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A five-year retrospective descriptive study on the clinical characteristics and outcomes of candidaemia at a tertiary hospital in South Africa

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ABSTRACT

Objectives: To describe the clinical features, microbiological profiles and outcome of patients with candidaemia at a tertiary hospital in South Africa.

Methods: A retrospective study of blood cultures isolating *Candida* species at Tygerberg Hospital from 2014 to 2019.

Results: We identified 108 patients with candidaemia. The most frequent species cultured were *Candida albicans* (51; 47.2%) followed by *C. glabrata* (32; 29.6%), *C. parapsilosis* (11; 10.2%), then *C. tropicalis* (5; 4.6%). No treatment was given in 31 patients (28.7%), of whom 22 (71%) demised. Few patients were screened for complications. Of 14 screened by ophthalmoscopy, none had complications of ophthalmitis, 1 of 23 who underwent echocardiography had infective endocarditis, and 1 of 3 screened had hepatosplenic abscess. Case fatality rate was 59 of 108 (55%). Multivariable logistic regression for predictors of mortality showed that patients with diabetes mellitus were twice as likely to die from candidaemia (odds ratio (OR) 2.43; $P=0.079$). Failure to consult with Infectious Diseases increased the likelihood of mortality 3 times (OR 2.99; $P=0.041$).

Conclusions: The all-cause mortality of patients with candidaemia was high. Many patients did not have follow up on blood cultures performed, were not screened for complications, nor had antifungal treatment. The study highlighted the role of Infectious Diseases consultation for candidaemia.

Introduction

Candida are yeasts that exist as commensals in anatomical sites such as the skin, female genital tract, and gastrointestinal tract, and may be found as colonising organisms in expectorated sputum and the urine of patients with indwelling catheters (Achkar & Fries, 2010). Candidaemia refers to the presence of *Candida* species in the bloodstream. Invasive candidiasis refers to bloodstream infections with *Candida* species (candidaemia) and deep-seated infection such as intra-abdominal abscess, peritonitis or osteomyelitis with or without candidaemia (Pappas et al., 2018). The fourth most common cause of nosocomial bloodstream infections in the USA is candidaemia, accounting for 9% of all nosocomial bloodstream infections, with an associated high mortality rate of 57% (Wisplinghoff et al., 2004; Fraser et al., 2018). In South Africa (SA), the annual burden of candidaemia is estimated at 5421 cases per year

(Schwartz et al., 2019), with a reported crude mortality of 60% (Kreusch & Karstaedt, 2013).

There are more than 150 species of *Candida*; the most frequent pathogens in humans are *C. albicans*, *C. krusei*, *C. parapsilosis*, *C. tropicalis* and *C. glabrata* (Shoham & Levitz, 2005). In SA, *C. albicans* used to be the most common species, followed by *C. glabrata* then *C. parapsilosis* (Kreusch & Karstaedt, 2013, Mnge et al., 2017). However, a national survey in SA for 2016–2017 showed that *C. parapsilosis* had become the lead species, followed by *C. albicans* then *C. krusei* (Van Schalkwyk et al., 2019). *C. auris* is a multidrug-resistant species, resistant to common disinfectants and desiccation, responsible for nosocomial infection causing invasive disease. Since its emergence only a decade ago, infection has been reported in 42 countries (Chakrabarti & Sood, 2021). The most recent reports (2019–2020) are from Italy, Sudan, Costa Rica and Mexico (Chakrabarti & Sood, 2021). In SA, *C. auris* incidence was highest in

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Gauteng province during 2016–2017 in private hospitals (Van Schalkwyk et al., 2019).

The risk factors for candidaemia include haematological malignancies, solid organ tumours, abdominal surgery, prolonged intensive care unit (ICU) stay, use of broad-spectrum antibiotics, haemodialysis, use of immunosuppressant drugs, central venous pressure (CVP) catheters and total parenteral nutrition (TPN) (Masur et al., 1977; Kullberg & Arendrup, 2015). The complications of candidaemia include ophthalmitis, endocarditis and hepatosplenic abscesses (Kaufmann, 2015; Masood and Sallah, 2005). Manifestations of invasive candidiasis include central nervous system candidiasis, pyelonephritis and osteomyelitis (Kullberg & Arendrup, 2015). The ability of *Candida* to form drug-resistant biofilms is a contributing factor for disease (Giannini, 2018). Biofilms contribute to the difficulty in treating patients with systemic infections due to their higher resistance to antifungal drugs and host immune response (Ramage et al., 2005). Devices, such as catheters and heart valves, provide suitable surfaces for adhesion and subsequent anchoring of biofilms (Lim et al., 2012).

