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Review Article

Emerging Role of PCR-based surveillance in the Diagnosis of invasive candidiasis

Colombo G^{1*}, Romano A² and Ricci F³

¹Department of Epidemiology, Congo Center for Vaccinology, Spain

²Department of Infectious Diseases, Parana Academy of Vaccinology, Greece

³Division of Clinical Microbiology, Ebro Center for Clinical Microbiology, Spain

*Address for Correspondence: Giulia Colombo, Department of Epidemiology, Congo Center for Vaccinology, Spain; E-mail: giulia.colombo@congo.edu

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Abstract

Background: Blood culture, the reference standard for invasive candidiasis, takes two to three days to turn positive and misses roughly half of patients with deep-seated disease, a delay tied to the disease's high attributable mortality [1,2].

Objective: This review synthesizes the accuracy of PCR-based detection of Candida DNA in blood relative to blood culture, beta-D-glucan, and the T2Candida panel, and its role in specific high-risk populations.

Methods: We reviewed meta-analyses and comparative diagnostic-accuracy studies of Candida PCR, beta-D-glucan, and T2Candida, together with population-specific studies and current IDSA and ESCMID guideline positions.

Findings: Pooled PCR sensitivity reaches approximately 95% with specificity around 92% [10], comparing favorably with beta-D-glucan (77-80% sensitivity) [15,16] and complementing T2Candida, which returns a result in 4.4 hours against more than two days for culture [18]; combined PCR/beta-D-glucan strategies outperform either alone in neonatal and intra-abdominal cohorts [12,22].

Conclusions: PCR-based surveillance offers a substantial sensitivity and turnaround advantage over blood culture and is best deployed alongside beta-D-glucan or T2Candida; the principal barrier to guideline endorsement remains assay standardization rather than accuracy [24,25].

Keywords: invasive candidiasis; polymerase chain reaction; beta-D-glucan; T2Candida; candidemia

1. Introduction

Invasive candidiasis kills a substantial fraction of the patients who develop it even when treatment starts promptly, and the biggest reason is not a shortage of effective antifungal drugs but a shortage of time: blood culture, still the reference standard in most hospitals, takes on average two to three days to turn positive and misses roughly half of patients with autopsy-proven deep-seated disease [1,2]. *Candida* species are among the leading causes of healthcare-associated bloodstream infection in the United States and much of Europe, and epidemiologic surveys of critically ill, non-immunosuppressed patients have shown that candidemia in the ICU carries mortality comparable to severe bacterial sepsis despite occurring in patients without the classic host-defense defects long assumed to be a prerequisite for invasive fungal disease [3]. The population at risk disproportionately includes patients with long indwelling catheters, recipients of broad-spectrum antibiotics, and transplant recipients whose blunted immune response obscures the fever and hemodynamic signals clinicians rely on to trigger empiric therapy [4,5]. Each additional day of inappropriate or absent antifungal therapy after candidemia onset has been repeatedly associated with rising attributable mortality: delaying empiric treatment until blood culture returns positive is an independent risk factor for hospital death [6], and among patients with septic shock attributed to *Candida* infection, both the timing of effective antifungal therapy and adequate source control independently predicted survival [7]. Empiric strategies built around clinical prediction rules and colonization indices, useful as they are, still miss patients who progress to invasive disease while treating many who never would have [8,9].

That mismatch between the patient's clock and blood culture's clock has pushed non-culture diagnostics, and nucleic acid amplification specifically, to the center of research effort over the past two decades. PCR assays that

detect *Candida* DNA directly in whole blood, serum, or plasma do not require the organism to grow to a countable density before signaling a result, so in principle they return an answer in hours rather than days and detect organisms at densities blood culture bottles routinely miss [10,11]. This review synthesizes the accuracy data from meta-analyses of blood PCR, comparative studies against blood culture and beta-D-glucan, population-specific evidence from neonatal and intra-abdominal candidiasis cohorts, the T2Candida nanodiagnostic panel, and current IDSA and ESCMID guideline positions, before turning to the barriers that have kept PCR out of most clinical laboratories despite two decades of encouraging data.

2. The diagnostic gap non-culture methods address

Blood culture's central weakness is sensitivity, not specificity. Autopsy and clinical correlation studies have long shown that patients with histologically confirmed deep-organ candidiasis, particularly hepatosplenic and other intra-abdominal disease, often never generate a positive peripheral blood culture, because fungal burden in blood at any given moment can fall below a culture bottle's volume-limited detection threshold even while tissue invasion is established [2]. Pfaller and Diekema's epidemiologic synthesis frames the resulting burden: candidemia and invasive candidiasis affect tens of thousands of patients annually in the United States alone, carry mortality commonly reported between 25% and 55%, and concentrate in ICU, oncology, and transplant units where diagnostic uncertainty is highest and delay is most costly [1].

