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Research Article

Clinical Outcomes of combination antimicrobial therapy in Patients with fungal pathogenesis

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Abstract

Background: Combination antimicrobial therapy, pairing agents from different antifungal classes, has long been proposed to improve survival over monotherapy in invasive fungal disease, but the strength of that evidence differs sharply across pathogens.

Objective: To synthesize published clinical-outcomes evidence on combination antifungal therapy for cryptococcal meningitis, invasive mould disease, and candidemia.

Methods: We synthesized randomized trials, prospective cohorts and society guidelines reporting mortality or mycological clearance for combination versus monotherapy antifungal regimens in adults with confirmed fungal infection.

Results: Amphotericin B plus flucytosine reduced two-week mortality in cryptococcal meningitis to roughly 8-11%, against approximately 25% with monotherapy; voriconazole-echinocandin combinations showed only subgroup-limited benefit in aspergillosis; polyene-echinocandin combinations improved survival in mucormycosis cohorts; and monotherapy performed adequately in candidemia.

Conclusions: Combination therapy improves outcomes in fungal pathogenesis in a syndrome-specific rather than uniform manner, and stewardship should match combination intensity to each syndrome's evidence base.

Keywords: combination antifungal therapy; cryptococcal meningitis; invasive aspergillosis; candidemia; antifungal stewardship

1. Introduction

Invasive fungal disease remains a leading cause of mortality among immunocompromised patients, and the antifungal armamentarium is far narrower than the antibacterial one, with only four major drug classes -- polyenes, azoles, echinocandins and flucytosine -- in routine use [1]. Polyenes and azoles disrupt ergosterol-dependent membrane function, echinocandins inhibit beta-1,3-glucan synthase [2], and flucytosine interferes with fungal nucleic acid synthesis; combining agents from different classes has long been proposed to achieve faster fungicidal activity, broader empirical coverage, and a lower probability that emerging resistance to one drug compromises the whole regimen [3]. The slow pace at which genuinely new antifungal classes have reached the clinic is itself part of the rationale for combining existing agents more effectively [4]. The rationale is strongest for cryptococcal meningitis and invasive mould disease, where monotherapy alone leaves unacceptably high mortality, and weakest for candidemia in non-neutropenic hosts, where single-agent therapy already performs well [5].

Clinical evidence has accumulated unevenly across pathogens. For *Cryptococcus neoformans*, amphotericin B plus flucytosine has been studied since the 1970s and is now guideline-endorsed induction therapy [6,7]. For invasive aspergillosis, azole-echinocandin combinations show more modest, population-dependent benefit [8,9]. For mucormycosis, only retrospective cohorts support polyene-echinocandin combinations, reflecting the disease's rarity and lethality [10,11]. This heterogeneity means combination therapy cannot be treated as one intervention with a single expected effect size.

This article synthesizes the published clinical-outcomes literature on combination antimicrobial therapy across the three fungal syndromes with the largest evidence base -- cryptococcal meningitis, invasive mould disease, and candidemia -- to clarify where combination therapy

measurably improves outcomes and what this means for antifungal stewardship.

2. Methods

We conducted a narrative synthesis of randomized trials, prospective cohorts, and major society guidelines addressing combination antimicrobial therapy for invasive fungal disease, drawing on the cryptococcal, aspergillosis, mucormycosis and candidemia literature indexed through 2018. Eligible studies compared a two-drug antifungal regimen against monotherapy with a clinically meaningful outcome -- mortality, mycological clearance, or time to clinical response -- in adults with confirmed fungal infection. Studies limited to prophylaxis or to in-vitro synergy testing without clinical outcomes were excluded from the primary synthesis but referenced where they inform mechanistic interpretation [12,13].

For each syndrome we extracted comparator regimens, populations, and outcome measures, then grouped studies by pathogen to allow within-syndrome comparison. Because trial designs and endpoints differ across the cryptococcal, mould and candida literatures, no formal meta-analytic pooling was attempted; findings are presented descriptively, consistent with prior narrative reviews of combination antifungal therapy [1,14].

