					Survival (%)[d]
			10^1	10^2	10^3	10^4	$>10^5$	
1	13	100	7.7	69.3	23			100
2	13	100	7.7	53.8	38.5			94.1
3	11	100		27.3	27.3	36.4	9	70.6
4	4	100		25	25		50	23.5
5	2	100			100			11.8
6	1	100			100			5.9
7	1	100					100	5.9
8	1	100					100	5.9
9	1	100					100	5.9
10	1	100					100	5.9
11	1	100					100	5.9
12								
13								
14								

[a] *C. albicans* blastoconidia (10^7 to 10^8 CFU) were administered i.v. to each rabbit.

[b] Percentage of urine specimens positive by culture for *C. albicans*/all specimens obtained per day of infection.

[c] Percentage of positive cultures with different concentrations of *C. albicans* per milliliter of urine.

[d] Percentage of surviving rabbits/infected rabbits.

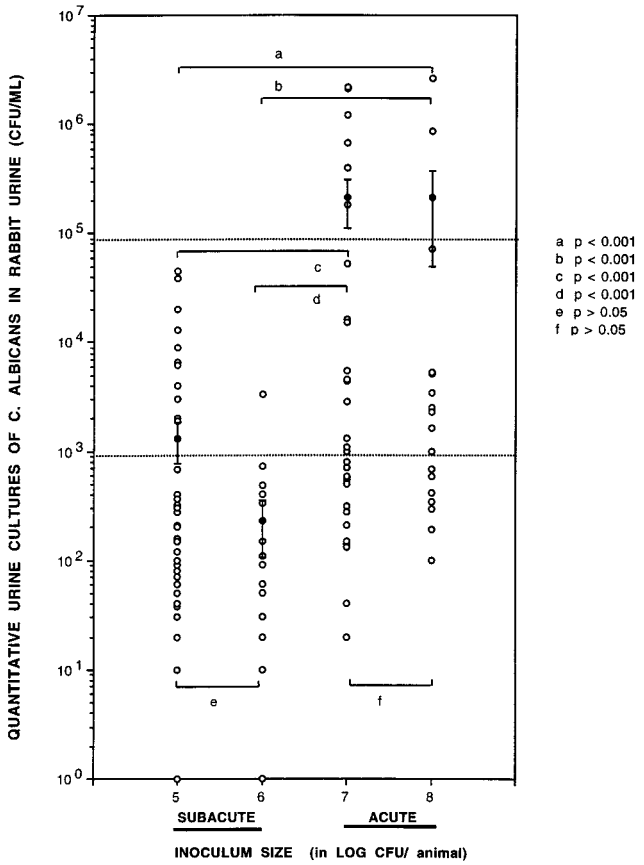

FIG. 1. Range of colony counts in quantitative urine cultures from rabbits with renal candidiasis. Open circles represent individual urine samples; closed circles indicate means (error bars, SEM). The means and SEM for rabbits with subacute candidiasis (10^5 and 10^6 CFU of *C. albicans*) differed significantly from those with acute renal candidiasis.

mained at $<10^3$ CFU/ml until day 7 of infection. Thereafter, a rise in urinary concentrations of *C. albicans* was seen, to a maximum of 10^4 CFU/ml of urine after day 9.

By comparison, all urine cultures from the animals with acute renal candidiasis were positive throughout the course of infection (Table 2). Cultures of urine from rabbits with acute renal candidiasis had higher concentrations of *C. albicans* than those of urine from rabbits with subacute renal candidiasis. Additionally, urinary concentrations of *C. albicans* rapidly rose to concentrations of $>10^3$ CFU/ml of urine early in the course of this lethal infection.

Variation in urinary concentrations of *C. albicans*. Figure 1 depicts the means, SEM, and ranges of urinary concentrations of *Candida* from study animals given various sizes of inoculum to establish subacute and acute renal candidiasis. The mean urinary concentrations of *C. albicans* from rabbits with subacute renal candidiasis differed significantly from those from rabbits with acute renal candidiasis ($P < 0.001$). Additionally, in the animals with subacute renal candidiasis, only 12 of 148 (8.1%) urine cultures had concentrations above the level of detection by standard microbiologic techniques for processing urine specimens (10^3 CFU/ml), 4 of 148 (2.7%) samples had concentrations of 10^4 CFU/ml, and none had 10^5 CFU/ml or greater.

The concentrations of *C. albicans* in urine of surviving animals with subacute renal candidiasis increased significantly over time (Fig. 2) ($P = 0.014$). However, urine cultures obtained from individual rabbits on different days were intermittently positive (Table 1). This variable yield of urine cultures, as well as the wide range of concentrations of *C. albicans* in urine over the duration of infection, precludes reliable prediction of the presence of renal candidiasis from a single quantitative urine culture.

