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Management and outcome of intracranial fungal infections in children and adults in Africa: a scoping review

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Abstract

Introduction Intracranial fungal infections' (IcFIs) varying clinical manifestations lead to difficulties in diagnosis and treatment. African populations are disproportionately affected by the high burden of the disease. There is a lack of clarity as to the diagnostic and treatment modalities employed across the continent. In this review, we aim to detail the management, and outcome of IcFIs across Africa.

Methods This scoping review was conducted using the Arksey and O'Malley framework. MEDLINE, EMBASE, Cochrane Library, African Index Medicus, and African Journals Online were searched for relevant articles from database inception to August 10th, 2021. The Preferred Reporting Items for Systematic Review and Meta-Analysis extension for Scoping Reviews guidelines were used to report the findings of the review.

Results Of the 5,779 records identified, 131 articles were included. The mean age was 35.6 years, and the majority (56.4%) were males. The majority (*n* = 8,433/8,693, 97.0%) of IcFIs presented as a meningitis, the most common communicable predisposing factor of IcFIs was HIV/AIDS (*n* = 7,815/8,693, 89.9%), and the most common non-communicable risk factor was diabetes mellitus (*n* = 32/8,693, 0.4%). *Cryptococcus species* was the most common (*n* = 8,428/8,693, 97.0%) causative organism. The most commonly used diagnostic modality was cerebrospinal (CSF) cultures (*n* = 4,390/6,830, 64.3%) for diffuse IcFIs, and MRI imaging (n = 12/30, 40%) for focal IcFIs. The most common treatment modality was medical management with antifungals only (*n* = 4,481/8,693, 51.6%). The most commonly used antifungal agent in paediatric, and adult patients was amphotericin B and fluconazole dual therapy (51.5% vs 44.9%). The overall mortality rate was high (*n* = 3,475/7,493, 46.3%), and similar for both adult and paediatric patients (47.8% vs 42.1%).

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Conclusion Most IcFIs occurred in immunosuppressed individuals, and despite the new diagnostic techniques, CSF culture was mostly used in Africa. Antifungals regimens used was similar between children and adults. The outcome of IcFIs in Africa was poor for both paediatric and adult patients.

Keywords Africa, Antifungal agents, Cryptococcus Neoformans, HIV, Meningitis, Mycoses

Introduction

Intracranial fungal infections (IcFIs) refer to the intra-axial, extra-axial or intraventricular presence of fungi [1]. Their clinical presentations vary making them difficult to diagnose and treat [2]. Although they are rare in the general population, they are common opportunistic infections in immunocompromised patients [2]. A person may be immunocompromised because of a disease or an infection, such as Human Immunodeficiency Virus (HIV). 75% of worldwide HIV infections occur in Africa [3, 4]. Globally, cryptococcal meningitis accounts for 181,100 annual deaths with approximately 75% of this mortality occurring in sub-Saharan Africa - these figures are likely underestimated - indicating the significant burden in this region [3, 4]. Other patients at risk are those who are on chemotherapy or corticosteroids, chronically ill, transplant recipients, or suffering from haematological disorders [5]. However, there is a lack of clarity as to the contribution of each of these risk factors to the incidence of IcFIs in African countries and the type of fungal infections (FIs) they predispose an individual to.

The most common fungus involved in IcFIs is *Cryptococcus neoformans* [5]. *Candida species* and *Aspergillus species* have also been reported in high-income countries (HICs); however, the presence of other types of FIs in Africa could mean that the spectrum of IcFIs differs in the African continent [6]. Accurate information on the fungi causing IcFIs in Africa is needed.

Diagnostic modalities for detecting IcFIs have advanced over the course of the 21st century with serological, immunofluorescent and molecular tools being increasingly used in HICs [5]. Similarly, new classes of antifungal agents are being increasingly used in HICs [2]. There have been pleas over the last two decades from the international community to ensure countries in Africa also have equitable access to gold-standard diagnostic and treatment modalities [7]. However, there has currently been no review that syntheses how patients with suspected or confirmed IcFIs are managed across Africa.

This study primarily aimed to report the diagnosis and treatment of IcFIs amongst paediatric (<18 years) and adult (≥18 years) populations across Africa. The secondary aims of this study were to identify risk factors among participants with IcFIs, record the types of fungi involved in these infections, and document the outcome of patients with IcFIs.

Methods

This review was conducted as per the published and registered protocol [8]. The Arksey and O'Malley scoping review framework was used to guide the scoping review [9]. The findings from this review were reported using the Preferred Reporting Items for Systematic Review and Meta-Analysis extension for Scoping Reviews (PRISMA-ScR) guidelines [10].

Inclusion and exclusion criteria

Only studies that discussed the management or outcome of IcFIs in Africa were included. Only articles that were peer-reviewed journal articles were included. There was no restriction on the study design with case reports, case series, cross-sectional studies, cohort studies, audits and trials included. There were no restrictions on the year or the language of the publications. This ensured all relevant articles published from database inception to the date of the search were captured. We excluded studies that (a) were reviews, meta-analyses, and conference abstracts, (b) did not have accessible full-texts, (c) did not include IcFIs (or did not have disaggregated data about IcFIs), and (d) did not have patients managed in Africa (or did not have disaggregated data about patients managed in Africa).