3. Antifungal regimens evaluated across major trials

The combination regimens that have reached randomized or large prospective comparison fall into a small number of drug pairings, summarized in Table 1. In cryptococcal meningitis, amphotericin B deoxycholate plus flucytosine is the best-studied pairing, from the earliest controlled trials through the modern ACTA trial [6,15,16]; amphotericin B plus fluconazole has also been tested as a flucytosine-sparing alternative [17,18,19]. In invasive aspergillosis, voriconazole plus an echinocandin (anidulafungin or caspofungin) is the principal combination studied, first in retrospective salvage cohorts and later in a randomized primary-therapy trial [20,8,9]. In

mucormycosis, liposomal amphotericin B plus an echinocandin has been evaluated only in retrospective cohorts, given the ethical difficulty of randomizing a rapidly lethal infection to monotherapy [10,21].

Table 1: Combination antifungal regimens with clinical-outcome data across the three fungal syndromes reviewed [6,15,8,10].

Syndrome	Combination regimen	Evidence base	Principal outcome studied
Cryptococcal meningitis	Amphotericin B + flucytosine	Multiple RCTs, 1979-2018	Mortality, CSF fungicidal activity
Cryptococcal meningitis	Amphotericin B + fluconazole	RCT (flucytosine-sparing)	Mortality, fungicidal activity
Invasive aspergillosis	Voriconazole + anidulafungin/caspofungin	Observational cohorts + 1 RCT	90-day mortality
Mucormycosis	Liposomal amphotericin B + echinocandin	Retrospective cohorts only	Overall survival

4. Outcomes in cryptococcal meningitis

Cryptococcal meningitis provides the strongest evidence that combination therapy improves outcomes. Bennett and colleagues' original comparison found that adding flucytosine to amphotericin B reduced relapse, establishing the combination as first-line induction for the following four decades [6]. Bicanic and colleagues quantified this pharmacodynamically, showing amphotericin B-based induction achieves faster early fungicidal activity than fluconazole-based induction [22]. Day and colleagues' pivotal Vietnamese trial compared amphotericin B alone, amphotericin B plus fluconazole, and amphotericin B plus flucytosine, finding two-week mortality lowest with amphotericin B-flucytosine, at approximately 8-11%, against roughly 25% with monotherapy [15]. The ACTA trial extended this to Africa, showing a shortened one-week amphotericin B-flucytosine induction achieved 10-week mortality of roughly 24%, lower than a fully oral fluconazole-flucytosine regimen at roughly 35% [16]. Jarvis and colleagues' pooled analysis of 501 patients confirmed induction regimen as among the strongest

independent predictors of mortality [23]. Loyse and colleagues found flucytosine again produced the fastest fungicidal activity among second-line combination partners [18]. Where flucytosine is unavailable, Nussbaum and colleagues' Malawi trial showed flucytosine plus high-dose fluconazole outperformed fluconazole monotherapy on early clearance [19]. Dromer and colleagues' French national cohort reached the same conclusion from real-world data [24], and van der Horst and colleagues provided earlier corroborating evidence of faster CSF sterilization with amphotericin B-based induction [25]. Society guidelines have since incorporated this evidence into first-line recommendations [7].

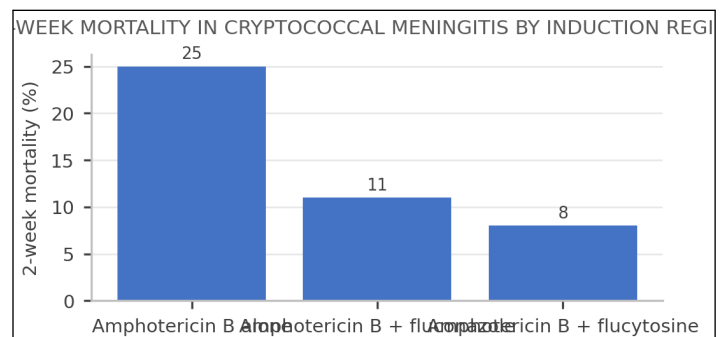


Figure 1: Two-week mortality in HIV-associated cryptococcal meningitis by induction regimen in a randomized comparison of amphotericin B monotherapy against amphotericin B combined with fluconazole or with flucytosine, approximately 25% with amphotericin B alone against roughly 11% and 8% respectively with the two combination regimens [15,22].