Correlation between quantitative urine cultures and renal concentrations. Urinary concentrations of *C. albicans* were not predictive of the amount of *Candida* infection established in the kidney. The highest concentrations of *C. albicans* measured in the urine of each individual animal, as well as the colony counts in urine obtained terminally, were compared to the burden of *Candida* in the kidney (Fig. 3). Neither the maximal ($r = 0.11$; $P = 0.53$) nor the terminal ($r = 0.49$; and $P = 0.004$) concentrations of *C. albicans* in urine correlated with the amount of renal candidiasis measured in CFU of *Candida* per gram of tissue. Additionally, neither the maximal nor the terminal urinary concentrations of *C. albicans* correlated with survival.

Correlation between renal concentrations of *C. albicans* and survival. There was no correlation between urinary concentrations of *C. albicans* and survival ($r^2 = 0.0232$; $P = 0.3486$).

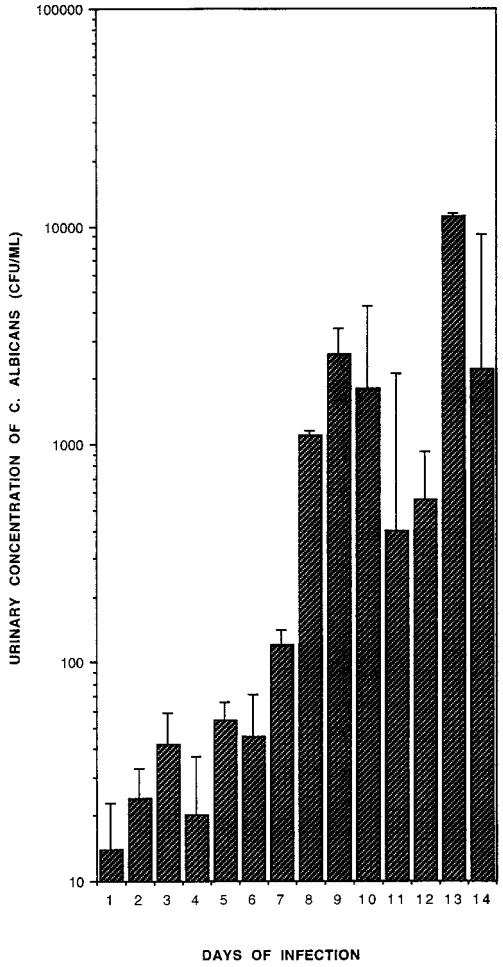

FIG. 2. Course of urine concentrations of *C. albicans* in subacute renal candidiasis. Shaded bars (*x* axis) represent means from urine cultures obtained daily over the course of subacute renal candidiasis (*y* axis) (error bars, SEM; $P = 0.0141$ [Kruskal-Wallis nonparametric analysis of variance]).

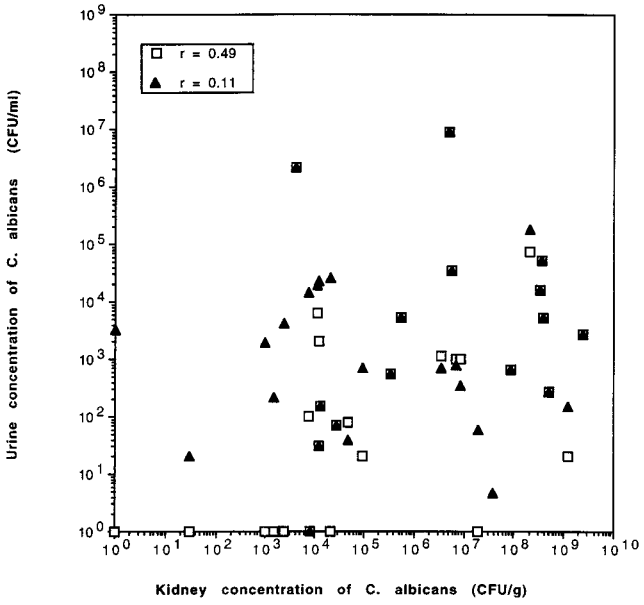

FIG. 3. Lack of correlation between quantitative urine cultures (*y* axis) and renal concentrations (*x* axis) of *C. albicans*. Open squares represent the maximum urinary concentrations of *C. albicans* for each animal. Triangles represent terminal urinary concentrations of *C. albicans.* Solid squares represent terminal urinary concentrations of *C. albicans* that were also the maximum urinary concentrations.

