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Clinical Utility of Routine Use of Fungal Blood Cultures

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Fungemia, including candidemia, is associated with substantial morbidity and mortality.[1] Certain fungi are relatively slow-growing, and are therefore more difficult to detect via standard 5-day incubation on automated blood-culture instruments. Lysis-centrifugation, also known as isolator blood cultures, is utilized for detection of intracellular pathogens such as mycobacteria and dimorphic fungi. In this method, host cells in the blood are lysed to release intracellular pathogens, and the sample is centrifuged to concentrate any organisms which are present. The pellet is then seeded onto appropriate solid media for fungal culture and incubated for up to 4-6 weeks at 30°C. [2, 3] With different vendor options, solid-media choices, and incubation times, fungal-isolator cultures are not standardized across different laboratories. The purpose of this article is to assess the clinical utility of fungal-isolator blood cultures and to provide informed practical guidance to clinicians regarding their use in clinical practice.

Previous work performed by Telenti et al in 1989 described their single-center experience utilizing lysis-centrifugation for isolation of fungi.[4] At that time, they found that this method improved diagnosis of fungemia, primarily for *Candida* species, *Cryptococcus* species, and two important dimorphic endemic fungi, *Histoplasma capsulatum* and *Coccidioides immitis*. The authors' recommendations were to increase use of fungal blood cultures when there is a high degree of clinical suspicion for fungemia, especially in post-surgical and immunocompromised populations.[4] Other studies have similarly demonstrated that this fungal-blood-culture technique allows higher sensitivity in detection of fungal organisms as compared to routine blood cultures, but only in controlled laboratory assays outside of clinical practice.[5]

While isolator systems have remained mostly unchanged over the last two decades, routine blood-culture techniques have improved and now allow for faster growth with improved identification algorithms. Modern blood cultures can now detect *Candida spp* with

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approximately 50% sensitivity with a median time to positivity of 2–3 days compared to autopsy-proven infection. [1] This knowledge is useful in addressing the general misconception that *Candida spp* are slow-growing. At the present time, routine blood-culture techniques and the previously described lysis-centrifugation method are essentially equivalent in the clinical assessment of suspected candidemia.[6]

In modern clinical practice, a clinician might consider ordering fungal blood cultures as part of a comprehensive infectious evaluation for fever or a systemic inflammatory syndrome, often seeking an answer when routine blood cultures do not isolate a causative pathogen by attempting to identify a pathogenic fungus. Another reason that fungal blood cultures might be ordered is for diagnostic evaluation in certain immunocompromised hosts, when *Cryptococcus*, *Histoplasma capsulatum* or other opportunistic molds might cause disease more frequently. However, fungal blood cultures are often ordered without knowledge of the culture process, indications, and limitations when interpreting test results. As described earlier, *Candida spp* can be readily identified via routine blood cultures. Other fungal infections such as histoplasmosis and coccidioidomycosis can be diagnosed by utilizing a thorough history and physical exam, laboratory and radiographic findings, targeted advanced diagnostics, such as fungal antigen and serological testing, and, in certain instances, histopathological examination of tissue specimens.[1] For example, *Histoplasma capsulatum* can be diagnosed with the urine antigen test with high sensitivity, and the sensitivity and specificity of the serum *Cryptococcus* lateral flow assay for antigen detection are both 98%.[7] In addition, a negative fungal blood culture can also provide false reassurance during clinical assessment. The test result might be a false-negative, as the sensitivity is not 100% for detection of invasive fungal infections. Also, for many potential fungal infections, empirical therapy might be warranted long before culture-result data are

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available. Awaiting results of fungal blood culture might be the incorrect clinical decision for certain patients.

Importantly, there are no large randomized controlled trials (RCTs) evaluating the utility of fungal blood cultures in diagnosing suspected disseminated fungal infections. Even prior to development of modern blood-culture techniques, the available data were sparse and less robust in adults compared to pediatric populations. A summary of available data is shown in Figure 1. Overall, the yield of positive cultures was low, there were many clinically insignificant cultures, and many of the clinically significant fungi were identified via other methods. Improvement in techniques for routine bacterial blood cultures will likely only continue to improve detection of fungal organisms, as it has for detection of *Candida spp*. Additionally, use of fungal blood cultures can also add unnecessary cost in patient care. Overall, available data suggest that routine use of fungal blood cultures is not needed, and a well-designed RCT with relevant clinical endpoints is likely needed to demonstrate their utility as a part of routine diagnostic evaluation.

