Towards shorter therapy for candidaemia: defining uncomplicated candidaemia in adults

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Although the characteristics of complicated candidaemia are well known, uncomplicated disease remains undefined. Recommended treatment duration for candidaemia is 14 days after bloodstream infection is cleared. Longer treatment duration might be required if candidaemia is complicated by deep organ involvement or by immunocompromising conditions such as neutropenia, uncontrolled haematological malignancy, or in the context of haematopoietic stem-cell transplantation. Complicated candidaemia might further be assumed in prolonged and high-dose glucocorticosteroid exposure, candidaemia recurrence, or with echinocandin-resistant pathogens. In this Review, outcome data were analysed to identify criteria differentiating between complicated and uncomplicated candidaemia in adults. We propose defining uncomplicated candidaemia by controlled source, clinical response, and clearance of the bloodstream within 5 days of appropriate antifungal treatment. Further data are needed to support or challenge our proposed definitions. Shorter treatment courses in this population meeting the definition criteria for uncomplicated candidaemia warrant evaluation in randomised controlled clinical trials.

Introduction

Candidaemia is defined by isolation of *Candida* species from at least one blood culture.[1] However, the disease course of candidaemia can vary individually depending on the duration of bloodstream infection, which can range from 1 day to several days.[2] Regardless of the individual course, current guidelines recommend a uniform treatment duration of 14 days after *Candida* clearance from the bloodstream.[1] The tradition of this 14-day standard has remained unchallenged since it was first applied in a randomised controlled trial more than 30 years ago.[3]

For bacterial infections, traditional standard treatment durations have been challenged and adapted successfully based on clinical trials.[4] Candidaemia that is complicated by deep-seated infections requires antifungal treatment for several weeks, and can include other treatments, such as surgery, or other interventions yielding source control.[1] Candidaemia without such deep organ involvement is clinically referred to as uncomplicated candidaemia,[5] but no precise definition has been proposed to date. In 1993, a comparative study of 29 patients with candidaemia without neutropenia and without deep-seated candidiasis were selected for a shorter than standard treatment duration based on the duration of positive blood cultures and clinical findings.[6] No relapse or worse clinical cure rate of the shorter treatment was documented, but generalisability of these findings was limited due to the small sample size.[6] Since this study, no other systematic approach has been published to adapt the current treatment strategy for candidaemia.

In this Review, we aim to define uncomplicated candidaemia by identifying factors that distinguish it from cases requiring a treatment duration of 14 days or more. If these patient-derived factors or disease characteristics are not present, candidaemia might possibly be treated sufficiently with a shorter course of treatment. A clear definition of uncomplicated candidaemia could guide clinicians on distinguishing these cases from potentially complicated courses of candidaemia that require timely diagnostics to rule out deep-seated infection. We propose a definition of uncomplicated candidaemia to characterise patients who might ultimately be considered for a shorter treatment duration.

Methods

A total of 5347 articles were retrieved. Titles were screened for relevant articles on studies including analysis of candidaemia or other forms of invasive candidiasis followed by screening of abstracts. Paediatric patients were excluded from further selection. All primary publications, case reports, and review articles

Key messages

- The spectrum of candidaemia ranges from one single positive blood culture to persistence over several days, whereas, per current guidelines, treatment lasts a uniform 14 days after clearance of blood cultures.
- Although candidaemia might appear uncomplicated in some people, there is no definition distinguishing uncomplicated candidaemia from complicated candidaemia.
- This Review analysed patient characteristics, mycological criteria, antifungal treatment, and management strategies predicting outcome of candidaemia.
- Uncomplicated candidaemia was defined as *Candida* spp clearance from blood with documented appropriate source control and clinical response within 5 days of antifungal treatment.
- Complicated candidaemia was indicated by any criteria of prolonged bloodstream infection, immunosuppression, intravenous drug use, extra-abdominal organ candidiasis, echinocandin-resistant species, or recurrence.
- Current treatment duration in people with uncomplicated candidaemia warrants evaluation in randomised controlled trials.

Lancet Infect Dis 2026; 26: e112–23

Published Online August 20, 2025 https://doi.org/10.1016/S1473-3099(25)00409-8

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See Online for appendix

were evaluated for relevance. Articles for which the selected criteria for predictive outcomes were assessed were further analysed. Full-text articles were retrieved when the title and abstract did not provide sufficient information to establish their suitability. Further publications were identified through an analysis of references within relevant articles. In the absence of relevant studies on the topic, consensus articles were used as a source. Guidelines on candidiasis were reviewed regarding additional relevant publications.[7,8]

Although complicated candidaemia is generally well characterised, we assessed potential host, clinical, and microbiological criteria predictive for complicated candidaemia (figure 1). Screening of host characteristics regarding immunosuppression were based on host factors defined in the consensus definition for invasive fungal disease by the European Organization for Research and Treatment of Cancer (EORTC) and the Mycoses Study Group Education and Research Consortium (MSGERC).[9] The studies were reviewed for all available outcome data, including attributable and all-cause mortality, duration of hospitalisation, rates of candidaemia recurrence, and rates of invasive candidiasis. Studies were ranked by design (prospective study ranks higher than retrospective), size, and adjustment for key confounding factors. Where findings were contradictory, the outcome results and conclusion were discussed among the authors in online group meetings. The proposed definition for uncomplicated candidaemia is outlined in the panel, and relevant time intervals to distinguish uncomplicated from complicated cases are provided in figure 2 (a detailed review of the litereature is provided in the appendix).

