Review

Childhood acute non-traumatic coma: aetiology and challenges in management in resource-poor countries of Africa and Asia

Samson Gwer[1,2], Clifford Chacha[3], Charles R. Newton[4,5,6], Richard Idro[7,8]

[1]Department of Medical Physiology, School of Health Sciences, Kenyatta University, and [2]Clinical Research, Afya Research Africa, Nairobi, [3]Thika Level-5 Hospital, Thika, and [4]Centre for Geographic Medicine Research, Kenya Medical Research Institute, Kilifi, Kenya; [5]Neurosciences Unit, The Wolfson Centre, Institute of Child Health, University College London Institute of Child Health, and [6]Department of Psychiatry, University of Oxford, UK; [7]Department of Paediatrics and Child Health, Mulago Hospital, Makerere University, Kampala, Uganda; [8]Centre for Tropical Medicine, Nuffield Department of Clinical Medicine, University of Oxford, UK

Objective: This review examines the best available evidence on the aetiology of childhood acute non-traumatic coma in resource-poor countries (RPCs), discusses the challenges associated with management, and explores strategies to address them.

Methods: Publications in English and French which reported on studies on the aetiology of childhood non-traumatic coma in RPCs are reviewed. Primarily, the MEDLINE database was searched using the keywords coma, unconsciousness, causality, aetiology, child, malaria cerebral, meningitis, encephalitis, Africa, Asia, and developing countries.

Results: 14 records were identified for inclusion in the review. Cerebral malaria (CM) was the commonest cause of childhood coma in most of the studies conducted in Africa. Acute bacterial meningitis (ABM) was the second most common known cause of coma in seven of the African studies. Of the studies in Asia, encephalitides were the commonest cause of coma in two studies in India, and ABM was the commonest cause of coma in Pakistan. *Streptococcus pneumoniae* was the most commonly isolated organism in ABM. Japanese encephalitis, dengue fever and enteroviruses were the viral agents most commonly isolated.

Conclusion: Accurate diagnosis of the aetiology of childhood coma in RPCs is complicated by overlap in clinical presentation, limited diagnostic resources, disease endemicity and co-morbidity. For improved outcomes, studies are needed to further elucidate the aetiology of childhood coma in RPCs, explore simple and practical diagnostic tools, and investigate the most appropriate specific and supportive interventions to manage and prevent infectious encephalopathies.

Keywords: Child, Coma, Aetiology, Resource-poor countries, Outcomes

Introduction

Acute non-traumatic coma is a common presentation of childhood illness in resource-poor settings.[1–4] In sub-Saharan Africa and Asia, this is mostly attributed to central nervous system infections, cerebral malaria (CM), acute bacterial meningitis (ABM) and viral encephalitides.[1,2,4] Other causes include metabolic disorders and poisoning. Notwithstanding the diverse geographical contexts, these diseases have consistently been associated with poor clinical outcomes, high case fatalities, and significant occurrence of persistent neurological and cognitive sequelae in survivors.[1,3,5,6] The latter type of outcome is subtle and poorly described but has significant deleterious effects on a child's social and educational functioning and long-term achievements.[6] Thus, the negative impact of these encephalopathies on child survival in resource-poor countries (RPCs) is far greater than is apparent from health facilities' statistics.

There is considerable mis-diagnosis in childhood coma in RPCs, partly because of similarity in clinical presentation of the various causes of coma, limited diagnostic resources, and, in malaria-endemic areas, a high prevalence of asymptomatic parasitaemia.[7,8] The consequence of mis-diagnoses is sub-optimal treatment of life-threatening clinical scenarios, mis-attribution of disease burden, mis-prioritization of

Correspondence to: S Gwer, Department of Medical Physiology, College of Health Sciences, Kenyatta University, PO Box 43844, 00100, Nairobi, Kenya. Fax: +254 41 752 2390; email: samgwer@gmail.com

DOI 10.1179/2046905513Y.0000000068

public health strategies, and inability to accurately determine the effectiveness and harmfulness of interventions under investigation.

In this review of childhood acute coma in RPCs, we sought to examine the best available evidence on the aetiology of childhood acute non-traumatic coma in RPCs, discuss the challenges associated with management, and suggest possible strategies to surmount these challenges.

Review Method

Search strategy

Randomized controlled trials, quasi-randomized clinical trials, non-randomized controlled trials, case control studies, cohort studies and observational studies were reviewed. Specifically, publications in English and French which reported on studies of children with acute non-traumatic coma in RPCs and on the aetiology of illness were sought. Studies that specifically examined ABM and encephalitides and provided information on coma status and the species of organisms involved were also considered. The 2011 World Bank classification of economic categorization of different countries of the world was used to identify RPCs from Africa and Asia, selecting countries that were classified as 'low-income' and 'lower middle-income countries'.[7] The MEDLINE database was primarily searched. The Cochrane and Joanna Briggs Institute libraries were also searched. The search for grey literature and unpublished literature included Proquest Dissertation Abstracts International, WHO's Global Health Library, Theses Canada Portal, and the Australasian Digital Theses Program. Initial keywords used were coma, unconsciousness, causality, aetiology or etiology, child, malaria cerebral, meningitis, encephalitis, Africa, Asia, and developing countries. An initial search was undertaken in the various databases using these keywords and appropriate papers identified by examining the titles and abstracts. Full texts of papers considered to be relevant to the review were retrieved. A secondary search was conducted by examining the reference lists of all identified reports and articles for additional studies. Studies that focussed on children in the neonatal age group or gave diverse age groups but did not provide details specific to the age group beyond the neonatal age were excluded.

Assessment and data collection

Two reviewers assessed the publications identified for methodological validity prior to inclusion in the review using standardized critical appraisal instruments from the Joanna Briggs Institute Meta-Analysis of Statistics Assessment and Review Instrument (JBI-MAStARI).[8] Any disagreement between the reviewers was resolved through discussion and, if no consensus was achieved, a third reviewer was involved. Data from the papers included in the review were entered into an MsAccess2007™-based database. Data on populations, study period, setting, diagnostic methods, profile of aetiological agents, and information on clinical outcomes, if any was provided, were extracted.