Search strategy

The search for this scoping review was run on EMBASE (Ovid), PUBMED, Cochrane library, African Index Medicus, and African Journals Online covering the period from database inception to August 10th 2021. The search strategy used variants and combinations of search terms related to "fungi", "intracranial infection", and "Africa" to identify relevant articles on IcFIs. The exact content and order of the search string query used are available in the Appendix of our published protocol [8].

Study selection

All of the articles from the search were transferred to Rayyan, where duplicates were identified and deleted [11]. The study selection process consisted of multiple steps. Firstly, an online calibration exercise was organised to ensure an understanding of the pre-defined inclusion and exclusion criteria by the study screeners. Next, at least two reviewers (from BDT, SZYO, CBE, CSG, OED, SB, YCHD, MK, ED, DUD, AKA, ÖK, JE, and NDAB)

independently screened each title and abstract of the identified articles based on the criteria. Any disagreement between the two reviewers' decisions prompted further discussion. The full texts of the remaining articles were retrieved and screened independently by two reviewers from BDT, SZYO, CBE, CSG, SB, YCHD, MK, ED, DUD, AKA, ÖK, JE, and NDAB. Any disagreement between two screeners' decisions prompted a further discussion between all reviewers until consensus was achieved.

Data extraction

Prior to data extraction, a predefined data-extraction sheet made in Microsoft Excel (Microsoft, Richmond, Virginia, USA) was used to ensure all participants in the data extraction step were extracting data homogeneously. The Excel sheet included columns of specific interest for data extraction such as study design, patient demographics/characteristics, type of intervention and outcomes of care as detailed in the published protocol [8]. Data extraction was performed in two stages: a proper stage preceded by a pilot stage. The pilot stage consisted of having multiple authors, each going through the same ten randomly selected articles to extract data. This was to ensure an accurate and homogenous data extraction by all participating authors. Feedback from the pilot stages was used to modify the data collection sheet so that it was reflective of the included studies.

Data analysis

The extracted data was analysed by SPSS v.26 (IBM, USA), with descriptive frequencies used to present data. Pooled statistics were calculated using measures of central tendency and spread.

Results

We identified 5,779 records from the database search. We excluded 768 articles (13.3%) at deduplication, 4,504 (77.9%) at the title and abstract screening and 376 (654%) at full-text screening. 131 (2.3%) articles were eligible for inclusion (Fig. 1).

Eight thousand six hundred and ninety-three patients whose management was reported were included in this review [12–142] (Supplementary Table 1). The reported age of the patients ranged from 2 days to 75 years old. Of 73 studies (1,924 patients) that reported the mean age of the patients, the overall mean age was 35.6 years. 118 studies (8,002 patients) reported the sex of the patients, most patients with IcFIs were male (n = 4,512, 56.4%, 95% confidence interval [CI] = 55.3-57.5%). 29 (22.0%) studies reported on the management and outcomes of IcFIs in South Africa, 20 (15.1%) in Uganda and 10 (7.6%) in Zimbabwe (Table 1). The 2010-2019 decade saw the highest number of publications (n = 72, 55.0%) and the majority of studies were case reports (n = 50, 38.2%) (Table 1).

The majority of IcFIs presented with meningitis (n = 8,433, 97.0%, 95% CI = 96.9-97.4%) (Table 2). Fungal granulomas were the most common focal IcFIs (n = 14, 0.2%, 95% CI = 0.1-0.3%) (Table 2). The most common predisposing risk factor was HIV/AIDS (n = 7,815, 89.9%, 95% CI = 89.3-90.5%) followed by tuberculosis (n = 641, 7.4%, 95% CI = 6.8-7.9%), and diabetes mellitus (n = 32, 0.4%, 95% CI = 0.3-0.5%) (Table 3). *Cryptococcus species* was the most common causative organism (n = 8,428, 97.0%, 95% CI = 96.6-97.3%), followed by *Candida species* (n = 15, %, 95% CI = 96.6-97.3%) (Table 4).

The results showed that the most commonly used diagnostic modality of diffuse IcFIs was cerebrospinal fluid (CSF) cultures (n = 4,390, 64.3%, 95% CI = 63.1-65.4%), followed by CSF cryptococcal antigen (n = 4,328, 63.4%, 95% CI = 62.2-64.5%) and CSF India ink stain (n = 2,063, 30.2%, 95% CI = 29.1-31.3%) (Table 5). Also, MRI imaging (n = 12, 40.0%, 95% CI = 22.7-59.4%) followed by brain biopsy and CT scan (each n = 9, 30.0%, 95% CI = 14.7-49.4%) were commonly used diagnostic modality of localised IcFIs (Table 6). The majority of patients were managed medically with antifungals only (n = 4,481, 51.6%, 95% CI = 50.5-52.6%), followed by serial lumbar taps (n = 818, 9.4%, 95% CI = 8.8-10.0%) (Table 6).