5. Outcomes in invasive mould disease

Evidence for combination therapy in aspergillosis and mucormycosis is more heterogeneous. Herbrecht and colleagues established voriconazole monotherapy as superior to amphotericin B for invasive aspergillosis, a high monotherapy benchmark [26]. Marr and colleagues' retrospective cohort suggested voriconazole-caspofungin salvage combination lowered mortality versus voriconazole alone [20], and Singh and colleagues' transplant cohort found reduced 90-day mortality with combination primary therapy [9]. However, Marr and colleagues' subsequent randomized trial of voriconazole plus anidulafungin versus voriconazole alone found only a

non-significant overall mortality trend, with benefit concentrated in a biomarker-confirmed subgroup, suggesting the earlier observational signal was inflated by confounding [8]. Cornely and colleagues' AmBiLoad trial showed dose-intensified polyene monotherapy added nephrotoxicity without survival benefit [27], and society guidelines have stopped short of recommending routine combination primary therapy [28,29]. In mucormycosis, Reed and colleagues' retrospective cohort found polyene-caspofungin combination associated with better survival than polyene monotherapy, while Chamilos and colleagues emphasized that delay in starting any amphotericin B-based therapy predicted death more strongly than regimen choice [10,30]. Kontoyiannis and Lewis concluded combination therapy is reasonable in non-responders but should never delay surgical debridement [21].

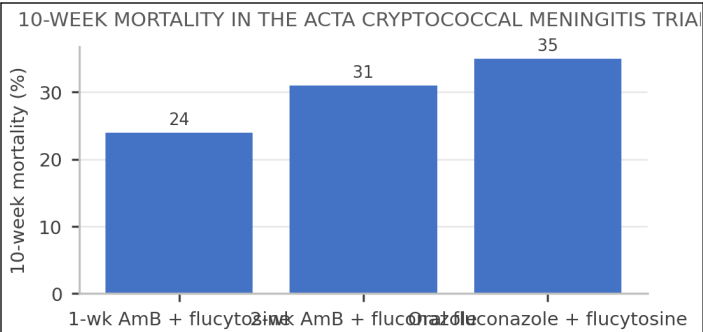


Figure 2: Ten-week mortality in HIV-associated cryptococcal meningitis in the ACTA trial comparing a shortened one-week amphotericin B plus flucytosine induction, a fully oral fluconazole-flucytosine regimen, and the historical two-week amphotericin B plus fluconazole regimen, approximately 24%, 35% and 31% respectively [16].

6. Outcomes in candidemia and candidiasis

Candidemia in non-neutropenic hosts is the syndrome with the weakest combination-therapy rationale, since monotherapy already performs well in randomized trials. Rex and colleagues found fluconazole equivalent to amphotericin B with less toxicity [31]. Mora-Duarte and colleagues' caspofungin trial and Kullberg and colleagues' voriconazole trial both confirmed modern single-agent therapy performs at least as well as historical sequential

strategies [32,33], and Reboli and colleagues' anidulafungin trial reinforced the same conclusion [34]. Pappas and colleagues' 2016 guideline recommends echinocandin or azole monotherapy for most candidemia, reserving combination for complications such as endocarditis [35]. This pattern -- strong benefit in cryptococcal meningitis, modest benefit in mould disease, and little benefit in candidemia -- is the central empirical finding of this synthesis.

Table 2: Monotherapy versus combination-era trial comparisons in candidemia, showing consistent adequacy of single-agent modern antifungal therapy [31,32,33,34].			
Trial	Comparator regimen	Population	Finding
[31]	Fluconazole vs amphotericin B	Non-neutropenic candidemia	Equivalent success, less toxicity with azole
[32]	Caspofungin vs amphotericin B	Invasive candidiasis	Caspofungin non-inferior, better tolerated
[33]	Voriconazole vs amphotericin B/fluconazole	Non-neutropenic candidemia	Non-inferior, fewer renal events
[34]	Anidulafungin vs fluconazole	Invasive candidiasis	Anidulafungin superior on global response