Data synthesis

The data from the studies identified were not pooled because they were heterogeneous, with diverse study methods and inconsistent diagnostic schemes. In some studies, proportions were re-calculated to determine the prevalence of various diseases and causative organisms. The findings are presented in narrative form and summarised in tables and graphs.

Aetiology

In reviewing the aetiology of childhood acute coma in RPCs, the search in MEDLINE using the search phrase '(coma OR unconsciousness) AND (Africa OR Asia) AND ('1963/01/01'[PDat]: '2013/03/31'[PDat]) AND Humans [Mesh] AND (infant[MeSH] OR child[MeSH] OR adolescent[MeSH])' revealed 915 records (Fig. 1). Seventy-three abstracts were reviewed and 14 records identified for inclusion in the review: nine from Africa, four from Asia, and one from Papua New Guinea (PNG). All publications identified focussed on coma in general, apart from one which was on coma in viral encephalitides.[9] One study on childhood ABM that included data on coma was excluded because data on coma in relation to aetiology had been requested from the authors but had not been provided by the time the report was written.[10] All studies that satisfied the entry criteria were included, notwithstanding the various shortcomings in methodological quality (Table 1).[11]

Cerebral malaria was the commonest cause of childhood coma in all but two of the studies conducted in Africa – one in Nigeria and another in Egypt, both of which were based in tertiary health facilities (Fig. 2).[3,12] In the Nigerian study, ABM was the commonest cause of coma.[12] In Egypt, CM was rare and metabolic conditions were the commonest cause of coma, perhaps attributable to the tertiary nature of the health facility in which the study was undertaken, the availability of diagnostic schemes to facilitate diagnosis, and socio-cultural practices such as consanguineous marriage.[3]

ABM was the second most common known cause of coma in seven of the African studies, all of which had CM as the commonest cause of coma. Three studies in Africa reported on encephalitides but none of them indicated use of any specific viral diagnostic methods or provided a profile of organisms isolated.

Of the three studies of coma in Asia, encephalitides were the commonest cause of coma in two studies in India, and ABM was the commonest cause of coma in Pakistan (Fig. 2).[4,13,14] Viral diagnostic studies