The most commonly used antifungal monotherapy was fluconazole (n = 1,891, 21.8%, 95% CI = 20.9-22.6%). More common was a dual therapy combination of amphotericin B and fluconazole (n = 2,287, 26.3%, 95% CI = 25.4-27.3%) (Table 6). Eighteen studies representing 33 patients reported on the type of antifungals for paediatric patients (0-17 years). The most commonly used antifungal agent in this age group was amphotericin B and fluconazole dual therapy (n = 17, 51.5%, 95% CI = 33.5%-69.2%) followed by Amphoteric B monotherapy (n = 6, 18.2%, 95% CI = 7.0%-35.0%) (Fig. 2). There have been a gradual increase in the use of amphotericin B and fluconazole monotherapies, and dual therapy of these drugs from 1980 (Fig. 3). However, since the 20th century fluconazole monotherapy and a combination of amphotericin B and fluconazole are the most commonly used regimens (Fig. 3).

The neuro-intensive care admission rate was 0.7% (n = 66, 95% CI = 0.6-0.9%). The readmission rate was 2.6% (n = 231, 95% CI = 2.2-2.9%). Mortality rate was reported in 93 studies with an overall population of 7,493. The overall mortality rate was 46.3% (n = 3475, 95% CI = 45.2-47.5%). The mortality rate was similar for adults (71 studies, 5647 patients) and paediatric patients (11 studies, 38 patients) [47.8% (95% CI = 46.5-49.2%)vs 42.1% (95% CI = 26.3-59.2%)]. In addition, only 104 articles

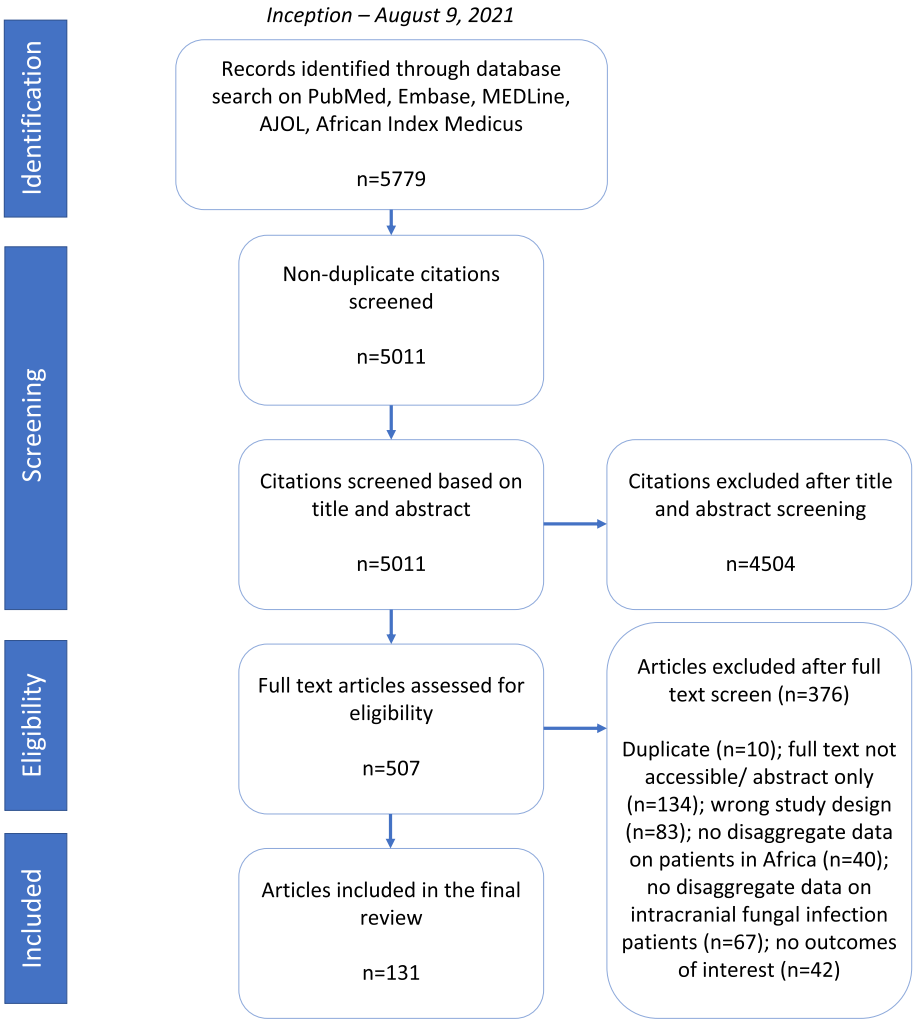

Fig. 1 PRISMA flow chart

with 5,371 patients reported on the clinical presentation of IcFIs (Supplementary Table 2).

Discussion

In this study, we summarised and described the management and outcomes of IcFIs from 27 African countries. The average age of patients was 35.7 years, with an almost equal proportion of males and females affected. A larger number of IcFIs were due to meningitis and the majority had HIV/AIDS as the predisposing factor. *Cryptococcus species* were the most common causative agents. A CSF culture and a CSF cryptococcal antigen test were the common diagnostic modalities employed. Most patients were treated solely with dual antifungal therapy. Magnetic resonance imaging and brain biopsy were the most common diagnostic modalities employed for patients with focal IcFIs. Overall IcFIs have a high rate of mortality in Africa for both adult and paediatric patients.