7. Discussion

The literature supports a syndrome-specific, rather than uniform, approach to combination antimicrobial therapy. The strongest survival benefit is in cryptococcal meningitis, where amphotericin B plus flucytosine has outperformed every alternative across four decades of trials [6,15,16]. Two fungicidal agents acting through independent mechanisms clear organism burden faster than a fungicidal-fungistatic pairing, a mechanistic story supported by fungicidal-activity data and by the consistency of the mortality benefit across Southeast Asian, African, and earlier North American and European cohorts [22,23]. This consistency justifies amphotericin B-flucytosine as a genuine standard of care, with flucytosine access and cost the principal remaining barrier rather than clinical uncertainty [19,7].

Invasive mould disease presents a more cautionary picture. The gap between the encouraging observational signal for voriconazole-echinocandin therapy and the modest, subgroup-limited randomized-trial benefit illustrates a recurring problem in combination-antimicrobial research: retrospective comparisons against historical monotherapy controls are vulnerable to confounding by indication, since sicker patients are often selected for combination salvage therapy [20,9,8]. This does not mean combination therapy for aspergillosis lacks value -- the randomized subgroup finding suggests real benefit in biomarker-confirmed disease -- but it should not be adopted as a blanket primary strategy, consistent with current guidance [28,29]. For mucormycosis, the literature is unanimous that timely diagnosis and surgical source control matter more to survival than which two-drug regimen is chosen [10,30,21].

For candidemia, the absence of an added combination benefit is itself useful, letting stewardship efforts focus on monotherapy selection and de-escalation rather than dual-agent regimens that add cost and toxicity without a survival advantage [35,5]. These three syndrome-specific pictures argue against extrapolating combination-therapy evidence from one fungal disease to another, a point made in prior reviews and reinforced by every trial summarized here [3,1,14]. Clinicians should match combination intensity to each syndrome's own evidence: aggressive dual fungicidal therapy for cryptococcal meningitis, selective use guided by severity and biomarkers in mould disease, and monotherapy with combination reserved for defined complications in candidemia.

8. Conclusion

Combination antimicrobial therapy improves clinical outcomes in fungal disease, but the magnitude depends heavily on the pathogen treated. Amphotericin B plus flucytosine reduces mortality in cryptococcal meningitis

with a consistency spanning four decades and multiple continents, and now anchors international guidelines [6,15,16,7]. Azole-echinocandin combinations for aspergillosis and polyene-echinocandin combinations for mucormycosis show real but more modest, population-dependent benefit, best reserved for severe or salvage presentations [8,10]. Candidemia in non-neutropenic hosts responds adequately to modern monotherapy, and routine combination adds toxicity without demonstrated benefit [35]. Antifungal stewardship in fungal pathogenesis is best served by treating combination therapy as a syndrome-specific decision grounded in the strength of the underlying trial evidence, not a single strategy applied indiscriminately across invasive fungal disease.

9. References

1. Johnson, M.D., MacDougall, C., Ostrosky-Zeichner, L., Perfect, J.R., Rex, J.H. (2004) Combination antifungal therapy. *Antimicrobial Agents and Chemotherapy*, 48(3): 693-715.
2. Denning, D.W. (2003) Echinocandin antifungal drugs. *Lancet*, 362(9390): 1142-1151.
3. Mukherjee, P.K., Sheehan, D.J., Hitchcock, C.A., Ghannoum, M.A. (2005) Combination treatment of invasive fungal infections. *Clinical Microbiology Reviews*, 18(1): 163-194.
4. Perfect, J.R. (2017) The antifungal pipeline: a reality check. *Nature Reviews Drug Discovery*, 16(9): 603-616.
5. Baddley, J.W., Pappas, P.G. (2005) Antifungal combination therapy: clinical potential. *Drugs*, 65(11): 1461-1480.
6. Bennett, J.E., Dismukes, W.E., Duma, R.J., Medoff, G., Sande, M.A., Gallis, H., et al. (1979) A comparison of amphotericin B alone and combined with flucytosine in the treatment of cryptococcal meningitis. *New England Journal of Medicine*, 301(3): 126-131.
7. Perfect, J.R., Dismukes, W.E., Dromer, F., Goldman, D.L., Graybill, J.R., Hamill, R.J., et al. (2010) Clinical practice