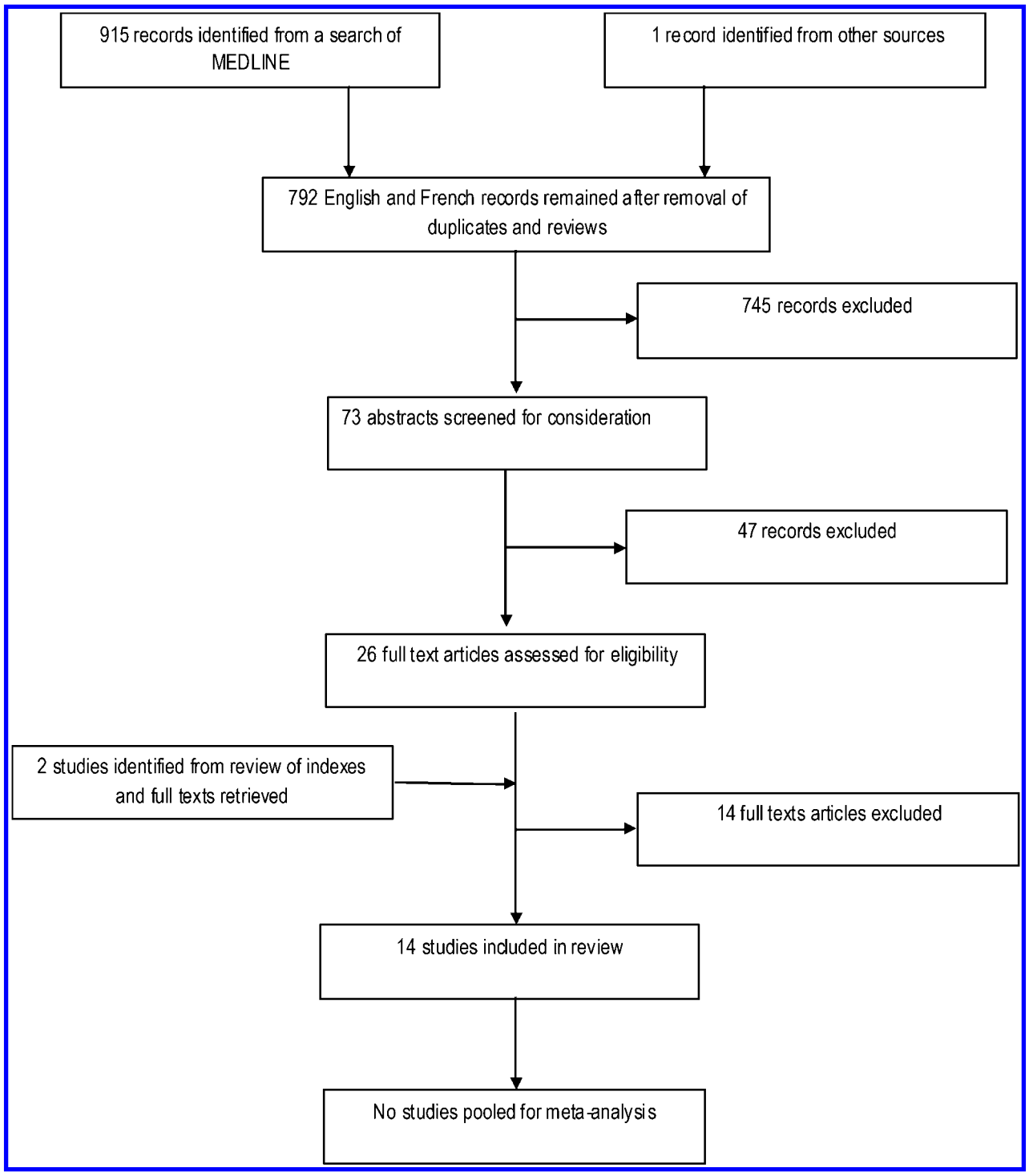

Figure 1 Flow of information through the systematic review

were not indicated as having been done in any of these studies and the profile of organisms for encephalitides was not provided. In Pakistan and in one of the studies in India, CM was the second most common cause of coma.[4,13] In PNG, the commonest cause of coma was ABM, followed by CM.[1] Viral studies were undertaken, although not consistently, and flaviviruses, Japanese encephalitis (n=2, 33%) and dengue fever (n=2, 33%) were the viral agents most commonly isolated.[1] In another study in Asia which focussed primarily on viral encephalitides, Japanese encephalitis (n=50, 63%), enteroviruses (n=18, 23%) and dengue fever (n=9, 11%) were the most commonly isolated viral agents in children with confirmed viral aetiology.[9]

Only five studies provided a profile of bacterial organisms isolated, including one that focussed only on coma in association with ABM: three from Kenya, one from Pakistan and another from Papua New Guinea.[1,13,15–17] The commonest organism isolated in all these studies was *Streptococcus pneumoniae* (Fig. 3). *Haemophilus influenzae* was the second most common isolate in two studies based in PNG and Kenya which were also the only studies in which it

Table 1 Assessment of methodological quality for the selected descriptive studies

	Assessment criterion	Ahmed 2011[13]	Akpede 1996[63]	Anga 2010[1]	Bansal 2005[14]	Berkley 1999[15]	Bondi 1991[64]	Chaturvedi 2001[4]	Fouad 2011[3]	Gwer 2012[16]	Ibekwe 2011[2]	Jitta 1984[17]	Le 2010[9]	Ogunmekan 1983[12]	Taylor 2004[26]
1	Was the study based on a random or pseudo-random sample?	Y	Y	Y	Y	Y	U	Y	U	Y	U	Y	Y	Y	U
2	Were criteria for inclusion in the sample clearly defined?	Y	Y	Y	Y	Y	Y	U	Y	Y	Y	Y	U	N	Y
3	Were confounding factors identified and strategies to deal with them stated?	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	U	U	N
4	Were outcomes assessed using objective criteria?	Y	Y	Y	Y	Y	U	Y	Y	Y	Y	Y	Y	U	Y
5	If comparisons are being made, were there sufficient descriptions of the groups?	N/A	N/A	N/A	N/A	Y	N/A	U	N/A	N/A	N/A	N/A	N/A	N/A	N
6	Was follow-up carried out over a sufficient time period?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
7	Were the outcomes of the people who withdrew described and included in the analysis?	N	Y	N	U	N/A	N/A	U	Y	N/A	N/A	U	N	N/A	N
8	Were outcomes measured in a reliable way?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
9	Was appropriate statistical analysis used?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	Y
10	Overall appraisal: Y/N?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y

Y, yes; N, no; N/A, not applicable; U, unclear

Figure 2 Profile of the aetiology of childhood coma

was identified as a cause of ABM.[1,15] A second study at the same site in Kenya conducted at a later period did not identify *H. influenzae* as a cause of ABM.[16] Notably, universal *H. influenzae* B vaccination had been introduced in the set-up by then.[18]

The findings presented here need to be considered with the following considerations in mind. Many children in RPCs die before accessing health facilities.[19,20] The burden of aggressive and rapidly progressing disease conditions such as ABM, metabolic disease and poisoning may not be accurately reflected by the profile of encephalopathic disease in those who are able to access health facilities. Thus, the sample population for these hospital-based studies in RPCs may be biased.

Diagnostic resources are limited in RPCs and this is reflected in the studies that were reviewed in which diagnostic schemes were neither comprehensive nor consistent. Most notably, there were almost no metabolic investigations for inborn errors of metabolism, and viral studies were undertaken in only two studies, both in Asia.[1,9] The importance of viral studies is underscored in a study in Kilifi, Kenya in which 9% of children with a diagnosis of CM were found to have evidence of herpes simplex infection in their cerebro-spinal fluid (CSF) samples.[21] In Malawi,

Figure 3 Profile of species aetiology of acute bacterial meningitis associated with impaired consciousness

12% of the fatal encephalopathic cases which were originally attributed to CM were found on autopsy to be caused by rabies.[22] Seven of the studies reviewed indicated diagnoses of encephalitis on the basis of clinical presentation, CSF biochemistry and cell count (Table 1). In our own study in Kilifi, Kenya, we demonstrated an apparent decrease in the absolute and relative numbers of comatose children with malaria parasitaemia over a period of documented decline in malaria transmission, in the context of an accompanying increase in the number of children with coma of unknown cause.[16] We speculated that this increasing number of unknown encephalopathies represented other causes of coma previously masked by malaria parasitaemia. Considering that these children were previously well and of normal growth and development, an un-investigated infectious aetiology was more likely. These studies suggest a significant burden of viral diseases in coma causation. Beyond viral investigations, diagnosis of other disease conditions is similarly challenging. Even under optimal conditions and practices, body fluid cultures for bacteria, although highly specific, are minimally sensitive.[23] Further, organism yield can be altered by partial antibiotic treatment, low-density bacteraemia, low volume cultures, and other technical factors.[23] In a series of children with clinically-defined sepsis, only 26% of 815 had proven bacteraemia but there was no difference in mortality between culture-positive and culture-negative children.[24] Among Gambian children with lobar pneumonia or empyema, blood culture alone yielded a bacterial pathogen in 18% of the cases, while the addition of percutaneous lung aspiration or pleural aspiration increased the yield to 52%.[25]

In Malawi, 23% of children with an initial diagnosis of CM were found at autopsy to have died of other causes, including pneumonia, meningitis, Reye's syndrome, ruptured arterio-venous malformation, hepatic necrosis, severe anaemia and other causes.[26] Thus, in the absence of consistent systematic diagnostic schemes to investigate for metabolic conditions, viral and bacterial infections, and other causes, our findings may be subject to detection bias and might not reflect the actual burden of the various diseases in the causation of coma.

