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ORIGINAL ARTICLE

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EQUAL Candida Score: An ECMM score derived from current guidelines to measure QUAlity of Clinical Candidaemia Management

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Summary

Candida species frequently cause blood stream infections and are reported to be the third to tenth most commonly isolated pathogens. Guidelines and standardised treatment algorithms provided by professional organisations aim to facilitate decision-making regarding diagnosis, management and treatment of candidaemia. In routine clinical practise, however, it may be challenging to comply with these guidelines. The reasons include lack of familiarity or feasibility to adherence, but also their length and complexity. There is no tool to measure guideline adherence currently. To provide such a tool, we reviewed the current guidelines provided by the *European Society for Clinical Microbiology and Infectious Diseases (ESCMID)* and by the *Infectious Diseases Society of America (IDSA)*, and selected the strongest recommendations for management quality as the bases for our scoring tool. Factors incorporated were diagnostic (blood cultures, echocardiography, ophthalmoscopy, species identification) and follow-up procedures (repeat blood cultures until negative result) as well as key treatment parameters (echinocandin treatment, step down to fluconazole depending on susceptibility result, CVC removal). The EQUAL Candida Score weighs and aggregates

factors recommended for the ideal management of candidaemia and provides a tool for antifungal stewardship as well as for measuring guideline adherence.

KEYWORDS

Candida, Candida treatment, candidaemia, guideline adherence, score

1 | INTRODUCTION

Candida species are among the most frequently isolated causes of hospital-acquired blood stream infections .[1-4] Candidaemia causes significant morbidity and mortality [5-8] and affects particularly immunocompromised patients as well as patients treated in intensive care units .[9,10] Most *Candida* blood stream infections are caused by *Candida albicans*, followed by *Candida glabrata*, *Candida tropicalis*, *Candida parapsilosis* and *Candida krusei* depending on the geographical region and patient population.[11,12] Echinocandin resistance of *Candida* spp. has been emerging and may be promoted by the expanding use of these drugs .[12,13] To date, it occurs most frequently in *C. glabrata*.[14]Apart from immunosuppression and ICU stay, most important predisposing factors for candidaemia are use of broad-spectrum antibiotics, central vascular catheters (CVC), extremes of age, haemodialysis, mechanical ventilation, neutropenia and abdominal surgery .[15-18] Echinocandins, liposomal amphotericin B, fluconazole and voriconazole are recommended for treatment. Any delay of targeted treatment profoundly increases mortality in patients with candidaemia .[19-21] Guidelines provided by scientific societies as well as standardised treatment algorithms are available ,[6,22-26] but not always followed in everyday clinical routine practice. Reasons include lack of familiarity or feasibility of adherence. A further issue may be complexity of current guidelines providing very detailed specific recommendations but failing to give a simplified overview of the key recommendations that can be viewed at a glance.

We reviewed the current guidance documents of the *European Society for Clinical Microbiology and Infectious Diseases (ESCMID*) and the *Infectious Diseases Society of America (IDSA)* and designed a score emphasising the most important recommendations and also to provide a simple tool to assses guideline adherence.

2 | CURRENT RECOMMENDATIONS FOR DIAGNOSIS AND MANAGEMENT OF CANDIDAEMIA

Candidaemia is defined as isolation of *Candida* spp. in a blood culture drawn peripherally or from a central line.[27] Sensitivity of blood culture for detection of *Candida* spp. ranges between 50% and 75% depending on the number of bottles taken.[28]

2.1 | Diagnosis

It is essential to draw at least two pairs of blood cultures (40 mL) for diagnosis of candidaemia and due to differing susceptibility profiles to identify the *Candida* to species level.[28]

Furthermore clinical diagnostic work-up includes echocardiography and ophthalmoscopy. Ocular involvement complicating candidaemia is a rare event and mostly asymptomatic and with favourable outcome .[29] Regular performance of ophthalmoscopy has been questioned recently, but is currently recommended for all patients with candidaemia: moderate recommendation, moderate level of evidence according to the ESCMID guideline, and strong recommendation, low-quality evidence according to the IDSA guideline .[30,31] A recent post hoc analysis of a prospective, multicentre, population-based candidaemia surveillance in Spain evaluated the benefits of this and led the authors to conclude that the need for ophthalmoscopy in patients without ocular symptoms should be reconsidered.[31]

Endocarditis may be suspected when follow-up blood cultures persist to be positive, in case of persistent fever despite appropriate treatment, or when the patient has new cardiac symptoms such as a new heart murmur, signs of heart failure, or embolisms during candidaemia [32,33] The current European guidance moderately supports a recommendation of echocardiography in all patients to exclude endocarditis .[22] A prospective cohort of 187 patients showed that at least 4.2 % of candidaemia patients have *Candida* infective endocarditis. The authors highly recommend performing echocardiography due to the initially, mostly hidden nature of *Candida* endocarditis .[34] Echocardiography can be performed transthoracically but should be complemented by a transesophageal echocardiography if the transthoracic echocardiography is negative.

