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Review Article

Appropriate Duration of Intravenous Treatment of Candidemia and Timing of Step Down to Oral Therapy in Non-neutropenic Patients

Rita Wilson Dib, Ray Hachem, Anne-Marie Chaftari* and Issam Raad.

The University of Texas M. D. Anderson Cancer Center, Department of Infectious Diseases, Infection Control and Employee Health, 1515 Holcombe, Unite 1460, Houston, Texas, 77030.

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Abstract. In this review, we have analyzed the available literature pertaining to the total duration of intravenous (IV) therapy and the appropriate timing of step down to oral therapy in the management of candidemia. Overview of the guidelines and literature seem to indicate that a minimum of 14 days of antifungal therapy is required in the treatment of candidemia without deeply seated infection. However, this was never based on evidence. Furthermore, step down to oral therapy seems to be dependent on the clinical stability criteria of the patient with candidemia after 4 to 7 days of IV therapy. Further studies are required to evaluate the appropriate total duration of IV therapy, appropriate timing of step down to oral therapy and to validate the clinical criteria that would allow the switch to happen.

Keywords: Candidemia, Non-nuetropenic patients, Intravenous treatment.

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Correspondence to: Dr. Anne-Marie Chaftari, Department of Infectious Diseases, Infection Control and Employee Health, Unit 1460, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Blvd., Houston, TX 77030. Tel: (713) 792-3491; Fax: (713) 742-7943. E-mail: achaftar@mdanderson.org

Introduction. Candidemia is the most common form of invasive candidiasis and one of the leading causes of bloodstream infections (BSI) in critically ill and immunosuppressed patients.[1,2] It is widely recognized for its high morbidity and mortality rates ranging between 10 to 47%.[3,4] Furthermore, candidemia has an added severity in immunosuppressed and critically ill patients. Given the high risk it poses, appropriate treatment and eradication of the organism remain crucial.

The most recent guidelines for the management of Candidemia without deeply seated complications (published by the Infectious Diseases Society of America (IDSA) in 2016) recommended a minimum of 14 days of antifungal therapy after documented blood culture clearance in a clinically stable state.[5] In the case of neutropenia, the guidelines also entail recovery of the white cell count.[5] However, these recommendations are based on limited clinical evidence grounded on the results of a number of trials in which this practice has been implied and routinely applied both in the non-neutropenic and less often the neutropenic population.[6-9]

In a milestone study by Rex et al. published in the New England Journal of Medicine in 1994 showing the equivalence of fluconazole to amphotericin B in the treatment of candidemia, the duration of therapy in both arms was mandated to be 2 weeks after the last negative blood culture.[7] Unfortunately, this practice has been carried through routinely as norm through the literature

and guidelines over the last three decades in the absence of other studies to compare the impact of total duration of therapy and appropriate time to step down to oral therapy.