Definitions of uncomplicated and complicated candidaemia applied in the literature

We identified six publications that defined uncomplicated or complicated candidaemia. In a retrospective cohort analysing treatment duration for *Candida* bloodstream infection, uncomplicated candidaemia was defined as the absence of clinically evident metastatic infection or deep-seated infection—in particular, endophthalmitis, endocarditis, thrombophlebitis, joint infection, or other secondary manifestations involving a foreign body.[5] A questionnaire developed by a European study group on the management of uncomplicated bloodstream infection included patients who are immunocompetent, without endocarditis, without implantable material, after removal of vascular catheters (if present), and no secondary complications or deep-seated infections.[55,56]

Endocarditis or other endovascular infections, septic metastases, recurrent bloodstream infection, or attributable mortality during follow-up were defined as complicated candidaemia in a prospective microbiological study analysing the persistence of *Candida* DNA in blood.[57] Invasive diseases (eg, endovascular focus, deep-seated abscess, urinary tract infection, or retinal findings) or

Evaluated criteria

Host characteristics		Uncomplicated	Complicated
Neutropenia <500 cells per μL		≤10 days in the past 30 days	>10 days in the past 30 days
Glucocorticosteroids		<3 weeks prednisone equivalent to ≥0·3 mg/kg per day	≥3 weeks prednisone equivalent to ≥0·3 mg/kg per day
Haematological malignancy		In remission	No remission
Allogeneic HSCT		No	Yes
Acute GvHD grade III or IV		No	Yes
Intravenous illicit drug use		No	Yes
History of invasive candidiasis or candidaemia		No	Yes
Source control		**Uncomplicated**	**Complicated**
Central venous line		Removal within 48 h after diagnosis	No removal
Intracardiac devices		No	Yes
Extracorporeal membrane oxygenation		No	Yes
Intra-abdominal candidiasis		Source control within 5 days	No source control >5 days
Extra-abdominal organ involvement		No	Yes
Microbiological factors		**Uncomplicated**	**Complicated**
Duration of candidaemia		Candidaemia <120 h	Candidaemia ≥120 h
Susceptibility		Echinocandin-susceptible *Candida* spp	Echinocandin-resistant *Candida* spp

Figure 1: **Clinical and microbiological criteria evaluated to distinguish uncomplicated from complicated candidaemia**
The following criteria were also evaluated, but did not differentiate between uncomplicated and complicated candidaemia: solid organ transplant recipient, T-cell depleting therapy, chronic GvHD, use of vasopressors, time from blood culture sampling to treatment initiation, time to positivity of initial blood culture, serum markers, and other assays for candidaemia diagnostics. GvHD=graft-versus-host disease. HSCT=haematopoietic stem-cell transplantation.

having a clinically significant underlying condition (eg, neutropenia [<500 cells per µL]) were defined as complicated candidaemia in a pilot study that evaluated an amphotericin B treatment strategy.[6] Complicated candidaemia was also defined as the presence of *Candida* endocarditis, *Candida* endophthalmitis, or CNS candidiasis in a review on the transition from intravenous to oral antimicrobial therapy.[58]

Host characteristics

Recent history of neutropenia

Neutrophils are crucial to the elimination of *Candida* species.[2,59] Guidelines recommend longer antifungal treatment duration of candidaemia in the presence of neutropenia with treatment continued until resolution of neutropenia.[7] In a systematic review of 17 randomised controlled trials on treatment of invasive candidiasis in patients with neutropenia, profound and prolonged neutropenia was associated with poor outcome of candidaemia cases.[10] In a multicentre observational cohort study on 100 patients, neutropenia was a considerable predictor for prolonged hospitalisation to complete intravenous antifungal treatment.[11]

In the presence of neutropenia (<500 cells per µL for more than 10 days occurring in the past 30 days), we propose to define candidaemia as complicated. The timeframe of 10 days was chosen based on the EORTC–MSGERC host criteria. The exact duration of recently recovered neutropenia is often missing in studies. Therefore, 30 days is based on a cutoff chosen that appears to be a safe interval for functional neutrophil recovery.

Solid organ transplant recipients

Few studies are available on candidaemia in solid organ transplant recipients, despite *Candida* species being the most common cause of invasive fungal disease in this population (except for lung transplant recipients).[60] Liver transplant recipients appear to be at higher risk for invasive candidiasis than other solid organ transplant recipients.[61–63] In two multicentre studies with candidaemia, the prospective data showed that the rate of unsuccessful treatment outcome was 25·5% and 30-day all-cause mortality was 15 (27·3%) of 55 solid organ transplant recipients.[61]

In the studies reviewed, outcome depended on transplant organ type, intensity of immunosuppression, and severity of candidaemia—namely, septic shock, and was directly linked to the time elapsed since transplantation and graft rejection. Most studies even showed a lower all-cause mortality rate than in the non-solid organ transplant population with candidaemia. A potential explanation for this lower rate was the immunomodulatory response due to post-transplant immunosuppression, which offers a survival advantage in bacterial sepsis.[64] Careful evaluation upon candidaemia should be conducted in liver transplant recipients and small bowel transplant recipients, as candidaemia in these patients is often associated with deep-seated infections.[63] Solid organ transplant recipients, as such, do not define complicated candidaemia, but additional risk factors for complicated candidaemia should be carefully assessed in this patient population.