2.2 | Treatment

Both, ESCMID and IDSA guidelines suggest an echinocandin as first-line therapy (strong recommendation; high-quality evidence). Echinocandins are active against a wide spectrum of *Candida* spp., are active against biofilms and are generally safe drugs .[22,35,36] However, the local epidemiology must always be considered and echinocandins may not be an appropriate choice in countries where *C. parapsilosis* is common. Step-down to fluconazole may be considered if the isolate is susceptible to it. In patients who are not critically ill and had no prior exposure to either azoles or echinocandins and do not have any biofilm-baring indwelling devices, fluconazole may be considered as first-line treatment. The IDSA accepts fluconazole as first line treatment and as an alternative for these patients while only giving a weak recommendation with low-quality evidence. Based on the results of multiple RCT, candidaemia (without metastatic complications) shall be treated 14 days from the first negative culture with systemic antifungal agents.[36-40] In general, this has been associated with few complications and relapses to date. In case of metastatic foci, treatment must be adapted depending on the organ involved.

TABLE 1 EQUAL Candida Score

Quality indicator	ESCMID/IDSA guidance		Score	
	Strength of recommendation	Level of evidence	Patients with CVC	Patients without CVC
Initial blood culture (40 mL)[6,28]	Essential	n/a	3	3
Species identification[6,28]	Essential	n/a	3	3
Susceptibility testing[6,28]	Recommended	I[28]/III[6]	2	2
Echocardiography[6,22]	B	II	1	1
Ophthalmoscopy[22,31]	B	II[22]/III[6]	1	1
Echinocandin treatment[6,22]	A	I	3	3
Step down to fluconazole depending on susceptibility result[6,22]	B	II	2	2
Treatment for 14 days after first negative follow-up culture[6,22]	A[6]/B[22]	II	2	2
CVC removal[6,22,41]	A	II		n/a
≤24 hours from diagnosis			3	
>24 < 72 hours from diagnosis			2	
Follow-up blood culture (at least one per day until negative)[6,22]	B	III	2	2
Maximum score			22	19

A, Strong recommendation; B, Moderate recommendation; I, Evidence from at least 1 properly designed randomised controlled trial; II, Evidence from at least 1 well designed clinical trial, without randomisation, from cohort or case–control analytic studies, from multiple time series, or from dramatic results of uncontrolled experiments; III, Evidence from opinions of respected authorities, based on clinical experience, descriptive case studies or reports of expert committees.

Following IDSA guidance, central venous catheters (CVC) should be removed as early as possible in patients with candidaemia, whenever the CVC is the presumed source of infection and removal is safely feasible. This decision should be taken individually for each patient (strong recommendation; moderate-quality evidence).[22,35] An analysis of seven prospective randomised controlled trials for treatment of candidaemia showed an association of CVC removal with decreased mortality .[41] Yet, assessing the effects of CVC removal by observational studies is challenging and CVC removal should be decided individually for each patient.

2.3 | Follow-up period

The aim of treatment in candidaemia patients with no organ involvement is to clear the infection and to prevent deep-organ involvement. Therefore, it is recommended to treat for 14 days after the end of candidaemia. According to both the ESCMID and the IDSA guidelines, at least one blood culture per day should be obtained until culture results turn negative (moderate recommendation, low quality evidence).

3 | EQUAL-CANDIDA SCORE

To highlight the most important recommendations from both guidelines the ECMM QUALity of Clinical Candidemia Management score (Table 1) was designed. It quantifies candidaemia guideline adherence as a surrogate marker of diagnostic and therapeutic management quality when treatment is intended to cure. It is not applicable to patients who receive treatment limited to best supportive care. The EQUAL Candida Score weighs and aggregates items recommended for ideal management of candidaemia .[6,22,28,31,41] The maximum score is 20 points for CVC carriers, and 17 points for non-CVC carriers. Whether a high score correlates with outcome remains to be explored.