Only seven of the included studies were conducted after the year 2000. It is important to consider the diverse periods of these studies. Public health interventions such as *H. infleunzae* vaccination and malaria control strategies, changing socio-economic circumstances and changes in weather patterns have altered the burden of important aetiologies and diseases over time.[18,27] New diagnostic modalities might improve detection of hitherto under-reported disease conditions. Only one of the included studies synthesised the changing profile of diagnosis over a significant period of time.[16] Other issues for consideration include the fact that coma aetiology might vary with seasons. For instance, a changing burden of malaria disease during rainy and dry seasons has been clearly demonstrated in some regions.[28,29] Some of the studies included in the review were undertaken over short periods of time or captured small samples and might have failed to describe such seasonal variations in the burden of infectious aetiology.[3,17]

The definition of coma varied in different circumstances. It is likely that tertiary facilities provided patient profiles different from those in lower-level health facilities. Other studies even included chronic encephalopathies and febrile convulsions, conditions which have different implications for practice and clinical outcomes than do acute encephalopathies.[2,13]

These challenges in diagnosing and defining the burden of various coma-causing diseases in RPCs are further complicated by co-morbidity and disease endemicity. In malaria-endemic areas, as many as 80% of children might be parasitaemic and asymptomatic.[30] Thus, even where there is reliable and timely malaria microscopy, encephalopathic illness in a parasitaemic child might not always be caused by malaria. HIV disease, malnutrition and diarrhoeal diseases causing severe dehydration, endemic in many RPCs, may themselves cause coma and predispose children to other infectious diseases resulting in coma. The need to investigate and treat other causes of coma such as bacterial and opportunistic infections is greater in HIV-infected children.[23] Increased risk of infection and an altered profile of the aetiology of meningitis have been described in childhood HIV disease.[31,32] A number of studies have also reported altered risk of childhood severe malaria with HIV co-infection.[33,34] Recently, a review of clinical and laboratory data from a cohort of children involved in a clinical trial of artesunate and quinine indicated higher malaria parasite burden, greater likelihood of deterioration of coma status, a more severe clinical course, and worse outcome of severe malaria disease with HIV co-infection compared with non-infection.[35] The effects of anti-retroviral drugs on the course of severe malaria, have not been well elucidated.[23]

The interaction between childhood malnutrition, which is commonly under-diagnosed, and diseases causing coma in children, is not well described either.[36] Protein energy malnutrition is associated with impaired immunity and probably increased susceptibility to infectious encephalopathies.[37] Indeed, a high prevalence of bacteraemia, particularly gram-positive isolates, and increased resistance to commonly used antibiotics has been demonstrated in severely malnourished Ethiopian children.[38] Early studies suggested a protective effect of malnutrition against cerebral

malaria.[39,40] However, no further studies have clarified this relationship. Importantly, co-diagnosis of malnutrition in the context of encephalopathy requires consideration of possible metabolic aetiology, careful assessment of fluid homeostasis, and cautious fluid resuscitation and enteric feeding.

Clearly, accurate diagnosis and consideration of co-morbidities is an important first step in facilitating appropriate clinical management of coma and prioritizing public health interventions. Improving diagnostic resources and human resource skills is part of the solution, an intervention which is dependent on socio-economic progress and governments' goodwill in the management of health systems. The exploration of simple clinical techniques to improve diagnostic ascertainment might also be useful. Recently, a number of studies in Malawi have indicated the value of malaria retinopathy, determined by indirect fundoscopy, in confirming diagnosis of CM.[26,41] However, in Ghana, significant overlap in malaria retinopathy between patients with CM and those with non-CM malaria syndromes has been described.[42] In addition to the consideration that indirect fundoscopy is a procedure that requires skilled training and experience lacking in most RPCs, the value of malaria retinopathy findings in determining accurate diagnosis of CM needs further clarification. The use of clinical syndromes defined by the World Health Organization's Integrated Management of Childhood Illness and Inpatient Guidelines has been shown to be useful in predicting invasive bacterial infection and increased risk of death.[43] However, such practice is likely to be subjective, dependent on clinical experience, and would still require sound laboratory support for optimality. The common practice is that of empirical use of antibiotics and anti-malarial drugs until a diagnosis is confirmed or negated. Antiviral drugs are rarely used in RPCs and, anyway, have not been shown to be consistently effective beyond timely use of acyclovir in herpes simplex and CMV encephalitides. Maintained without proper guidelines and information on local microbial sensitivities, such practice may fuel antimicrobial resistance.

With such difficulties in accurate diagnosis and in the background of limited skilled human resources for health care, childhood coma presentation in RPCs almost surely portends a fatal consequence or lifelong disability for its sufferer.

Outcome and Risk Factors for Poor Outcome

This review did not systematically search for studies on outcome and risk factors for poor outcome. Such a task would ideally have entailed inclusion of studies focussing on specific disease entities such as CM, various specific viral encephalitides and specific meningitides, disease conditions which may have unique risk factors for poor outcome. Among the studies identified for review, mortality ranged between 15% and 58% (Table 2). Case fatality for the various diseases varied in the different studies. Neurological sequelae were reported in six studies and varied between 31% and 67%. Follow-up assessments after discharge were not consistently performed in these studies and were mostly not necessary for the primary objectives of the studies.

Depth of coma, observed in eight studies, was the most frequently reported clinical factor associated with poor outcome. Other factors associated with poor outcome included hypotension, neurological features of raised intracranial pressure or intracranial herniation, each reported in three studies, and aetiology associated with bacterial infection, young age and breathing difficulties at presentation, each demonstrated in two studies. Seizures, developing after 48 hours of hospitalisation, were associated with poor outcome in only one study.[3] In another study, seizures occurring within 24 hours before admission or at presentation were actually associated with better odds of survival.[16] A number of studies have indicated the association between multiple or prolonged seizures and poor outcome. However, simple seizures are common in neurologically intact children with fever and might reduce time to admission in encephalopathy, with an apparently better outcome in these children. It is also possible that the association between seizures and adverse outcome may be specific to disease or related to recurrence or persistence.