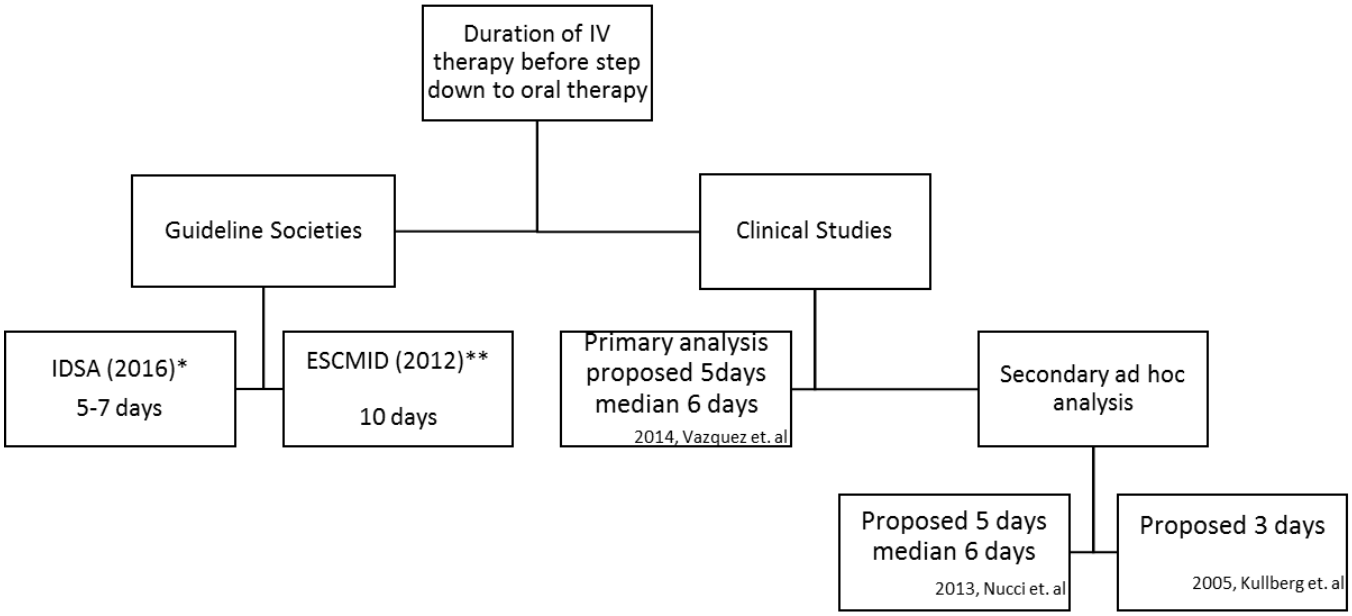
Duration of Therapy. Early initiation of antifungal agents in this population has been associated with favorable survival outcome[10] but the question remains as to when it should be stopped. To our knowledge, there were no randomized studies in the literature comparing different duration of treatment and a limited number looked at the appropriate timing of the step down from intravenous (IV) to oral antifungal therapy.

Hence, it is necessary to evaluate the available data on the total duration of therapy of uncomplicated candidemia given the importance of the subject matter.

One would argue that a long duration of therapy is useful for prevention or unintentional treatment of undiscovered foci of infection given the fact that up to 16% of candidemic patients have some exhibition of ocular involvement, with devastating consequences in inappropriately treated patients.[11] In a study by Blennow et al., two to three weeks of antifungal treatment was found to be adequate to treat undetected ocular infections in the setting of candidemia without signs of metastatic infection at onset. In this cohort, 21 patients received <=14 days of therapy. Among them, only one patient developed proven endophthalmitis after having received only 2 days (total) of therapy.[12] However, we cannot draw conclusions from this study on the effect of duration of therapy since the patients could be treated longer as a consequence to having a possible or probable ocular candidiasis. In addition, the authors did not distinguish the duration of IV versus oral therapy.

Step Down to Oral Therapy. A suggested strategy to keep the balance between the need for aggressive therapy and not overdoing it, is to do step down to oral therapy. It was recommended by the IDSA to step down within 5 to 7 days once the patient achieves symptom resolution and clearance of the blood cultures (**Figure 1**).[5] In 2012, the European Society for Clinical Microbiology and Infectious Diseases (ESCMID) proposed stepping down to oral fluconazole after 10 days of therapy if the patient was stable and the isolated candida species demonstrate appropriate minimal inhibitory concentrations (MICs) to the drug.[13]
In the actual practice, physicians are applying the step down therapy as per their clinical judgment. Setting clinical stability is not uniformly defined. Some studies relied on the hemodynamic status and microbiologic eradication, while others relied on the improvement in clinical signs and symptoms (defervescence for 24 hours) along with microbiological eradication.[14,15]

Figure 1. Proposed timing of step down to oral therapy in the medical literature:



*Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America. **ESCMID* guideline for the diagnosis and management of Candida diseases 2012: non-neutropenic adult patients.

