Questioning the 14-day dogma in candidemia treatment duration

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Abstract: The growing threat of antimicrobial resistance (AMR) is a global concern. With AMR directly causing 1.27 million deaths in 2019 and projections of up to 10 million annual deaths by 2050, optimising infectious disease treatments is imperative. Prudent antimicrobial use, including treatment duration, can mitigate AMR emergence. This is particularly critical in candidemia, a severe condition with a 45% crude mortality rate, as the 14-day minimum treatment period has not been challenged in randomised comparison. A comprehensive literature search was conducted in August 2023, revealing seven original articles and two case series discussing treatment durations of less than 14 days for candidemia. No interventional trials or prospective observational studies assessing shorter durations were found. Historical studies showed varying candidemia treatment durations, questioning the current 14-day minimum recommendation. Recent research observed no significant survival differences between patients receiving shorter or longer treatment, emphasising the need for evidence-based guidance. Treatment duration reduction post-blood culture clearance could decrease exposure to antifungal drugs, limiting selection pressure, especially in the context of emerging multiresistant Candida species. Candidemia's complexity, emerging resistance and potential for shorter in-hospital stays underscore the urgency of refining treatment strategies. Evidence-driven candidemia treatment durations are imperative to balance efficacy with resistance prevention and ensure the longevity of antifungal therapies. Further research and clinical trials are needed to establish evidence-based guidelines for candidemia treatment duration.

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Questioning the 14-day dogma in candidemia treatment duration

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Abstract

The growing threat of antimicrobial resistance (AMR) is a global concern. With AMR directly causing 1.27 million deaths in 2019 and projections of up to 10 million annual deaths by 2050, optimising infectious disease treatments is imperative. Prudent antimicrobial use, including treatment duration, can mitigate AMR emergence. This is particularly critical in candidemia, a severe condition with a 45% crude mortality rate, as the 14-day minimum treatment period has not been challenged in randomised comparison. A comprehensive literature search was conducted in August 2023, revealing seven original articles and two case series discussing treatment durations of less than 14 days for candidemia. No interventional trials or prospective observational studies assessing shorter durations were found. Historical studies showed varying candidemia treatment durations, questioning the current 14-day minimum recommendation. Recent research observed no significant survival differences between patients receiving shorter or longer treatment, emphasising the need for evidence-based guidance. Treatment duration reduction post-blood culture clearance could decrease exposure to antifungal drugs, limiting selection pressure, especially in the context of emerging multiresistant *Candida* species. Candidemia's complexity, emerging resistance and potential for shorter in-hospital stays underscore the urgency of refining treatment strategies. Evidence-driven candidemia treatment durations are imperative to balance efficacy with resistance prevention and ensure the longevity of antifungal therapies. Further research and clinical trials are needed to establish evidence-based guidelines for candidemia treatment duration.

KEYWORDS
antimicrobial resistance, *Candida*, *Candida albicans*, *Candida glabrata*, *Candida* spp., *Candida tropicalis*, candidemia, drug resistance, patient quality of life, treatment duration

1 | INTRODUCTION

The emerging crisis of antimicrobial resistance (AMR) poses a serious threat to modern society. AMR was directly responsible for 1.27 million deaths worldwide in 2019.[1] In the year 2050, estimates foretell a potential annual loss of up to 10 million lives globally due to AMR-related factors if coordinated and sustainable intervention against the emergence and diffusion of AMR pathogens is not made.[2] These resistances can be linked in large part to the improper use of antimicrobials. The prudent application of infectious disease treatments, optimising their duration to achieve maximum cure rates while avoiding unnecessarily extending them, is one strategy to mitigate the emergence of AMR that stands out. For instance, in the treatment of pneumonia, urinary tract infections and intra-abdominal infections, this method has proven to be reliable and secure.[3] Turning our attention to fungal infections, the responsible use of antifungals is a key element of antimicrobial stewardship programmes as well, as their excessive application not only promotes the development of resistance but also has the potential to fuel the spread of fungal strains harbouring mutations that potentially lead to resistance to antifungals, both in yeasts, such as *Candida auris*, *Candida glabrata* or *Candida parapsilosis*, and in moulds like *Aspergillus fumigatus*.[4–8] Furthermore, prolonged antifungal therapy, especially in immunocompromised individuals, might result in the selection of opportunistic fungal diseases like Mucorales or *Fusarium* spp. These prolonged regimens of antifungal medication upset the microbial equilibrium, allowing less common but more aggressive fungi to grow and cause illnesses. These secondary infections can be difficult to control since they are frequently resistant to regular antifungal medications. When determining treatment duration, a careful balance must be struck between effectively treating the initial infection and minimising the risk of selecting for secondary, potentially more resistant infections, with special consideration for immunocompromised patients' vulnerability and the need for ongoing research to inform evidence-based guidelines for fungal infection management.[9]