Supportive Care and Management

Risk factors such as volume deficits or shock, multiple seizures, raised intracranial pressure (ICP) and breathing difficulties are associated with ischaemic neuronal damage, partly owing to diminished cerebral blood flow, altered cerebral auto-regulation, hypoxia and intracranial herniation.[44,45] They present ideal targets for practical interventions to improve outcome. However, the clinical signs are often difficult to detect and occur late in the illness. For example, papilloedema is a late sign of raised ICP in children and is associated with significant inter-observer variation among clinicians.[46] Low blood pressure occurs late in shock and is not a reliable indicator of childhood haemodynamic deficit in severely ill children.[47] Significant occurrence of subtle and electrographic seizures has been demonstrated in children with CM, ABM and other encephalopathies.[48,49]

In better resourced settings, intensive, often invasive, monitoring to detect raised ICP, seizures and hypovolaemia, and facilities for mechanical ventilation, allow for early recognition and better management for improved outcome. In RPCs, the challenge

Table 2 Outcome and risk factors for poor outcome

Citation	Profile	Country	Mortality %	CF CM, %	CF ABM, %	CF encephalitides, %	CF metabolic, %	CF unknown, %	Neuro-cognitive sequalae, %%	Risk factors for poor outcome
Ahmed 2011[13]	Coma	Pakistan	29				20		41	Hypothermia, hypotension, bradycardia, altered breathing pattern, non-reacting pupils, low GCS, hypotonia, hyporeflexia, muscle power of 2
Akpede 1996[63]	Coma	Nigeria	15	12	15			6		
Bansal 2005[14]	Coma	India	35	0	25	28	64		62 (57% moderate + severe)	Age <3 years, low pulse volume, absent oculocephalic reflex and presence of papilloedema – risk facors for death
Berkley 1999[15]	Coma	Kenya	23.4	11.1	17.2					
Bondi 1991[64]	Coma	Nigeria	36						31	Aetiology, severe anaemia, hypoglycaemia, pneumonia
Chaturvedi 2001[4]	Coma	India	29.1							Coma as defined by the modified GCS score
Fouad 2011[3]	Coma	Egypt	50		67	47	50		57.7 (31% moderate + severe)	Poor GCS ont admission, abnormal respiratory pattern, and seizures after 48 hours of admission were independent significant predictors of mortality
Gwer 2012[16]	Coma	Kenya	25	16	35			33		Vomiting, breathing difficulties, bradycardia, profound coma (BCS=0), bacteraemia and clinical signs of meninigtis associated with poor outcome
Ibekwe 2011[2]	Coma	Nigeria	32.5							No independent predictors of mortality found
Jitta 1984[17]	Coma	Kenya	58	29	40	100		80	35 (Mild + moderate)	
Le Van Tan 2010[9]	Encephalitis	Vietnam	29			29				Low GCS and young age (1 year) associated with death
Ogunmekan 1983[12]	Coma	Nigeria	26.7						28 (14.7% moderate + severe)	Complete absence of occular motility and fixed dilated pupils associated with poor outcome

CF, case fatality; CM, cerebral malaria; ABM, acute bacterial meningitis; SBP, systolic blood pressure; GCS, Glasgow coma score; BCS, Blantyre coma score; Metabolic conditions = inborn errors of metabolism, diabetic keto-acidosis, hypoglycaemia, hypocalcaemia, hyponatraemia

is that of limited resources and expertise to facilitate optimal management.

Part of the strategy to surmount these challenges is to explore the use of simple tools for intensive care monitoring. In a recent study in which we demonstrated significant occurrence of electrographic seizures in African children with coma, we observed that 93% of seizures on EEG could be detected by the placement leads used for the two channel cerebral function analyser monitor (CFAM).[49] Devices with 1–4 EEG channels such as the CFAM are cheaper than standard EEG machines, can easily be interpreted by less experienced clinicians and nurses, and would be of greater use in RPCs. We have also been interested in exploring techniques for non-invasive monitoring of ICP. One of the candidate techniques includes the tympanic membrane displacement analyser which might be useful in monitoring intracranial dynamics in children with coma.[50] Mechanical ventilation would be appropriate for children in deep coma, with repeated seizures and in those with respiratory difficulties. However, options for mechanical ventilation in infectious encephalopathies are not widely available in RPCs and, even if made available, the challenge would be that of identifying patients who are most likely to benefit in the context of overwhelming need.[51]

Another strategy would be that of empirical supportive treatment. Thus, children in coma could empirically receive prophylactic anticonvulsants for prevention of seizures. Phenobarbital has previously been investigated for such use and, although it was associated with significant prevention of seizures, it caused greater mortality from respiratory arrest than the placebo.[52] We are currently analysing results of a placebo-controlled trial on the use of fosphenytoin to prevent seizures in coma (ISRCTN11862726) (http://www.controlled-trials.com/ISRCTN11862726) and believe that other newer and safer anticonvulsants such as leviracetam should also be explored for this purpose. Osmotic agents may be useful for preventing and managing raised ICP. In our systematic review on the efficacy and effectiveness of osmotic agents for treatment ICP, we observed great potential for continuous hypertonic saline infusions and oral glycerol.[53] These osmotic agents need to be explored further for widespread empirical use to prevent raised ICP.

