REVIEW ARTICLE

Finding the "Missing 50%" of Invasive Candidiasis: How Nonculture Diagnostics Will Improve Understanding of Disease Spectrum and Transform Patient Care

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Blood cultures are limited for diagnosing invasive candidiasis by poor sensitivity and slow turn-around time. New diagnostics are needed to complement cultures, in particular to identify the "missing 50%" of patients who are blood culture-negative. Mannan/anti-mannan immunoglobulin G, β-D-glucan (BDG) and polymerase chain reaction (PCR) assays can diagnose candidemia before blood cultures and show promising sensitivity/specificity, but they are not widely investigated in blood culture–negative, deep-seated candidiasis. In a recent study, BDG and PCR were superior to blood cultures in deep-seated candidiasis, suggesting they may identify currently undiagnosed patients and expand our understanding of disease spectrum. Positive predictive values of nonculture tests are limited by the low prevalence of invasive candidiasis, which mandates that results be interpreted judiciously. When used as biomarkers that assess a patient's risk of having invasive candidiasis, tests will facilitate preemptive antifungal strategies. Because negative predictive values are excellent, tests will also be useful for ruling out invasive candidiasis and discontinuing unnecessary antifungal therapy.

Keywords. invasive candidiasis; candidemia; diagnostic; PCR; β-D-glucan.

Mortality among patients with candidemia and other invasive *Candida* infections is as high as 40% despite antifungal therapy [1]. The poor outcomes stem, at least in part, from the inadequate sensitivity of blood and sterile-site cultures, the current diagnostic gold standards. Improved diagnostic tests for invasive candidiasis are among the most pressing needs in infectious diseases [2]. In this article, we review the performance of cultures and nonculture diagnostics for invasive candidiasis, and consider the impact of the latter on our understanding of disease spectrum and patient care.

WHAT ARE WE TRYING TO DIAGNOSE?

Invasive candidiasis encompasses candidemia and deep-seated candidiasis (infections of tissue sites beneath mucosal surfaces). Deep-seated candidiasis may stem from hematogenous dissemination or direct introduction of *Candida* to a sterile site. Deep-seated infections may remain localized, spread to contiguous sites, or lead to secondary candidemia. In diagnosing invasive candidiasis, therefore, there are 3 entities that must be considered: (1) candidemia in the absence of deep-seated candidiasis; (2) candidemia associated with deep-seated candidiasis; and (3) deep-seated candidiasis that is not associated with candidemia (Figure 1). Animal models show that deep-seated infections in group 2 generally persist after clearance of *Candida* from the bloodstream [3].

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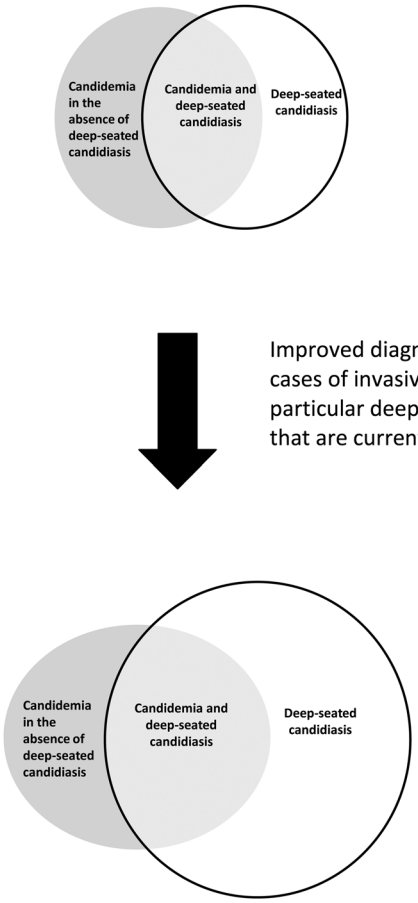

Figure 1. Impact of nonculture diagnostics on identifying different types of invasive candidiasis. The 3 entities that must be considered when diagnosing invasive candidiasis are shown from left to right in the Venn diagrams. At present, data suggest that the 3 groups are roughly similar in size (top Venn diagram). A reasonable estimate from the literature is that blood cultures are approximately 50% sensitive in diagnosing invasive candidiasis, missing roughly half of the deep-seated candidiasis in the second group and all cases in the third group. Moving from left to right across the groups, the relative impact of nonculture diagnostics on identifying previously unrecognized invasive candidiasis is increased. Nonculture diagnostics, for the most part, will identify new cases of deep-seated candidiasis (bottom Venn diagram), primarily by detecting *Candida* nucleic acid and cellular components that persist in the blood or that are released from deep tissue sites. By identifying previously unrecognized infections, nonculture diagnostics will improve our understanding of the clinical spectrum of invasive candidiasis.