Implications

In keeping with existing literature, our review found that the most commonly encountered predisposing factor for IcFIs in Africa was HIV/AIDS infection. A proportion of those with IcFIs in our review had an associated confirmed tuberculosis infection. Although this review is not designed to ascertain a causal relationship, the syndemic interaction between tuberculosis and HIV is known to be an important driver for FIs in low-resource settings like Africa [6]. Our review also highlights the importance of non-communicable diseases such as diabetes mellitus as risk factors for IcFIs in Africa. Acknowledging that HIV/AIDs contributes to the majority of the cases, it is imperative that innovative and targeted models for primary HIV prevention, education, screening and early identification, adherence to treatment, stigmatization and discrimination prevention - especially for at-risk groups - should be put in place [143]. Similarly, more research and

Table 1 Characteristics of studies on the management and outcome of intracranial fungal infections in Africa

Characteristic	Frequency (percentage)
Study setting (n=132 as one study was conducted in two countries)	
South Africa	29 (22.0)
Uganda	20 (15.1)
Zimbabwe	10 (7.6)
Nigeria	9 (6.8)
Malawi	8 (6.1)
Morocco	8 (6.1)
Tunisia	6 (4.5)
Ivory coast	5 (3.8)
Egypt	5 (3.8)
Kenya	4 (3.0)
Senegal	3 (2.3)
Ethiopia	3 (2.3)
Botswana	3 (2.3)
Tanzania	3 (2.3)
Central African Republic	2 (1.5)
Gabon	2 (1.5)
Rwanda	2 (1.5)
Algeria	1 (0.7)
Burkina Faso	1 (0.7)
Equatorial Guinea	1 (0.7)
Guinea-Bissau	1 (0.7)
Lesotho	1 (0.7)
Libya	1 (0.7)
Madagascar	1 (0.7)
Mali	1 (0.7)
Mozambique	1 (0.7)
Republic of Congo	1 (0.7)
Year of publication	
1970-1979	2 (1.5)
1980-1989	4 (3.0)
1990-1999	12 (9.2)
2000-2009	28 (21.4)
2010-2019	72 (55.0)
2020-2021	13 (9.9)
Study design	
Case report	50 (38.2)
Prospective cohort study	27 (20.6)
Retrospective cohort study	21 (16.0)
Case series	13 (10.0)
Randomised controlled trials	10 (7.6)
Cross-sectional study	5 (3.8)
Cohort study	3 (2.3)
Nested study	1 (0.8)
Audit	1 (0.8)

Table 2 Types of intracranial fungal infections in Africa. (Some patients had more than one type of IcFI; a = diffuse infection; b = localised infection; *N*=8693)

Type of infection	Number (percentage, %)	Lower limit 95% CI (%)	Upper limit 95% CI (%)
Meningitis[a]	8,433 (97.0)	96.6	97.4
Meningoencephalitis[a]	210 (2.4)	2.1	2.8
Rhino-orbito-cerebral mucormycosis	22 (0.3)	0.2	0.4
Fungal granuloma[b]	14 (0.2)	0.1	0.3
Brain abscess[b]	10 (0.1)	0.1	0.2
Fungal vasculitis[b]	6 (0.1)	0.0	0.2

Table 3 Predisposing factors for intracranial fungal infections in Africa

Risk factors	Number (percentage, %)	Lower limit 95% CI (%)	Upper limit 95% CI (%)
HIV/AIDS	7,815 (89.9)	89.3	90.5
Tuberculosis	641 (7.4)	6.8	7.9
Diabetes mellitus	32 (0.4)	0.3	0.5
Corticosteroids	4 (0.0)	0.0	0.1
Chemotherapeutic agents	3 (0.0)	0.0	0.1
Cancer	2 (0.0)	0.0	0.1
Unspecified or not recorded	494 (5.7)	5.2	6.2

HIV Human immunodeficiency virus, *AIDS* Acquired immunodeficiency syndrome, *N*=8693. (Some patients had more than one risk factor)

investment should be made toward the creation of new antiretroviral therapies in Africa which are cheaper and have fewer side effects [143].

CSF culture is the current gold standard for diagnosing cryptococcal meningitis, and this was the most common diagnostic tool for IcFIs identified in this review [144]. This diagnostic mode is faced with multiple disadvantages: can take days to weeks 7-10 days to grow, can produce false-negative results when the fungal burden is low or the sample is non-available for culture, and different techniques may yield different results [144]. This depicts the need for the use of multimodal diagnostic options as was the case in almost all studies in our review. The important use of cryptococcal antigen and Indian ink test in this study can be explained by cryptococcal meningitis being the predominating IcFIs identified. They however fail to identify non-cryptococcal fungi identified in this study. Serological tests and immunofluorescence techniques have developed significantly over the years [145–147]. A more accurate diagnostic confirmation has been achieved by polymerase chain reaction assays with most protocols developed for the diagnosis of invasive

Table 4 Causative organisms of intracranial fungal infections in Africa (*N*=8693)