In the absence of intensive monitoring, fluid management in childhood coma in RPCs presents a major challenge. In infectious encephalopathy, in which the integrity of the blood/brain barrier might be impaired, therapy aimed at correcting volume deficits and improving tissue perfusion carries the risk of cerebral oedema. Volume resuscitation with colloids might be safer than crystalloid solutions, as the latter freely equilibrate in the extracellular compartment and thus have the potential risk of aggravating ICP. This possibility was initially supported by a randomised trial on children with severe malaria that demonstrated that volume expansion with 4.5% human albumin solution was associated with significantly lower mortality (4%) than saline (18%) in children with acidosis, especially amongst those admitted in coma (5% *vs* 46%, respectively).[54] Gelofusine, a modified gelatin and a much cheaper colloid, showed no beneficial effect on survival.[55] A larger multicentre clinical trial on fluid boluses in severely ill African children has since demonstrated greater mortality with saline and albumin bolus fluid administration than no fluid bolus administration.[56] However, the criteria used for volume deficit in this study is in contention and the implications of these findings for practice are still under discussion and may require other studies for clarification.[57] Normal saline remains the fluid of choice for resuscitation of encephalopathic children.[58] It may be that hypertonic saline may be useful for volume resuscitation and maintenance in childhood infectious encephalopathy considering that it boosts volume load and is useful in the prevention and treatment of raised ICP. Fluid resuscitation in malnutrition, highly prevalent in RPC children and often presenting as a co-morbidity in infectious encephalopathy, may be complicated by congestive cardiac failure and electrolyte derangement, and presents a great management challenge with no clear guidance to date.

Other considerations in supportive management in childhood coma in RPCs include timing of enteral feeding and micronutrient supplementation. A recent clinical trial has indicated that early enteral feeding in non-intubated children with CM may be deleterious.[59] Whilst the use of iron supplementation in active bacterial or malaria infection is known to be detrimental, the value of other micronutrient supplementations such as zinc, magnesium and vitamin A is not so well established. In developed countries, the use of corticosteroids in childhood ABM has been shown to improve outcome.[60] However, in RPCs, studies on the benefits of corticosteroids have been equivocal, probably because of late presentation and a high HIV infection prevalence.[61,62] The clinical implications of corticosteroid use in better resourced settings within urban areas in RPCs and on other infectious encephalopathies such as CM are not clear.

Research Priorities

There is significant paucity of knowledge on the aetiology, pathophysiology, risk factors, outcomes and appropriate interventions for childhood acute coma in RPCs. Understanding the aetiology of childhood acute non-traumatic coma is necessary in order to direct research, prioritize public health interventions and guide routine clinical management.

Prospective observational studies in malaria and non-malaria-endemic areas that incorporate viral, bacterial and metabolic studies, imaging and detailed clinical observations will be useful in elucidating the aetiology and pathophysiology of disease. Clearly, infectious encephalopathies have a significant effect on child survival in RPCs. Universal vaccination and malaria control strategies have been shown to significantly alter the burden of disease. It seems obvious that universal vaccine initiatives against malaria, *S. pneumoniae*, Japanese encephalitis and dengue fever will significantly alter the burden of disease causing coma. If previously unappreciated infectious agents are found to cause a significant proportion of childhood encephalopathies, it makes sense to extend these studies by investigating useful biomarkers to aid development of simple techniques such as rapid diagnostic kits and allow for widespread and accurate diagnoses, even in RPCs. Rapid diagnostic kits for malaria and HIV disease have already been shown to improve diagnosis and management.

Developing simple tools for monitoring ICP, seizures and shock would greatly aid supportive management of coma and the investigation of other appropriate supportive interventions. Such supportive interventions that are a priority for investigation include prophylactic anticonvulsants, osmotic agents for treatment of ICP, fluids for resuscitation and supplementary micronutrients. As we strive to determine the best-practice evidence for managing coma in RPCs, it seems appropriate to use the WHO's definitions of clinical syndromes, to at least attempt accurate laboratory diagnoses of malaria parasitaemia and bacteraemia, and to provide empirical antimicrobial treatment as guided by local disease endemicity and microbial sensitivities.

Acknowledgment

We are grateful to the Joanna Briggs Institute for permitting us to use their systematic review tools in conducting our review. Charles Newton is supported by a Wellcome Trust fellowship award (070114).