However, the renal concentration of *C. albicans* (in CFU/gram) inversely correlated with the duration of survival (in days) of rabbits with renal candidiasis ($r = 0.76$; $P < 0.001$) (Fig. 4). Rabbits with higher concentrations of *C. albicans* in kidney died earlier (on days 2 to 5) than the animals with lesser concentrations of *Candida* in kidney, many of which survived to day 14.

DISCUSSION

Clinical case reviews of candiduria have suggested a range of urinary concentrations of *C. albicans* as being correlated with significant renal infection (15, 19, 24, 32, 39), but this issue has never been addressed under controlled conditions in animal models of renal candidiasis (3, 5, 29). Quantitative urine cultures have been historically utilized in the evaluation of urinary tract infections (2, 17, 27). As a standard of care, leading textbooks of infectious diseases, nephrology, and clinical microbiology cite the importance of 10^5 CFU/ml as a critical breakpoint for significant bacteriuria (14, 34, 36), and algorithms in the classic texts suggest that workup for urethritis be pursued when members of the family *Enterobacteriaceae* are detected at concentrations below this. Such breakpoints, however, may have limited validity for different patient populations or organisms other than the *Enterobacteriaceae* (21, 25), organisms vastly different from *Candida* in their size, biology, virulence, and pathogenicity. Furthermore, clinical laboratories process urine specimens and report results in a standard fashion, and these CFU/milliliter thresholds are therefore extrapolated to candiduria. The recommended procedure for culturing fungal pathogens requires concentrating a sample to improve the yield (14, 34, 36), but this procedure is not routine and is time- and labor-intensive. In this animal model of upper urinary tract candidiasis, however, quantitative urine cultures were not sufficiently sensitive to detect renal candidiasis, even when the lowest detectable concentration was 10 CFU/ml. Urine cultures were only intermittently positive over time for rabbits with subacute renal candidiasis but were consistently positive for those with acute candidiasis. Moreover, the concentration of *C. albicans* in renal tissue but not that in urine correlated with survival. Thus, there appears to be no threshold of quantitative urine cultures of *C. albicans* which can reliably exclude a diagnosis of renal candidiasis, and the presence or absence of *C. albicans* in urine cultures may be all that is necessary for clinical laboratories to determine.

The method of quantitative urine cultures utilized in this study allowed detection of as little as 10 CFU of *C. albicans* per ml of urine. The sensitivity of such cultures in detecting true upper urinary tract infection was 73%, although the apparent sensitivity of urine cultures may be influenced by the size of the inoculum administered and the severity of renal infection established, as well as the duration of infection. Urine cultures were intermittently positive for *C. albicans* and, even when positive, had wide fluctuations in concentration on a daily basis, even for the same animal monitored over time. Furthermore, no evidence of lower urinary tract candidiasis was seen in the animals, which limits the translation of the findings of this animal study into humans, in whom lower urinary tract infections, particularly in hospitalized patients with indwelling Foley catheters, are common.

The kidney is among the most frequently infected organs involved in hematogenous disseminated candidiasis, and the presence of candiduria may be the first microbiologic evidence of renal infection. At the same time, asymptomatic colonization or localized infection of the urinary bladder, particularly in the catheterized patient, is very frequent. The applicability of the findings of this study to infection in humans may be limited by the fact that lower urinary tract colonization or infection with *C. albicans* was not modeled into the study. Nevertheless, these data indicate that there is no concentration of *C. albicans* below which renal candidiasis can be considered unlikely. The significance of a positive urine culture for *C. albicans* depends upon assessing the status of the host, with the most immunocompromised patient—such as the organ transplant recipient, the very low birth weight infant in the ICU, the neutropenic

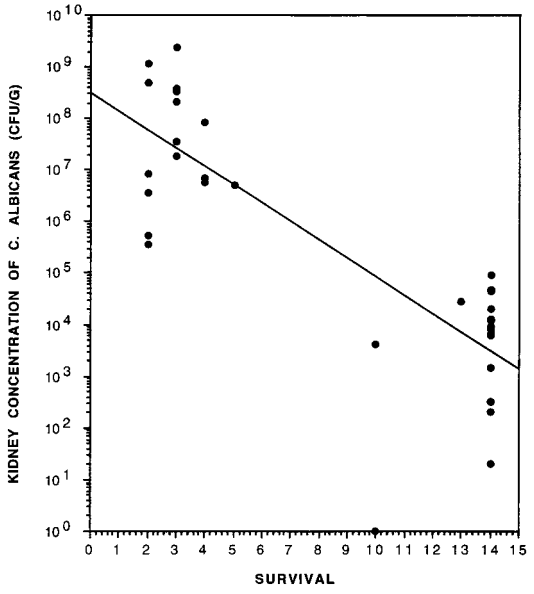

FIG. 4. Inverse correlation of duration of survival (*x* axis) with renal concentrations of *C. albicans* (*y* axis) ($r = 0.76$; $P < 0.001$). Circles represent individual animals with acute or subacute renal candidiasis.