Clinicians consequently choose between waiting for a culture that may never turn positive or starting empiric therapy on clinical suspicion, guided by scoring systems such as the *Candida* score and the clinical prediction rule refined by Ostrosky-Zeichner and colleagues, neither designed to substitute for a positive microbiologic result [8,9]. Clancy and Nguyen's influential framing of invasive

candidiasis's "missing 50%" argued that non-culture diagnostics were necessary, not merely incremental, because culture-based case definitions systematically under-ascertain a form of disease that behaves differently from the bloodstream infections culture reliably captures [2], an argument that anticipated much of the momentum since built around PCR and T2Candida (Figure 1).

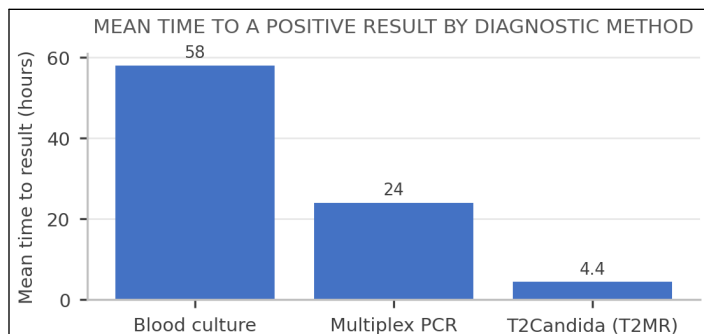


Figure 1: Reported mean time to a positive result for blood culture versus PCR-based and T2 magnetic resonance detection of *Candida* in blood, drawn from a multicenter clinical trial and comparative diagnostic-accuracy studies [18,12,1].

3. PCR performance against blood culture

PCR-based detection of *Candida* DNA has been assessed across systematic reviews spanning assay chemistries, sample types, and populations, and the aggregate picture is a sensitivity advantage over blood culture bought at a modest cost in specificity. Avni, Leibovici, and Paul's meta-analysis pooled 54 studies and 4,694 patients and reported pooled sensitivity for whole-blood PCR of approximately 95% against a proven or probable reference standard, with pooled specificity around 92%, figures that held whether the comparator was blood culture alone or a composite standard incorporating autopsy and biopsy findings [10]. Those numbers are the strongest quantitative case for PCR's central claim: recovering culture-negative but genuinely infected patients that blood culture, by its nature, cannot detect.

Head-to-head studies refine that picture by testing PCR against blood culture and beta-D-glucan in the same cohort. Nguyen and colleagues prospectively evaluated multiplex real-time PCR alongside the Fungitell

beta-D-glucan assay and blood culture in 236 at-risk patients, and found that combining PCR with beta-D-glucan substantially improved sensitivity over blood culture alone, with PCR positivity often preceding blood culture positivity by a day or more [12]. Seminested PCR applied directly to blood has shown comparable or superior sensitivity to culture and biochemical identification, with same-day species discrimination that culture cannot match without additional days [13]. Arvanitis and colleagues' review situates these figures within the broader diagnostic landscape, concluding that no single assay currently performs well enough to be used in isolation, and that combination strategies are likely to remain the practical standard [11].

4. Beta-D-glucan and combination strategies

Serum 1,3-beta-D-glucan, a fungal cell wall component shared across most pathogenic *Candida* species, has the largest evidence base of any non-culture biomarker and is the essential comparator for judging PCR's incremental value. Obayashi and colleagues' original 1995 description established proof of concept that a rise in circulating glucan tracked with invasive deep mycosis across a mixed hematology and surgical cohort [14]. Two meta-analyses have since refined pooled accuracy: Karageorgopoulos and colleagues, pooling 16 studies and nearly 3,000 patients, reported sensitivity around 77% and specificity around 85% across invasive fungal infections broadly, while Onishi and colleagues, restricting analysis to studies with a rigorous reference standard, reported sensitivity near 80% and specificity near 82% specifically for invasive candidiasis [15,16].