A recent study suggests that approximately one-third of patients with invasive candidiasis fall into each group [4]. In keeping with these findings, older data indicate that roughly half of patients with candidemia do not have deep-seated infections [5]. Unfortunately, clinicians are unable to reliably identify candidemic patients who may develop deep-seated complications or suffer poor outcomes [6]. Given these considerations, an ideal diagnostic test for invasive candidiasis should fulfill the criteria in Table 1.

Table 1. Characteristics of an Ideal Diagnostic Test for Invasive Candidiasis

Test performance
Minimally invasive (eg, blood test rather than test of a deep tissue sample)
Requires low volume samples
Rapid turn-around time
Requires minimal labor and fits within the normal flow of activities in clinical microbiology laboratories
Sensitive and specific
Provides speciation and antifungal susceptibility data
Multiplex capabilities
Testing goals
Identify patients early in the course of invasive candidiasis
Identify patients with candidemia who have deep-seated candidiasis
Identify patients with candidemia who are likely to develop deep-seated candidiasis
Identify patients with deep-seated candidiasis but negative blood cultures
Provide prognostic information (eg, identify patients who are likely to have poor outcomes or fail antifungal therapy)

HOW BAD ARE CULTURES?

In fact, blood cultures are sensitive at detecting viable *Candida* cells. The median *Candida* concentration within a first positive blood culture is 1 colony-forming unit (CFU)/mL [7]; 26%–65% of positive blood cultures have <1 CFU/mL [7, 8]. Indeed, the limit of detection for blood cultures is comparable to methods such as polymerase chain reaction (PCR) [7]. A concentration of 1 CFU/mL corresponds to approximately 5.6×10^3 CFU in the blood volume of a typical adult, but a 10-mL culture captures only 0.2% of the systemic circulation. As such, negative blood cultures may reflect the absence of viable *Candida* within the circulation, concentrations of viable *Candida* that are insufficient to be detected within a collected sample, or intermittent or transient release of viable cells into the bloodstream.

In studies of autopsy-proven invasive candidiasis, the sensitivity of antemortem blood cultures ranged from 21% to 71% (Table 2). The sensitivity among all patients in these studies was 38% (156/415). These data come with important caveats. Most notably, the studies were largely comprised of patients with deep-seated infections that were likely to result from hematogenous seeding (group 2 above). Patients who had positive antemortem blood cultures but no evidence of organ infections on autopsy were not included (group 1). By including

Table 2. Performance of Blood Cultures in Autopsy Studies of Invasive Candidiasis

Reference	Year	No. of Patients	Underlying Disease	Sensitivity
Louria (from [13])	1962	19	Hematologic malignancies, solid tumors, medical and surgical conditions	42%
Bodey (from [13])	1966	61	Acute leukemia	25%
Taschdjian (from [13])	1969	17	Malignancies and other medical conditions	47%
Hart (from [13])	1969	16	Hematologic malignancies, solid tumors, transplant, medical and surgical conditions	44%
Bernhardt (from [13])	1972	14	Transplant and surgical conditions	36%
Gaines (from [13])	1973	26	Hematologic malignancies, solid tumors, medical and surgical conditions	54%
Myerowitz (from [13])	1977	39	Hematologic malignancies, solid tumors, medical and surgical conditions	44%
Ness [9]	1989	7	Hematologic malignancies and bone marrow transplant recipients	71%
Singer [37]	1977	16	Hematologic malignancies	31%
Berenguer [13]	1993	37	Mostly hematologic malignancies and solid tumors	43%
Van Burik [38]	1998	62	Bone marrow transplant recipients	52%
Kami [39]	2002	91	Hematologic malignancies	21%
Thorn [40]	2010	10	Hematologic malignancies, gastrointestinal disease, transplant, prematurity	50%

