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Clinical Studies

Diagnosing candidemia with the T2Candida panel: an instructive case of septic shock in which blood cultures were negative

Cornelius J. Clancy [a,b,*], M. Hong Nguyen [a]

[a] University of Pittsburgh, Division of Infectious Diseases, Pittsburgh, PA
[b] VA Pittsburgh Healthcare System, Infectious Diseases Section, Pittsburgh, PA

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ABSTRACT

T2Candida that was positive for *C. albicans*/*C. tropicalis* supported antifungal treatment of a patient with hematogenously disseminated candidiasis and septic shock in whom blood cultures were negative. T2Candida, used and interpreted as a Bayesian biomarker, can identify patients with candidemia who are missed by blood cultures, including those receiving antifungal treatment.

A 27-year-old distant double-lung transplant recipient (cystic fibrosis) developed fever (38.9°C) and leukocytosis (13,000 cells/μL) during hemodialysis using a newly matured arteriovenous fistula (AVF). He had a history of tacrolimus-induced renal failure and line-associated *Enterococcus faecalis* and coagulase-negative *Staphylococcus, Candida glabrata*, and *S. aureus* bloodstream infections (24, 15, 12, and 10 months previously, respectively). He was discharged from hospital 5 days earlier to complete treatment for *Enterobacter cloaceae* bacteremia. A tunneled catheter was removed during hospitalization; ciprofloxacin was administered for 13 of planned 14 days through a peripherally inserted central catheter (PICC). Immunosuppression consisted of cyclosporine and low-dose prednisone. Vancomycin and meropenem were given at hemodialysis and admission, respectively. Shortly after admission, he developed hypotension requiring norepinephrine and respiratory failure necessitating mechanical ventilation. Micafungin was initiated within 2 h; the PICC was discontinued. T2Candida collected concurrently with blood cultures 4 h after micafungin dosing was positive in 4.5 h for *C. albicans*/*C. tropicalis*. The patient defervesced, and he was weaned from norepinephrine and extubated within 72 h. Antibiotics were discontinued. AVF ultrasound was negative. Ophthalmologic exam (hospital day 5) was consistent with *Candida* chorioretinitis. PICC tip and blood cultures (hemodialysis, admission, in-hospital) were negative. Micafungin was switched to fluconazole after 2 weeks to complete 6 weeks of treatment.

Candidemia is associated with mortality rates of 25–40% (Andes et al., 2012). Treatment of candidemia is often delayed because blood culture, the gold standard diagnostic, is <50% sensitive for hematogenously disseminated candidiasis and turnaround time is several days (Clancy and Nguyen, 2013). The T2Candida panel (T2 Biosystems, Lexington, MA) is cleared by the Food and Drug Administration for diagnosing candidemia. T2Candida identifies *Candida* cells directly in whole blood using a self-contained, fully automated instrument that detects amplified, agglomerated ribosomal DNA through T2 magnetic resonance (Clancy et al., 2018; Mylonakis et al., 2015). Results are reported as positive or negative for *C. albicans*/*C. tropicalis*, *C. glabrata*/*C. krusei*, or *C. parapsilosis*, groupings based on typical antifungal susceptibility patterns. The limit of detection is 1–3 CFU/mL, superior to that generally reported for polymerase chain reaction (Avni et al., 2011; Clancy and Nguyen, 2013). Mean time to *Candida* detection and species identification (or negative results) is 4.4 ± 1.0 h (Mylonakis et al., 2015). In prospective multicenter trials, T2Candida sensitivity and specificity for candidemia were 90% and 98%, respectively (Clancy et al., 2018; Mylonakis et al., 2015). T2Candida was significantly more likely to be positive than blood cultures among candidemic patients who were receiving antifungal treatment (50% vs. 21%; $P < 0.0001$).

In using T2Candida, clinicians must understand that the test is a Bayesian biomarker that assigns a probabilty of candidemia rather

* Corresponding author. Tel.: +1-412-648-8510; fax: +1-412-648-8455.
E-mail address: cjc76@pitt.edu. (C.J. Clancy).

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Table 1
Anticipated positive and negative predictive values of T2Candida in different clinical settings.