In summary, our recommendations for use of fungal blood cultures in daily clinical practice include the following:

1) Avoid use of fungal blood cultures in the evaluation of suspected disseminated yeast infections due to *Candida spp.* and *Cryptococcus spp.* These organisms are detectable via routine blood cultures and there are alternate diagnostic methods with more robust evidence such as the magnetic resonance assay
2) Consider risk factors for candidemia and treat empirically with echinocandins if *Candida spp* are unable to be isolated via routine blood cultures and there remains persistent clinical concern for invasive candidal infection.

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3) Carefully consider which specific fungi could be causing a particular clinical syndrome, and evaluate each patient individually based on host risk factors and clinical presentation. Utilize targeted testing, such as serum cryptococcal antigen, serum *Aspergillus* galactomannan, and urine *Histoplasma* antigen, or undertake other syndrome-specific evaluation, such as tissue biopsy or bronchoscopy.
4) If there is significant clinical concern for a disseminated fungal infection other than one caused by *Candida spp*, consultation with an infectious disease practitioner is recommended to assist with assessment, diagnostic evaluation, and empirical treatment.
    a. Fungal blood cultures could be recommended when evaluating for *Fusarium spp*, other filamentous fungi, *Histoplasma capsulatum*, and *Coccidioides immitis* if alternate testing methods are not available or clinically feasible.

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Table 1: Literature Review of Clinical Experience with Fungal Blood Cultures

Study Group (Years Evaluated)	Population	Total Fungal Cultures Obtained	Frequency of Candida Uniquely by Fungal Cultures	Crypto-coccus	Molds	Dimorphic Fungi	Excess Cost
Campigotta et al. (2003-2013) [8]	Pediatric Population at 2 Academic Centers	9,442	13/134 (9.7%)	0	9/25 (36%) clinically significant 6 filamentous fungi (4 episodes Aspergillus spp - 1 isolated from lung biopsy 1 Bipolaris - isolated from pleural fluid 1 Curvularia 1 Exherohilum) 1 Fusarium oxysporum (also identified on routine blood culture) 2 dimorphic fungi (see next column)	1 episode Histoplasma capsulatum: (focal liver lesion culture positive and positive Histoplasma antibody) 1 episode Coccidiodes, isolated from bone lesion culture as well	Not Calculated
Mess et al. (1992-1994) [9]	Advanced HIV at 1 Academic Center	1162	0 (out of 5 positive)	7 unique episodes, all had positive serologic makers	1 dimorphic Fungi	1 Coccidiodes immitis (positive serology)	Not Calculated
Kumar et al (2010-2017) [10]	Pediatric oncology and stem-cell transplant unit at 1 Academic Center	1980	3 (1 colony on 2 different patients)	0	18 5 *Cladosporium spp.*, 6 *Penicillum spp.*, 1 *Aspergillus spp. (*not fumigatus, flavus, or niger), 1 Bipolaris (1 colony), 1 Rhodotorula mucillaginosa 4 unidentified molds	N/A	$182,000, $350,000 adjusted for inflation

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					Impression: Most clinically insignificant		
Creger et al. (56 months; unknown study period, published 1998) [11]	Immunosuppressed patients with cancer at 1 Academic Center	Unknown; 41/42 false positive cultures were from fungal cultures	2 *Candida parapsilo-sis*	14	1 Aspergillus flavus, 1 Aspergillus spp.	N/A	Not Calculated
Morrell et. Al (14 months, unknown study period, published 1996) [12]	All cultures at 1 Adult Hospital at Academic Center	5196 (1.6%+)	10/56 (17.9%)	Neoformans: 9 (all identified using other methods and 0 affected therapy) Albidus: 1 which affected therapy	Unclear significance 2 Aspergillus flavus (1 isolated elsewhere, 0 affected therapy) 3 Fusarium (3 isolated elsewhere, 0 affected therapy) 2 affected therapy (Rhodotorula rubra, Penicillium sp.)	N/A	$300,000 annually, >$550,000 adjusted for inflation

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