such patients, the sensitivity of blood cultures in cases associated at some point with candidemia increases to 63%–83% [9]. Furthermore, only 1 study assessed a standardized blood culture collection strategy. In this study, daily blood cultures and additional sets during febrile episodes among patients with hematologic malignancies were 71% sensitive [9]. Therefore, it is reasonable to conclude that blood cultures identify a majority of patients with candidemia. Within this cohort, they perform less well among the subgroup with deep-seated infections, who may be cultured after *Candida* is cleared from the bloodstream. Of course, blood cultures will not diagnose deep-seated candidiasis that is not associated with candidemia (group 3). If blood cultures identify approximately 75% of patients in groups 1 and 2, the overall sensitivity for invasive candidiasis may be estimated as approximately 50%. Nonculture diagnostics may identify cases that are missed by blood cultures by detecting components of *Candida* cells that are remnants of prior candidemia or released from infected tissue sites.

The sensitivity of blood cultures is limited by the fact that viable *Candida* cells are rapidly eliminated from the circulation [3]. The mechanism of pathogenesis and *Candida* species also impact sensitivity. Candidemia is believed to result most commonly from translocation across the gastrointestinal mucosa into the vasculature, or from direct inoculation via intravascular catheters. Central venous catheter–related candidemia is associated with higher organism burdens than candidemia stemming from extravascular sources [8, 10]. *Candida* cells translocating across the gastrointestinal mucosa are immediately transported to the liver, which is an efficient microbial filter. *Candida parapsilosis*, which often causes line-associated candidemia in neonates, is associated with higher burdens than *Candida albicans* [7]. *Candida glabrata* candidemia, which has been linked to gastrointestinal portals of entry [11], typically presents with lower burdens [7, 10].

Even if blood cultures recover *Candida* species, they have other shortcomings. The median time to positivity is 2–3 days, and can take as long as 8 days [7, 9]. *Candida glabrata* and *C. parapsilosis* candidemia are often associated with longer and shorter times to positivity than *C. albicans*, respectively, in keeping with typical bloodstream concentrations [7, 10]. As described below, blood cultures may take up to 4 weeks longer than nonculture tests to diagnose invasive candidiasis. These considerations are important because delays in antifungal therapy are associated with poor outcomes [12]. Finally, cultures do not provide meaningful quantitative data, as burdens within initial positive samples do not correlate with patient outcomes [7, 10, 13].

The gold-standard tests for deep-seated candidiasis are sterilely collected cultures of infected tissues. Unfortunately, the sensitivity of deep-seated cultures is limited in its own right, which may reflect challenges in identifying optimal sampling sites or uneven distributions/low burdens of viable organisms. In a study of hepatic candidiasis, for example, the sensitivity of biopsy cultures was only 42%, including 30% and 61% in the presence and absence of antifungal therapy, respectively [14]. Moreover, collecting samples from deep-seated sites requires surgery or other invasive procedures, which carry significant risks and are often precluded by underlying medical conditions.

Table 3. Potential Advantages and Disadvantages of Nonculture Diagnostic Tests

Potential Advantages	Potential Disadvantages
Rapid turn-around time	Do not recover organisms
Not dependent on viable organisms[a]	May not speciate *Candida* or distinguish between fungi
May be positive prior to cultures, and stay positive during antifungal therapy[a]	Narrow-spectrum (may detect only *Candida* among multiple pathogens)
May offer quantitative data with prognostic significance	May need to be run in batch by clinical microbiology laboratory due to limited number of samples
Multicopy targets and amplification may improve sensitivity	May have low threshold for contamination
May be coupled with detection of markers for drug resistance or other relevant phenotypes	Financial costs to patients and clinical microbiology laboratory

[a] These are listed as potential advantages, but depending on circumstances, they may also be liabilities. For example, not being dependent upon viable *Candida* may allow nonculture tests to identify deep-seated infections if nucleic acids or cellular components are released into the circulation, as demonstrated for polymerase chain reaction in rabbit models of invasive candidiasis [26, 27]. At the same time, nonculture diagnostics may detect dead organisms or remnants of old infections. In these cases, a positive test may not signify an active disease. Similarly, the ability to follow the kinetics of a nonculture assay may allow clinicians to gauge responses to therapy or determine prognosis. However, persistence of positivity may confound interpretations if kinetics are not linked to outcomes, and may limit the subsequent ability to diagnose recurrent or relapsing infections.

HOW GOOD ARE NONCULTURE DIAGNOSTICS?

