

Aetiology and outcome of non-traumatic coma in African children: protocol for a systematic review and meta-analysis

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Protocol

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Abstract

Background: Non-traumatic coma is a common acute childhood presentation to healthcare facilities in Africa and is associated with high morbidity and mortality. Historically, the majority of cases were attributed to cerebral malaria (CM), but with the recent drastic reduction in malaria incidence, non-malarial coma is a larger proportion of cases, and determining the aetiology is diagnostically challenging, particularly in resource-limited settings. The purpose of this paper is to provide a protocol for a systematic review on the aetiology and clinical outcome of non-traumatic coma in African children.

Methods: The following databases will be searched: MEDLINE, Embase, and Scopus. Published articles of all languages and publication date on non-traumatic coma in African children will be included. Disease-specific articles will also be included, providing that coma is associated. Two authors will independently assess the studies for risk of bias, following which the data will be analysed, synthesised, and discussed.

Discussion: This systematic review will provide a summary of the best available evidence on the aetiology and outcome of non-traumatic coma in African children. This review is registered in PROSPERO International Prospective Register of Systematic Reviews (CRD42020141937).

Background

Non-traumatic coma is a common acute childhood presentation to healthcare facilities throughout Africa. Infectious causes of deep coma (defined as Blantyre Coma Scale (BCS) ≤ 2) include cerebral malaria (CM), acute bacterial meningitis (ABM), viral encephalitides, and HIV-associated opportunistic pathogens, such as Tuberculosis and Cryptococcal disease, and non-infectious causes include metabolic abnormalities and toxins (1-3). In malaria-endemic regions, CM is diagnosed in children with coma and peripheral malarial parasitaemia with no other identifiable cause (1). Limited diagnostic resources in many African settings and the phenomenon of asymptomatic malarial parasitaemia have both rendered the alternate diagnoses of childhood coma under-described, resulting in a poor epidemiological understanding of this clinical presentation (4,5). A study in Kenya revealed that less than half of children admitted with acute non-traumatic coma had an identified cause (6). With the recent drastic reduction in malaria incidence, it is postulated that non-malarial coma represents a larger proportion of coma cases (6). Non-traumatic coma in children is associated with high mortality (15-58%) and significant neurological sequelae (31-68%) (7-9). The long-term effects of coma on cognition and educational achievement is less commonly described, and existing literature primarily focuses on CM (10,11). Yet, these effects play an important role in the social and economic development of low-resource countries (12).

There is a paucity of data in the aetiology of non-malarial coma in Africa (3). Given the high burden of morbidity and mortality associated with this clinical presentation, an overview of the literature to date is vital to direct further research. Gwer *et al.* (2013) performed a review of fourteen studies on childhood

non-traumatic coma in both Africa and Asia (9). However, there have subsequently been multiple larger studies that have used molecular diagnostics and other adjuvant diagnostic capacities, such as magnetic resonance imaging (MRI) and electroencephalogram (EEG). Non-traumatic coma outcomes in Africa are heterogenous between studies and long term follow up is sparse. A systematic review on outcome of non-traumatic coma has not yet been investigated (9).

Using the Population, Intervention, Comparator, Outcome and Study Designs (PICOS) framework, we will aim to examine the best available evidence on the aetiology of acute non-traumatic coma in African children, including specific syndromic cohorts in comatose children to broaden the search of studies and maximise the evidence base (13). In this systematic review, we will also quantify the associated morbidity and mortality of disease-specific non-malarial coma in this setting. Lastly, we will suggest direction for future research in this important yet under-researched area.

Methods/design

Outcomes of Interest

The primary outcome of this study is to determine the aetiology of non-traumatic coma in African children. The secondary outcome is to determine the overall morbidity (particularly neurological and cognitive-behavioural sequelae) and mortality of disease-specific states with non-traumatic coma in African children. These outcomes will provide critical data needed to inform future directions for research.

Protocol Development and Registration

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) was used to develop this protocol (14) (Table 1), and we will use elements of the Cochrane Handbook of Systematic Reviews to guide the systematic review (15). The Population, Intervention, Comparator, Outcome and Study Designs (PICOS) framework was used to develop the inclusion and exclusion criteria (13). This review is registered in PROSPERO International Prospective Register of Systematic Reviews (CRD42020141937).

Eligibility Criteria

Studies of all design methods, including cohort studies and randomised-controlled trials, that are either prospective or retrospective will be included. Studies from any country in Africa will be considered, including those from multi-centre trials with data for children from African countries which can be uniquely identified. Publication dates and language will not be restricted. However, case reports, case series, commentaries and editorials will be excluded from the review. We will exclude all publications which do not contain primary data.