Glucocorticosteroid treatment

In a meta-analysis of 18 cohort studies, patients with candidaemia receiving glucocorticosteroid therapy had significantly worse clinical outcomes, including higher mortality than those not receiving glucocorticosteroids.[14] Survival rates at 42 days after initiation of micafungin were lower in patients who had received glucocorticosteroids at baseline, as shown in pooled data from two randomised trials.[12] Glucocorticosteroids were associated with significantly higher mortality in a

***Panel:* Definition criteria for uncomplicated candidaemia after 5 days of treatment**

Absence of relevant immunosuppression

- No neutropenia (<500 cells per µl) for more than 10 days in the last 30 days[9–13]
- No recent or newly initiated ongoing use of glucocorticosteroids (≥0·3 mg/kg per day for ≥3 weeks)[9,12–17]
- No haematological malignancy without remission[18–24]
- No allogeneic haematopoietic stem-cell transplantation[25,26]
- No acute graft-versus-host disease grade III or IV[16,27]

Absence of active illicit intravenous drug use[28–33]

Controlled source

- Central venous line, if any, is removed within 24–48 h after diagnosis of candidaemia[1,13,34–37]
- No implantable cardiac electronic device, ventricular assist device, extracorporeal membrane oxygenation, or indwelling intravascular foreign body that cannot be removed present at onset of candidaemia[38–43]
- Intra-abdominal candidiasis (eg, abdominal abscess or peritonitis) is surgically or interventionally controlled[44–49]

Absence of extra-abdominal deep-seated candidiasis

- No central nervous system infection, chorioretinitis, endophthalmitis, intravascular infection, endocarditis, renal abscess, osteomyelitis, or joint infection[1,50,51]

Clinical response

- No attributable signs or symptoms for persistent candidaemia 120 h or more after treatment initiation
- No signs, symptoms, or indicative imaging for deep-seated candidiasis 120 h or more after treatment initiation

Mycological response

- Candidaemia less than 120 h between blood draws of the index blood culture and the first negative blood culture[52,53]

Antifungal susceptibility testing available

- Absence of echinocandin-resistant *Candida* species[54]

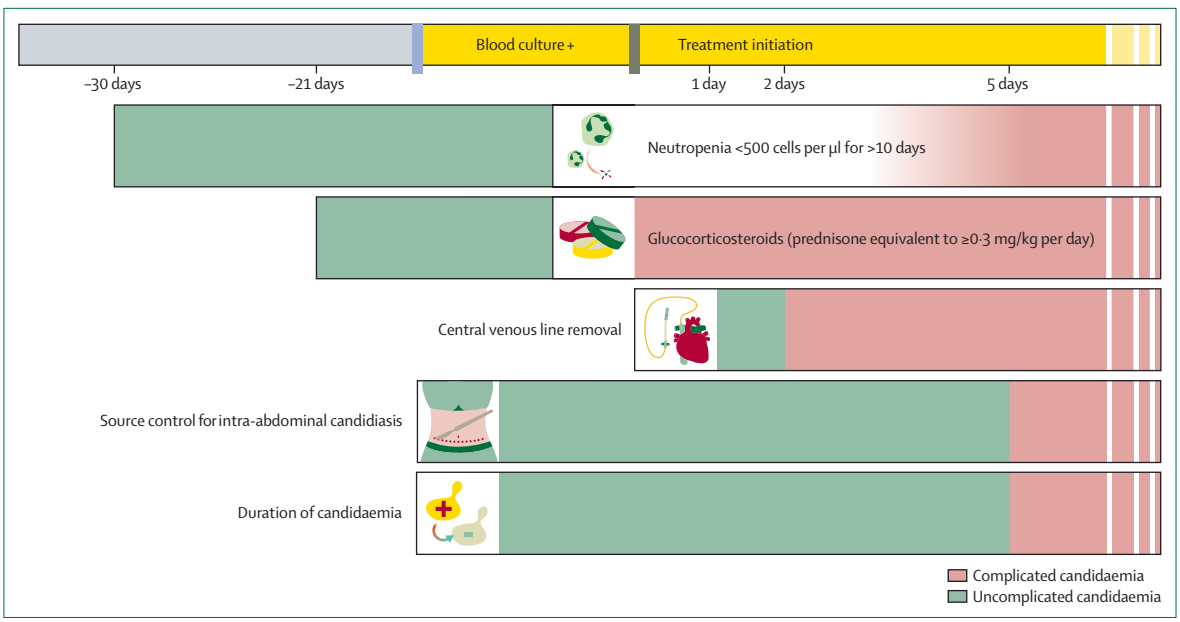

Figure 2: **Time-dependent criteria proposed to distinguish uncomplicated from complicated candidaemia**
Timeline depicting the onset of candidaemia (upper blue rectangle), timing of antifungal treatment initiation (upper grey rectangle), and time-dependent criteria. Day 0 refers to initiation of antifungal treatment. Criteria proposed to enter definition of complicated candidaemia are: neutropenia for over 10 days in the past 30 days, ongoing use of glucocorticosteroids for 21 days or more, missing removal of central venous line for over 48 h, missing source control of intra-abdominal candidiasis for over 5 days, and duration of candidaemia for 120 h or more.