References

1 Anga G, Barnabas R, Kaminiel O, Tefuarani N, Vince J, Ripa P, *et al*. The aetiology, clinical presentations and outcome of febrile encephalopathy in children in Papua New Guinea. Ann Trop Paediatr. 2010;30:109–18.
2 Ibekwe RC, Ibekwe MU, Onwe OE, Nnebe-Agumadu UH, Ibe BC. Non-traumatic childhood coma in Ebonyi State University Teaching Hospital, Abakaliki, South Eastern Nigeria. Niger J Clin Pract. 2011;14:43–6.
3 Fouad H, Haron M, Halawa EF, Nada M. Nontraumatic coma in a tertiary pediatric emergency department in Egypt: etiology and outcome. J Child Neurol. 2011;26:136–41.
4 Chaturvedi P, Kishore M. Modified Glasgow Coma Scale to predict mortality in febrile unconscious children. Indian J Pediatr. 2001;68:311–14.
5 Carter JA, Neville BG, Newton CR. Neuro-cognitive impairment following acquired central nervous system infections in childhood: a systematic review. Brain Res Brain Res Rev. 2003;43:57–69.
6 Kihara M, Carter JA, Holding PA, Vargha-Khadem F, Scott RC, Idro R, *et al*. Impaired everyday memory associated with encephalopathy of severe malaria: the role of seizures and hippocampal damage. Malar J. 2009;8:273.
7 The World Bank. Country and Lending Groups, 2011.
8 System for the Unified Management, Assessment and Review of Information. University of Adelaide, Joanna Briggs Institute, 2013.
9 Le VT, Phan TQ, Do QH, Nguyen BH, Lam QB, Bach VC, *et al*. Viral etiology of encephalitis in children in southern Vietnam: results of a one-year prospective descriptive study. PLoS Negl Trop Dis. 2010;4:e854.
10 Laman M, Manning L, Greenhill AR, Mare T, Michael A, Shem S, *et al*. Predictors of acute bacterial meningitis in children from a malaria-endemic area of Papua New Guinea. Am J Trop Med Hyg. 2012;86:240–5.
11 Ahuja GK, Mohan KK, Prasad K, Behari M. Diagnostic criteria for tuberculous meningitis and their validation. Tuberc Lung Dis. 1994;75:149–52.
12 Ogunmekan AO. Non-traumatic coma in childhood: etiology, clinical findings, morbidity, prognosis and mortality. J Trop Pediatr. 1983;29:230–2.
13 Ahmed S, Ejaz K, Shamim MS, Salim MA, Khans MU. Non-traumatic coma in paediatric patients: etiology and predictors of outcome. J Pak Med Assoc. 2011;61:671–5.
14 Bansal A, Singhi SC, Singhi PD, Khandelwal N, Ramesh S. Non traumatic coma. Indian J Pediatr. 2005;72:467–73.
15 Berkley JA, Mwangi I, Mellington F, Mwarumba S, Marsh K. Cerebral malaria versus bacterial meningitis in children with impaired consciousness. QJM. 1999;92:151–7.
16 Gwer S, Thuo N, Idro R, Ndiritu M, Boga M, Newton C, *et al*. Changing trends in incidence and aetiology of childhood acute non-traumatic coma over a period of changing malaria transmission in rural coastal Kenya: a retrospective analysis. Br Med J Open. 2012;2:e000475.
17 Jitta JN, Wafula EM, Wasunna A. The comatose child in the Paediatric Observation Ward of Kenyatta National Hospital, Nairobi, Kenya. East Afr Med J. 1984;61:917–24.
18 Cowgill KD, Ndiritu M, Nyiro J, Slack MP, Chiphatsi S, Ismail A, *et al*. Effectiveness of *Haemophilus influenzae* type b conjugate vaccine introduction into routine childhood immunization in Kenya. JAMA. 2006;296:671–8.
19 Mung'ala VO, Snow RW. Death registration on the Kenyan Coast. East Afr Med J. 1994;71:747–50.
20 Greenwood BM, Bradley AK, Greenwood AM, Byass P, Jammeh K, Marsh K, *et al*. Mortality and morbidity from malaria among children in a rural area of The Gambia, West Africa. Trans R Soc Trop Med Hyg. 1987;81:478–86.
21 Schubart CD, Mturi N, Beld MG, Wertheim PM, Newton CR. Role of viruses in Kenyan children presenting with acute encephalopathy in a malaria-endemic area. Am J Trop Med Hyg. 2006;75:1148–50.
22 Mallewa M, Fooks AR, Banda D, Chikungwa P, Mankhambo L, Molyneux E, *et al*. Rabies encephalitis in malaria-endemic area, Malawi, Africa. Emerg Infect Dis. 2007;13:136–9.
23 Gwer S, Newton CR, Berkley JA. Over-diagnosis and co-morbidity of severe malaria in African children: a guide for clinicians. Am J Trop Med Hyg. 2007;77 (6 suppl):6–13.
24 Saez-Llorens X, Vargas S, Guerra F, Coronado L. Application of new sepsis definitions to evaluate outcome of pediatric patients with severe systemic infections. Pediatr Infect Dis J. 1995;14:557–61.
25 Falade AG, Mulholland EK, Adegbola RA, Greenwood BM. Bacterial isolates from blood and lung aspirate cultures in Gambian children with lobar pneumonia. Ann Trop Paediatr. 1997;17:315–19.
26 Taylor TE, Fu WJ, Carr RA, Whitten RO, Mueller JS, Fosiko NG, *et al*. Differentiating the pathologies of cerebral malaria by postmortem parasite counts. Nat Med. 2004;10:143–5.
27 O'Meara WP, Bejon P, Mwangi TW, Okiro EA, Peshu N, Snow RW, *et al*. Effect of a fall in malaria transmission on morbidity and mortality in Kilifi, Kenya. Lancet. 2008; 372:1555–62.
28 Rumisha SF, Smith T, Abdulla S, Masanja H, Vounatsou P. Assessing seasonal variations and age patterns in mortality during the first year of life in Tanzania. Acta Trop. 2013;126:28–36.
29 Bigoga JD, Nanfack FM, Awono-Ambene PH, Patchoke S, Atangana J, Otia VS, *et al*. Seasonal prevalence of malaria vectors and entomological inoculation rates in the rubber