Organisms	Number (percentage, %)	Lower limit 95% CI (%)	Upper limit 95% CI (%)
Opportunistic fungi			
Cryptococcus species	8,428 (97.0)	96.6	97.3
Candida species	15 (0.2)	0.1	0.3
Rhizopus species	12 (0.1)	0.1	0.2
Mucor species	11 (0.1)	0.1	0.2
Aspergillus species	9 (0.1)	0.1	0.2
Conidiobolus coronatus	5 (0.1)	0.0	0.1
Acremonium specie	1 (0.0)	0.0	0.1
Petriellidium boydii	1 (0.0)	0.0	0.1
Cladosporium specie	1 (0.0)	0.0	0.1
Phaeohyphomycosis specie	1 (0.0)	0.0	0.1
Pseudallescheria boydii	2 (0.0)	0.0	0.1
Scopulariopsis specie	1 (0.0)	0.0	0.1
Trichophyton rubrum	1 (0.0)	0.0	0.1
Xylohypha bantiana	1 (0.0)	0.0	0.1
True pathogenic fungi			
Blastomyces species	2 (0.0)	0.0	0.1
Histoplasma specie	1 (0.0)	0.0	0.1
Unspecified or not recorded	130 (1.5)	1.3	1.8

Table 5 Diagnostic modalities of intracranial fungal infections in Africa

Diagnostic modality	Number (percentage, %)	Lower limit 95% CI (%)	Upper limit 95% CI (%)
For diffuse fungal infections (N= 6830)			
CSF culture	4390 (64.3)	63.1	65.4
CSF cryptococcal antigen	4,328 (63.4)	62.2	64.5
CSF India ink stain	2,063 (30.2)	29.1	31.3
Peripheral blood culture	80 (1.2)	0.9	1.5
Serum cryptococcal antigen	228 (3.3)	2.9	3.8
Gram stain	212 (3.1)	2.7	3.5
CSF immunodiffusion	136 (2.0)	1.7	2.4
CT imaging	17 (0.2)	0.2	0.4
CSF acid-fast stain	62 (0.9)	0.7	1.2
CSF opening pressure	50 (0.7)	0.5	1.0
CSF polymerase chain reaction	44 (0.6)	0.5	0.9
MRI imaging	17 (0.2)	0.2	0.4
Brain biopsy	11 (0.2)	0.1	0.3
Unspecified	457 (6.7)	6.1	7.3
For localised fungal infections (N = 30)			
MRI imaging	12 (40.0)	22.7	59.4
Brain biopsy	9 (30.0)	14.7	49.4
CT imaging	9 (30.0)	14.7	49.4
CSF culture	5 (16.7)	5.6	34.7
CSF cryptococcal antigen	4 (13.3)	3.8	30.1
CSF India ink stain	3 (10.0)	2.1	26.5
Pus culture	2 (6.7)	0.8	22.1
CSF immunodiffusion	1 (0.3)	0.1	17.2
Peripheral blood culture	1 (0.3)	0.1	17.2
Unspecified	10 (33.3)	17.3	52.8

CT Computed tomography, *MRI* Magnetic resonance imaging, *CSF* Cerebrospinal fluid

FIs. Other molecular diagnostic tools for the detection of fungi directly from CSF, have proved promising in clinical trials but still need to undergo standardisation before clinical use [147–149]. These modern diagnostic techniques are not always available in the African setting [150–152]. There are now numerous methods for diagnosing IcFIs secondary to *Cryptococcus species* [153]. For example, a study identified in this review showed a similar specificity between gram stain and Indian ink test in diagnosing cryptococcal meningitis [86]. Furthermore, more specific and sensitive diagnostic tools like detecting cryptococcal antigen in blood, and Saliva are now available [154]. In addition, lateral flow assay as a point-of-care test for detecting cryptococcal antigen introduces a new paradigm in managing cryptococcal disease [155]. However, these techniques are yet to be widely utilised in Africa as evident in (Table 5). This could be due to a lack of advocacy for these new tools in the region, rather than a cost problem as they have been shown to be cost-effective [156]. Finally, our study showed that neuroimaging was lacking (Table 5). MRI is a valuable tool to detect ischemic stroke and vasculitis as complication of fungal infection, and also to detect granulomas and necrotising lesions. As this diagnostic tool was hardly available, there is likely to be an under-estimation of the proportion of patients with fungal space occupying lesions, necrotising lesions, granulomas and vascular complication associated with fungal infections.Although, imaging of mycosis on computed tomographic scan or magnetic resonance imaging may be non-specific and usually negative for candidiasis or cryptococcosis; these often have unique imaging patterns [145, 146]. The diagnosis of invasive mycosis requires a biopsy of the involved tissue (brain, meninges, and CSF or ventricular fluid), followed by culture and histopathology of these samples [17]. Central nervous system (CNS) biopsies are regarded as too risky in severely ill patients, and those with haematological disorders, hence the need for specialised neurosurgical centres which are often not equitably available in Africa [157].