retrospective cohort of 720 patients with candidaemia, however, dosing information was not reported.[13] Previous glucocorticosteroid exposure of more than 10 mg/d methylprednisolone for more than 5 days was not associated with early mortality in a retrospective univariate analysis of 752 patients who were critically ill with candidaemia.[15]

Use of glucocorticosteroids remains difficult to assess as a criterion for uncomplicated candidaemia. We regard patients receiving at least 0·3 mg/kg per day prednisone equivalent for 3 weeks or more at risk for a complicated candidaemia course, independent of the indication. This precise dosage and timeframe was chosen according to the consensus of the EORTC–MSGERC criteria, as better quality of evidence is not available.[9,65]

T-cell depleting therapies

Since most of the reviewed studies did not specify previous T-cell depleting drugs in their multivariate analyses, it is difficult to assess effects of T-cell suppression on the outcome of candidaemia.[66,67] Outcome might differ between primary diseases leading to T-cell depleting treatment whereas patients with haematological malignancies are likely to develop a complicated course of candidaemia due to concurrent factors, such as neutropenia or glucocorticosteroid use. Candidaemia during interleukin inhibitor treatment in autoimmune conditions can be regarded as uncomplicated. Currently, T-cell depleting or modulating therapy alone is not sufficient to define complicated candidaemia.

Haematologic malignancy

There is a significant overlap with data on the outcome of patients with neutropenia with candidaemia, especially during induction chemotherapy.[18–21,68,69] In a retrospective cohort with haematological malignancy and candidaemia, lymphoma and mulitple myeloma were associated with significantly higher all-cause mortality rates in multivariate analysis.[22] Haematological malignancy not in remission is indicative of complicated candidaemia, in view of the poor outcomes.

Allogeneic haematopoietic stem-cell transplantation

Since fluconazole prophylaxis became standard of care, incidence of invasive candidiasis after allogeneic haematopoietic stem-cell transplantation (HSCT) declined.[69] Allogeneic HSCT was independently associated with poor outcome in a retrospective cohort analysing patients who were critically ill and immunocompromised with candidaemia.[25]

Studies on outcome regarding invasive candidiasis in the allogeneic HSCT population are characterised by heterogeneity (ie, different haematological malignancies, therapy regimens, low granularity of fungal infection reporting, and focus on incidence of invasive fungal disease rather than outcome).[25,26] Therefore, these studies are difficult to guide the decision-making process for

definition criteria. As allogeneic HSCT often results in clinically significant neutropenia during pre-engraftment and is followed by impaired cellular immunity, candidaemia after allogeneic HSCT is considered complicated.

Acute graft-versus-host disease

In a retrospective analysis of 469 HSCT recipients with candidaemia, acute graft-versus-host disease (GvHD), from grade III to IV, independently predicted all-cause mortality, whereas no association was observed for GvHD of grade II. Grade I was not explicitly analysed. The overall incidence of candidaemia was 1·7%, mostly presenting as breakthrough infection during antifungal prophylaxis or treatment.[27] Acute GvHD, from grade III to IV, has been identified as an independent negative prognostic factor in patients with candidaemia and, therefore, is considered a criterion for complicated candidaemia.

Chronic GvHD

Chronic GvHD predisposes for candidaemia in the late phase after allogeneic HSCT, but was not identified as a significant risk factor for mortality.[27] Therefore, chronic GvHD does not define complicated candidaemia, but additional risk factors for complicated candidaemia should be carefully assessed in this patient population.

Active illicit intravenous drug use

Candidaemia in patients with intravenous drug use was frequently associated with deep-seated infections. Surveillance programmes have reported increased incidences of disseminated candidiasis with end-organ involvement, including cases of osteomyelitis.[28–30] Endocarditis was found to be ten times more likely in patients with intravenous drug use (30 [39%] of 77 patients) than in patients without (three [3%]) in a retrospective analysis. Candidaemia was more frequently associated with late recurrent candidaemia as observed in surveillance analyses.[31,32] Candidaemia in patients with active illicit intravenous drug use has a high risk for deep-seated infections and, therefore, qualifies as complicated candidaemia.

Previous invasive candidiasis or candidaemia

Recurrent episodes of candidaemia or invasive candidiasis were heterogeneously defined in studies including the terms of early versus late recurrence—usually after 30 days, and differentiating between relapse or reinfection. Relapse could be distinguished from reinfection by molecular typing of *Candida* strains.[70] A second episode of candidaemia after more than 30 days was reported in 326 (6%) of 5428 patients with candidaemia in surveillance data.[31] Predisposing factors for recurrent candidaemia were similar to those for a first episode and included abdominal surgery, gastrointestinal disease, intravenous drug use, and total parenteral nutrition.[31,32,71] Recurrent candidaemia suggested an uncontrolled source of infection, such as an intravascular focus or abdominal abscess. Mortality at 1 year was eight (50%) of 16 patients with candidaemia that recurred after more than 1 month, compared with 8 (25%) for control patients without recurrence in a retrospective study of 1219 candidaemia episodes.[72]

Recurrent invasive candidiasis is considered complicated candidaemia as it is commonly associated with an uncontrolled source of infection and higher mortality rates compared with the first episode. We define recurrent candidaemia as a second episode within 90 days to allow for late relapse scenarios and to ensure a safety margin.