Focusing on a crucial aspect of this problem, candidemia, a severe condition that primarily affects immunocompromised and critically ill people, calls for thorough investigation.[10] A population-based incidence rate of 3.88 cases per 100,000 people in Europe as of 2023 is reported, which equates to about 29,000 cases per year. As opposed to intensive care units (ICU), where the incidence rate is at 5.5 cases per 1000 ICU admissions, the pooled incidence rate in European hospitals is 0.83 cases per 1000 admissions.[11] Candidemia has a roughly 45% crude mortality rate, with even higher rates in ICU, underscoring its seriousness.[11] In the nosocomial setting, *Candida* spp. are major causes of bloodstream infections.[12,13]

Candidemia implies several physical stress factors for patients, by causing longer hospital stays, more invasive procedures and a higher risk of mortality.[13–15] Adherence to a specific set of guidelines is recommended for effective management.[12] These include interventions such as transoesophageal echocardiography and fundoscopy,[16] essential for detecting metastatic lesions as a possible result of candidemia. Additionally, candidemia has a significant impact on healthcare systems, resulting in prolonged hospital stays, interventions and higher costs, which are directly related to the recommended minimum treatment period.[14,15] Guidelines are endorsing initial empirical treatment with an echinocandin with transition to an azole therapy if the isolates are susceptible, blood culture negative and the patient clinically stable. Currently, in non-neutropenic patients, without deep-seated candidiasis or metastatic lesions, the recommended treatment duration is 14 days after documented clearance of blood cultures.[17,18] These recommendations are based on a crucial 1994 study comparing fluconazole with amphotericin B for candidemia in non-neutropenic patients.[19] However, this treatment duration was set arbitrarily. Recently, it has revealed that extended therapy with echinocandins in patients experiencing urinary tract infections caused by *Candida auris* can lead to the emergence of resistance.[20] Thus, further research is warranted because this 14-day regimen lacked the necessary empirical support. In this review, we aim to verify all the evidence currently available regarding a potential shortening of treatment duration after blood culture clearance in patients with candidemia.

2 | METHODOLOGY

In August 2023, an extensive literature search was conducted on PubMed, clinicaltrials.gov and cochranelibrary.com to gather relevant manuscripts. The primary focus of this search was to investigate available literature on the suitability of following with the currently recommended 14-day antifungal treatment duration after bloodstream clearance in patients with uncomplicated candidemia or on the contrary reduce this length. The following search strings were utilised: "(candidemia AND duration)", "(candidemia AND treatment AND duration)" and "(candidemia AND short treatment)". Studies were considered if published in English, French, German, Italian or Spanish within the last 30 years (1993–2023).

Titles and abstracts were screened to identify information on reduced treatment duration. Subsequently, full papers were assessed when the title and/or abstract hinted at pertinent data. We identified nine manuscripts consisting of seven original articles and two case series that mentioned treatment durations of less than 14 days. We did not identify any interventional trials or relevant observational studies investigating a shorter treatment duration.

2.1 | Insights from candidemia studies over the years

In 2000, a study sought to understand the epidemiological patterns and clinical presentations of late recurrent candidemia. It uncovered data on five cases with late recurrences, revealing varying treatment durations: one patient received an 11-day regimen, another received no antifungal therapy and three were treated for over 14 days. This early investigation highlighted the potential for late recurrences despite extended therapeutic efforts.[21] Moving forward to 2007,