These figures argue for combination testing rather than a single winning assay. Beta-D-glucan's principal weakness is a well-documented set of false-positive triggers, including hemodialysis with cellulose membranes, intravenous immunoglobulin, surgical gauze exposure, and certain bacteremias, none of which meaningfully affect PCR specificity, while PCR's principal weakness

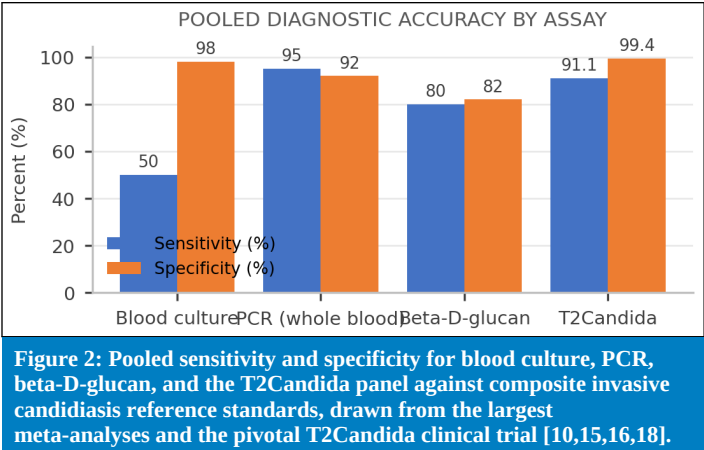
remains a lack of standardization across in-house assays and extraction protocols that has slowed regulatory clearance more than it has slowed single-center accuracy [15,11]. Nguyen and colleagues found that combining PCR and beta-D-glucan captured more true infections than either alone, at an acceptable cost in additional false positives, a pattern replicated in population-specific studies discussed below [12,17] (Table 1).

Table 1: Diagnostic characteristics of non-culture assays for invasive candidiasis, including principal sources of false results, drawn from meta-analytic and comparative studies [10,15,16,12,18].			
Assay	Pooled/reporter d sensitivity	Pooled/reporter d specificity	Principal limitation
Blood culture	~50% (autopsy-confirmed disease)	High (when positive)	Slow (2-3 days); misses deep-seated disease
PCR (whole blood)	~95%	~92%	Assay/extraction standardization varies by laboratory
Beta-D-glucan	77-80%	82-85%	False positives (dialysis, IVIG, gauze, some bacteremia)
T2Candida (T2MR)	91.1%	99.4%	Panel covers five Candida species; platform-dependent

5. T2Candida as a nanodiagnostic alternative

T2Candida occupies an intermediate position between conventional PCR and culture: it amplifies Candida DNA directly from whole blood without a separate extraction step, then detects amplicons by T2 magnetic resonance rather than fluorescence, collapsing hours of hands-on processing into a largely automated workflow. Mylonakis and colleagues' pivotal trial evaluated the panel against blood culture in 1,801 hospitalized at-risk patients and reported sensitivity of 91.1% and specificity of 99.4% against a composite reference standard, with a mean time to result of approximately 4.4 hours compared with more than two days for blood culture, a difference of clinical rather than statistical magnitude [18]. The panel's FDA clearance rested on this and related validation work and has since supported earlier discontinuation of empiric antifungal therapy in ICU patients who would otherwise

remain on broad-spectrum agents while awaiting culture, a stewardship benefit that accrues even when the assay never returns a true positive, though the same rapid-diagnostic momentum carries a risk of unintended overtreatment when a positive result is acted on without integrating the pretest clinical probability [19,11,20]. Camp, Spettel, and Willinger's review situates T2Candida alongside conventional PCR as complementary rather than competing technologies, with the choice between them depending more on existing infrastructure and cost structure than on any large residual accuracy gap [21] (Figure 2).



6. Population-specific evidence and standardization barriers

Two populations illustrate where PCR-based surveillance has moved furthest toward tailored clinical evidence: very-low-birth-weight neonates and patients at risk for intra-abdominal candidiasis, a syndrome notoriously hard to diagnose by blood culture alone because infection is often confined to the peritoneal cavity with only intermittent bloodstream spillover. Ramos and colleagues' CANDINEO study evaluated quantitative PCR together with beta-D-glucan in very-low-birth-weight preterm neonates, where blood volume constraints limit culture sampling and clinical sepsis signs are nonspecific; the combination identified invasive candidiasis earlier and more sensitively than blood culture alone [22]. Fortún

and colleagues evaluated multiplex real-time PCR with beta-D-glucan in a high-risk surgical and critically ill population for intra-abdominal candidiasis; PCR performed on peritoneal fluid and blood identified cases blood culture missed entirely, reinforcing that source-proximate molecular sampling has a distinct role where bloodstream sampling is mechanistically the wrong compartment [17]. Pfeiffer and colleagues' quantitation of *Candida* colony-forming units in initial positive blood cultures adds a complementary point: fungal burden at the time of a first positive culture is frequently very low, often below one CFU/mL, helping explain why blood culture sensitivity is intrinsically volume-limited and why PCR has a structural advantage at exactly this burden range [23] (Table 2).