Use of vasopressors

Large prospective cohort studies on candidaemia did not analyse vasopressor therapy as a risk factor. However, intensive care unit admission was associated with worse outcomes of patients with candidaemia, and the use of vasopressors might be a surrogate for intensive care treatment.[66,73] Vasopressor use, as such, does not define complicated candidaemia, however, additional risk factors for complicated candidaemia should be carefully assessed

Source control

Candidaemia can lead to secondary biofilm formation on surfaces of indwelling vascular catheters or medical devices present at diagnosis, which poses challenges for effective antifungal treatment. Consequently, risk of persistent infection is increased.[74] Intra-abdominal candidiasis, including abscesses and peritonitis, are further clinical scenarios where source control is a cornerstone of successful candidaemia treatment.[1,7] The optimal timing of source control as a predictor of outcome differs based on the type of infection, with distinct considerations seen between catheter-related infections and intra-abdominal candidiasis. Missing source control makes any episode of candidaemia complicated.

Central venous lines

In a meta-analysis, central venous catheter removal was associated with improved survival in patients with candidaemia in 40 of 73 observational studies. The analysis pooled several outcome measures, including overall mortality and the time until bloodstream clearance.[34] In a patient-level quantitative review of seven randomised controlled trials of 1915 patients with candidaemia, invasive candidiasis, or both, central venous catheter removal was associated with decreased all-cause mortality at 30 days after treatment initiation. Removal within 48 h after onset of candidaemia was associated with improved outcome in a retrospective cohort including 720 patients.[13] By contrast, removal within 48 h after diagnosis of candidaemia had no effect on mortality.[75] Removal within 24–48 h after treatment initiation was not associated with clinical benefit in 842 patients from two randomised controlled trials on candidaemia.[76]

Data on the effect of removing specific types of central venous access devices—such as peripherally inserted central catheters, Hickman and Broviac lines, or implanted port systems—were not explicitly reported. Given the similar risk of biofilm formation across these device types[77] and their similar roles in central venous access, we propose that central venous lines should not be differentiated in the definition criteria. Central venous lines should be removed to increase likelihood of uncomplicated candidaemia. If removal is conducted within 24–48 h after diagnosis of candidaemia, it is considered uncomplicated. If removal is not feasible, candidaemia is considered complicated.

Intracardiac medical devices

In a systematic review, pooled outcome data of 48 patients with fungal infection of cardiac implantable electronic devices showed increased mortality in patients (four [44·4%] of nine) when the device was retained compared with extraction (three [7·7%] of 39). Duration of antifungal treatment in most patients after extraction was more than 6 weeks.[38] In a retrospective cohort of 300 patients with ventricular assist devices, 23 (7·6%) developed *Candida*-related device infections. In these 23 patients, clinical and mycological cure was reached in four (17·4%) and five (21·7%) patients, respectively, corresponding to an all-cause mortality of 21 (91%) patients and a ventricular assist device infection-related mortality of 15 (65%) patients.[39] If the device cannot be removed, current European Confederation of Medical Mycology and Infectious Diseases Society of America guidelines recommend removing all intracardiac devices in conjunction with antifungal treatment for 4–6 weeks or more.[7,8] Candidaemia in patients with a cardiac implantable electronic device or ventricular assist device should be regarded as complicated.

Extracorporeal membrane oxygenation

In a cohort of 368 patients on venovenous extracorporeal membrane oxygenation (ECMO) support, incidence of invasive candidiasis was reported in 20 (5·4%) of patients. Clearance of infection was reached in 12 (54·5%) of 22 patients after a median of 3·5 days. In ten patients, invasive fungal disease persisted despite adequate antifungal treatment. In-hospital mortality of patients with candidaemia was 16 (80%) compared with nine (40·9%) of 22 control patients with matched non-invasive fungal disease.[40] Patients who are critically ill and receiving ECMO support showed a high variability in pharmacokinetics due to alterations in the volume of distribution and in clearance, as well as drug sequestration in the ECMO circuit. Evidence on optimal antifungal dosing is scarce, increasing the risk of subtherapeutic drug concentrations.[41] Candidaemia in patients receiving ECMO should be considered complicated.

Intra-abdominal candidiasis

Intra-abdominal candidiasis mainly presents as abdominal abscess or peritonitis and is associated with high mortality.[78,79] As concurrent candidaemia is only found in a small subset of patients with intra-abdominal candidiasis, diagnosis remains challenging and requires regular re-evaluation and risk stratification of patients.[44,78,79] Limited penetration of antifungal treatment into the peritoneal cavity might increase the risk of unsuccessful treatment in patients with intra-abdominal candidiasis.[80–82] Optimal duration of antifungal treatment in intra-abdominal candidiasis remains unclear. Treatment duration should be guided by individual circumstances and, in most cases, antifungal treatment should be continued for at least 2 weeks with longer treatment durations where there are persistent signs and symptoms or imaging findings.[7] A multidisciplinary expert panel suggested continuing antifungal treatment after clinical improvement for at least 10–14 days in patients who are immunocompetent.[7,83] Early source control within 5 days after collection of samples positive for *Candida* species independently predicted survival in 163 patients who were critically ill in a retrospective study. 100-day mortality ranged from seven (88%) of eight patients with primary peritonitis to 11 (19%) of 59 patients with intra-abdominal abscesses.[44] Source control within 5 days, in conjunction with antifungal treatment, was associated with improved outcomes in most of the reported studies, particularly 30-day mortality for patients who were critically ill. It was identified as the sole independent risk factor for 30-day mortality in another study.[45–47] Intra-abdominal candidiasis should define complicated candidaemia unless source control is performed by surgery or other interventions within 5 days and if adequate antifungal treatment is administered.