A trial conducted in several centers in Latin America, patients were eligible for step down after at least 5 days of anidulafungin if they had "stable blood pressure" and at least two negative blood cultures. Only 14 out of 44 qualified for step down to voriconazole with a median duration of IV therapy of six days. They were all found to have lower APACHE II score and lower incidence of solid tumors compared with others making them less sick. Global response and overall mortality were significantly lower in the step down group.[15] Even though the number of enrolled patients is small, this study showed the feasibility of the step down therapy but it did not give us an idea on the efficacy of stepping down the therapy to oral formulation in high risk patients especially that the two approved/used agents (fluconazole and voriconazole) show >90% oral bioavailability.

An open-label non-comparative trial evaluated global response rates, defined by clinical improvement and microbiological eradication, of patients with candidemia who were treated with anidulafungin followed by oral fluconazole (if baseline cultures revealed C. *albicans* or C. *parapsilosis*) or voriconazole (all other species) after a minimum of 5 days of anidulafungin provided that the patients were clinically stable.[16] The step down criteria consisted of 24 hours off fever, hemodynamic stability and documentation of sterile blood cultures and resolved neutropenia. A total of 150 patients underwent a step down to oral therapy, 56% of them qualified for the switch to oral therapy within 6 days with a median of 5 days [range, 1-6]. On the other hand, 44% did not meet the criteria within the first 6 days of therapy and the median duration of their IV therapy was 10 days [range, 7-27]. The overall response in the group of patients who underwent early step down versus the modified intention to treat (MITT) population did not differ.[16] Again it was noted that the patients who were switched to oral therapy before 7 days from onset had lower APACHE scores. This study shows that early step down to oral therapy within 6 days is dependent on certain clinical stability criteria (**Table 1**).

Another study compared voriconazole to amphotericin B therapy whereby the protocol allowed switch from IV voriconazole to oral voriconazole and from IV amphotericin to oral fluconazole. The median duration of amphotericin B was 4 days.[17] Even though the authors did not mention the median duration of IV voriconazole therapy and the percentage of patients switched to the oral formulation, there was no significant difference in overall response between the two groups.

Another concern with the current proposed step down strategies was raised by Glockner et.al which is the vague definition of the timing of documented negative blood culture. This timing may vary depending on how often the blood cultures are taken and the fact that they are known to have slow turnaround times with median time to positivity of 2–3 days reaching 7 days in some situations.[18,19] Glockner at al., therefore, suggest to consider the timing of collection of the first negative blood culture as a starting point to initiate step down strategies.

What is notable in many of the conducted studies is that microbiologic eradication ranged

Table 1. Proposed clinical criteria to determine the eligibility to step down to oral antifungal therapy.

Guideline society / Study title (year)	Qualifying clinical criteria	References
IDSA (2016)	- Patient improved clinically - documented clearance of *Candida* from the bloodstream - organism that is susceptible to fluconazole or voriconazole	- [5]
ESCMID (2012)	- Clinically stable - Appropriate MIC for the isolated candida species	- [13]
An open-label study of anidulafungin for the treatment of candidaemia/invasive candidiasis in Latin America (2013)	- Stable blood pressure - Can tolerate oral therapy - ≥ two negative blood cultures - Voriconazole not contraindicated	- [15]
Evaluation of an early step-down strategy from intravenous anidulafungin to oral azole therapy for the treatment of candidemia and other forms of invasive candidiasis: results from an open-label trial (2014)	- Ability to tolerate oral therapy - Afebrile for 24 hours - Hemodynamically stable - Not neutropenic - Documented clearance of candida from bloodstream	- [16]

Voriconazole versus a regimen of amphotericin B followed by fluconazole for candidaemia in non-neutropenic patients: a randomised non-inferiority trial (2005)	- ALL patients if isolate was susceptible to fluconazole
	- Earlier switch to oral therapy if
	  - C. *Lusitaniae* isolated
	  - Unable to tolerate Amphotericin B
		- [17]

between 2 and 5 days regardless of the antimicrobial agent and the route of administration.[16,17,20] This finding could be used to set an appropriate time to consider stepping down or de-escalating the treatment safely.

