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

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ABSTRACT

Introduction The protocol presents the methodology of a scoping review that aims to synthesise contemporary evidence on the management and outcomes of intracranial fungal infections in Africa.

Methods and analysis The scoping review will be conducted in accordance with the Arksey and O'Malley's framework. The research question, inclusion and exclusion criteria and search strategy were developed based on the Population, Intervention, Comparator, Outcome framework. A search will be conducted in electronic bibliographic databases (Medline (OVID), Embase, African Journals Online, Cochrane Library and African Index Medicus). No restrictions on language or date of publication will be made. Quantitative and qualitative data extracted from included articles will be presented through descriptive statistics and a narrative description.

Ethics and dissemination This study protocol does not require ethical approval. Findings will be reported in a peer-reviewed medical journal and presented at local, regional, national and international conferences.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This scoping review will describe the literature on the management and outcomes of intracranial fungal infections in Africa.
⇒ This protocol is reported in accordance with the guidance of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Protocols and will ensure transparency in the methodology of the scoping review, which will reduce the likelihood of reviewing bias.
⇒ The search strategy will be conducted in five electronic databases covering academic peer-reviewed literature.
⇒ The scoping review will be guided by the rigorous methodology and reporting set by the Arksey and O'Malley's framework relevant reporting guidelines.
⇒ There will be no formal assessment on the quality of the included studies.

INTRODUCTION

Intracranial fungal infections (IcFIs) or mycoses refer to the presence of fungi in the intra-axial and extra-axial spaces.[1] They can present with a range of clinical signs and symptoms, causing difficulties in diagnosis and treatment. More importantly, they commonly cause opportunistic infections in immunosuppressed patients such as those with HIV infection.[2] Africa, with an estimated population of 1.3 billion people accounts for 75% of all 37 million individuals living with HIV.[3] It is estimated that 50% of fungal-related deaths in the setting of HIV infections probably occur in Africa; however, there are inaccurate statistics from most African countries. Similarly, other high-risk groups include transplant recipients and immunosuppressed patients treated with chemotherapeutics and corticosteroids as well as those suffering from haematological disorders and chronically ill patients.[4]

Further dissemination of fungal infections is worsened by poor working conditions, lack of finance and poor health-seeking behaviour which is applicable in Africa.[5] Interestingly, only 10%–15% of pathological fungi cause systemic or central nervous system (CNS) mycosis. The most commonly identified fungi in IcFIs include *Cryptococcus neoformans*, *Candida* spp, and *Aspergillus* spp.[4] Annual global deaths from cryptococcal meningitis were estimated at 181 100, with 135 900 (75%) deaths in sub-Saharan Africa, indicating a significant burden of the disease in this region.[6] However, these figures may be an under-representation of the actual fact due to under-reporting. Irrespective of these burdens, management guidelines for IcFIs are lacking in some African countries.[7]

The mortality and morbidity rates associated with CNS fungal infections are higher

when compared with other microorganisms. Immunocompetent hosts are not excluded as the cure rate for these patients receiving antifungal therapy for cryptococcal meningitis is 75% and is only 25% for CNS aspergillosis and mucormycosis.[2 5] Africa is likely to have a greater impact given its relatively greater burden, and scarcity of modern diagnostic techniques able to detect the disease in its early stages.[6 8–10] It cannot be overemphasised that prompt recognition and commencement of appropriate surgical and medical management are essential for improving the overall prognosis of CNS mycosis in this setting.[2 5]

Diagnosing and treating IcFIs in Africa can be challenging and this is compounded by the limited availability of CT or MRI.[11] A key part of the diagnosis of IcFIs requires a biopsy of the involved tissue (brain, meninges and CSF or ventricular fluid), followed by culture and histopathology of these samples.[12] Performing CNS biopsies in severely ill patients, and those with coagulation disorders, can be challenging and require specialised neurosurgical centres which are not readily available in most parts of Africa.[13]

The past decade has brought about quicker and more accurate diagnostic techniques, which include molecular testing, serological test and immunofluorescence, which is used in high-income countries.[12 14–16] These newer techniques ensure timely identification of causative organisms and prompt commencement of appropriate antifungal agents. There is, however, a lack of data on the availability and accessibility of these novel approaches in Africa. Therefore, the need for our present study aims to map out the management and outcomes of IcFIs in the African continent.

Review aims

The protocol describes the methodology of an up-to-date scoping review of the literature on the management and outcomes of IcFIs. The primary and secondary aims of the review are described in box 1. The proposed scoping review work will be valuable in informing policymakers, stakeholders, governments and healthcare organisations that govern the provision of care to patients with IcFIs. The knowledge gaps identified will be the first step to focus on key research priorities that will inform the development of a larger research project, within a higher hierarchy of evidence.