The clinical course of a patient with candidaemia is difficult to predict. All patients with candidaemia should receive intervention, including antifungal therapy and the removal of contaminated catheters and devices (Evans, 2010). It is important to remove the source of *Candida*, for example, by removing CVP and haemodialysis catheters. However, it should never be assumed that removal of a catheter alone is adequate therapy for candidaemia, and treatment with the appropriate antifungal agent must be commenced (Pappas et al., 2015). *Candida* found in blood cultures should never be viewed as a contaminant as candidaemia may manifest as reversible intravascular catheter contamination to life-threatening sepsis (Evans, 2010).

According to the Infectious Diseases Society of America guidelines (Pappas et al., 2015), the recommended duration of therapy for candidaemia without obvious metastatic complications is for 2 weeks after documented clearance of *Candida* species from the bloodstream, as evidenced by a negative surveillance culture. Therefore, follow-up blood cultures should be done every day or every other day to establish the time point at which the candidaemia has been cleared. Blood cultures that are persistently positive should result in radiological imaging, such as abdominal ultrasound or computed tomography to look for intra-abdominal abscesses and echocardiography to detect endocarditis (Pappas et al., 2015). In non-neutropenic patients with candidaemia, fundoscopy should be done in the first week to look for chorioretinitis, macular involvement and vitritis (Pappas et al., 2015). For neutropenic patients, it is recommended to delay the examination until neutrophil recovery.

We aimed to describe the *Candida* species, risk factors, management and outcomes of patients with candidaemia admitted to the adult wards of a tertiary hospital in Cape Town, South Africa.

Materials and methods

Study design and setting

We conducted a single centre retrospective, observational study on all blood cultures isolating a *Candida* species at Tygerberg Hospital from January 2014 to December 2018. Tygerberg Hospital is a public tertiary academic hospital located in Cape Town, Western Cape. It is the largest hospital in the Western Cape and the second largest in SA, serving an urban and rural population of over 3.4 million people. The hospital has 1384 beds and 67 wards.

Inclusion and exclusion criteria

Patients older than 18 years with a blood culture isolating *Candida* species were included in the study.

Data collection and processing

Cases were identified through the electronic microbiology laboratory database. Candidaemia from patients outside of Tygerberg Hospital, duplicated results and ascitic fluid in culture medium were not included in the database. Electronic medical notes and pharmacy records were reviewed for each patient. Baseline data including age, gender, ward, species and resistance to antifungals were recorded. The risk factors of ICU duration, prior antibiotics, abdominal surgery, CVP catheters, haemodialysis, haematological malignancies, corticosteroids, diabetes, HIV and diabetes mellitus were noted. Complications of ophthalmitis, infective endocarditis and hepatosplenic abscesses were documented. We examined management in the wards and specifically looked at whether an Infectious Diseases opinion was obtained, if the correct dosage and treatment of antifungals were administered, if follow up blood cultures were done, whether echocardiography and fundoscopy were performed, and whether central lines were removed. The outcome of in-hospital death or discharge was noted.

Data were collected on a specifically designed data collection form and then entered into a REDCap database. Data were then exported into Statistical Package for the Social Sciences software (SPSS) for analysis.

Data analysis

Descriptive analysis was done using frequency tables and summary statistics using SPSS software. Univariate and multivariable logistic regression models were generated to assess risk factors and predictors of mortality from candidaemia. Crude and adjusted odds ratios, 95% CIs and *P* values were reported.

Results

We identified candidaemia in 175 specimens from adult patients. After excluding duplicate samples and specimens other than blood submitted in blood culture bottles (e.g., ascitic fluid), 108 patients were entered into the final database (Figure 1). The mean patient age was 50 (SD 16.8) years. The gender distribution was 56 female (51.9%) and 52 male (48.1%). Patients were managed in the internal medicine wards ($n=32$, 29.6%) and surgical wards ($n=32$, 29.6%), ICU ($n=22$, 20.4%), urology ward ($n=11$, 10.2%), haematology-oncology ($n=8$, 7.4%) and general oncology ($n=3$, 2.8%). The risk factors were previous antibiotic usage in ($n=62$, 58.5%), liver dysfunction (41, 39.4%), CVP catheter usage ($n=35$, 35.3%), diabetes mellitus ($n=29$, 28.4%), HIV ($n=13$, 12.6%), haemodialysis ($n=13$, 12.3%), haematological malignancy ($n=10$, 9.6%), TPN ($n=10$, 9.5%), malignancy ($n=9$, 8.8%) and corticosteroid use ($n=9$, 8.6%) (Table 1).