No studies showed superiority of any agent, however, both the ESCMID and the IDSA guidelines suggest the initiation of echinocandins with a later step down to an appropriate agent based on the susceptibility pattern and the patient's clinical status.[5,13] The reason that these agents have become the common practice is their fungicidal activity whereby susceptibility studies have shown low MIC for Candida species including *C. glabrata* and *C. krusei*.[21,22] Furthermore, echinocandins demonstrated a survival advantage in non-neutropenic patients.[23] In addition, they are only available in intravascular formulation which puts the patients in situations where they have to stay as inpatients to receive their treatment or face the hurdles of home IV therapies. In addition, they reportedly have minimal adverse effects with limited drug interactions.[24]

However, recent case series have described treatment failure associated with growing resistance among strains comprising *C. glabrata* and C. *tropicalis*.[25,26]

Hence, it is important to establish the feasibility of a step down therapy from echinocandins in order to avoid the increasing risk of resistance. On the other hand, stepping down from IV therapy when feasible might also positively affect the healthcare cost in this subset of patients while maintaining the successful clinical outcome as shown in previous des-escalation cost effective analysis from studies from the UK and China.[27,28]

Conclusions. In conclusion, the current practice in the management and treatment of candidemia and invasive candidiasis is based on inference rather than evidence. This incites the need for more comprehensive studies comparing the different management strategies and their outcomes. Such strategies should ideally account for specific risk factors and comorbidities which will help identify candidates for early step down. However, based on the available data and the occurrence of clinical response, step down to oral therapy between days 4-7 after initiation of IV therapy seems to be reasonable in most cases. Additional studies are needed to further validate and define the clinical criteria that would allow early step down to oral therapy.

References:

1. Vincent JL, Rello J, Marshall J, Silva E, Anzueto A, Martin CD, et al. International study of the prevalence and outcomes of infection in intensive care units. JAMA. 2009;302(21):2323-9. PubMed PMID: 19952319. https://doi.org/10.1001/jama.2009.1754
2. Martin GS, Mannino DM, Eaton S, Moss M. The epidemiology of sepsis in the United States from 1979 through 2000. New Engl J Med. 2003;348(16):1546-54. PubMed PMID: WOS:000182248900005. https://doi.org/10.1056/NEJMoa02213
3. Gudlaugsson O, Gillespie S, Lee K, Vande Berg J, Hu J, Messer S, et al. Attributable mortality of nosocomial candidemia, revisited. Clin Infect Dis. 2003;37(9):1172-7. PubMed PMID: 14557960. https://doi.org/10.1086/378745
4. Pappas PG, Rex JH, Lee J, Hamill RJ, Larsen RA, Powderly W, et al. A prospective observational study of candidemia: epidemiology, therapy, and influences on mortality in hospitalized adult and pediatric patients. Clin Infect Dis. 2003;37(5):634-43. PubMed PMID: 12942393. https://doi.org/10.1086/376906
5. Pappas PG, Kauffman CA, Andes DR, Clancy CJ, Marr KA, Ostrosky-Zeichner L, et al. Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America. Clin Infect Dis. 2016;62(4):e1-50. PubMed PMID: 26679628; PubMed Central PMCID: PMCPMC4725385. https://doi.org/10.1093/cid/civ933
6. Kuse ER, Chetchotisakd P, da Cunha CA, Ruhnke M, Barrios C, Raghunadharao D, et al. Micafungin versus liposomal amphotericin B for candidaemia and invasive candidosis: a phase III randomised double-blind trial. Lancet. 2007;369(9572):1519-27. PubMed PMID: 17482982. https://doi.org/10.1016/S0140-6736(07)60605-9
7. Rex JH, Bennett JE, Sugar AM, Pappas PG, Vanderhorst CM, Edwards JE, et al. A Randomized Trial Comparing Fluconazole with Amphotericin-B for the Treatment of Candidemia in Patients without Neutropenia. New Engl J Med. 1994;331(20):1325-30. doi: PubMed PMID: WOS:A1994PR21600001.
8. Pappas PG, Rotstein CM, Betts RF, Nucci M, Talwar D, De Waele JJ, et al. Micafungin versus caspofungin for treatment of candidemia and other forms of invasive candidiasis. Clin Infect Dis. 2007;45(7):883-93. PubMed PMID: 17806055. https://doi.org/10.1086/520980
9. Betts RF, Nucci M, Talwar D, Gareca M, Queiroz-Telles F, Bedimo RJ, et al. A Multicenter, double-blind trial of a high-dose caspofungin treatment regimen versus a standard caspofungin treatment regimen for adult patients with invasive candidiasis. Clin Infect Dis. 2009;48(12):1676-84. PubMed PMID: 19419331. https://doi.org/10.1086/598933
10. Morrell M, Fraser VJ, Kollef MH. Delaying the empiric treatment of Candida bloodstream infection until positive blood culture results are obtained: a potential risk factor for hospital mortality. Antimicrob Agents Ch. 2005;49(9):3640-5. PubMed PMID: WOS: 000231542900006. https://doi.org/10.1128/AAC.49.9.3640-3645.2005
11. Oude Lashof AM, Rothova A, Sobel JD, Ruhnke M, Pappas PG, Viscoli C, et al. Ocular manifestations of candidemia. Clin Infect Dis. 2011;53(3):262-8. PubMed PMID: 21765074. https://doi.org/10.1093/cid/cir355
12. Blennow O, Tallstedt L, Hedquist B, Gardlund B. Duration of treatment for candidemia and risk for late-onset ocular candidiasis. Infection. 2013;41(1):129-34. PubMed PMID: 23212461. https://doi.org/10.1007/s15010-012-0369-8
13. Cornely OA, Bassetti M, Calandra T, Garbino J, Kullberg BJ, Lortholary O, et al. ESCMID* guideline for the diagnosis and management of Candida diseases 2012: non-neutropenic adult patients. Clin Microbiol Infect. 2012;18 Suppl 7:19-37. PubMed PMID: 23137135. https://doi.org/10.1111/1469-0691.12039
14. Reboli AC, Rotstein C, Pappas PG, Chapman SW, Kett DH, Kumar D, et al. Anidulafungin versus fluconazole for invasive candidiasis. N