Extra-abdominal deep-seated candidiasis

Extra-abdominal deep-seated invasive candidiasis includes CNS infection, chorioretinitis, endophthalmitis, intravascular infection, endocarditis, renal abscess, osteomyelitis, and joint infection. In the event of persistently positive blood cultures or persistent fever despite appropriate antifungal treatment, deep-seated candidiasis should be ruled out by echocardiography and other imaging studies. Current guidelines endorse a prolonged course of antifungal treatment for deep-seated candidiasis due to the formation of biofilms and as source control can often only be achieved by surgery or other interventions.[1,7]

Extra-abdominal deep-seated candidiasis defines complicated candidaemia, and prolonged treatment is required. Most entities of deep-seated candidiasis should be investigated within 5 days after the start of antifungal treatment.[1] Therefore, we propose that uncomplicated candidaemia can be confirmed when deep-seated candidiasis is ruled out within 5 days after treatment initiation.

Time from blood culture sampling to treatment initiation

Timely initiation of antifungal treatment, irrespective of the specific antifungal drug used, was associated with improved outcomes in multiple studies.[84–86] The effect of timing varied with the cutoff points selected. A retrospective cohort study showed a reduced mortality rate of one (11·1%) of nine patients when treatment was initiated within 12 h from the first blood culture drawn versus 49 (33·1%) of 148 patients when treatment was initiated after 12 h. Multivariate analysis identified a delay of more than 12 h between blood culture draw and initiation of antifungal treatment as an independent predictor of mortality.[84] The strongest association with unfavourable outcomes was observed for treatment delays of 24 h or more between blood culture draw and initiation of appropriate antifungal treatment.[84–86] Diagnosis of candidaemia should result in prompt initiation of appropriate antifungal treatment. The specific topic of time from blood culture turning positive to treatment initiation has scarcely been evaluated when compared with studies that analyse time to treatment initiation after first blood culture draw.[87–89] Favourable outcomes were seen in patients receiving empirical antifungal treatment—an approach that should not be included as a generalised treatment strategy of candidaemia. A precise timepoint to start antifungal treatment upon diagnosis of candidaemia is not retained as definition criterion for uncomplicated candidaemia. Nevertheless, antifungal treatment should be started as promptly as possible upon diagnosis of candidaemia.

Time to positivity of initial blood culture

No correlation between time to positivity of the initial blood culture and mortality was found in a meta-analysis of 24 studies.[90] In a retrospective study over 5 years and 100 episodes of candidaemia, survival did not differ between episodes with time to positivity of less than 24 h compared with more than 24 h.[91] A shorter time to positivity was associated with increased 30-day mortality in an analysis of 415 candidaemia episodes.[92] There was no clear association of time to positivity with patient outcome in most studies and results are conflicting.[90–94] Furthermore, the difference in time to positivity for different *Candida* species was statistically significant, confounding the interpretation of outcome data.[93] A short time to positivity of the initial blood culture alone does not define complicated candidaemia.

Mycological response to treatment

Persistent candidaemia, despite appropriate treatment, defined clinical failure in large prospective studies.[59] Cohorts and clinical trials reported various median or mean durations of candidaemia lasting 2–5·6 days during antifungal treatment with amphotericin B, caspofungin, fluconazole, or micafungin.[2,15,95–99] An analysis of a cohort of 773 patients who were critically ill with candidaemia found no association between persistent candidaemia of more than 3 days and mortality.[15] A population-based surveillance study of 752 candidaemia episodes treated in 2010 and 2011 supported this result.[20] Randomised clinical trials comparing anidulafungin with fluconazole[96] and rezafungin with caspofungin[100,101] found differences in mycological response without clinically significant effect on mortality.

We propose defining persistent candidaemia as persistent bloodstream infection with ongoing microbiological evidence of *Candida* species with a duration of 120 h or more—ie, the time between the first blood draw of a positive culture and the first blood draw of a negative blood culture. This cutoff has been used in recent cohorts on persistent candidaemia,[102–105] as well as secondary outcome measures recommended by the European Medicines Agency and US Food and Drug Administration for clinical trials.[100,101,106,107] The presence of persistent candidaemia defines complicated candidaemia. Candidaemia lasting less than 120 h between blood draws of the index blood culture and the first negative blood culture is considered uncomplicated candidaemia.