Although nonculture diagnostics offer potential advantages over cultures, they also have relative weaknesses (Table 3). The great strengths of cultures are that they recover the infecting organism, which permits assessments of phenotypes such as drug susceptibility, and they detect multiple pathogens. In the end, nonculture tests will complement rather than replace cultures.

Antigen and Antibody Detection

There is a long history of serum *Candida* antigen and antibody detection assays. In general, the former are limited by rapid clearance from the bloodstream [15]. Although concerns about the impact of immunosuppression on antibody detection are common, a number of studies indicate that these assays perform well in patients with neutropenia and cell-mediated immune defects (including bone marrow and solid organ transplant recipients) [15, 16]. Interestingly, serum immunoglobulin G (IgG) responses against specific antigens have generally performed better than IgM, suggesting that many patients mount amnestic responses or have ongoing, subclinical tissue invasion [16]. Patients infected with non–*C. albicans* species can be identified by responses against recombinant *C. albicans* antigens [16].

The best results have been obtained with a combined mannan/anti-mannan antibody assay (Platelia, Bio-Rad). In a meta-analysis of 14 studies, the sensitivity and specificity of mannan and anti-mannan IgG were 58% and 93% and 59% and 83%, respectively. Values for the combined assay were 83% and 86%, with best performances for *C. albicans*, *C. glabrata*, and *Candida tropicalis* infections [17]. In one study of candidemia, at least 1 test was positive before blood culture in 73% of patients (median for mannan and anti-mannan IgG: 6 and 7 days, respectively) [18]. Early diagnoses of candidemia were corroborated in other studies [17]. In a study of hepatosplenic candidiasis, at least 1 test was positive before radiographic changes in 86% of patients [19].

β-D-Glucan Detection

β-D-glucan (BDG) is a cell wall constituent of *Candida* species and other fungi. Several detection assays have been developed that are based upon activation of the coagulation cascade by BDG. They differ in methods of measurement and definitions of positivity; there are no conclusive data about performance differences. The Fungitell assay (Associates of Cape Cod) is available in the United States.

The sensitivity and specificity of serum BDG testing for diagnosing invasive candidiasis have ranged from 57% to 97% and 56% to 93%, respectively. In a recent meta-analysis of 11 studies, sensitivity was 75% [20]. Optimal results are achieved if 2 consecutive tests are positive [21]. The major uncertainties for BDG detection are specificity and false-positivity, particularly among high-risk populations. False-positive results are rare in healthy controls, but common in patients with gram-positive and gram-negative bacteremia and intensive care unit (ICU) residents [22]. Specificity and positive predictive value were extremely poor in a study of lung transplant recipients, particularly those with respiratory mold colonization or undergoing hemodialysis [23]. Several other causes of false-positivity have been identified (Table 4). True-positive results are not specific for invasive candidiasis, as the test detects BDG from other pathogenic fungi.

BDG kinetics within the circulation are poorly understood, but there are reports of positivity prior to positive blood cultures and in antemortem samples from patients with autopsy-proven disease and negative blood cultures [24]. A negative slope for serial BDG levels was associated with successful echinocandin

Table 4. Causes of False-positive β-D-Glucan Results for Invasive Candidiasis

False-positive Results	Fungi That Yield Positive β-D-Glucan Results
Human blood products (albumin, immunoglobulin, coagulation factors, plasma protein fractions)	Yeasts: *Candida* spp, *Trichosporon* spp, *Saccharomyces cerevisiae*
[a]Hemodialysis	Molds: *Acremonium*, *Aspergillus* spp, *Fusarium* spp
Surgical gauze or other materials containing glucan	Dimorphic fungi: *Coccidioides immitis*, *Histoplasma capsulatum*, *Sporothrix schenckii*
Antibiotics such as piperacillin-tazobactam and ampicillin-clavulanate	Others: *Pneumocystis jiroveci*
Systemic bacterial infections	
Excess manipulation of sample	
Severe mucositis	

Source: Adapted from Wheat [22].

[a] Initial reports ascribed false-positive results to cellulose membranes, but more recent studies have described associations with hemodialysis in the absence of such membranes [21, 23]. The etiology of false-positive β-D-glucan results among patients undergoing hemodialysis remains uncertain.

therapy in one study, but sensitivity and specificity were only 62% and 61%, respectively, and correlations were not evident among patients with deep-seated candidiasis [25]. The impact of antifungal therapy on test performance is unclear.