4 | CONCLUSION

Guidelines are fundamental for evidence based medicine. Yet, following these guidelines in daily clinical practice may be challenging. By designing the EQUAL-Candidaemia score, we aim to provide a tool for quick and simple (self-) audit for treating physicians. In addition, the score will facilitate the evaluation of guideline adherence in antifungal stewardship and future studies.

CONFLICTS OF INTEREST

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REFERENCES

1. Hoenigl M, Wagner J, Raggam RB, et al. Characteristics of hospital-acquired and community-onset blood stream infections, South-East Austria. *PLoS ONE*. 2014;9:e104702.
2. Wisplinghoff H, Ebbers J, Geurtz L, et al. Nosocomial bloodstream infections due to Candida spp. in the USA: species distribution, clinical features and antifungal susceptibilities. *Int J Antimicrob Agents*. 2014;43:78-81.
3. Wisplinghoff H, Bischoff T, Tallent SM, Seifert H, Wenzel RP, Edmond MB. Nosocomial bloodstream infections in US hospitals: analysis of 24,179 cases from a prospective nationwide surveillance study. *Clin Infect Dis*. 2004;39:309-317.
4. Lass-Flörl C. The changing face of epidemiology of invasive fungal disease in Europe. *Mycoses*. 2009;52:197-205.
5. Gudlaugsson O, Gillespie S, Lee K, et al. Attributable mortality of nosocomial candidemia, revisited. *Clin Infect Dis*. 2003;37:1172-1177.
6. Pappas PG, Kauffman CA, Andes DR, et al. Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2016;62:e1-e50.
7. Wey SB, Mori M, Pfaller MA, Woolson RF, Wenzel RP. Hospital-acquired candidemia. The attributable mortality and excess length of stay. *Arch Intern Med*. 1988;148:2642-2645.
8. Cornely OA, Gachot B, Akan H, et al. Epidemiology and outcome of fungemia in a cancer Cohort of the Infectious Diseases Group (IDG) of the European Organization for Research and Treatment of Cancer (EORTC 65031). *Clin Infect Dis*. 2015;61:324-331.
9. Shorr AF, Wu C, Kothari S. Outcomes with micafungin in patients with candidaemia or invasive candidiasis due to Candida glabrata and Candida krusei. *J Antimicrob Chemother*. 2011;66:375-380.
10. 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;41:1232-1239.
11. Falagas ME, Roussos N, Vardakas KZ. Relative frequency of albicans and the various non-albicans Candida spp among candidemia isolates from inpatients in various parts of the world: a systematic review. *Int J Infect Dis*. 2010;14:e954-e966.
12. Mellinghoff SC, Panse J, Alakel N, et al. Primary prophylaxis of invasive fungal infections in patients with haematological malignancies: 2017 update of the recommendations of the Infectious Diseases Working Party (AGIHO) of the German Society for Haematology and Medical Oncology (DGHO). *Ann Hematol*. 2017;97:197-207.
13. Goncalves SS, Souza ACR, Chowdhary A, Meis JF, Colombo AL. Epidemiology and molecular mechanisms of antifungal resistance in Candida and Aspergillus. *Mycoses*. 2016;59:198-219.
14. Arendrup MC, Perlin DS. Echinocandin resistance: an emerging clinical problem? *Curr Opin Infect Dis*. 2014;27:484-492.
15. Wenzel RP. Nosocomial Candidemia: risk Factors and Attributable Mortality. *Clin Infect Dis*. 1995;20:1531-1534.
16. Blumberg HM, Jarvis WR, Soucie JM, et al. Risk factors for candidal bloodstream infections in surgical intensive care unit patients: the NEMIS prospective multicenter study. The National Epidemiology of Mycosis Survey. *Clin Infect Dis*. 2001;33:177-186.
17. Almirante B, Rodriguez D, Park BJ, et al. Epidemiology and predictors of mortality in cases of Candida bloodstream infection: results from population-based surveillance, barcelona, Spain, from 2002 to 2003. *J Clin Microbiol*. 2005;43:1829-1835.
18. Michalopoulos AS, Geroulanos S, Mentzelopoulos SD. Determinants of candidemia and candidemia-related death in cardiothoracic ICU patients. *Chest*. 2003;124:2244-2255.
19. Garey KW, Rege M, Pai MP, et al. Time to initiation of fluconazole therapy impacts mortality in patients with candidemia: a multi-institutional study. *Clin Infect Dis*. 2006;43:25-31.
20. Blot SI, Vandewoude KH, Hoste EA, Colardyn FA. Effects of nosocomial candidemia on outcomes of critically ill patients. *Am J Med*. 2002;113:480-485.
21. 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 Chemother*. 2005;49:3640-3645.
22. Cornely OA, Bassetti M, Calandra T, et al. ESCMID* guideline for the diagnosis and management of Candida diseases 2012: non-neutropenic adult patients. *Clin Microbiol Infect*. 2012;18:19-37.
23. Bow EJ, Evans G, Fuller J, et al. Canadian clinical practice guidelines for invasive candidiasis in adults. *Can J Infect Dis*. 2010;21:e122-e150.
24. Karthaus M, Ruping MJ, Cornely OA, et al. Current issues in the clinical management of invasive candida infections–the AGIHO, DMykG, OGMM and PEG web-based survey and expert consensus conference 2009. *Mycoses*. 2011;54:e546-e556.
25. Ruhnke M, Rickerts V, Cornely OA, et al. Diagnosis and therapy of Candida infections: joint recommendations of the German Speaking Mycological Society and the Paul-Ehrlich-Society for Chemotherapy. *Mycoses*. 2011;54:279-310.
26. Koehler P, Tacke D, Cornely OA. Our 2014 approach to candidaemia. *Mycoses*. 2014;57:581-583.
27. De Pauw B, Walsh TJ, Donnelly JP, et al. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. *Clin Infect Dis*. 2008;46:1813-1821.
28. Cuenca-Estrella M, Verweij PE, Arendrup MC, et al. ESCMID* guideline for the diagnosis and management of Candida diseases 2012: diagnostic procedures. *Clin Microbiol Infect*. 2012;18(Suppl 7):9-18.

