BRIEF REPORT

Performance of the T2Candida Panel for the Diagnosis of Intra-abdominal Candidiasis

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Performance of T2Candida for detecting intra-abdominal candidiasis (IAC) was assessed in 48 high-risk patients. T2Candida sensitivity/specificity and positive/negative predictive values were 33%/93% and 71%/74%, respectively. IAC was present in 100% of cases with concordant positive T2Candida/1,3-beta-d-glucan and absent in 90% of concordant negative results. Combination T2Candida/1,3-beta-d-glucan may help guide treatment decisions.

Keywords. invasive candidiasis; candidemia; T2 magnetic resonance; blood cultures; beta-glucan.

Candida spp. frequently cause sepsis and invasive infections in intensive care unit (ICU) patients [1]. Intra-abdominal candidiasis (IAC), manifesting most often as peritonitis and/or abscesses, is common among ICU patients who have undergone complicated abdominal surgery or with other gastrointestinal (GI) tract disorders. Blood cultures represent the diagnostic gold standard for invasive candidiasis but remain sterile in >80% of patients with IAC [2, 3]. Cultures of intra-abdominal samples generally are required to diagnose IAC, but they are limited by low sensitivity, slow turnaround, and need for invasive procedures. Reliance upon cultures may delay antifungal treatment of IAC, which can contribute to high mortality rates [2, 3]. Current nonculture diagnostic methods, such as detection of 1,3-beta-d-glucan (BDG) in serum, identify some patients with IAC who are missed by cultures. However, serum BDG assays are limited by lack of specificity and high false positivity [4, 5]. The development and validation of rapid diagnostic tests for IAC and other invasive candidiasis are a pressing priority.

The T2Candida panel (T2C; T2 Biosystems, Lexington, MA, USA) is a fully automated magnetic resonance–based molecular test for direct detection of the 5 major pathogenic *Candida* spp. (*C. albicans*/*C. tropicalis*, *C. glabrata*/*C. krusei*, and *C. parapsilosis*) in whole-blood samples within 5 hours [6]. T2C was cleared by the Food and Drug Administration (FDA) and received the "Conformité Européenne" (CE) certification for diagnosis of candidemia, based largely on clinical trial data demonstrating sensitivity and specificity of ~90% and ~98%, respectively, for detecting target *Candida* spp. [7, 8]. Data on T2C performance for diagnosis of noncandidemic invasive candidiasis, such as IAC, are scant [9]. Our objective was to assess the performance of T2C for detection of IAC compared with blood cultures and BDG testing.

METHODS

Cases were included from a previous prospective cohort study by the Fungal Infection Network of Switzerland (FUNGINOS) [5]. Adults (≥18 years old) in ICUs of 2 university hospitals were enrolled consecutively if they exhibited the following risk factors for IAC: (i) recurrent GI tract perforation (anastomotic leakage or recurrent surgical transection of the gut), (ii) acute necrotizing pancreatitis (Balthazar grade D-E), or (iii) recent abdominal surgery (<3 days) and *Candida* colonization of nonsterile sites (eg, mouth, urine, stool, skin, or respiratory tract). A diagnosis of IAC was established if a *Candida* spp. was isolated by perioperative intra-abdominal culture, as previously described [5]. Blood cultures (2 sets of BACTEC Plus aerobic/F and Lytic anaerobic/F bottles, Becton Dickinson, Sparks, MD, USA) were performed in cases of fever or clinical suspicion of infection. Blood and serum samples were collected twice weekly from inclusion until 2 weeks after ICU discharge. Sera underwent BDG testing (Fungitell, Associates of Cape Cod, Falmouth, MA, USA; positivity cutoff ≥80 pg/mL) as part of the previous study [5]. T2C testing was performed on archived frozen blood samples that were thawed and in which sufficient volume was available (≥3 mL). Samples collected within 72 hours of IAC diagnosis, or between days 7 and 10 from study inclusion for patients without

IAC, were analyzed. Performance of T2C for the diagnosis of IAC was compared with that of BDG and blood cultures.

This study was approved by the local ethics committee, and written informed consent was obtained from patients or their legal representatives [5].

RESULTS

Valid T2C results were obtained for 48 ICU patients who were at risk for IAC, including 18 patients with IAC and 30 patients who did not fulfill IAC criteria as defined above. The clinical characteristics of the patients are presented in the Supplementary Data (Supplementary Table 1).

C. albicans was the causative agent of IAC in 72% (13/18) of patients. *C. tropicalis* (n = 2), *Candida* spp. not included in the T2C panel (*C. kefyr*, *C. lusitaniae*), and *C. albicans/C. glabrata* (n = 1) were involved in the remaining cases. Eleven percent (2/18) of patients with IAC were diagnosed with candidemia by blood culture. T2C was positive in 33% (6/18) of IAC patients, including the 2 patients with candidemia. *Candida* spp. detected by T2C matched those from intra-abdominal cultures. Eleven percent (2/18) of patients had been receiving antifungal treatment for 4 days at the time of IAC diagnosis; T2C was negative in these patients. T2C was negative in 93% (28/30) of patients without IAC. The 2 patients in whom T2C was positive had negative BDG results in follow-up samples despite *Candida* colonization at multiple sites, did not receive antifungal therapy, and survived until hospital discharge.