cancer patient, or the bone marrow transplant recipient—at highest risk for renal candidiasis. The clinical microbiologist may suggest that other diagnostic studies, such as blood cultures, urinary cytology to demonstrate yeast in renal casts, and imaging techniques to demonstrate renal lesions or fungal bezoars, be pursued in the appropriate setting. Non-culture-based diagnostic systems have been studied with urinary tract infections due to bacteria (6) and *Candida* spp. (30, 38, 40); however, these methods remain investigational.

Quantitative urine cultures did not reliably reflect the concentration of *C. albicans* in the kidneys. The presence of renal abscesses on gross and histopathologic examination, as well as the microbiologic quantitation of *Candida* per gram of kidney homogenate, was not geometrically proportional to the urinary concentration of *C. albicans*. That some rabbits demonstrated sterile urine terminally despite large *Candida* abscesses persisting in the kidneys underscores the lack of predictive power of urine cultures for renal candidiasis.

The lack of correlation between urinary concentrations of *C. albicans* and the extent of infection demonstrated microbiologically may be due to several mechanisms: (i) the degree of mechanical destruction of renal tissue and the disruption of tubular integrity may prevent the egress of fungal elements from the kidney into the urine; (ii) the marked inflammatory response surrounding the abscesses may limit the extension of *C. albicans* into the tubular lumen; and (iii) the extensive mycelial network in a *Candida* renal abscess may not be reflected by relatively smaller numbers of blastoconidia and pseudohyphae in the urine.

The low urinary concentrations of *C. albicans* in this study are unlikely to be attributable to the saline- and furosemide-induced diuresis. Concentration occurs efficiently in urine, even as solute cycling and water absorption vary over wide limits. In saline diuresis, urine/plasma osmolar ratios do not drop below unity. Even in diseased states, such as diabetes insipidus, the urine/plasma osmolar ratios do not drop below 0.4 (18). While some degree of urinary dilution may be attributed to saline- and furosemide-induced diuresis, it is unlikely that this would result in a dilution of 100- to 1,000-fold, given the physiologic limits of the countercurrent mechanism. In addition, the practice of hydration and saline diuresis is standard in ICUs, where candiduria is being reported with greater frequency.

The urinary concentration of *C. albicans* met or exceeded the traditional benchmark of 10^5 CFU/ml for diagnosing urinary tract infection only in the animals with acute renal candidiasis established with the larger inocula (10^7 to 10^8 CFU per animal). This concentration, however, accounted for a mere 16.7% (8 of 49) of the total urine specimens obtained from these rabbits, all of which died within 4 days of infection, indicating a lethal infection in this noncatheterized, nonneutropenic model. In humans, random urine cultures from asymptomatic volunteers have been reported to have similar concentrations of *C. albicans* without any significant morbidity, especially in the subset of patients with factors known to predispose them to fungal colonization, e.g., females, those who are undergoing antibiotic therapy, and those with diabetes mellitus (1, 37).

Renal candidiasis is difficult to diagnose on clinical grounds, often requiring the demonstration of radiologically detectable abscesses in the presence of candidiasis or histological evidence of parenchymal invasion with yeasts. There are no autopsy series correlating urinary concentrations of *Candida* and renal infection. A colony cutoff of 10^4 CFU of *C. albicans*/ml has been proposed by some investigators to discriminate upper versus lower urinary tract infections (20, 33) and was felt to correlate with increased mortality in at least one study (43). Despite the histopathological evidence indicating well-established renal abscesses in this study, 92% of urine cultures disclosed concentrations well below 10^4 CFU/ml, and as much as one-quarter of urine specimens had less than 10 CFU of *C. albicans*/ml. Furthermore, the urinary concentration of *C. albicans* was often less than 10^3 CFU/ml and would theoretically not be evident by regular quantitative urine culture techniques. The extrapolation of these findings to humans suggests that negative urine cultures or low colony counts of *C. albicans* do not reliably exclude significant renal infection, a clinical phenomenon inferred by several case reports (16, 22, 24, 29). Thus, a negative urine culture in this rabbit model does not reliably exclude a diagnosis of renal candidiasis, and no threshold of urinary concentration of *C. albicans* can be established to reliably identify renal candidiasis.

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