- guidelines for the management of cryptococcal disease: 2010 update by the Infectious Diseases Society of America. *Clinical Infectious Diseases*, 50(3): 291-322.
8. Marr, K.A., Schlamm, H.T., Herbrecht, R., Rottinghaus, S.T., Bow, E.J., Cornely, O.A., et al. (2015) Combination antifungal therapy for invasive aspergillosis: a randomized trial. *Annals of Internal Medicine*, 162(2): 81-89.
 9. Singh, N., Limaye, A.P., Forrest, G., Safdar, N., Munoz, P., Pursell, K., et al. (2006) Combination of voriconazole and caspofungin as primary therapy for invasive aspergillosis in solid organ transplant recipients: a prospective, multicenter, observational study. *Transplantation*, 81(3): 320-326.
 10. Reed, C., Ibrahim, A., Edwards, J.E. Jr., Walot, I., Spellberg, B. (2008) Combination polyene-caspofungin treatment of rhino-orbital-cerebral mucormycosis. *Clinical Infectious Diseases*, 47(3): 364-371.
 11. Spellberg, B., Ibrahim, A.S. (2010) Recent advances in the treatment of mucormycosis. *Current Infectious Disease Reports*, 12(6): 423-429.
 12. Groll, A.H., Piscitelli, S.C., Walsh, T.J. (2001) Antifungal pharmacodynamics: concentration-effect relationships in vitro and in vivo. *Pharmacotherapy*, 21(8 Pt 2): 133S-148S.
 13. Cuenca-Estrella, M. (2004) Combinations of antifungal agents in therapy--what value are they? *Journal of Antimicrobial Chemotherapy*, 54(6): 854-869.
 14. Vazquez, J.A. (2008) Combination antifungal therapy for mold infections: much ado about nothing? *Clinical Infectious Diseases*, 46(12): 1889-1901.
 15. Day, J.N., Chau, T.T.H., Wolbers, M., Mai, P.P., Dung, N.T., Mai, N.H., et al. (2013) Combination antifungal therapy for cryptococcal meningitis. *New England Journal of Medicine*, 368(14): 1291-1302.
 16. Molloy, S.F., Kanyama, C., Heyderman, R.S., Loyse, A., Kouanfack, C., Chanda, D., et al. (2018) Antifungal combinations for treatment of cryptococcal meningitis in Africa. *New England Journal of Medicine*, 378(11): 1004-1017.
 17. Larsen, R.A., Bozzette, S., Jones, B.E., Haghighat, D., Leal, M.A., Forthal, D., et al. (1994) Fluconazole combined with flucytosine for treatment of cryptococcal meningitis in patients with AIDS. *Clinical Infectious Diseases*, 19(4): 741-745.
 18. Loyse, A., Wilson, D., Meintjes, G., Jarvis, J.N., Bicanic, T., Bishop, L., et al. (2012) Comparison of the early fungicidal activity of high-dose fluconazole, voriconazole, and flucytosine as second-line drugs given in combination with amphotericin B for the treatment of HIV-associated cryptococcal meningitis. *Clinical Infectious Diseases*, 54(1): 121-128.
 19. Nussbaum, J.C., Jackson, A., Namarika, D., Phulusa, J., Kenala, J., Kanyemba, C., et al. (2010) Combination flucytosine and high-dose fluconazole compared with fluconazole monotherapy for the treatment of cryptococcal meningitis: a randomized trial in Malawi. *Clinical Infectious Diseases*, 50(3): 338-344.
 20. Marr, K.A., Boeckh, M., Carter, R.A., Kim, H.W., Corey, L. (2004) Combination antifungal therapy for invasive aspergillosis. *Clinical Infectious Diseases*, 39(6): 797-802.
 21. Kontoyiannis, D.P., Lewis, R.E. (2011) How I treat mucormycosis. *Blood*, 118(5): 1216-1224.
 22. Bicanic, T., Wood, R., Meintjes, G., Rebe, K., Brouwer, A., Loyse, A., et al. (2007) Fungal burden, early fungicidal activity, and outcome in cryptococcal meningitis in antiretroviral-naïve or antiretroviral-experienced patients treated with amphotericin B or fluconazole. *Clinical Infectious Diseases*, 45(1): 76-80.
 23. Jarvis, J.N., Bicanic, T., Loyse, A., Namarika, D., Jackson, A., Nussbaum, J.C., et al. (2014) Determinants of mortality in a combined cohort of 501 patients with HIV-associated cryptococcal meningitis: implications for improving outcomes. *Clinical Infectious Diseases*, 58(5): 736-745.