The mean duration of treatment was 16 days (SD 11). No treatment was given in 31 patients (29, 2%), of whom 22 demised (71%). Follow up blood cultures were done on 41 patients (38%) and 29 patients (26.9%) had an Infectious Diseases consultation. Ophthalmological examination was undertaken in 14 patients (13.2%) and echocardiography in 23 patients (21.7%). Of the 14 patients who had fundoscopy, none had complications of ophthalmitis. Of the 2 patients who had echocardiography, 1 patient (0.9%) had developed infective endocarditis, and out of 3 patients who had imaging, 1 (0.9%) had hepatosplenic abscesses.

The most frequent *Candida* species encountered were *C. albicans* (51 patients, 47.2%), *C. glabrata* ($n=32$, 29.6%) and *C. parapsilosis* ($n=11$, 10.2%) followed by *C. tropicalis* ($n=5$, 4.6%). Other *Candida* species were found in 9 patients (8.3%) (Figure 2). Fluconazole resistance was found in 35 isolates (31.5%), 32 in *C. glabrata* (91.4%) and 3 in *C. krusei* (8.6%).

The mortality rate was 55% ($n=59$). Univariate analysis on the predictors of mortality showed that TPN ($P=0.042$), abdominal surgery ($P=0.002$), diabetes mellitus ($P=0.0011$), liver dysfunction ($P=0.043$)