This review highlights that antifungals are the cornerstone of the management of IcFIs in Africa. Fluconazole and Amphotericin B - either in isolation or in

Table 6 Treatment modalities of intracranial fungal infections in Africa, including the spectrum of antifungal agents used (*N*=8693)

Treatment	Number (percentage, %)	Lower limit 95% CI (%)	Upper limit 95% CI (%)
Antifungals only	4,481 (51.6)	50.5	52.6
Serial lumbar taps	818 (9.4)	8.8	10.0
Sertraline	401 (4.6)	4.2	5.1
Dexamethasone	115 (1.3)	1.1	1.6
Interferon gamma therapy	57 (0.7)	0.5	0.9
Craniotomy	6 (0.1)	0.0	0.2
Burr hole aspiration	1 (0.0)	0.0	0.1
Insertion of drain	1 (0.0)	0.0	0.1
Unspecified	2,359 (27.1)	26.2	28.1
Antifungals prescribed			
Monotherapy	3,011 (34.6)	33.6	35.7
Fluconazole only	1,891 (21.8)	20.9	22.6
Amphotericin B only	1,106 (12.7)	12.0	13.4
Itraconazole only	4 (0.0)	0.0	0.1
Voriconazole only	3 (0.0)	0.0	0.1
Flucytosine only	3 (0.0)	0.0	0.1
Ketoconazole only	3 (0.0)	0.0	0.1
Nystatin only	1 (0.0)	0.0	0.1
Dual therapy	2,617 (30.1)	29.1	31.1
Amphotericin B + Fluconazole	2,287 (26.3)	25.4	27.3
Amphotericin B + Flucytosine	240 (2.8)	2.4	3.1
Fluconazole + Flucytosine	23 (0.3)	0.2	0.4
Amphotericin B + miconazole	1 (0.0)	0.0	0.1
Amphotericin B + ketoconazole	1 (0.0)	0.0	0.1
Triple therapy			
Amphotericin B + Flucytosine + Fluconazole	65 (0.8)	0.6	1.0

combination - were identified to be the most commonly used antifungals for both adult and paediatric patients. Both drugs have several characteristics associated with optimal entry into the CNS [158]. However, *Cryptococcal species* were found to be the most common causative organism of IcFIs (97.1%), and the gold standard treatment for cryptococcal meningitis is a triple antifungal therapy which consists of at least two weeks of amphotericin B intravenously in combination with oral flucytosine at a dose of 0.7–1.0 mg/kg and 100 mg/kg (in four divided doses) daily respectively followed by 400mg (6mg/kg) daily of oral fluconazole for at least eight weeks [159]. This combination can cost between $700 and $800 per day for adults in Africa [160]. This compares with an average monthly pay of $758 in Africa, with South Africa having the highest average monthly salary at $2088 [161]. The cheaper cost of fluconazole made it historically attractive to use, with data favouring the use of amphotericin B (0.7mg/kg daily for two weeks) in combination with fluconazole (800 mg/day for at least 10 weeks) when flucytosine is not available [159]. However, there is increasing evidence of fluconazole resistance in Africa, which can be due to the increasing use of fluconazole (800-2000mg daily for 10-12 weeks) as the sole therapy in the management of IcFIs as reported in this study despite it being at the base of the ladder in terms of effectiveness [159, 162]. This will make the management of IcFIs increasingly difficult in Africa unless steps - outlined almost a decade ago - are taken to improve access to essential antifungal medications [7]. Alternatively, costs are reducing for other antifungals - e.g., voriconazole-, and they are becoming more widely available; it may be pertinent to conduct cost-effectiveness and efficacy studies to evaluate their utility in countries where fluconazole resistance is rising [163, 164]. The scarcity of treatments and the increasing resistance to current therapeutics highlight the need for the development of antifungal agents which have novel mechanisms of action and are suitable for clinical use. Repurposing existing drugs as antimycotic therapeutics is a promising strategy for the rapid development of such new treatments. Our review suggests that some centres in Africa are doing