another study compared adherence to guideline recommendations to nonadherence. In their results, the investigators showed how clinicians often initiated candidemia therapy based on clinical suspicion before microbiologic confirmation. Nonetheless, the results indicated that neither treatment duration nor inappropriate dosing significantly influenced survival outcomes.[22] Concerns about the duration of antifungal treatment were raised in 2015, highlighting that late recurrent candidemia can occur in patients who have intracardiac devices, retained surgical mesh, thromboembolism, stents, pacemakers or other electronic intracardiac devices that were not initially considered potential sources of infection during the first episode of candidemia.[23] In 2017, a subsequent study explored this topic further. Instead of specifying an exact treatment duration, it categorised treatments as appropriate or not according to candidemia guidelines. Notably, it observed no discernible difference in survival between these two categories.[24] Additionally, in 2019, researchers analysed the outcomes of patients receiving care from infectious disease physicians. Those under infectious disease consultation received notably longer candidemia antifungal treatment courses, averaging 18 days compared with the 14 days for those without such consultation. This extended duration could be attributed to various factors, according to authors, including a higher incidence of complications associated with candidemia in the infectious disease consult group. It is worth mentioning that the practice of considering the first day of the prescribed treatment course as the day when documented negative blood cultures were established, following treatment guidelines, could have also played a role. In summary, the ID consultation group displayed an overall more favourable outcome, potentially influenced by multiple contributing factors.[25] Later, in 2020, another research reported no significant differences in mortality between patients receiving early and appropriate antifungal therapy and those who did not. Of note, treatment duration was just one component within a comprehensive care bundle, with successful outcomes associated with adherence to all elements of this bundle.[26] More recently, in 2021, an analysis examined the treatment duration of 134 patients who did not adhere to the recommended guidelines. It found that 27% received treatment for 7 days or less, 41% for 7–13 days and 28% for 14 days or more. Notably, the study showed no higher mortality or recurrence based on treatment duration but highlighted that the most common reason for failure to receive appropriate initial antifungal treatment was omission of the loading dose (Table 1).[27]

3 | EXPLORING THE IDEAL TREATMENT DURATION

3.1 | Antifungal exposure and resistance management

Shortening the duration of candidemia treatment following culture clearance may offer the potential advantage of minimising patients' exposure to antifungal drugs, which in turn could contribute to the reduction of the risk of drug-resistant strains emerging. This approach becomes particularly pertinent in light of the increasing prevalence of *Candida glabrata*, *Candida parapsilosis* and multiresistant *Candida auris*.[6,16] And this concern becomes even more pronounced when transitioning from newer antifungal agents like echinocandins to oral alternatives such as fluconazole in which the emergence of drug resistance is a more obvious phenomenon.[7,8,28] A well-considered approach to adequate antifungal selection[29] is crucial to forestall the potential development of resistant strains, especially in the context

TABLE 1 Studies reporting treatment finalisation within 14 days post-blood culture clearance since 2000.

Year	Study aim	Key findings	Reference
2000	Epidemiological patterns and clinical presentations of late recurrent candidemia	• Late recurrences observed despite extended therapy • Treatment duration varied (11 days, no therapy, >14 days), but not outcome	21
2007	Comparison of guideline adherence vs. nonadherence	• Candidemia therapy often initiated based on clinical suspicion before microbiologic confirmation • Survival not significantly influenced by treatment duration or dosing	22
2017	Comparison of guideline adherence vs. nonadherence	• No discernible difference in survival between appropriate and inappropriate treatments according to guidelines	24
2019	Analysis of outcomes for patients under infectious disease consultation	• Infectious disease consultation associated with longer treatment (18 days vs. 14 days) • Potential factors influencing extended duration • No differences in outcome	25
2020	Comparison of guideline adherence vs. nonadherence	• No significant mortality differences • Comprehensive care bundle adherence associated with successful outcomes • Therapy part of the bundle	26
2021	Comparison of guideline adherence vs. nonadherence	• Treatment duration distribution: 27% ≤7 days, 41% 7–13 days, 28% ≥14 days • No higher mortality or recurrence based on duration • Common failure: omission of loading dose	27

of fluconazole usage, which has already been associated with the emergence of multiresistant species.

3.2 | Risk of relapse and mortality

While investigating late recurrence of candidemia, defined by two episodes of candidemia at least 30 days apart, several available reports suggest that treatment duration might not exert a significant impact on recurrence rates or even survival outcomes.[21,27] This finding highlights the intricate nature of candidemia as a medical entity and emphasises the need for a comprehensive assessment when determining the optimal treatment duration for individual patients. It also reinforces the understanding that candidemia is influenced by multifaceted factors that extend beyond treatment duration, prompting clinicians to embrace a holistic approach in their decision-making.[30] While not directly linked to late recurrent candidemia, it is essential to consider specific risk factors associated with this condition, including nosocomial cases, gastrointestinal diseases and a history of intravenous drug abuse. Other conditions might also be acknowledged as major risk factors, such as indwelling central venous catheter (CVCs), cardiac pacemakers, ventricular assist devices, vascular grafts and vascular endoprostheses that have not been removed.[17] In this decision-making process, the indispensable role of infectious disease physicians, is evident. Indeed, a recent publication from 2019 conducted a comparison between cases with infectious disease consultation and those without, underscoring the substantially improved outcomes observed in the former group.[25] Also related to controlling candidemia progression, recent research suggests that biomarkers such as BDG and T2MR may be useful for distinguishing between complicated and uncomplicated cases of candidemia.[31–33] However, more research is needed to validate their use in clinical practice.