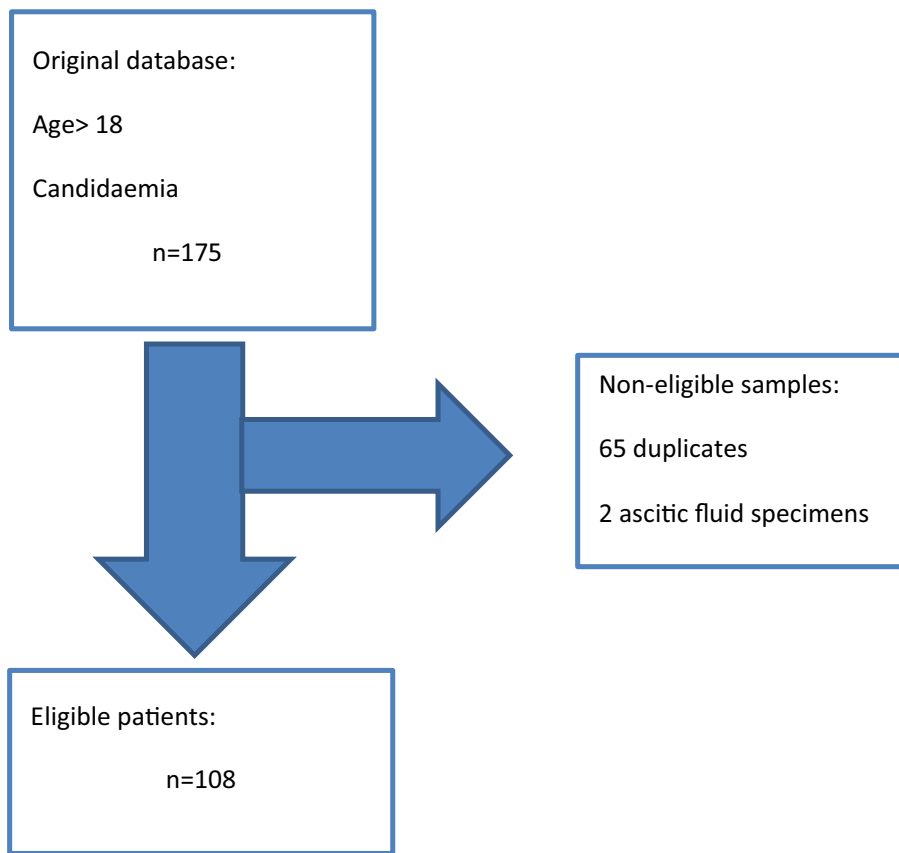


Figure 1. Study participation flowchart

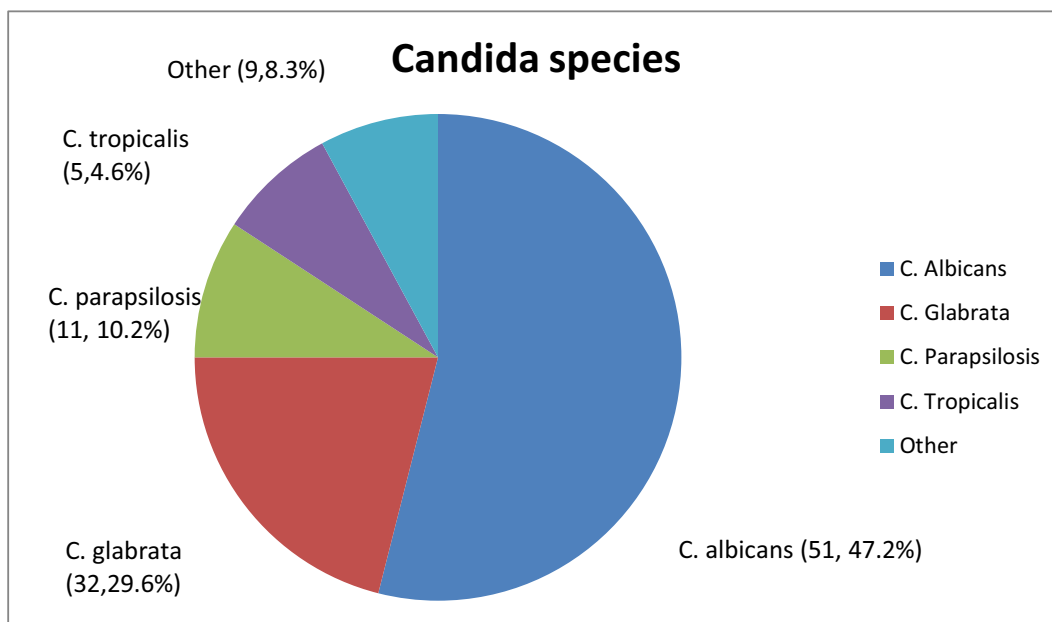


Figure 2. Candida species pie chart

and no consultation with an Infectious Diseases specialist ($P=0.11$) were predictors for mortality (Table 2). TPN therapy was confounded by abdominal surgery, and after adjusting for abdominal surgery, it was not a significant risk factor, although numbers of patients with TPN were very small ($n=10/9.52\%$). Abdominal surgery, diabetes mellitus, liver dysfunction and cases without consultation with an Infectious Diseases specialist were entered into a multivariable analysis which showed that patients without consultation with an Infectious Diseases specialist were

3 times more likely to die (95% CI, 1.05–8.57) and those with abdominal surgery were 73% less likely to die ($P=0.01$) (Table 3).

Discussion

Our study found that a significant number of patients with candidaemia did not have follow up blood cultures done, were not screened for complications of candidaemia or did not have antifungal treatment

Table 1
Risk factors for Candidaemia

	n	%
Antibiotics (n=106)		
Yes	62	58,5
No	39	36,8
Not documented	5	4,7
Abdominal surgery (n=103)		
No	68	66
Yes	35	34
Central venous catheter (n=99)		
Yes	35	35,4
No	37	37,4
Not documented	27	27,3
Total parenteral nutrition (n=105)		
Yes	10	9,5
No	90	85,7
Not documented	5	4,8
Haemodialyses (n=105)		
No	92	87,6
Yes	13	12,4
Haematological malignancies (n=104)		
No	94	90,4
Yes	10	9,6
Malignancy (n=102)		
Yes	9	8,8
No	93	91,2
Corticosteroids (n=105)		
Yes	9	8,6
No	94	89,5
Not documented	2	2
Diabetes (n=102)		
No	73	71,6
Yes	29	28,4
HIV (n=103)		
Yes	13	12,6
No	45	43,7
Unknown	45	43,7
Liver dysfunction (n=104)		
Yes	41	39,4
No	32	30,8
Not documented	31	29,8