Polymerase Chain Reaction

Polymerase chain reaction fulfills many of the criteria in Tables 1 and 3. In rabbit models of disseminated candidiasis, cell-free *C. albicans* DNA was released into the bloodstream from target organs, and PCR remained positive after sterilization of blood cultures [26, 27]. PCR clinical studies are limited by a lack of methodologic standardization and multicenter validation. Investigators have used different detection platforms, blood fractions, and gene targets. Nevertheless, in a recent meta-analysis, the pooled sensitivity and specificity of PCR for suspected invasive candidiasis were 95% and 92%, respectively [28]. In probable invasive candidiasis, sensitivity of PCR and blood cultures was 85% and 38%, respectively. Data among patients colonized with *Candida* were surprisingly limited, but there was a trend toward lower specificity.

Clinicians have used PCR to initiate *Candida* species–specific antifungal therapy as early as 6 hours after the onset of sepsis [29]. In several studies, PCR results preceded positive blood cultures by 1 day to 4 weeks [28]. In one of these studies, PCR-directed therapy was initiated a median of 3 days (range, 0–8 days) before the diagnosis of candidemia. PCR may have prognostic value, as persistently positive results were associated with death in 5 studies [28].

In Europe, a whole-blood, multiplex real-time PCR assay that detects 19 bacteria and 6 fungi (*C. albicans*, *C. glabrata*, *C. parapsilosis*, *C. tropicalis*, *Candida krusei*, and *Aspergillus fumigatus*) has been investigated in sepsis and neutropenic fever (SeptiFast, Roche). Among patients with candidemia, the sensitivity of the test was 94%; the only negative result was observed with *Candida famata* candidemia [30].

FINDING THE "MISSING 50%": DIAGNOSING BLOOD CULTURE–NEGATIVE INVASIVE CANDIDIASIS

The overwhelming majority of patients in diagnostic studies have had candidemia. As such, there are limited data about test performances among the so-called "missing 50%"—that is, patients with invasive candidiasis who are not diagnosed by blood cultures. In a recent study of prospectively enrolled patients with candidemia, deep-seated candidiasis but negative blood cultures, or both deep-seated candidiasis and candidemia [31], the sensitivity of a real-time quantitative PCR assay (ViraCor-IBT) was superior to Fungitell BDG (Figure 2). In 24 patients with deep-seated candidiasis, samples were collected at the same time for cultures, BDG, and PCR. The respective sensitivities were 17%, 62%, and 88% ($P = .005$ and .003 for blood cultures vs BDG and PCR, respectively). The combination of blood culture and BDG or PCR had sensitivity of 79% and 98%, respectively. The data suggest that BDG and, in particular, PCR may be useful adjuncts to blood cultures, and identify some patients who are currently undiagnosed.

The specificity of BDG and PCR was 73% and 70%, respectively, which may have been impacted by a high-risk control group largely comprised of patients with mucosal candidiasis or colonized with *Candida* species. Indeed, it is plausible that some controls had unrecognized invasive candidiasis, as many were immunosuppressed, in ICUs, and had signs and symptoms of infection but negative cultures. Therefore, the study highlights the central challenge in assessing diagnostics for invasive candidiasis: How do you evaluate performance when the gold standard is inadequate? Specifically, it may be impossible to know if positive results despite negative blood cultures are false-positives or true-positives that are missed by blood cultures.

IMPACT OF NONCULTURE DIAGNOSTICS ON UNDERSTANDING THE CLINICAL SPECTRUM OF INVASIVE CANDIDIASIS

By identifying invasive candidiasis that is currently missed, nonculture diagnostics will expand our understanding of