Box 1 Primary and secondary aims of the review

Primary:
1. Characterise the treatment modalities of IcFIs in Africa.

Secondary:
1. Assess the availability of diagnostic modalities such as cerebrospinal fluid and serum studies and neuroimaging (MRI, CT scan).
2. Assess the clinical outcome of patients primarily defined as rates of mortality and morbidity.

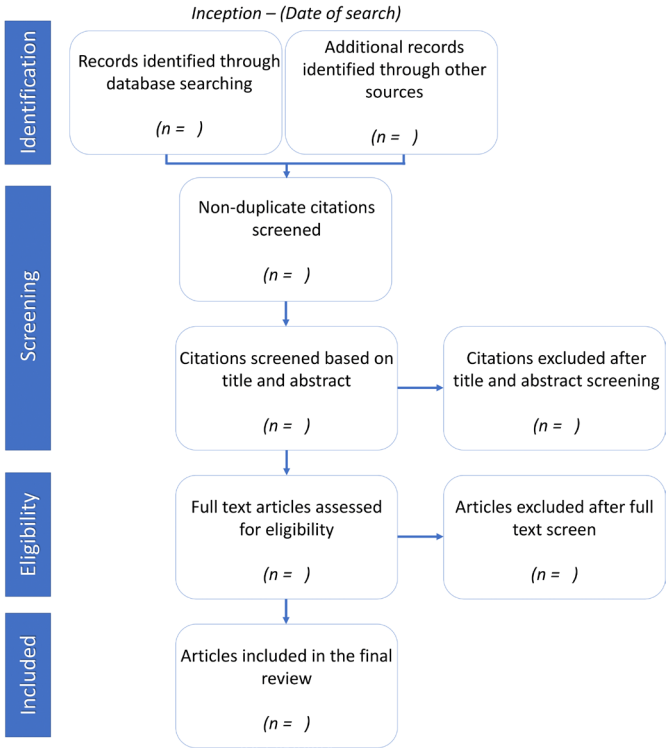

Figure 1 PRISMA flow diagram for scoping review process. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

METHODS AND ANALYSIS

The protocol for the present scoping review is reported as guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Protocols.[17] The design of the proposed scoping review methodology was informed by Arksey and O'Malley's framework, which includes five stages to conduct a scoping review.[18] All study types will be included to ensure the inclusion of the majority of relevant literature.

Stage 1: identifying the research question

The Patient, Intervention, Comparison, Outcome (PICO) framework was used to define the title, scoping review objective, scoping review question and inclusion criteria. Our main research question is: How are IcFIs managed in Africa?

Stage 2: identifying relevant studies

The authors discussed the keywords that will be used for the search strategy and the eligibility criteria of the studies based on the PICO strategy.

Databases and search strategy

Two reviewers (BDT and CBE) developed the search strategy by testing various combinations of keywords and Medical Subject Headings (MESH) terms in different electronic bibliographic databases, followed by all members of the review team reviewing, discussing and finalising the search strategy. This search strategy broadly includes intracranial AND fungi AND Africa. No restrictions on language or date of publication will be made. The full search strategy is found in online supplemental appendix 1.

Box 2 Key information to be extracted

Study details
⇒ First author.
⇒ Year of publication.
⇒ Country of first author.
⇒ Country where the study was conducted.
⇒ Language of publication.
⇒ Study design.
⇒ Sample size.

Data relevant to the PICO term
⇒ Population: age, sex, predisposing factors, immunocompromised status of patients.
⇒ Intervention: (1) organisms identified from the infection, (2) diagnostic modalities of IcFIs, (3) conservative, medical and/or surgical treatment given to patients.
⇒ Comparison: outcomes of patients receiving various combinations of conservative, medical and/or surgical intervention.
⇒ Outcome: (1) mortality rate, (2) neurointensive-care admission, (3) functional outcome (both short and long term), (4) length of hospital admission, (5) readmission rate, (6) symptoms resolved/reduced/unchanged/worsened and/or (7) complications from the IcFI.

The search will be conducted in the following databases: Medline (OVID), Embase, African Journals Online, Cochrane library and African Index Medicus. Additional resources such as references from included studies will be hand searched by a reviewer (BDT) to ensure that all relevant evidence in the literature are included.

