

Kinetic Patterns of *Candida albicans* Germ Tube Antibody in Critically Ill Patients: Influence on Mortality[∇]

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The influence of kinetic patterns of *Candida albicans* germ tube antibodies (CAGTA) on mortality was analyzed in six intensive care units. Statistically significant lower mortality rates were found in patients with patterns of increasing CAGTA titers who had been treated with antifungal agents. Thus, antifungal treatment should be considered when CAGTA titers are increasing in critically ill patients.

Invasive candidiasis (IC) in critically ill patients represents a diagnostic challenge. The mortality rate of patients with IC remains excessively high (10) and is associated with difficulty in making a prompt microbiological diagnosis (11) and a delay in antifungal treatment (2, 7). Until now, no single serological test has found widespread clinical acceptance (8). Recently, an immunofluorescence test for *Candida albicans* germ tube antibody (CAGTA) detection has been marketed to help with the IC diagnosis. A recently published mortality analysis by our group showed a significant diminution of mortality in those patients with a CAGTA-positive result (12), although the significance of a CAGTA-positive result without other evidence of IC (serological candidiasis) remained unknown. For these reasons, the aims of the present study of critically ill patients with risk factors of developing IC were to describe the kinetic patterns of CAGTA-positive patients and to analyze the outcome of these patients according to CAGTA detection, dynamic profiles of patients, and the administration of antifungal therapy.

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A retrospective subanalysis of mortality extracted from a prospective observational multicenter study was conducted at six Spanish university hospitals over a period of 2 years (2005 to 2006) (12). Inclusion criteria were as follows: (i) acute pancreatitis of >7 days of evolution, (ii) a prolonged intensive care unit (ICU) stay (>14 days) and three or more risk factors (diabetes mellitus, extrarenal depuration, parenteral nutrition, more than 7 days of broad-spectrum antibiotic therapy, and

major abdominal surgery), (iii) liver transplant, (iv) neutropenia or bone marrow transplant, and (v) a high level of *Candida* colonization. Exclusion criteria were as follows: (i) pregnancy, (ii) an age of <18 years, (iii) previous IC, or (iv) a life expectancy of <7 days. A CAGTA detection assay (*Candida albicans* immunofluorescence assay immunoglobulin G; Vircell, Spain) was performed twice a week, and a positive result was determined to be a serum titer of $\geq 1/160$ in at least one sample. Blood cultures were processed with automated systems (BACTEC [Becton Dickinson] or BacT/Alert [bioMérieux, Spain]). Identification of yeasts was made with the API 32C or Vitek system (bioMérieux). At each institution, the decision to add antifungal therapy for patients with suspected IC was at the discretion of the prescribing physician based on clinical criteria, but it was not influenced by CAGTA results. The chi-square or Fisher's exact test was used to compare categorical variables. For patients who had at least one positive result, the increase or decrease of CAGTA titers was also described. A *P* value of ≤ 0.05 was considered statistically significant.

Fifty-three critically ill nonneutropenic patients (37.7% post-surgery) were included. Twenty-two patients (10 patients had one positive sample, 8 patients had two, and 4 patients had three or more) had CAGTA-positive results, none of them with positive blood cultures for *Candida* isolates. There were no differences in the antifungal treatment rates between the CAGTA-positive and CAGTA-negative groups. Two patients determined to be CAGTA positive on the basis of only one determination were excluded since it was impossible to determine any change in their titers. Three patterns in CAGTA-positive patients were detected: increasing titers (31.8%), decreasing titers (36.4%), and no change in titer kinetics (22.8%) (Table 1). The intra-ICU mortality rate was significantly lower (*P* = 0.004) in CAGTA-positive patients (22.7% versus 61.2% in CAGTA-negative patients), as had been previously described by our group (12).

A tendency toward lower mortality rates was found in patients with a pattern of increasing CAGTA titers, in contrast with those patients who did not show an increase in CAGTA

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TABLE 1. Mortality of CAGTA-positive patients according to their dynamic patterns and the administration of antifungal treatment

Dynamic pattern	No. (%) of patients with indicated outcome			
	Total	Died	Treated with antifungals	Treated with antifungals and died
CAGTA positive	22 (100)	5 (22.7)	10 (45.4)	4 (40)
Not determinable	2 (9)	0 (0)	0 (0)	
Increasing titers	7 (31.8)	1 (14.2)	4 (57.1)	0 (0)
No change	5 (22.7)	1 (20)	2 (40)	1 (50)
Decreasing titers	8 (36.3)	3 (37.5)	4 (50)	3 (75)

titers (14.3% versus 30.7%; $P = 0.08$). This finding was statistically significant when only treated patients were analyzed (0% versus 66.6%; $P = 0.04$) (Table 1). On the other hand, when the number of positive serum samples was studied, this tendency was not observed.

The high prevalence of CAGTA-positive results in the population studied (41.5%) corroborated the adequacy of the inclusion criteria used in this study as a predictive biomarker of *Candida* infection and the need to consolidate the CAGTA determinations in a well-defined ICU population. To our knowledge, no association between a positive serological result and mortality has been reported previously in a prospective study in ICU patients with IC. The significance of antibody responses to other antigens (especially heat shock proteins) has been reported previously in animal models (1, 5). Furthermore, the value of dynamic patterns of a serological test had never been described as a possible prognostic factor in critically ill patients. Another biomarker, like soluble triggering receptor expressed on myeloid cells-1, has also been recently described in an ICU setting associated with a higher rate of survival (3).

In our study, the decision to add antifungal empirical therapy for patients with suspected IC was at the discretion of the prescribing physician based on clinical criteria, but it was never guided by CAGTA results. Thus, there were no differences in the antifungal treatment rates between the two groups of patients. Intra-ICU mortality was significantly lower in CAGTA-positive patients. Though CAGTA-positive and -negative patients received antifungal treatment (the decision of treatment was based on clinical data), the lower mortality observed in the CAGTA-positive group might be related to the correct empirical treatment administered to these patients. This fact could be supported by the surprising finding of lower mortality rates demonstrated in patients with increasing CAGTA titers who had received antifungal therapy. The possibility that the increased CAGTA titers in patients could represent true IC episodes makes this finding more realistic. In addition, detection of CAGTA may be useful for the therapeutic monitoring of patients with IC (4, 6, 9). Due to these results, antifungal treatment might be considered when a patient has an increasing pattern of CAGTA titers. However, several limitations must be noted in this study: the small number of patients due to the difficulty of enrolling these kinds of patients with re-

defined criteria, the lack of demonstration of any true episode of IC, and finally the fact that the antifungal treatment was not guided by the CAGTA result.

In conclusion, the rate of CAGTA-positive results in this group of ICU patients is high and the presence of this biomarker is associated with a lower mortality rate. The possibility that increased CAGTA titers in patients might represent true IC episodes could explain the lower mortality rates demonstrated when receiving antifungal treatment. Further studies are warranted to confirm these initial findings.

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