Table 2
Univariate analysis-risk factors with mortality

Risk factor	Crude OR	95% C.I.	P value
Gender (reference : Male)			
Female	1.75	0.80 - 3.80	0.61
ICU stay (reference: No)			
Yes	0.41	0.10 - 1.65	0.21
Antibiotics (reference: No)			
Yes	1.50	0.67 - 3.40	0.33
Central Venous Catheter (reference: No)			
Yes	0.72	0.28 - 1.82	0.48
Total Parenteral Nutrition (reference: No)			
Yes	0.11	0.13 - 0.92	0.04
Haemodialysis (reference: No)			
Yes	2.17	0.66 - 7.20	0.20
Haematological malignancies (reference: No)			
Yes	1.29	0.35 - 4.80	0.70
Corticosteroids (reference: No)			
Yes	2.59	0.60 - 11.04	0.20
Diabetes (reference: No)			
Yes	3.24	1.31 - 8.01	0.01
Liver dysfunction (reference: No)			
Yes	2.86	1.03 - 7.88	0.04
Abdominal surgery (reference: No)			
Yes		0.09 - 0.59	0.00
Discussion with ID (reference: Yes)			
No	2.12	0.84 - 5.34	0.11
Not documented	0.56	0,14 - 2.16	0.40

ICU: Intensive Care Unit, ID: Infectious Diseases.

Table 3
Multivariable logistic regression model of predictors of mortality

Risk factor	Adjusted OR	95% C.I.	P value
Abdominal surgery (reference: No)*			
Yes	0.27	0.01 - 0.74	0.01
Diabetes (reference: No)			
Yes	2.43	0.90 - 6.58	0.08
Discussion with ID (reference: Yes)			
No	3.00	1.05 - 8.57	0.04
Undocumented	0.69	0.16 - 2.94	0.62

* Adjusted for Total Parenteral Nutrition and liver dysfunction

prescribed. We also found an increased risk of mortality when an Infectious Diseases consultation was not done.

Of concern is that the proportion of patients who had no antifungal treatment prescribed in this study was higher than previously reported (Tedeschi et al., 2016). Untreated candidaemia is associated with increased mortality (Fraser et al., 2018). A retrospective, multicentre observational study on candidaemia in Italy found that 13.8% of patients did not receive any treatment at all, which contributed disproportionately to mortality (Tedeschi et al., 2016). We hypothesise that the reasons for the absence of treatment may be a lack of follow up on culture results before a patient is discharged, or patients may have died before fungal culture results were released.

Only half of the patients had follow up blood cultures performed, and an Infectious Diseases consultation was done in less than half of the patients, with increased mortality if not referred. Evidence suggests that candidaemia management is more appropriate, with a resulting benefit to in-hospital mortality, in hospitals that have Infectious Diseases consultation available (Tedeschi et al., 2016, Kobayashi et al., 2020).

Although this study shows a low rate of complications such as endocarditis, intra-abdominal abscesses and ophthalmitis, we are concerned that such cases may have been missed due to a low proportion of patients being referred for fundoscopy or screened for infective endocarditis or intra-abdominal abscesses. This lack of screening and referral suggests a lack of awareness on how to manage candidaemia, highlighting the need for antifungal stewardship. An Italian study of candidaemias in internal medicine wards found that a low proportion of patients had their central catheters removed, underwent fundoscopy and echocardiography, or were treated with an antifungal, confirming insufficient knowledge of guidelines and recommendations on candidaemia management (Tedeschi et al., 2016).

In our study, *C. albicans* was the most frequently cultured Candida species, followed by *C. glabrata*, then *C. parapsilosis*. This finding is consistent with recent studies in SA and the USA, Northern Europe and Australia, which show an increased number of *C. glabrata* cases (Mnge et al., 2017, Guinea, 2014, Chapman et al., 2017). More than half of the patients in our study had a history of prior antibiotic usage, and the emergence of *C. glabrata* has been linked to widespread antibiotic use. All *C. glabrata* isolates and *C. krusei* isolates were resistant to fluconazole, consistent with the known association of these species with fluconazole resistance. This finding contrasts with a local study in Eastern Cape, SA, which showed fluconazole resistance in *C. albicans* and *C. tropicalis* and in 81% of *C. glabrata* isolates (Mnge et al., 2017), which may reflect inappropriate antifungal usage. There were no isolates of nosocomial *C. auris* infections during our study.

Liver disease and diabetes mellitus were major risk factors associated with mortality in this study, consistent with previous studies (De Rosa et al., 2013, Cortés et al., 2021). In a single-centre cohort study in Soweto, SA, the most frequent risk factors for candidaemia were HIV, abdominal surgery and diabetes mellitus (Kreusch & Karstaedt, 2013).