3.3 | Cost-effectiveness and resource allocation

The implications of varying treatment durations for candidemia extend beyond the clinical realm to encompass significant economic considerations.[14,34] The choice between shorter and longer treatment durations impacts hospitalisation periods, thereby influencing costs, the allocation of scarce healthcare resources and also the direct correlation between extended duration of hospitalisation with an increase in the rates of healthcare-associated infections.[2] Striking an optimal balance between delivering effective treatment and optimising resource allocation is a complex task that requires careful evaluation of the clinical and economic outcomes.

3.4 | Drug toxicity, adverse effects profile

While azole-related drug toxicity is commonly associated with prolonged treatment, shorter courses of treatment can still result in hepatotoxicity, phototoxic reactions or neurotoxic effects.[35,36] Additionally, azole therapy can impact by drug–drug interactions, making it possible to mitigate these adverse effects by reducing treatment duration. Similarly, despite the potential for adverse effects such as infusion-related reactions, gastrointestinal issues, liver abnormalities and skin reactions with echinocandins, these side effects are typically mild and controllable,[37] making it feasible to minimise them by shortening the duration of treatment.

3.5 | Patient quality of life

Prolonged hospital stays, necessitated by extended treatment durations,[13] introduce a range of challenges that extend beyond the clinical realm.[14] The risk of hospital-acquired infections and the potential deterioration of patients' quality of life underscore the delicate balance required when determining the appropriate treatment duration. Minimising the adverse impact on patients' well-being becomes a crucial consideration in optimising the balance between therapeutic efficacy and treatment duration. With this regard, the once-weekly administration of echinocandins is a promising therapeutic strategy for azole-refractory candidiasis, with the potential to improve patient outcomes by facilitating earlier discharge from the hospital.[38]

3.6 | Limitations to treatment shortening strategies

There are some limitations to be considered in specific patients when evaluating a treatment shortening of less than 14 days, apart from deep organ candidiasis, chronic disseminated candidiasis or metastatic infection sites, where longer treatment periods are warranted. As neutrophil function is crucial in eliminating *Candida* spp., treatment duration should not be shortened in neutropenic patients during ongoing neutropenia.[39] This is also endorsed by current guidelines, which only support a discontinuation of antifungal treatment if neutropenia has resolved.[17,18] Furthermore, in case of uncertain duration of ongoing candidemia, which is, for example typically the case in patients with intravenous drug use, the relative risk for occult metastatic infection sites or deep-seated tissue candidiasis[40,41] is elevated. Moreoever, it is also recommended to avoid treatment reducing in patients with suppurative thrombophlebitis, pacemakers, intraventricular devices and endovascular prostheses.[17] Thus, treatment duration in this patient population should only be considered in a case-by-case evaluation.

4 | CONCLUSION

In light of the escalating threat of AMR, optimising infectious disease treatment practices, including treatment duration, is crucial. Candidemia severity and mortality rates necessitate rigorous investigation into appropriate treatment approaches. The current 14-day

minimum treatment recommendation should be adhered to, although lacking empirical support, prompting the need for evidence-based clinical trials evaluating shorter treatment durations. The intricate nature of candidemia, the emergence of resistant *Candida* strains and the potential of shortening in-hospital duration emphasise the urgency of refining treatment strategies. As AMR looms, evidence-driven candidemia treatment durations are imperative for balancing efficacy with resistance prevention and ensuring the longevity of antifungal therapies.

AUTHOR CONTRIBUTIONS

Jon Salmanton-García: Investigation; writing – original draft; resources; writing – review and editing; visualization. **Ilana Reinhold:** Writing – original draft; writing – review and editing; resources; investigation. **Juergen Prattes:** Investigation; writing – review and editing; resources. **Nico Bekaan:** Investigation; writing – review and editing; resources. **Philipp Koehler:** Investigation; writing – review and editing; resources. **Oliver A. Cornely:** Conceptualization; investigation; funding acquisition; writing – review and editing; resources.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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