Studies with a primary focus of acute non-traumatic coma in children (1 month-16 years old), particularly those diagnosed with febrile encephalopathy or suspected central nervous system infection (as defined

by $BCS \leq 2$, or equivalent as per a coma assessment tool) will be included. Disease-specific studies will also be included providing coma is associated and reported.

Electronic Search Strategy

We will search the following databases: (1) MEDLINE, (2) Embase, and (3) Scopus from inception. The complete search strategy for MEDLINE is included in Table 2. We will search conference proceedings and databases of ongoing studies to identify studies not found in the databases listed above. Reference lists of eligible studies and relevant systematic reviews will be searched to identify additional studies to be considered for inclusion. All records identified from the search will be imported to EndNote X9.3.1 (Clarivate Analytics, Philadelphia, PA), a citation management programme, following which duplicates will be removed.

Screening and Selection Criteria

Two authors (SR and CF) will independently screen the title and abstract of each publication. Those articles obviously irrelevant to the review, or which do not clearly meet the inclusion criteria will be excluded. The number of records screened and excluded will be recorded. The full text of the identified studies will then be individually assessed for eligibility against the pre-determined criteria, by three reviewers (CF, SR, and AB). Discrepancies will be resolved by internal discussion and consultation with an additional author (MG) if required. The reasons for exclusion of full-text articles will be documented.

Data Extraction

We will use the Cochrane Effective Practice and Organisation of Care (EPOC) standard data collection form and adapt it for study characteristics and outcome data (17). Two review authors will pilot the form on a randomly selected subset of 10% of included studies.

The following information will be extracted from each included trial:

1. Author and Publication Details: Name of first author, corresponding author, publication year and journal, PubMed and registration ID, and funding source.
2. Study Characteristics: Study design, duration, location(s), setting, timing of data collection (prospective or retrospective), methods of recruitment, duration of follow-up and statistical methods, completeness of outcome data, and Cochrane variables of bias (16).
3. Participants: Number, age range, mean age, gender, definition of coma, inclusion and exclusion criteria, withdrawals and exclusions, method of diagnosis (microbiological methods used, including culture and polymerase chain reaction (PCR) methods), co-morbidities, and other relevant characteristics, such as human immunodeficiency virus (HIV) and nutritional status.
4. Outcome: Clinical diagnosis, microbiological diagnosis, clinical outcome, such as fatality or neurological and/or neurocognitive sequelae for each clinical syndrome, and microbiological

diagnosis. Neurological sequelae stratified into subtypes including motor, vision, hearing, epilepsy, and cognitive-behavioural.

Attempts to contact authors will be made for missing outcome data or of key study characteristics.

Assessment of Risk of Bias

Three reviewers (CF, SR, and AB) will independently conduct a bias risk assessment at the study level in order to assess the quality of the included studies. The validated Cochrane Collaboration Risk of Bias tool (16) will be used as a framework upon which to guide quality assessments for randomised controlled trials. The Newcastle-Ottawa Scale (NOS) will be used for case-control and cohort studies. Critical Appraisal Skills Programme (CASP) checklists will be used for other study types (18,19).

Risk of bias for each domain will be recorded as high, low, or unclear. Any disagreements will be discussed with a third reviewer (MG).

Data Synthesis

Because of concerns about meta-analysis of proportions on very heterogeneous populations, we plan a meta-analysis of outcome stratified by inclusion criteria where possible. A narrative synthesis of the data will also be provided including summary and explanation of characteristics and findings of included studies per outcome. Mortality will be presented as a simple proportion with exact binomial confidence intervals, and pooled mortality estimates will be calculated using generalised linear mixed models (a normal-binomial model). For interventional studies, the outcomes in the usual care arm of the study only will be included in these estimates. Heterogeneity will be quantified with τ^2 , I^2 , and Cochran's Q test. Exploratory meta-regression will be undertaken to explore heterogeneity by including covariates as fixed effects (e.g. year of recruitment, proportion of patients infected with HIV, median age) and testing for improved model fit by likelihood ratio testing of nested models. A p value of < 0.05 will be considered a statistically significantly improved fit. Summary estimates of one month mortality, where available, will be considered together and presented in the same way. Pooled prevalence estimates of malaria, acute bacterial or viral meningitis, encephalitis and bloodstream infection, will be calculated using random effects meta-analysis as above. For these aetiology analyses, we will include all studies, regardless of coma definition, and will include both usual care and intervention arms of RCTs. A sensitivity analysis will also be performed at the outcome level using the high-quality studies only (15). A table of study characteristics will be provided and the risk of bias for included studies will be described throughout the synthesis.