The limitations of the study include that it was a retrospective, single-centre study with a small study population. Data collection was reliant on electronic patient records captured by the primary caregiver,

which may have influenced the quality of data obtained. In addition, the incidence of candidaemia may have been underestimated as deep-seated candidiasis may be blood culture negative (Clancy & Nguyen, 2013). There may also have been referral bias, with a larger proportion of less seriously ill patients referred for an Infectious Diseases consultation and more seriously ill patients dying before a consultation could take place. Further research is needed to address any potential selection bias.

Conclusion

Our study highlights the urgent need for antifungal stewardship in our hospital setting. In this single-centre study in a large academic hospital, a significant number of patients with candidaemia did not have follow up blood cultures, were not screened for complications or did not have antifungal treatment prescribed. Candidaemia should never be viewed as a ‘contaminant’. There was an increased risk of mortality when Infectious Diseases consultation was not done, highlighting the role of involving an Infectious Diseases specialist when managing a patient with candidaemia.

Declaration of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Author contributions

MH and AP conceptualised the study. MH conducted the data collection. MH did the statistical analysis. MH prepared the first draft. AP and AW reviewed the manuscript. All authors approved the final manuscript.

Ethical approval

The protocol was approved by the Stellenbosch University Health Research Ethics Committee (Reference No: HEA-2020-10865).

References

Achkar JM, Fries BC. Candida infections of the genitourinary tract. *Clinical Microbiology Reviews* 2010;23(2):253–73. doi:[10.1128/CMR.00076-09](https://doi.org/10.1128/CMR.00076-09).