Prevalence	Representative patient	T2Candida[1] Sens/Spec: 90%/98%		T2Candida[2] Sens/Spec: 90%/90%	
		PPV (95% CI)[3]	NPV (95% CI)[3]	PPV	NPV
0.4%	Any hospitalized patient in whom a blood culture is collected (Mylonakis et al., 2015)	15% (10-27%)	>99.9% (>99.9%)	3%	>99.9%
1%	Patient admitted to intensive care unit (ICU) (Blumberg et al., 2001, Ng et al., 2015) Hemodialysis patient with acute infection (Sychev et al., 2009)	31% (22-48%)	99.9% (99.7->99.9%)	8%	99.9%
2%	Patient with febrile neutropenia, baseline rate of candidemia prior to empiric antifungal treatment (Boogaerts et al., 2001, Walsh et al., 1999, Walsh et al., 2002, Walsh et al., 2004)	47% (37-65%)	99.8% (99.6-99.9%)	16%	99.8%
3%	Patient with septic shock (Leon et al., 2009, Magill et al., 2006, Ng et al., 2015, Ostrosky-Zeichner et al., 2007)	67% (46-74%)	99.7% (99.6-99.8%)	22%	99.6%
5%	Patient with left ventricular assist device and evidence of active infection (Aslam et al., 2010, Shoham et al., 2007)	70% (59-82%)	99.5% (99.3-99.7%)	32%	99.4%
10%	ICU patient at high-risk for candidemia based on clinical prediction models (Ostrosky-Zeichner et al., 2014, Playford et al., 2016, Timsit et al., 2016)	82% (74-91%)	99% (98.6-99.3%)	50%	98.8%

Aslam et al., 2010; Blumberg et al., 2001; Boogaerts et al., 2001; Playford et al., 2016; Shoham et al., 2007; Timsit et al., 2016; Walsh et al., 1999; Walsh et al., 2002; Walsh et al., 2004.
Sens = sensitivity; Spec = specificity; PPV = positive predictive value; NPV = negative predictive value.
[1]T2Candida sensitivity and specificity in the DIRECT studies were 90% and 98%, respectively (Clancy et al., 2018; Mylonakis et al., 2015).
[2]T2Candida sensitivity and specificity of 90% and 90% are shown to highlight how small reductions in specificity would impact the interpretation of test results. Note that PPVs are significantly reduced, whereas NPV reductions are small and clinically irrelevant. PPVs and NPVs within the boxed-off areas signify patients in whom nonculture testing may have greatest clinical utility, assuming that antifungal treatment is justified at a threshold likelihood of invasive candidiasis of ≥~15–30%. For the patients indicated, a positive result is anticipated to move the likelihood of candidemia from below the treatment threshold to above the threshold. At the same time, negative results make candidemia extremely unlikely. The precise borders of the box may vary somewhat depending on where within the 15–30% range the threshold value is set. For example, an assay with 90% sensitivity and 90% specificity may have value in patients in septic shock (anticipated PPV: 22%) or with febrile neutropenia and not receiving an antifungal agent (PPV: 16%). Treatment interventions based on this conceptual framework warrant validation in clinical trials.
[3]95% CI: The 95% confidence intervals for sensitivity and specificity of T2Candida in the DIRECT study were 87–94% and 97–99%, respectively. The 95% CI range shown here was determined using sensitivity/specificity of 87%/97% and 94%/99%.

than a definitive diagnostic (Clancy and Nguyen, 2014, 2016). Positive and negative predictive values (PPVs, NPVs) are determined by sensitivity and specificity, and the pretest likelihood of candidemia. The likelihood of candidemia in patients with signs of infection can be estimated from published data, and anticipated PPVs and NPVs can be calculated (Table 1). These estimates can be adjusted based on local epidemiology and clinical information and as new data become available (Table 2).

Our patient was admitted with an infection during hemodialysis, which carries an ~1% risk of candidemia (Sychev et al., 2009). Since bacteria were the most likely pathogens, he was treated with broad-spectrum antibacterials. When he developed septic shock, micafungin was administered immediately. These decisions were reasonable since candidemia typically accounts for 3–10% of septic shock, (Leon et al., 2009; Magill et al., 2006; Ng et al., 2015; Ostrosky-Zeichner et al., 2007) and each hour delay in instituting an active antimicrobial reduces survival in both septic shock and candidemia (Rhodes et al., 2017). Ideally, T2Candida would have been collected prior to giving micafungin. However, testing after antifungal dosing retains value because T2Candida positivity is significantly less likely to be impacted by treatment than are blood culture results (Clancy et al., 2018). Assuming ~3% pretest likelihood, the anticipated PPV in our patient was 67%. Therefore, the result supported antifungal treatment and PICC removal even as blood cultures remained negative. Mycoses Study Group prediction criteria were fulfilled subsequently, which further increased the probability of candidemia (Ostrosky-Zeichner et al., 2014). The finding of chorioretinitis confirmed a diagnosis of deep-seated infection due to hematogenously disseminated candidiasis and justified both the switch from micafungin to fluconazole based on pharmacokinetics and a 4–6-week treatment course (Kauffman, 2015).