29. Munoz C, Carlet J, Fitting C, Misset B, Bleriot JP, Cavaillon JM. Dysregulation of in vitro cytokine production by monocytes during sepsis. *J Clin Invest*. 1991;88:1747-1754.
30. Vena A, Muñoz P, Padilla B, et al. Is routine ophthalmoscopy really necessary in candidemic patients? *PLoS ONE*. 2017;12:e0183485.
31. Munoz P, Vena A, Padilla B, et al. No evidence of increased ocular involvement in candidemic patients initially treated with echinocandins. *Diagn Microbiol Infect Dis*. 2017;88:141-144.
32. Card L, Lofland D. Candidal endocarditis presenting with bilateral lower limb ischemia. *Clin Lab Sci*. 2012;25:130-134.
33. Tacke D, Koehler P, Cornely OA. Fungal endocarditis. *Curr Opin Infect Dis*. 2013;26:501-507.
34. Fernandez-Cruz A, Cruz Menarguez M, Munoz P, et al. The search for endocarditis in patients with candidemia: a systematic recommendation for echocardiography? A prospective cohort. *Eur J Clin Microbiol*. 2015;34:1543-1549.
35. Pappas PG, Kauffman CA, Andes D, et al. Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2009;48:503-535.
36. Reboli AC, Rotstein C, Pappas PG, et al. Anidulafungin versus Fluconazole for Invasive Candidiasis. *N Engl J Med*. 2007;356:2472-2482.
37. Pappas PG, Rotstein CM, Betts RF, et al. Micafungin versus caspofungin for treatment of candidemia and other forms of invasive candidiasis. *Clin Infect Dis*. 2007;45:883-893.
38. Kuse E-R, Chetchotisakd P, da Cunha CA, et al. Micafungin versus liposomal amphotericin B for candidaemia and invasive candidosis: a phase III randomised double-blind trial. *Lancet*. 2007;369:1519-1527.
39. Betts RF, Nucci M, Talwar D, 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;48:1676-1684.
40. Cornely OA, Vazquez J, De Waele J, et al. Efficacy of micafungin in invasive candidiasis caused by common Candida species with special emphasis on non-albicans Candida species. *Mycoses*. 2014;57:79-89.
41. Andes DR, Safdar N, Baddley JW, et al. Impact of treatment strategy on outcomes in patients with candidemia and other forms of invasive candidiasis: a patient-level quantitative review of randomized trials. *Clin Infect Dis*. 2012;54:1110-1122.

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