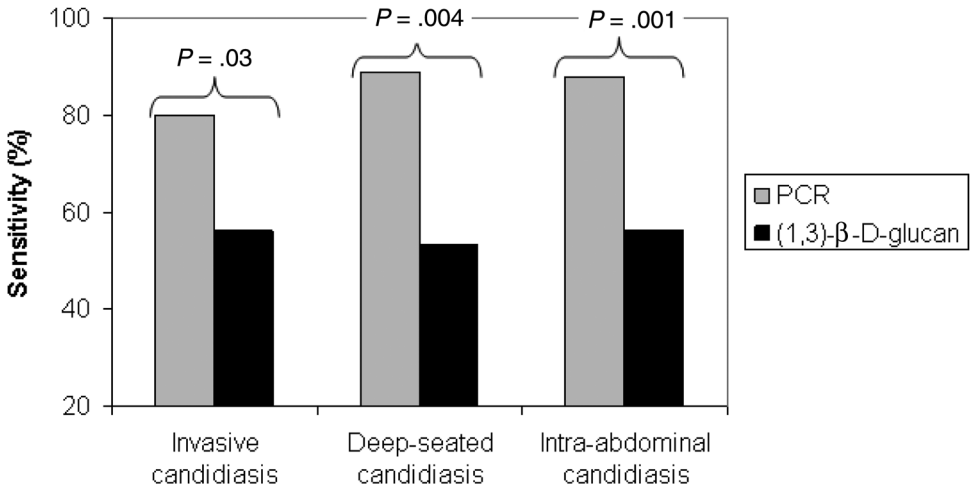

Figure 2. Sensitivity of serum polymerase chain reaction (PCR) and β-D-glucan (BDG) in diagnosing invasive candidiasis. PCR was superior to BDG, particularly among patients with deep-seated candidiasis. Overall, 55 patients with invasive candidiasis were enrolled. At the time of enrollment, 60% (33/55) of patients had deep-seated candidiasis in the absence of positive blood cultures (corresponding to group 3 in Figure 1). Thirty-one percent (17/55) had candidemia without evidence of deep-seated candidiasis (group 1), and 9% (5/55) had both candidemia and deep-seated candidiasis (group 2). Eighty-nine percent (34/38) of deep-seated candidiasis was intra-abdominal infections. Data shown for deep-seated and intra-abdominal candidiasis include patients with and without positive blood cultures. Results for deep-seated candidiasis without positive blood cultures did not differ from the data in the graph. (Adapted from [31].) Abbreviation: PCR, polymerase chain reaction.

disease spectrum. The major impact will come from diagnosing previously unrecognized deep-seated candidiasis. Careful consideration of the literature suggests that most candidemia is already diagnosed by blood cultures, and methods such as PCR are not likely to offer significantly lower thresholds of detection [7, 31]. Furthermore, the clinical manifestations of candidemia have been studied extensively. At present, deep-seated candidiasis is missed if patients were never candidemic or candidemia has cleared, and if infected tissue sites are falsely negative or invasive sampling procedures are contraindicated. The potential impact of blood-based, nonculture diagnostics is highlighted by the BDG and PCR study above, in which 60% of patients had deep-seated candidiasis in the absence of positive blood cultures. In a follow-up, observational study from the same center, intra-abdominal candidiasis was more common than candidemia and accounted for the majority of invasive disease [32]. The distribution of invasive candidiasis may vary across centers, depending on factors such as antifungal usage and volumes of gastrointestinal surgery, transplantation, and ICU care. Nevertheless, the data suggest that as nonculture tests are widely utilized, more cases of deep-seated candidiasis will be recognized. As a result, clinical descriptions of invasive candidiasis will be less skewed toward candidemia, and we are likely to learn that the "missing 50%" is larger than believed (Figure 1).

IMPACT ON PATIENT CARE

Despite the promise of nonculture diagnostics, they are not ready to be introduced into routine clinical practice. Indeed, the tests share a number of uncertainties that must be resolved prior to widespread use. Furthermore, there are specific questions about each test (Table 5).

The clinical utility of nonculture diagnostics will be shaped by the low prevalence of invasive candidiasis. In a typical ICU in which the pretest likelihood of invasive candidiasis is 3% [33], for example, the positive predictive value (PPV) and negative predictive value (NPV) for a test with sensitivity of 80% and specificity of 70% would be 8% and 99%, respectively. Increasing the pretest likelihood to 10%, as with the use of prediction models that consider risk factors for invasive candidiasis [33], only improves PPV to 23% whereas the NPV remains 97%. The low PPV limits these tests as definitive diagnostics, and mandates that they be interpreted judiciously. Along these lines, it is important to consider assays such as PCR and BDG as detection tests. They may detect the presence of *Candida*, but the diagnosis of invasive candidiasis requires that clinicians consider more than just the test result.