- Chakrabarti, A., & Sood, P. (2021). On the emergence, spread and resistance of *Candida auris*: host, pathogen and environmental tipping points. doi:[10.1099/jmm.0.001318](https://doi.org/10.1099/jmm.0.001318).
- Chapman B, Slavin M, Marriott D, Halliday C, Kidd S, Arthur I, ... Boan P. Changing epidemiology of candidaemia in Australia. *Journal of Antimicrobial Chemotherapy* 2017;72(4):1103–8. doi:[10.1093/jac/dkw422](https://doi.org/10.1093/jac/dkw422).
- Clancy CJ, Nguyen MH. Finding the missing 50% of invasive candidiasis: How nonculture diagnostics will improve understanding of disease spectrum and transform patient care. *Clinical Infectious Diseases* 2013;56(9):1284–92. doi:[10.1093/cid/cit006](https://doi.org/10.1093/cid/cit006).
- Cortés JA, Montañez AM, Carreño-Gutiérrez AM, Reyes P, Gómez CH, Pescador A, ... Rosso F. Risk factors for mortality in Colombian patients with candidemia. *Journal of Fungi* 2021;7(6). doi:[10.3390/jof7060442](https://doi.org/10.3390/jof7060442).
- De Rosa FG, Treacarichi EM, Montrucchio C, Losito AR, Raviolo S, Posteraro B, ... Tumbarello M. Mortality in patients with early- or late-onset candidaemia. *Journal of Antimicrobial Chemotherapy* 2013;68(4):927–35. doi:[10.1093/jac/dks480](https://doi.org/10.1093/jac/dks480).
- Evans SE. Coping with *Candida* infections. *Proceedings of the American Thoracic Society* 2010;7(3):197–203. doi:[10.1513/pats.200907-075AL](https://doi.org/10.1513/pats.200907-075AL).
- Fraser VJ, Jones M, Dunkel J, Storfer S, Clinical S, Diseases I, ... Louis S. *Candidemia in a Tertiary Care Hospital : Epidemiology, Risk Factors, and Predictors of Mortality* Medoff and W . Claiborne Dunagan Published by : Oxford University Press Stable URL : <https://www.jstor.org/stable/4456622>. *Candidemia in a Tertiary Care Hosp* 2018;15(3):414–21.
- Giannini, M. J. S. M. (2018). *Candida* species : current epidemiology, pathogenicity, biofilm formation, natural antifungal products and new therapeutic options, (2013), 10–24. <https://doi.org/10.1099/jmm.0.045054-0>
- Kaufmann CA. Complications of Candidemia in ICU Patients: Endophthalmitis, Osteomyelitis, Endocarditis. *Semin Respir Crit Care Med*. 2015;36(5):641–9. doi:[10.1055/s-0035-1562891](https://doi.org/10.1055/s-0035-1562891).
- Kobayashi T, Marra AR, Schweizer ML, Eyck PTen, Wu C, Alzunitan M, ... Diekema DJ. Impact of infectious disease consultation in patients with candidemia: A retrospective study, systematic literature review, and meta-analysis. *Open Forum Infectious Diseases* 2020;7(9):1–11. doi:[10.1093/ofid/ofaa270](https://doi.org/10.1093/ofid/ofaa270).
- Kreusch A, Karstaedt AS. Candidemia among adults in Soweto, South Africa, 1990–2007. *International Journal of Infectious Diseases* 2013;17(8):e621–3. doi:[10.1016/j.ijid.2013.02.010](https://doi.org/10.1016/j.ijid.2013.02.010).
- Kullberg BJ, Arendrup MC. Invasive Candidiasis. *New England Journal of Medicine* 2015;373:1445–56. doi:[10.1056/NEJMra1315399](https://doi.org/10.1056/NEJMra1315399).
- Lim, C. S., Rosli, R., Seow, H. F., & Chong, P. P. (2012). *Candida* and invasive candidiasis : back to basics, 21–31. <https://doi.org/10.1007/s10096-011-1273-3>
- Masood, A., & Sallah, S. (2005). Chronic disseminated candidiasis in patients with acute leukemia : emphasis on diagnostic definition and treatment, 29, 493–501. <https://doi.org/10.1016/j.leukres.2004.10.003>
- Masur H, Rosen PP, Armstrong D. Pulmonary disease caused by *Candida* species. *The American Journal of Medicine* 1977;63(6):914–25. doi:[10.1016/0002-9343\(77\)90546-0](https://doi.org/10.1016/0002-9343(77)90546-0).
- Mnge P, Okeleye BI, Vasaikar SD, Apalata T. Species distribution and antifungal susceptibility patterns of *Candida* isolates from a public tertiary teaching hospital in the Eastern Cape Province. *South Africa* 2017;50:1–7. doi:[10.1590/1414-431X20175797](https://doi.org/10.1590/1414-431X20175797).
- Pappas PG, Kauffman CA, Andes DR, Clancy CJ, Marr KA, Ostrosky-Zeichner L, ... Sobel JD. Executive Summary: Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America. *Clinical Infectious Diseases* 2015. doi:[10.1093/cid/civ1194](https://doi.org/10.1093/cid/civ1194).
- Pappas PG, Lionakis MS, Arendrup MC, Ostrosky-zeichner L, Kullberg BJ. Invasive candidiasis. *Nature Publishing Group* 2018;4(May):1–20. doi:[10.1038/nrdp.2018.26](https://doi.org/10.1038/nrdp.2018.26).
- Ramage G, Saville SP, Thomas DP, Lo L, Biofilms CA. (2005) *Candida* Biofilms- an Update.pdf 2005;4(4):633–8. doi:[10.1128/EC.4.4.633](https://doi.org/10.1128/EC.4.4.633).
- Schwartz IS, Boyles TH, Kenyon CR, Hoving JC, Brown GD, Denning DW. The estimated burden of fungal disease in South Africa. *South African Medical Journal* 2019;109(11):885. doi:[10.7196/samj.2019.v109i11.13718](https://doi.org/10.7196/samj.2019.v109i11.13718).
- Shoham S, Levitz SM. The immune response to fungal infections. *British Journal of Haematology* 2005;129(5):569–82. doi:[10.1111/j.1365-2141.2005.05397.x](https://doi.org/10.1111/j.1365-2141.2005.05397.x).
- Tedeschi S, Tumietto F, Giannella M, Bartoletti M, Cristini F, Cioni G, ... Viale P. Epidemiology and outcome of candidemia in internal medicine wards: A regional study in Italy. *European Journal of Internal Medicine* 2016;34:39–44. doi:[10.1016/j.ejim.2016.08.020](https://doi.org/10.1016/j.ejim.2016.08.020).
- Van Schalkwyk E, Mpembe RS, Thomas J, Shuping L, Ismail H, Lowman W, ... Govender NP. Epidemiologic shift in Candidemia driven by *Candida auris*, South Africa, 2016–2017. *Emerging Infectious Diseases* 2019;25(9):1698–707. doi:[10.3201/eid2509.190040](https://doi.org/10.3201/eid2509.190040).
- 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. *Clinical Infectious diseases* 2004;39(3):309–17.