T2Candida PPVs increase dramatically with small increases in pretest likelihoods of candidemia (Table 1). In contrast, anticipated NPVs remain exceptional (≥99%) in most settings in which the test will be employed. How, then, is T2Candida most likely to be useful in clinical practice? This question is difficult to answer because the threshold probability of candidemia that justifies antifungal treatment is not known. Numerous studies suggest that antifungal prophylaxis is beneficial if the baseline rate of invasive fungal infection is ≥15–30% (Clancy and Nguyen, 2014, 2016). Therefore, the PPV to trigger empiric treatment of candidemia is likely to fall within this range. T2Candida is not expected to be valuable if collected each time a blood culture is ordered because the anticipated PPV is unlikely to support routine antifungal treatment and a negative result will not appreciably lessen the probability of candidemia. However, in individuals at greater risk for candidemia, such as our patient with septic shock, a positive result increases disease likelihood above the putative treatment threshold, while a negative result virtually excludes the diagnosis. By these criteria, T2Candida may have been useful when our patient was febrile during hemodialysis, as the anticipated PPV was ~30%. Patient populations in which T2Candida should have greatest clinical utility are boxed-off in Table 1. The table highlights how a slight decrease in specificity, from 98% to 90%, would reduce PPVs such that testing is less broadly useful. Of course, clinicians must know their local epidemiology. Species in the T2Candida panel account for >95% of candidemia (Pfaller et al., 2011), but microbiology can differ by center (Jung et al., 2015).

Table 2
Changing likelihoods of candidemia in our case based on clinical events and new data.

Clinical events and data	Likelihood of candidemia	Clinical decision and rationale
Fever, leukocytosis, hemodialysis, PICC, broad-spectrum antibiotic, immunosuppression, past history of candidemia	~1%	An antifungal agent was not administered during hemodialysis or upon admission. The likelihood of candidemia in a hemodialysis patient with an infection is only ~1% (Sychev et al., 2009). The probability of candidemia in this patient likely was a bit higher due to other risk factors for candidemia such as presence of a PICC, current receipt of a broad-spectrum antibiotic, immunosuppression, and history of *C. glabrata* bloodstream infection. Nevertheless, the decision to withhold antifungal treatment was reasonable given the low relative risk of candidemia and the institution of appropriate antibiotic treatment with vancomycin and meropenem.
Septic shock, intensive care unit (ICU) patient	~3%	The likelihood of candidemia in patients with septic shock is 3–10% based on published data (Leon et al., 2009; Magill et al., 2006; Ng et al., 2015; Ostrosky-Zeichner et al., 2007). The prompt administration of an active antimicrobial agent is a crucial determinant of survival; each hour delay in initiating antimicrobial treatment is associated an increase in mortality (Rhodes et al., 2017). In this case, the health care team considered 2 options. One option was to give an antifungal agent and use positive or negative T2Candida results to guide a subsequent decision to continue or discontinue treatment, respectively. The alternative was to perform T2Candida testing and initiate antifungal treatment in response to a positive result. The PPVs, NPVs, and rapid turnaround time of T2Candida made these options feasible. The team opted for the first option.
T2Candida positive in patient with septic shock	~67%	The sensitivity and specificity of T2Candida for candidemia are 90% and 98%, respectively, based on data from the DIRECT clinical trials. Given these values, the anticipated PPV assuming a 3% likelihood of candidemia in an ICU resident with septic shock is 67%. T2Candida is significantly more likely to remain positive for *Candida* than blood culture in patients with candidemia who are receiving antifungal therapy, as in this case. Therefore, the data supported the decision to start micafungin.
T2Candida positive and fulfillment of clinical prediction criteria for candidemia in ICU	~80%	On hospital day 3, the patient fulfilled criteria of the Mycoses Study Group clinical prediction model, which assigns an ~10% probability of invasive *Candida* infection (Ostrosky-Zeichner et al., 2014). In this setting, the anticipated PPV of T2Candida would be ~80%.
Ophthalmologic exam consistent with *Candida* chorioretinitis	Approaching 100%	Ophthalmologic exam on hospital day 5 revealed discrete, focal, white, heaped-up retinal lesions, consistent with chorioretinitis. The retina was easily visualized, and there was no evidence of vitreal involvement. These findings are highly specific for *Candida* endopthalmitis in a setting of probable candidemia. The diagnosis of candidemia is further supported by the constellation of a positive T2Candida result, resolution of shock after institution of antifungal treatment, and the lack of an alternative diagnosis since repeated blood cultures were negative for bacteria. Fluconazole achieves more reliable penetration than echinocandins into the eye.

Our discussion provides a conceptual framework for interpreting T2Candida results and using the test rationally in clinical decision making. Studies are needed to validate these concepts, define T2Candida performance in routine practice, and demonstrate that testing can improve patients' outcomes and reduce inappropriate antifungal usage. Our case highlights how T2Candida can identify at least some candidemia cases that are missed by blood cultures, and guide early treatment. T2Candida may be particularly useful in targeting antifungal treatment to patients with septic shock who also have other risk factors for candidemia. To fully realize the benefits of T2Candida, clinicians will need to practice as Bayesians and make decisions based on the probability of candidemia.

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