Discussion

This systematic review will be published in accordance with PRISMA guidelines, and the review process will be recorded through use of the PRISMA flow diagram (20). This systematic review will provide a transparent review of the available evidence in order to provide a more accurate understanding of the

causes of non-traumatic coma in African children. In this section, the authors aim to discuss the conclusiveness of the data in addition to strengths and limitations of the review. We hope that this review will serve to raise awareness of this common presentation in African settings. This review will highlight gaps in the literature and therefore areas in which future research is required.

Abbreviations

CM: cerebral malaria

ABM: acute bacterial meningitis

MRI: magnetic resonance imaging

EEG: electroencephalogram

PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols

PICOS: Population, Intervention, Comparator, Outcome and Study Designs

PCR: polymerase chain reaction

HIV: human immunodeficiency virus

EPOC: Effective Practice and Organisation of Care

NOS: Newcastle-Ottawa Scale

CASP: Critical Appraisal Skills Programme

Declarations

Ethics Approach and Consent to Participate

Not applicable

Consent for Publication

Not applicable

Availability of Data and Materials

Not applicable

Competing Interests

The authors declare that they have no competing interests.

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Authors' Contributions

SR, MG, and CF conceived and designed the systematic review. SR and CF developed the search strategy, and LB developed the statistical strategy for the review. CF and AB drafted the protocol manuscript, and SR, KBS, MG and LB contributed to the critical revision of the manuscript for methodological and intellectual content. SR is the guarantor of the review. All authors approved the final version of the submitted manuscript.

Acknowledgements

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Amendments

In the event of protocol amendments, a description of the change and rationale will be documented with the date of amendment.

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Tables

Table 1. PRISMA-P Checklist

Section/Topic	#	Checklist Item	Information Reported		Line Number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	Yes		1-2
Update	1b	If the protocol is for an update of a previous systematic review, identify as such		No	N/A
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	Yes		4
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	Yes		6-37
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Yes		251-256
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments		No	N/A
Support					
Sources	5a	Indicate sources of financial or other support for the review	Yes		245-249
Sponsor	5b	Provide name for the review funder and/or sponsor	Yes		248-249
Role of Sponsor/ Funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	Yes		248-249
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	Yes		80-103
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Yes		104-110
METHODS					

Section/Topic	#	Checklist Item	Information Reported		Line Number(s)
			Yes	No	
Eligibility Criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	Yes		128-138
Information Sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	Yes		140-147
Search Strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Yes		Table 2 (Appendix)
STUDY RECORDS					
Data Management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Yes		145-147
Selection Process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	Yes		149-156
Data Collection Process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	Yes		158-176
Data Items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	Yes		162-175
Outcomes and Prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Yes		113-118; 162-175
Risk of Bias in Individual Studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Yes		178-186
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	Yes		188-207
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2 , Kendall's tau)	Yes		188-207
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	Yes		188-207
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned		No	N/A

Section/Topic	#	Checklist Item	Information Reported		Line Number(s)
			Yes	No	
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	Yes		205-207
Confidence in Cumulative Evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	Yes		188-207

Table 2. MEDLINE Search Strategy

Number	Search terms
1	Coma* OR consciousness OR unconscious OR "non-traumatic coma" OR "non traumatic coma" OR "nontraumatic coma" OR encephalopathy OR "febrile encephalopathy" NOT "head injury"
2	aetiology OR aetiologies OR etiology OR etiologies OR cause OR causes OR causality
3	Paediatric OR pediatric OR child*
4	Africa OR "sub Saharan Africa" OR "sub-Saharan Africa" OR Algeria OR Angola OR Benin OR Botswana OR "Burkina Faso" OR Burundi OR Cameroon OR "Cape Verde" OR "Central African Republic" OR Chad OR Comoros OR "Republic of the Congo" OR "Democratic Republic of the Congo" OR "Cote d'Ivoire" OR Djibouti OR Egypt OR "Equatorial Guinea" OR Eritrea OR Eswatini OR Ethiopia OR Gabon OR "The Gambia" OR Ghana OR Guinea OR "Guinea-Bissau" OR Kenya OR Lesotho OR Liberia OR Libya OR Madagascar OR Malawi OR Mali OR Mauritania OR Mauritius OR Morocco OR Mozambique OR Namibia OR Niger OR Nigeria OR Rwanda OR "Sao Tome and Principe" OR Senegal OR Seychelles OR "Sierra Leone" OR Somalia OR "South Africa" OR "South Sudan" OR Sudan OR Swaziland OR Tanzania OR Togo OR Tunisia OR Uganda OR Zambia OR Zimbabwe
5	#1 AND #2 AND #3 AND #4