24. Dromer, F., Bernede-Bauduin, C., Guillemot, D., Lortholary, O. (2008) Major role for amphotericin B-flucytosine combination in severe cryptococcosis. PLoS ONE, 3(8): e2870.
25. van der Horst, C.M., Saag, M.S., Cloud, G.A., Hamill, R.J., Graybill, J.R., Sobel, J.D., et al. (1997) Treatment of cryptococcal meningitis associated with the acquired immunodeficiency syndrome. New England Journal of Medicine, 337(1): 15-21.
26. Herbrecht, R., Denning, D.W., Patterson, T.F., Bennett, J.E., Greene, R.E., Oestmann, J.W., et al. (2002) Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. New England Journal of Medicine, 347(6): 408-415.
27. Cornely, O.A., Maertens, J., Bresnik, M., Ebrahimi, R., Ullmann, A.J., Bouza, E., et al. (2007) Liposomal amphotericin B as initial therapy for invasive mold infection: a randomized trial comparing a high-loading dose regimen with standard dosing (AmBiLoad trial). Clinical Infectious Diseases, 44(10): 1289-1297.
28. Walsh, T.J., Anaissie, E.J., Denning, D.W., Herbrecht, R., Kontoyiannis, D.P., Marr, K.A., et al. (2008) Treatment of aspergillosis: clinical practice guidelines of the Infectious Diseases Society of America. Clinical Infectious Diseases, 46(3): 327-360.
29. Patterson, T.F., Thompson, G.R. 3rd, Denning, D.W., Fishman, J.A., Hadley, S., Herbrecht, R., et al. (2016) Practice guidelines for the diagnosis and management of aspergillosis: 2016 update by the Infectious Diseases Society of America. Clinical Infectious Diseases, 63(4): e1-e60.
30. Chamilos, G., Lewis, R.E., Kontoyiannis, D.P. (2008) Delaying amphotericin B-based frontline therapy significantly increases mortality among patients with hematologic malignancy who have zygomycosis. Clinical Infectious Diseases, 47(4): 503-509.
31. Rex, J.H., Bennett, J.E., Sugar, A.M., Pappas, P.G., van der Horst, C.M., Edwards, J.E., et al. (1994) A randomized trial comparing fluconazole with amphotericin B for the treatment of candidemia in patients without neutropenia. New England Journal of Medicine, 331(20): 1325-1330.
32. Mora-Duarte, J., Betts, R., Rotstein, C., Colombo, A.L., Thompson-Moya, L., Smietana, J., et al. (2002) Comparison of caspofungin and amphotericin B for invasive candidiasis. New England Journal of Medicine, 347(25): 2020-2029.
33. Kullberg, B.J., Sobel, J.D., Ruhnke, M., Pappas, P.G., Viscoli, C., Rex, J.H., et al. (2005) Voriconazole versus a regimen of amphotericin B followed by fluconazole for candidaemia in non-neutropenic patients: a randomised non-inferiority trial. Lancet, 366(9495): 1435-1442.
34. Reboli, A.C., Rotstein, C., Pappas, P.G., Chapman, S.W., Kett, D.H., Kumar, D., et al. (2007) Anidulafungin versus fluconazole for invasive candidiasis. New England Journal of Medicine, 356(24): 2472-2482.
35. Pappas, P.G., Kauffman, C.A., Andes, D.R., Clancy, C.J., Marr, K.A., Ostrosky-Zeichner, L., et al. (2016) Clinical practice guideline for the management of candidiasis: 2016 update by the Infectious Diseases Society of America. Clinical Infectious Diseases, 62(4): e1-e50.