Per-patient sensitivity, specificity, positive and negative predictive values (PPV and NPV), and positive and negative likelihood ratios for T2C and BDG are provided in Table 1. Concordant positive T2C/BDG results were associated with IAC in 100% (5/5) of patients. Concordant negative results were associated with absence of IAC in 90% (18/20) of patients. Discordant T2C and BDG results were observed in 48% (23/48) of patients, 48% (11/23) of whom had IAC.

DISCUSSION

To our knowledge, this is the first study to determine T2C performance specifically for the diagnosis of IAC. T2C sensitivity

and specificity were 33% and 93%, respectively. Our findings are in keeping with those reported recently in a study from 2 ICUs in Denmark, in which T2C sensitivity and specificity for proven or likely noncandidemic invasive candidiasis (including a limited number with IAC, n = 6) were 45% and 96%, respectively [9]. Similar to the Danish study, our analysis demonstrated the ability of T2C to detect noncandidemic deep-seated invasive candidiasis.

The performance of T2C in diagnosing IAC, marked by high specificity and PPV, stands in contrast to that reported previously for serum BDG. In previous studies, BDG sensitivity and specificity for IAC ranged from 53% to 77% and 55% to 78%, respectively [5, 10–12]. The relative strengths of BDG for diagnosing IAC compared with T2C are improved sensitivity and excellent NPV. The complementary performance characteristics of T2C and BDG suggest that the tests might have the greatest clinical utility when used in combination. Indeed, concordant positive T2C and BDG results indicated IAC in 100% of cases, and concordant negative results could reliably exclude IAC in 90% of cases. The probability of IAC if 1 test was positive and the other was negative was 48%, which is likely sufficient to justify antifungal therapy in at-risk patients with signs of intra-abdominal infection in whom an alternative diagnosis is not apparent. For these patients, the need for ongoing antifungal therapy should be reassessed based on clinical evolution and microbiological results.

This study was limited by its small size and retrospective design. Use of freeze-thaw archived samples may account for the high rate of invalid T2C results (31%), which exceeded 7.6% and 9.2% for freshly collected and freeze-thawed samples, respectively, in clinical trials [7, 8]. A potential explanation for these findings is that the frozen samples were stored for several years, following their original collection during the FUNGINOS study. Indeed, even for samples giving putatively "valid" negative results, it is possible that test performance was impacted. The influence of antifungal therapy on T2C performance for diagnosing IAC remains unclear. Although only 11% of our patients were receiving an antifungal drug at the time of T2C testing, the corresponding figure was 77% among subjects in the Danish ICU study [9]. The low yield of blood cultures for IAC detection in the present study is comparable to that previously reported [2, 3]. Only standard blood cultures (aerobic and anaerobic vials) were used. It is unclear if the use of specific fungal culture vials increases the performance of blood culture for detection of candidemia [13].

T2C may have generated false-positive results in 2 patients who did not have clinical evidence of invasive candidiasis and in whom outcomes were favorable in the absence of antifungal therapy. However, we cannot exclude that T2C may have detected transient candidemia in these patients that was not diagnosed by blood cultures. Finally, in our study, 11% (2/18) of IAC was attributed to *Candida* species not included in the

Table 1. Performance of T2Candida and 1,3-Beta-D-Glucan for Detection of Intra-abdominal Candidiasis

	T2Candida	1,3-Beta-D-Glucan
Sensitivity,	33.3 (13.3–59.0)	83.3 (58.6–96.4)
Specificity, %	93.3 (77.9–99.2)	66.7 (47.2–82.7)
Positive predictive value,[a] %	71.1 (35.7–91.6)	55.2 (41.6–68.0)
Negative predictive value,[a] %	74.0 (66.9–80.0)	89.0 (73.7–95.9)
Positive likelihood ratio	5.00 (1.13–22.18)	2.50 (1.45–4.32)
Negative likelihood ratio	0.71 (0.51–1.00)	0.25 (0.09–0.72)

Values in brackets are 95% confidence intervals.

[a]Calculated for a disease prevalence of 33% in the original prospective cohort study [5].

T2C panel. The fact that the spectrum of detection of T2C is restricted to 5 *Candida* species is an intrinsic limitation of the test. These 5 species account for ≥95% of invasive candidiasis at most centers, but local epidemiology must be taken into account in determining the value of the panel at each hospital [7]. At present, T2C does not detect emerging *Candida auris*, which has been involved in nosocomial outbreaks. A research prototype T2C assay including this species has sensitivity and specificity comparable to those reported for the current panel [14].

In conclusion, T2C may detect at least some cases of noncandidemic IAC. Moreover, combination T2C/BDG testing may be useful in defining the probability of IAC as high (approaching 100%), moderate (~50%), or low (≤10%) based on concordant positive, discordant, and concordant negative results, respectively. Follow-up investigations of T2C in diagnosing IAC and other types of invasive candidiasis using freshly collected samples are needed, as are studies of the impact of T2C- and BDG-guided treatment on patient outcomes, antifungal stewardship, and hospital costs.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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