Candida species and antifungal susceptibility

Several studies from different geographical regions have found that candidaemia caused by *Candida albicans* is associated with lower mortality than infections caused by other *Candida* species. Data from seven randomised controlled trials showed a 30-day mortality of 601 (31·4%) of 1915 patients. Mortality for *C albicans* was 250 (29·9%) of 837 patients and for *Candida parapsilosis* 68 (22·7%) of 299 patients compared with candidaemia caused by *Candida glabrata*, *Candida tropicalis*, and *Candida krusei* mortality, which was 223 (37·3%) of 598 patients.[35] *C glabrata* (23·7–50%) and *C tropicalis* (41·4–81·2%) were associated with particularly high mortality rates in several studies, whereas *C parapsilosis* candidaemia was associated with lower mortality rates (7·7–28%).[35,108–111] Previous antifungal exposure, particularly to azoles, was identified as an independent risk factor for breakthrough infections primarily by *C glabrata*, but also by *C tropicalis*.[112,113] A retrospective analysis of candidaemia caused by fluconazole-resistant *C parapsilosis* in 196 patients and fluconazole-susceptible *C parapsilosis* in 261 patients found 30-day all-cause mortality was not associated with fluconazole-resistance nor initial antifungal treatment.[92] Mutations in the *FKS* genes of *C glabrata* and *Candida auris*, which lead to echinocandin resistance, were associated with higher mortality rates due to unsuccessful treatment. These genetic changes reduced the efficacy of echinocandins, complicating treatment and contributing to poor outcomes.[54] Mortality was higher in patients with infections caused by biofilm-forming *Candida* species (59·9–75%) than non-biofilm forming species (32·3–45·8%).[114,115] Uncomplicated candidaemia can be defined only after antifungal susceptibility testing has been reviewed. With echinocandins being the recommended first-line treatment for candidaemia, we propose to define

candidaemia with echinocandin-resistant strains as complicated.

Serum markers and other assays

Evidence directly comparing outcomes of beta-D-glucan (BDG)-positive and BDG-negative candidemia is limited, although several studies have explored whether subsequent BDG positivity or PCR-based detection correlates with poorer outcomes. Lower mortality was seen in 103 patients who were critically ill, with decreasing BDG concentrations over the course of treatment.[116] In a retrospective single centre study with 93 episodes of candidaemia, no significant differences between BDG-positive and BDG-negative groups were observed for 30-day mortality.[117] In most studies, initially increased biomarker concentrations, such as BDG, do not predict a poorer outcome. Therefore, a combination of positive biomarkers and standard culture cannot be used to define complicated or uncomplicated candidaemia.

Search strategy and selection criteria

PubMed was searched for articles and studies published in English, French, German, and Spanish between Jan 1, 1999, and March 1, 2025 using the following search terms: (uncomplicated AND (candidemia OR candidaemia)) OR ((candidemia OR candidaemia OR "invasive candidiasis") AND (neutropenia OR neutropenic) AND (outcome OR mortality)) OR ((candidemia OR candidaemia OR "invasive candidiasis") AND "solid organ transplantation") OR ((candidemia OR candidaemia) AND (corticosteroid OR steroid OR glucocorticoid OR prednisone)) OR ((candidemia OR candidiasis) AND (outcome OR mortality) AND (abatacept OR azathioprine OR basiliximab OR "calcineurin inhibitor" OR "TNF-alpha" OR ruxolitinib OR "JAK inhibitor" OR "IL-6 inhibitor" OR "IL-12 inhibitor" OR "IL-17 inhibitor" OR "IL-23 inhibitor" OR "anti-lymphocyte globulin" OR "anti-thymocyte globulin")) OR ((candidemia OR candidaemia) AND ("haematologic malignancy" OR "hematologic malignancy" OR neoplasia) AND (outcome OR mortality)) OR ((candidemia OR candidaemia OR candida) AND "graft versus host") OR ((candidemia OR candidaemia) AND ("intravenous drug use" OR "injection drug use")) OR ((recurrence OR recurrent OR relapse OR reinfection) AND (candidaemia OR candidemia)) OR (((candidemia OR candidiasis) AND (outcome OR mortality OR survival) AND ("central venous catheter" OR "central line" OR CVC)) AND ("cardiac implantable electronic devices" OR CIED OR pacemaker OR "ventricular assist device" OR VAD OR "extracorporeal membrane oxygenation" OR ECMO)) OR (("central line" OR broviac OR hickmann OR port OR PICC) AND ("blood stream infection" OR candidemia OR candidaemia)) OR ((candidemia OR candidiasis) AND (outcome OR mortality OR survival) AND ("invasive candidiasis" OR "intraabdominal candidiasis" OR IAC OR "abdominal abscess" OR peritonitis)) OR ("deep-seated candidiasis" OR candida AND (endocarditis OR osteomyelitis)) OR ((candidemia OR candidiasis) AND (outcome OR mortality) AND ("intensive care unit" OR vasopressor OR "hemodynamic support")) OR ((candidemia OR candidiasis) AND "treatment response") OR ((candidemia OR candidaemia) AND (auris OR glabrata OR parapsilosis OR tropicalis OR albicans OR krusei) AND (patient* OR mortality OR survival OR outcome OR study OR trial OR retrospective OR prospective OR multicenter)) OR ((candidemia OR candidaemia OR candida) AND "time to positivity") OR ((BDG OR "beta-D-glucan" OR ß-D-glucan) AND (outcome OR mortality) AND (candidaemia OR candidemia)) OR ((PCR OR molecular OR T2) AND (outcome OR mortality) AND (candidaemia OR candidemia)). Clinicaltrials.gov was searched for the terms "candidaemia, "candidemia", "candidiasis".

Limitations

Our Review found a high number of relevant studies, but is limited by the heterogeneity of populations and outcome measures. During our search, we found mainly retrospective analyses, with few randomised clinical trials and prospective studies, therefore restricting the clinical applicability of our proposed definition. Some studies included patients with candidaemia treated with fluconazole as first-line treatment, which is no longer recommended in guidelines.[1] Furthermore, mortality attributable to candidaemia was often not reported. The scarcity of statistical adjustment for confounders in several studies restricted the interpretation of the criterion's independent effect on the outcome. In some clinical settings, deep-seated infection cannot always be ruled out within 5 days, therefore limiting the use of our proposed definition.