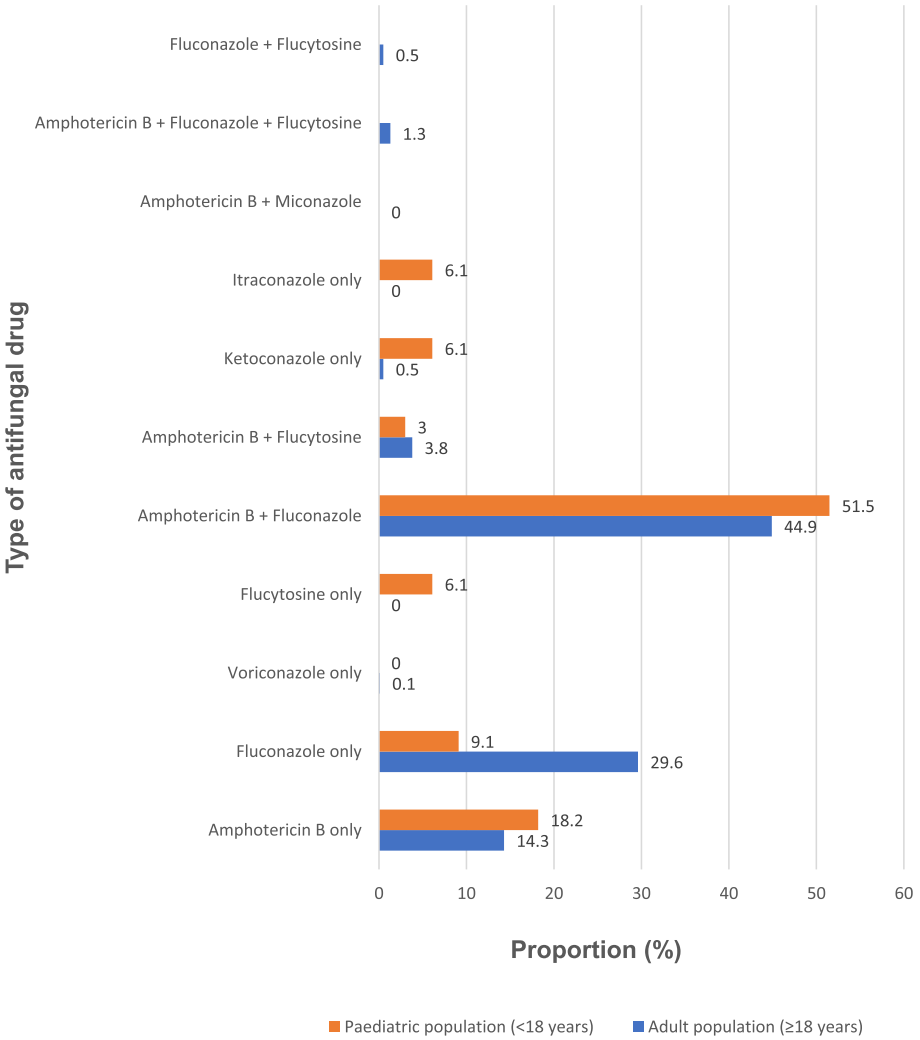

Fig. 2 Variations in antifungal drugs for intracranial fungal infections between paediatric (*N*=33) and adults (*N*=4839) populations in Africa

so by using sertraline [95, 112]- although this has only been shown to be efficacious in in vitro studies and has only been evaluated for the treatment of HIV-associated cryptococcal meningitis- and interferon-gamma [71, 165, 166]. Although further evidence is needed for both these therapies, as well as the therapeutic effect of serial lumbar punctures [167], given there is no evidence in the literature to our knowledge supporting its use to treat non-cryptococcal intracranial fungal infections.

Our review highlighted neuro-intensive care admission rate, readmission rate and mortality rate as the common criteria for assessing outcomes of IcFIs in Africa. The review showed that the overall mortality rate of IcFIs in Africa was about 46.3% (47.8% for adults and 42.1% for paediatric patients). This reflects the mortality reported in low- and middle-income countries which is higher compared to Europe and the United States of America [3, 5]. On a global scale, the mortality of CNS FIs in those with HIV/AIDs is lower in those on ARTs [3, 5]. However, there was no evidence of improved outcomes with early initiation of ART in HIV-infected patients with cryptococcal meningitis in our review [59, 75]. Furthermore, it has been reported that the amphotericin-flucytosine combination (treatment of choice) yields a better outcome in terms of mortality [168]. A randomised controlled trial conducted in Malawi showed that Fluconazole and Flucytosine combination were more fungicidal and had a lower mortality rate than fluconazole alone [62]. In a series of HIV-associated IcFIs, abnormal mental status and high organism load, measured by quantitative CSF culture or CSF antigen titre, are the most important determinants of death, while raised CSF opening pressure and low CSF white cell count are also associated with poor outcome [169, 170].