In fact, nonculture tests might be best viewed as biomarkers that assess a patient's risk of having invasive candidiasis. Incorporated into prediction models or other risk-assessment

Table 5. Issues to be Resolved for Nonculture Diagnostics Prior to Widespread Use

	Unresolved Issues for Specific Tests		
Unresolved Issues for All Tests	Mannan/Antimannan	β-D-Glucan	Polymerase Chain Reaction
How do tests perform in blood culture–negative cases?	How does the assay perform for infections caused by various *Candida* spp?	What is the specificity, and what are the positive predictive values (especially in high-risk populations)?	Will a standardized assay be developed?
How do tests perform in deep-seated candidiasis?	What is the impact of immunosuppression on performance?	What is the impact of β-D-glucan synthesis inhibition by echinocandins on performance?	Will an assay be validated in multicenter studies?
How do tests perform in specific patient populations?	What is the timeline of immunoglobulin G responses during the pathogenesis of invasive candidiasis? (Do some patients have ongoing, subclinical invasive disease?)		
What is the impact of antifungal therapy on performance?			
What is the impact of colonization, mucosal candidiasis, or prior invasive candidiasis on performance?			
What are the kinetics of the tests, and do baseline values or changes over time have prognostic value?			
How should tests be incorporated into patient management strategies?			
How do the tests perform in samples other than blood/serum?			

strategies, a positive *Candida* biomarker could be used to identify high-risk patients for preemptive antifungal therapy [21]. At present, many ICUs employ prophylactic or empiric antifungal strategies. In the former approach, all patients receive antifungal therapy. In the latter, antifungal therapy is initiated in patients who develop suggestive clinical findings. Prophylaxis can reduce fungal infections and mortality [34], but may impact institutional ecology and antifungal resistance. Moreover, cost-efficacy mandates more targeted approaches. Empiric strategies have not been validated [35]. The potential utility of preemptive strategies employing nonculture tests as biomarkers can be illustrated by considering the typical ICU in the previous paragraph. Antifungal prophylaxis for all ICU residents would benefit 1 of every 33 patients, whereas prophylaxis based on a prediction model assigning 10% pretest likelihood would benefit 1 of 10 patients. A preemptive strategy targeting patients identified by the prediction model and a positive biomarker would assign 23% pretest likelihood and benefit 1 of 4 patients. Indeed, a single-center study of BDG surveillance among high-risk ICU patients reported a PPV of 30% for invasive candidiasis, and found preemptive anidulafungin to be safe and associated with good outcomes [21]. Further studies are needed to validate biomarker-driven preemptive strategies. The feasibility of these approaches will require convincing clinicians to restrict antifungal usage among patients who do not fulfill the preemptive criteria [21], which may be challenging in certain ICUs.

An alternative approach is to use the excellent NPVs of nonculture tests to rule out invasive candidiasis and justify stopping unnecessary prophylactic or empiric antifungal therapy. Biomarker-driven antimicrobial discontinuation has been validated in studies of ICU patients with ventilator-associated pneumonia, in which procalcitonin results were used to reduce antibiotic consumption without adversely impacting outcomes [36]. The success of discontinuation protocols will depend upon educating clinicians so that they are comfortable stopping antifungal therapy, once started. The difficulty of this task is highlighted by the preemptive study mentioned in the previous paragraph, in which 21% of patients received anidulafungin despite repeatedly negative BCG results [21]. A practical limitation to biomarker-driven strategies at many centers will be the need for on-site testing on a regular basis, particularly if assays are labor intensive [21].

CONCLUSIONS

We now have a broad armamentarium of antifungals with good anti-*Candida* activity [2]. In the future, better outcomes for invasive candidiasis are less likely to result from new drugs than from early intervention strategies that incorporate nonculture tests as biomarkers. In this regard, we stand at the cusp of a new era, in which nonculture tests will transform patient care. Moving forward, the most important consideration in designing diagnostic studies will be the increased inclusion of patients with blood culture–negative, deep-seated candidiasis. Data from carefully designed, inclusive studies will improve our understanding of disease spectrum.

Note

Potential conflicts of interest. C. J. C. is a site principal investigator for a multicenter trial of the T2 Candida Bioassay for candidemia (T2 Biosystems; ClinicalTrials.gov identifier: NCT01525095). M. H. N. received investigator-initiated research funding from ViraCor-IBT Laboratories for the BDG/PCR study cited in this paper [31].

Both authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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