Conclusion

The definition we propose for uncomplicated candidaemia (panel; figure 2) could have two applications. In clinical practice, the definition might be used to identify patients at low risk for a complicated disease course, and lead to shorter treatment duration than what is currently recommended while acknowledging the aforementioned limitations. We do not yet advocate such individualised treatment at this stage. The second application of our criteria is to help define a patient population for comparative clinical trials, evaluating whether shorter is better for patients with candidaemia.

To validate our definition for uncomplicated candidaemia, the suggested criteria should be applied to cohorts of patients with candidaemia. This process would allow the comparison of outcome data between complicated and uncomplicated candidaemia, and also trigger adjustments to the criteria. Ultimately, only a double-blind, randomised controlled trial will provide evidence as to whether patients with uncomplicated candidaemia are currently overtreated.

Contributors

IR and OAC wrote the original manuscript draft. SP, BL, DS, JS, and RS substantially contributed to manuscript writing. SP, BL, DS, JS, RS, PK, and TR critically revised the draft. All authors approved the final manuscript.

Declaration of interests

IR declares a speaker fee from Menarini Group. SP declares travel support from Gilead Sciences. BL declares honoraria from AstraZeneca, Gilead, GSK, Johnson & Johnson, and Moderna. JS declares grants paid to his institution from the German Federal Ministry of Education and Research (BMBF), the Medical Faculty of the University of Cologne, Basilea Pharmaceutica, Noscendo, and Scynexis; consulting fees from Alvea Vax, Gilead, Mundipharma, and Micron Research; speaker fees from AbbVie, Akademie für Infektionsmedizin, Forum für Medizinische Fortbildung (FomF), Hikma, Gilead, Lilly, and Pfizer; and travel support from Page Medical. PK declares grants paid to his institution from BMBF, the Bundesweites Forschungsnetz Angewandte Surveillance und Testung, Nationales Pandemie Kohorten Netz, German National Pandemic Cohort Network, Netzwerk Universitätsmedizin, Network of University Medicine, the State of North Rine-Westphalia, and the

Dr Heinz Lux-Stiftung; consulting fees from Ambu, Gilead Sciences, Mundipharma, Noxxon, and Pfizer; honoraria from Akademie für Infektionsmedizin, Ambu, Astellas Pharma, BioRad Laboratories, European Confederation of Medical Mycology (ECMM), Gilead Sciences, GPR Academy Ruesselsheim, HELIOS Kliniken, Jazz Pharmaceuticals Germany, medupdate, MedMedia, MSD, Pfizer, Scilink Comunicación Científica, and University Hospital LMU Munich; board participation for Ambu, Gilead Sciences, Pfizer Pharma, Mundipharma, and Noxxon; honoraria for reviews and royalties from book authorships from Elsevier; and an unpaid role of Editor for *Mycoses* (Wiley) and *Annals of Medicine* (Taylor & Francis online). PK also declares a German patent application (DE 10 2021 113 007.7) has been filed by the University of Cologne, of which he is listed as one of three inventors. TR declares speaker fees from Akademie für Infektionsmedizin and Hikma. RS declares grants from the German Centre for Infection Research (DZIF) and Ministerium für Kultur und Wissenschaft des Landes Nordrhein-Westfalen paid to her institution; honoraria from Pfizer, Akademie für Infektionsmedizin, Hikma, Mundipharma, and FomF; travel support from ECMM, Pfizer, Page Medical, and the European Society of Clinical Microbiology and Infectious Diseases; and has board membership for Young ECMM and the Deutschsprachige Mykologische Gesellschaft Foundation. OAC declares grants paid to his institution from iMi, Ihi, BMBF, Cidara, DZIF, EU Directorate-General Research and Innovation, F2G, Gilead, MedPace, MSD, Mundipharma, Octapharma, Pfizer, and Scynexis; consulting fees from AbbVie, AiCuris, Basilea, Biocon, Cidara, Elion Therapeutics, Gilead, GSK, IQVIA, Janssen, Matinas, MedPace, Menarini, Molecular Partners, Melinta, Mycoses Study Group-Education and Research Consortium, Mundipharma, Noxxon, Octapharma, Pardes, Partner Therapeutics, Pfizer, PSI, Scynexis, Seres, and Seqirus; honoraria from Abbott, AbbVie, Akademie für Infektionsmedizin, Al-Jazeera Pharmaceuticals–Hikma, amedes, AstraZeneca, Deutscher Ärzteverlag, Gilead, GSK, Grupo Biotoscana–United Medical–Knight, Ipsen Pharma, Medscape–WebMD, MedUpdate, MSD, Moderna, Mundipharma, Noscendo, Paul-Martini-Stiftung, Pfizer, Sandoz, Seqirus, Shionogi, streamedup!, Touch Independent, and Vitis; payment for expert testimony from Cidara; and board participation for AstraZeneca, Boston Strategic Partners, Cidara, IQVIA, Janssen, MedPace, Melinta, PSI, Pulmocide, Shionogi, The Prime Meridian Group, and Vedanta Biosciences. DS declares no competing interests.

Acknowledgments

We thank Matteo Oliverio for his contribution of the figures and Ullrich Bethe for proofreading the manuscript.

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