Table 2: Population-specific PCR and beta-D-glucan diagnostic studies in patients for whom blood culture performs poorly [22,17,23].			
Study / population	Assay(s) evaluated	Comparator	Key finding
[22] CANDINEO, VLBW neonates	Quantitative PCR + beta-D-glucan	Blood culture	Earlier and more sensitive detection than culture alone
[17] high-risk intra-abdominal candidiasis	Multiplex real-time PCR + beta-D-glucan	Blood culture, peritoneal fluid	PCR identified cases blood culture missed entirely
[23] initial positive blood cultures	Quantitative CFU counting	--	Fungal burden often <1 CFU/mL, limiting culture sensitivity

Despite two decades of favorable accuracy data, PCR-based *Candida* detection is not a primary recommendation in either major guideline document. The IDSA's 2016 update acknowledges that non-culture diagnostics including PCR and beta-D-glucan can supplement blood culture in selected scenarios, but stops short of recommending routine PCR testing, citing the absence of a single standardized, widely validated

commercial assay [24]. ESCMID's 2012 guideline reaches a similar position, describing PCR as promising but not yet fully standardized and recommending beta-D-glucan as the more mature adjunct at that time [25]. The core barrier both bodies identify is standardization rather than accuracy: *Candida* PCR assays vary in target gene, sample type, extraction chemistry, and positivity threshold, a heterogeneity Avni and colleagues flagged as the largest source of between-study variance in their pooled estimates [10]. Arvanitis and colleagues note that in-house PCR assays, however well validated locally, cannot be compared across institutions the way an FDA-cleared platform such as T2Candida can, which is why T2Candida achieved guideline recognition years before any amplicon-based *Candida* PCR assay reached comparable clearance [11,19]. Bassetti and colleagues' EUCANDICU project, a large multicenter European surveillance effort, illustrates the consequence: cross-center comparisons remain difficult precisely because non-culture diagnostics are frequently locally developed and unevenly deployed [26]. The remaining obstacle to wider adoption is organizational and regulatory rather than scientific.

7. Discussion

The evidence assembled supports a fairly confident conclusion: PCR-based detection of *Candida* DNA meaningfully outperforms blood culture on sensitivity and turnaround time, performs comparably to or better than beta-D-glucan on specificity, and adds actionable information when combined with beta-D-glucan or used alongside T2Candida, particularly where blood culture is structurally disadvantaged, including neonates with limited sampling volume and patients with intra-abdominal disease that may never generate a positive peripheral culture [10,12,22,17]. The magnitude of the sensitivity gain in the largest meta-analyses, low-to-mid 90s against composite standards compared with blood culture's well-documented failure to detect autopsy-confirmed disease, is large enough that the case for incorporating PCR rests on more than marginal

improvement [10,2].

What tempers that conclusion is deployment rather than accuracy. The standardization gap that IDSA and ESCMID cited has not closed, and the heterogeneity across in-house PCR assays remains a live issue for laboratories considering adoption [24,25,10]. T2Candida's regulatory clearance illustrates what standardization accomplishes: a single validated platform, evaluated in a large multicenter trial, moved from publication to stewardship application within a few years, a path amplicon-based PCR has followed more slowly because no single commercial assay has undergone comparably definitive multicenter validation [18,19]. The practical implication is that adopting PCR-based surveillance is reasonable and evidence-supported, but currently requires either a cleared platform or rigorous local validation against the specific population a laboratory intends to serve. No single non-culture test is positioned to replace blood culture outright; the strongest evidence favors combination strategies, a pattern consistent enough across disparate populations to function as a general design principle for diagnostic algorithms rather than a population-specific quirk [12,17,22,8].

8. Conclusion

Two decades of accuracy studies and rigorous meta-analyses establish that PCR-based detection of *Candida* DNA in blood identifies invasive candidiasis with sensitivity in the low-to-mid 90s and specificity above 90% against composite reference standards, outperforming blood culture on both sensitivity and turnaround time while complementing beta-D-glucan and the T2Candida panel rather than duplicating either [10,18,15]. That accuracy has translated into clinical benefit in high-need populations, including very-low-birth-weight neonates and patients at risk for intra-abdominal candidiasis, where blood culture's structural weaknesses are most pronounced [22,17]. What has not caught up is standardization: the absence of a single, widely validated,

cross-institutionally comparable amplicon PCR platform, in contrast to the FDA-cleared T2Candida assay, remains the reason both IDSA and ESCMID describe PCR as a promising adjunct rather than a primary recommended test [24,25]. Closing that gap through commercial platform development, multicenter validation, and combination-testing algorithms is the next necessary step before PCR-based surveillance moves from a well-supported adjunct to a first-line diagnostic tool.

9. Declarations

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