Engl J Med. 2007;356(24):2472-82. PubMed PMID: 17568028. https://doi.org/10.1056/NEJMoa066906
15. Nucci M, Colombo AL, Petti M, Magana M, Abreu P, Schlamm HT, et al. An open-label study of anidulafungin for the treatment of candidaemia/invasive candidiasis in Latin America. Mycoses. 2014;57(1):12-8. PubMed PMID: 23710653. https://doi.org/10.1111/myc.12094
16. Vazquez J, Reboli AC, Pappas PG, Patterson TF, Reinhardt J, Chin-Hong P, et al. Evaluation of an early step-down strategy from intravenous anidulafungin to oral azole therapy for the treatment of candidemia and other forms of invasive candidiasis: results from an open-label trial. BMC Infect Dis. 2014;14:97. PubMed PMID: 24559321; PubMed Central PMCID: PMCPMC3944438. https://doi.org/10.1186/1471-2334-14-97
17. Kullberg BJ, Sobel JD, Ruhnke M, Pappas PG, Viscoli C, Rex JH, et al. Voriconazole versus a regimen of amphotericin B followed by fluconazole for candidaemia in non-neutropenic patients: a randomised non-inferiority trial. Lancet. 2005;366(9495):1435-42. PubMed PMID: 16243088. https://doi.org/10.1016/S0140-6736(05)67490-9
18. Glockner A, Cornely OA. Practical considerations on current guidelines for the management of non-neutropenic adult patients with candidaemia. Mycoses. 2013;56(1):11-20. PubMed PMID: 22574925. https://doi.org/10.1111/j.1439-0507.2012.02208.x
19. Zaoutis TE, Argon J, Chu J, Berlin JA, Walsh TJ, Feudtner C. The epidemiology and attributable outcomes of candidemia in adults and children hospitalized in the United States: a propensity analysis. Clin Infect Dis. 2005;41(9):1232-9. PubMed PMID: 16206095. https://doi.org/10.1086/496922
20. Reboli AC, Shorr AF, Rotstein C, Pappas PG, Kett DH, Schlamm HT, et al. Anidulafungin compared with fluconazole for treatment of candidemia and other forms of invasive candidiasis caused by Candida albicans: a multivariate analysis of factors associated with improved outcome. BMC Infect Dis. 2011;11:261. PubMed PMID: 21961941; PubMed Central PMCID: PMCPMC3203347. https://doi.org/10.1186/1471-2334-11-261
21. Pfaller MA, Boyken L, Hollis RJ, Kroeger J, Messer SA, Tendolkar S, et al. In vitro susceptibility of invasive isolates of Candida spp. to anidulafungin, caspofungin, and micafungin: six years of global surveillance. J Clin Microbiol. 2008;46(1):150-6. PubMed PMID: 18032613; PubMed Central PMCID: PMCPMC2224271. https://doi.org/10.1128/JCM.01901-07
22. Pfaller MA, Boyken L, Hollis RJ, Kroeger J, Messer SA, Tendolkar S, et al. Wild-type MIC distributions and epidemiological cutoff values for the echinocandins and Candida spp. J Clin Microbiol. 2010;48(1):52-6. PubMed PMID: 19923478; PubMed Central PMCID: PMCPMC2812271. https://doi.org/10.1128/JCM.01590-09
23. Mora-Duarte J, Betts R, Rotstein C, Colombo AL, Thompson-Moya L, Smietana J, et al. Comparison of caspofungin and amphotericin B for invasive candidiasis. N Engl J Med. 2002;347(25):2020-9. PubMed PMID: 12490683. https://doi.org/10.1056/NEJMoa021585
24. Bassetti M, Righi E, Montravers P, Cornely OA. What has changed in the treatment of invasive candidiasis? A look at the past 10 years and ahead. J Antimicrob Chemother. 2018;73(suppl_1):i14-i25. PubMed PMID: 29304208. https://doi.org/10.1093/jac/dkx445
25. Kontoyiannis DP, Vaziri I, Hanna HA, Boktour M, Thornby J, Hachem R, et al. Risk Factors for Candida tropicalis fungemia in patients with cancer. Clin Infect Dis. 2001;33(10):1676-81. PubMed PMID: 11568858. https://doi.org/10.1086/323812
26. Farmakiotis D, Tarrand JJ, Kontoyiannis DP. Drug-resistant Candida glabrata infection in cancer patients. Emerg Infect Dis. 2014;20(11):1833-40. PubMed PMID: 25340258; PubMed Central PMCID: PMCPMC4214312. https://doi.org/10.3201/eid2011.140685
27. Masterton RG, Casamayor M, Musingarimi P, van Engen A, Zinck R, Odufowora-Sita O, et al. De-escalation from micafungin is a cost-effective alternative to traditional escalation from fluconazole in the treatment of patients with systemic Candida infections. J Med Econ. 2013;16(11):1344-56. PubMed PMID: 24003830. https://doi.org/10.3111/13696998.2013.839948
28. Chen D, Wan X, Kruger E, Chen C, Yue X, Wang L, et al. Cost-effectiveness of de-escalation from micafungin versus escalation from fluconazole for invasive candidiasis in China. J Med Econ. 2018;21(3):301-7. PubMed PMID: 29303621. https://doi.org/10.1080/13696998.2017.1417312