cultivated area of Niete, South Region of Cameroon. Parasit Vectors. 2012;5:197.
30 Bodker R, Msangeni HA, Kisinza W, Lindsay SW. Relationship between the intensity of exposure to malaria parasites and infection in the Usambara Mountains, Tanzania. Am J Trop Med Hyg. 2006;74:716–23.
31 Wolzak NK, Cooke ML, Orth H, van Toorn R. The changing profile of pediatric meningitis at a referral centre in Cape Town, South Africa. J Trop Pediatr. 2012;58:491–5.
32 Nyasulu P, Cohen C, De Gouveia L, Feldman C, Klugman KP, von Gottberg A. Increased risk of death in human immunodeficiency virus-infected children with pneumococcal meningitis in South Africa, 2003–2005. Pediatr Infect Dis J. 2011;30:1075–80.
33 Cuadros DF, Branscum AJ, Crowley PH. HIV-malaria co-infection: effects of malaria on the prevalence of HIV in East sub-Saharan Africa. Int J Epidemiol. 2011;40:931–9.
34 Kalyesubula I, Musoke-Mudido P, Marum L, Bagenda D, Aceng E, Ndugwa C, *et al*. Effects of malaria infection in human immunodeficiency virus type 1-infected Ugandan children. Pediatr Infect Dis J. 1997;16:876–81.
35 Hendriksen IC, Ferro J, Montoya P, Chhaganlal KD, Seni A, Gomes E, *et al*. Diagnosis, clinical presentation, and in-hospital mortality of severe malaria in HIV-coinfected children and adults in Mozambique. Clin Infect Dis. 2012;55:1144–53.
36 Myatt M, Khara T, Collins S. A review of methods to detect cases of severely malnourished children in the community for their admission into community-based therapeutic care programs. Food Nutr Bull. 2006;27 (3 suppl):S7–23.
37 Taylor AK, Cao W, Vora KP, De La Cruz J, Shieh WJ, Zaki SR, *et al*. Protein energy malnutrition decreases immunity and increases susceptibility to influenza infection in mice. J Infect Dis. 2013;207:501–10.
38 Abrha A, Abdissa A, Beyene G, Getahun G, Girma T. Bacteraemia among severely malnourished children in jimma university hospital, ethiopia. Ethiop J Health Sci. 2011;21:175–82.
39 Murray MJ, Murray AB, Murray NJ, Murray MB. Diet and cerebral malaria: the effect of famine and refeeding. Am J Clin Nutr. 1978;31:57–61.
40 Edington GM. Pathology of malaria in West Africa. Br Med J. 1967;1:715–18.
41 Beare NA, Taylor TE, Harding SP, Lewallen S, Molyneux ME. Malarial retinopathy: a newly established diagnostic sign in severe malaria. Am J Trop Med Hyg. 2006;75:790–7.
42 Essuman VA, Ntim-Amponsah CT, Astrup BS, Adjei GO, Kurtzhals JA, Ndanu TA, *et al*. Retinopathy in severe malaria in Ghanaian children – overlap between fundus changes in cerebral and non-cerebral malaria. Malar J. 2010;9:232.
43 Berkley JA, Maitland K, Mwangi I, Ngetsa C, Mwarumba S, Lowe BS, *et al*. Use of clinical syndromes to target antibiotic prescribing in seriously ill children in a malaria endemic area: observational study. Br Med J. 2005;330:995.
44 Newton CR, Krishna S. Severe falciparum malaria in children: current understanding of pathophysiology and supportive treatment. Pharmacol Ther. 1998;79:1–53.
45 Czosnyka M, Pickard JD. Monitoring and interpretation of intracranial pressure. J Neurol Neurosurg Psychiatry. 2004;75:813–21.
46 Sinclair AJ, Burdon MA, Nightingale PG, Matthews TD, Jacks A, Lawden M, *et al*. Rating papilloedema: an evaluation of the Frisen classification in idiopathic intracranial hypertension. J Neurol. 2012;259:1406–12.
47 Lemson J, Nusmeier A, van der Hoeven JG. Advanced hemodynamic monitoring in critically ill children. Pediatrics. 2011;128:560–71.
48 Crawley J, Smith S, Muthinji P, Marsh K, Kirkham F. Electroencephalographic and clinical features of cerebral malaria. Arch Dis Child. 2001;84:247–53.
49 Gwer S, Idro R, Fegan G, Chengo E, Garrashi H, White S, *et al*. Continuous EEG monitoring in Kenyan children with non-traumatic coma. Arch Dis Child. 2012;97:343–9.
50 Gwer S, Sheward V, Birch A, Marchbanks R, Idro R, Newton CR, *et al*. The tympanic membrane displacement analyser for monitoring intracranial pressure in children. Childs Nerv Syst. 2013;29:927–33.
51 Gerardin P, Rogier C, Ka AS, Jouvencel P, Diatta B, Imbert P. Outcome of life-threatening malaria in African children requiring endotracheal intubation. Malar J. 2007;6:51.
52 Crawley J, Waruiru C, Mithwani S, Mwangi I, Watkins W, Ouma D, *et al*. Effect of phenobarbital on seizure frequency and mortality in childhood cerebral malaria: a randomised, controlled intervention study. Lancet. 2000;355:701–6.
53 Gwer S, Gatakaa H, Mwai L, Idro R, Newton CR. The role for osmotic agents in children with acute encephalopathies: a systematic review. BMC Pediatr. 2010;10:23.
54 Maitland K, Pamba A, English M, Peshu N, Marsh K, Newton C, *et al*. Randomized trial of volume expansion with albumin or saline in children with severe malaria: preliminary evidence of albumin benefit. Clin Infect Dis. 2005;40:538–45.
55 Akech S, Gwer S, Idro R, Fegan G, Eziefula AC, Newton CR, *et al*. Volume expansion with albumin compared to gelofusine in children with severe malaria: results of a controlled trial. PLoS Clin Trials. 2006;1:e21.
56 Maitland K, Kiguli S, Opoka RO, Engoru C, Olupot-Olupot P, Akech SO, *et al*. Mortality after fluid bolus in African children with severe infection. N Engl J Med. 2011;364:2483–95.
57 Duke T. What the African fluid-bolus trial means. Lancet. 2011;378:1685–7.
58 World Health Organization. Pocket Book of Hospital Care for Children – Guidelines for the Management of Common Illnesses with Limited Resources. Geneva: WHO, 2005.
59 Maude RJ, Hoque G, Hasan MU, Sayeed A, Akter S, Samad R, *et al*. Timing of enteral feeding in cerebral malaria in resource-poor settings: a randomized trial. PLoS One. 2011;6:e27273.
60 Borchorst S, Moller K. The role of dexamethasone in the treatment of bacterial meningitis – a systematic review. Acta Anaesthesiol Scand. 2012;56:1210–21.
61 Molyneux EM, Walsh AL, Forsyth H, Tembo M, Mwenechanya J, Kayira K, *et al*. Dexamethasone treatment in childhood bacterial meningitis in Malawi: a randomised controlled trial. Lancet. 2002;360:211–18.
62 Ciana G, Parmar N, Antonio C, Pivetta S, Tamburlini G, Cuttini M. Effectiveness of adjunctive treatment with steroids in reducing short-term mortality in a high-risk population of children with bacterial meningitis. J Trop Pediatr. 1995;41:164–8.
63 Akpede GO, Abiodun PO, Ambe JP. Aetiological considerations in the febrile unconscious child in the rainforest and arid regions of Nigeria. East Afr Med J. 1996;73:245–50.
64 Bondi FS. Childhood coma in Ibadan. Relationship to socio-economic factors. Trop Geogr Med. 1991;43:288–92.