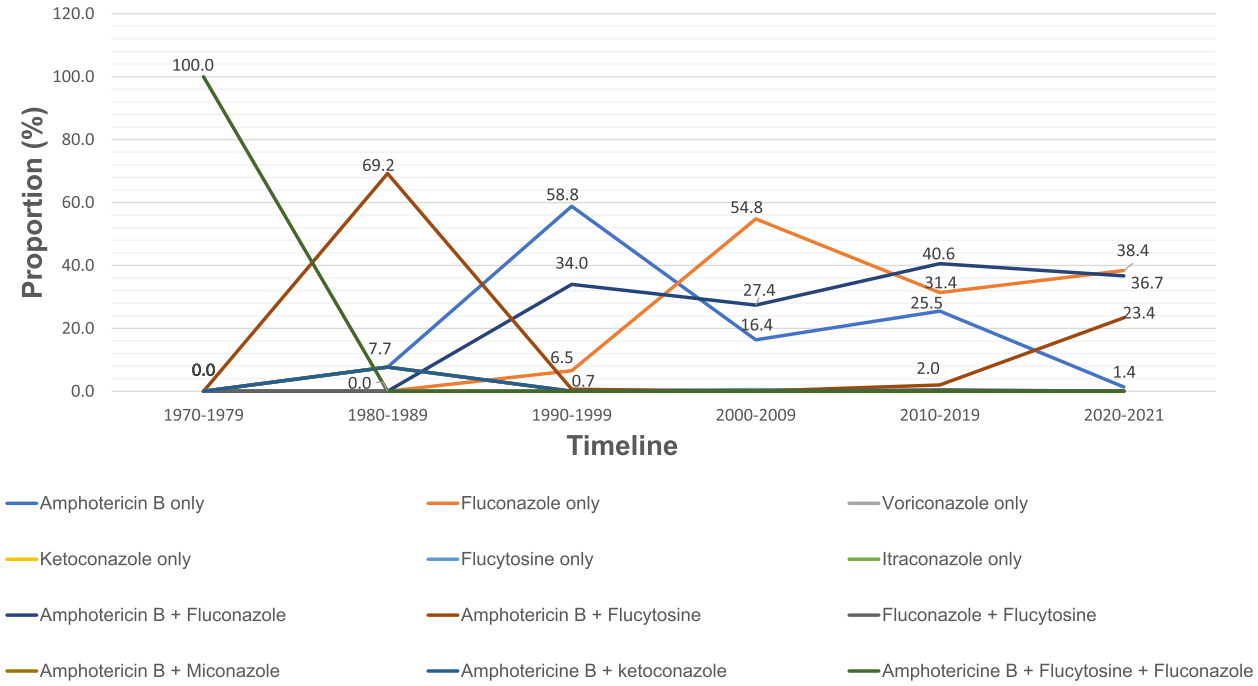

Fig. 3 Trends in antifungal agents for the management of intracranial fungal infections in Africa

Limitations

In addition to highlighting the inequities that exist regarding the diagnosis and management of IcFIs in Africa, this review underscores the majority of papers on IcFIs in Africa come from 4 countries: South Africa, Uganda, Zimbabwe, and Nigeria. In addition, published data is only readily available from 50% of the countries in Africa (n = 27/54). Therefore, the results showcased in this paper are unlikely to reflect the situation across the continent of Africa, especially given ecological niches are different across the African continent and this may result in differences in the aetiology and distribution of intracranial fungal infections. Furthermore, pooling data across disparate situations in different countries ignores the complexities of each country and the needs of each setting. However, it is beyond the scope of this review to identify specific issues related to each country and devise strategic solutions. This is because this review relies on pre-collected data, and is unable to thoroughly assess the barriers to access and utilisations of various diagnostic modalities and therapies at each centre. Future studies should aim to assess issues with horizontal and vertical equity responsible for the deviations from the gold standard care identified in this review. Furthermore, due to the heterogeneity of the study settings captured by this review and the difficulty of extrapolating the efficacy of treatments from HICs to low- and middle-income countries, it is not possible to accurately determine how intensive care admission, re-admission, and mortality rates would differ if each gold-standard measure was individually employed, and therefore the most important aspects to focus on. In addition, it may be that the use of diagnostic methods such as CSF culture delayed confirmation of diagnosis and delayed treatment, but the studies included did not stratify outcomes by diagnosis or record the delay to treatment starting. Also, it is difficult to delineate between intracranial meningitis and spinal meningitis due to the continuous flow of CSF between the brain and the spinal cord. Any study mentioning meningitis without mentions of spine or spinal cord was considered intracranial meningitis. Articles on spinal meningitis only were excluded from our review. Lastly, conclusions that can be drawn from this review are limited by the quality of evidence in the available literature as a large proportion of included articles were case reports and case series. Also, our study design which is that of a scoping review of the literature and doesn't typically include a risk of bias assessment. This is because this type of study design answers a broad research question, and helps inform future systematic review answering specific questions on the topic.

Conclusions

This scoping review provides an overview of the management and outcomes of IcFIs in Africa. The predominance of meningitis and HIV/AIDs as intracranial

distribution and predisposing factors for FIs matched previous literature, as did *Cryptococcus species* as the most common causative agent in Africa. Despite the new diagnostic techniques available, CSF culture was mostly used in Africa. This technique, despite being the gold standard, has some disadvantages which may contribute to delays in the diagnosis of IcFIs. Most patients were being managed with antifungal only. Monotherapy with fluconazole or amphotericin and a combination of both were the preferred antifungal regimen used. This differs from the recommended triple therapy with amphotericin, fluconazole and flucytosine which is costly. Unfortunately, the outcomes of IcFIs in Africa were poor. This may be a consequence of the common risk factor associated with IcFIs in Africa and difficulties in the diagnosis and optimal treatment mentioned earlier.

Abbreviations

CNS	Central Nervous System
CSF	Cerebrospinal Fluid
FI	Fungal Infection
HIC	High Income Country
HIV	Human Immune Virus
IcFI	Intracranial Fungal Infection

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12879-024-09694-2.

Supplementary Material 1: Supplementary Table 1. Studies included in the review. Supplementary Table 2. Clinical presentation of intracranial fungal infections in Africa. *N* = 5371.

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Conception: BDT, CE, SZYO Screening: ACC, AKA, BDT, CE, CG, CSG, DUD, JE, MK, NDAB, OED, ÖK, SB, SZYO, YCHD, Data extraction: ACC, BDT, CAI, CG, CSG, DUD, JE, NDAB, ÖK, SB, SZYO, YCHD Data analysis: BDT, SZYO Data curation: BDT, SZYO Writing: ACC, AKA, BDT, CAI, CG, CSG, DUD, JE, NDAB, OED, SB, SZYO, YCHD Reviewing and editing: BDT, CE, CG, NDAB, SB, SZYO Project administration: BDT, CE, SZYO Supervision: NDAB Visuals: BDT, CE, SZYO

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Availability of data and materials
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Declarations

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Soham Bandyopadhyay has an academic clinical fellowship by the National Institute for Health and Care Research (NIHR). All other authors declare they have no competing interests.

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