Eligibility criteria

The inclusion criteria of the study are based on the PICO strategy and are listed below:

- Participants: patients of all ages (adults and children) in Africa with a diagnosis of IcFI.
- Intervention: studies reporting on the method of diagnosing and/or treating IcFI patients.
- Comparison: methods of diagnosis and/or treatment.
- Outcome: studies reporting on (1) mortality rate, (2) neurointensive-care admission, (3) functional outcome, (4) length of hospital admission, (5) readmission rate, (6) symptoms resolved/reduced/unchanged/worsened and/or (7) complications from IcFI.
- Types of studies: peer-reviewed publications such as journal articles, cross-sectional studies, case reports, case series, cohort studies, trials and audits. Reports in any language will be included. Where needed, reports were translated to a suitable language for the multilingual authors using online translation platforms such as DeepL Translator (https://www.deepl.com/en/translator).

The following articles will be excluded:

- Do not include African patients or do not have disaggregated data about the African population.
- Do not discuss IcFIs or do not have disaggregated data about IcFIs.
- Do not discuss presentation, management or outcomes of patients with IcFIs.
- Conference abstracts (due to the lack of in-depth information available) and reviews (due to duplication of data; however, any relevant articles included in the review that are not already included in our search will be included).
- Theses from Masters and PhDs will not be included unless they were published in an academic peer-reviewed journal and are accessible through the named electronic databases.

Stage 3: study selection

The screening process of this proposed scoping review will comprise two phases. In the first phase, a calibration exercise will be carried out before title and abstract screening in order to ensure an adequate understanding of the inclusion criteria by study screeners.[19–21] Titles and abstracts will be reviewed by two independent reviewers following broad inclusion criteria, that is, studies looking at the management and outcomes of IcFIs in Africa. Papers identified by either or both reviewers will be included in the next phase, which is the full-text screening. The same reviewers will screen full-text studies using the eligibility criteria mentioned above. Disagreements will be discussed among the reviewers and in case of no resolution, an appeal will be made to a senior author (NDAB). A PRISMA flow diagram (figure 1) will be presented to reflect the search process.

Stage 4: charting the data

Data from the included studies will be extracted using a predefined data extraction sheet made in Microsoft Excel (Microsoft, Richmond, Virginia). Data extraction will also be performed with a pilot stage being conducted before the proper stage. In the pilot stage, all authors will review and extract data from the same 10 randomly selected articles to assure the reliability of the data extraction sheet and to ensure that all authors are able to accurately and homogeneously extract the necessary data. A meeting will be held among all authors after the pilot stage to discuss any necessary changes to be made to the proforma to ensure that it is reflective of the included studies. The expected information to be extracted is outlined in box 2.

Stage 5: collating, summarising and reporting the results

Data extracted will be presented in tabular form showing descriptive statistics. The tables may display data such as the distribution of studies per year or decade, countries where the study was conducted, patient clinical background status, treatment modalities and patient outcomes. Wherever appropriate, pooled analysis of the data will be presented in measures of central tendency and spread. A narrative description of the results will also be presented by grouping the data into meaningful summaries to allow comprehensive reporting of the findings.

Given the limited, heterogeneous evidence on IcFIs in Africa, a formal assessment of risk bias was deemed unnecessary for this scoping review as it will suffer from

the standard biases associated with new areas of clinical research.

Patient and public involvement

None.

Ethics and dissemination

Ethics

Since a scoping review involves a methodical integration and presentation of available resources, this study does not require ethics approval.

Dissemination

The main fundings of the completed scoping review will be disseminated via publication in a peer-reviewed medical journal. These findings will then be promoted via social media. The findings will also be presented at local, regional, national and international conferences. Colead authors will keep a record of the conferences at which the data are presented to avoid duplication of submissions and to comply with all conference regulations.

This work will provide a high-quality overview of the emerging evidence available on the management and outcomes of IcFIs in Africa and, thus, will be useful for the identification of key research priorities and uncovering of any disparities among countries in the continent. This review may provide focused areas of interest for policymakers, governments and healthcare organisations to invest in research and development, with the future aim to craft continentwide guidelines that inform best practice management of patients with IcFIs in Africa.

Twitter Chinedu Brian Egu @dr_alexbrianchi and Soham Bandyopadhyay @SohamBGlobal

Contributors BDT and CBE contributed to the conception and design of the study. BDT, CBE and SZYO drafted the manuscript. All authors (BDT, SZYO, CBE, CSG, SB, OED, YCHD, DUD, ACC, AKA, MK, JE, CAI, OK, NDAB) revised the manuscript critically for important intellectual content and approved for the manuscript to be published. BDT, CBE and SZYO contributed equally and are joint first authors. NDAB is the guarantor of the work.

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