The University of Nottingham

National Reyes Syndrome Foundation UK

The management of a child with a decreased conscious level

A nationally developed evidence-based guideline for hospital practitioners

Full technical document

Developed by
The Paediatric Accident and Emergency Research Group

Authors

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Mr and Mrs Fountain	(Patient representatives, Nottingham)

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The guideline was developed with a grant from the National Reye's Syndrome Foundation UK (Registered charity no. 288064).

Guideline Development Group

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Dr William Whitehouse	(Senior Lecturer in Paediatric Neurologist, University of Nottingham)
Mr and Mrs Fountain	(Patient representatives, Nottingham)

Parent / Patient representation

Parental contributions were provided by the lay members of the following organisations:

Children Living with Inherited Metabolic Diseases

The Encephalitis Society

The National Reye's Syndrome Foundation UK

These contributions were invaluable to the development of the good practice points. Further details are provided in Appendix E.

Stakeholder groups

The following organisations contributed to the development of the guideline:

The Association of Paediatric Anaesthetists of Great Britain and Ireland

British Association of Emergency Medicine

Association of Paediatric Emergency Medicine

Royal College of Paediatrics and Child Health - British Association of General Paediatricians

Royal College of Paediatrics and Child Health - Nephrology Interest Group

Royal College of Paediatrics and Child Health - Pathology Interest Group

Paediatric Intensive Care Society

The British Inherited Metabolic Disease Group

Royal College of Pathologist – Clinical Biochemistry

Royal College of Pathologists – Special Advisory Committee on Paediatric Pathology

Royal College of Pathologists – Special Advisory Committee on Medical Microbiology

Royal College of Pathologists – Special Advisory Committee on Medical Virology

Clinical Virology Network UK

British Paediatric Neurology Association

The Society of British Neurological Surgeons

The British Society for Clinical Neurophysiologists

Royal College of Nursing

Neonatal and Paediatric Pharmacy Group

Royal College of Radiologists

The British Society of Paediatric Radiology

National Reyes Syndrome Foundation

The Encephalitis Society

Children Living with Inherited Metabolic Diseases

The level of input helped tremendously with the substance and format of the final guideline recommendations and algorithm. Further details of their involvement are provided in Appendix D.

Delphi panellists

The Guideline Development Group would like to thank all the members of the Delphi panel, whose hard work and effort have created a series of best practice recommendations in the areas where evidence is lacking.

Name	Speciality
Dr Daniel Wallis	Emergency Medicine
Dr Andrew Volans	Emergency Medicine
Miss Lynn Williams	Emergency Medicine
Dr Tina Sajjanhar	Paed. Emergency Medicine
Dr Bridget Wilson	Paed. Emergency Medicine
Trevor Hammond (Nurse)	Paed. Emergency Medicine
Dr Krishnan Venkataraman	General Paediatrics
Dr Peter J Sebire	General Paediatrics
Dr Andy Raffles	General Paediatrics
Dr Janet Craze	General Paediatrics
Dr Kate Armon	General Paediatrics
Dr Robert Tasker	Paediatric ICU
Dr David Thomas	Paediatric ICU
Dr Linda Edwards	Paediatric ICU
Chris Dickson (Nurse)	Paediatric ICU
Dr Charles Newton	Paediatric Neurology
Dr Colin Ferrie	Paediatric Neurology
Dr Rob Forsyth	Paediatric Neurology
Dr Catharine White	Paediatric Neurology
Dr Evangeline Wassmer	Paediatric Neurology
Dr Fenella Kirkham	Paediatric Neurology
Dr Donald MacArthur	Paediatric Neurosurgery
Dr Peter Robinson	Metabolic Medicine
Dr Ed Wraith	Metabolic Medicine
Dr John Glasgow	Metabolic Medicine
Prof James Leonard	Metabolic Medicine
Dr Anupam Chakrapani	Metabolic Medicine
Dr Tracy Tinklin	Paediatric Endocrinology
Dr Anne Green	Paediatric Biochemistry
Dr Karl Johnson	Paediatric Radiology
Dr Alan Sprigg	Paediatric Radiology
Sue Jarvis	Paediatric Pharmacy
Dr Graham Smith	Paediatric Nephrology
Dr Martin Christian	Paediatric Nephrology
Prof Jangu Banatvala	Medical Virology
Dr Clive Graham	Medical Microbiology
Dr Jolyon Smith	Neurophysiology
Dr Zenobia Zaiwalla	Neurophysiology
Mrs Pamela Johns	Parent representative

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1. Introduction

Epidemiology of decreased conscious level in children

Reduced conscious level in children is a presenting problem which often causes concern for parents and health professionals. There are a number of different causes, some of which may be obvious (e.g. a head injury), while others may create significant diagnostic dilemmas (e.g. herpes simplex encephalitis or Reye's syndrome).

The epidemiology of decreased consciousness can be divided into two broad categories:

1) Traumatic conditions
2) Non-traumatic conditions

From hospital statistics in England in 2003-2004, there were 33,460 children admitted following a head injury(1). This suggests an annual incidence of traumatic causes of decreased conscious level of 338/100,000 children aged 0-15 (assuming that the children admitted with head injuries had decreased consciousness). For non-traumatic conditions, a UK epidemiological study estimated 30/100,000 children aged 0-16 per year presented to hospital with a reduced conscious level, which lasted for six hours or more(2). Although non-traumatic causes of reduced consciousness are less frequent than traumatic causes, the mortality rate of 50% makes the topic worthy of attention.

Diagnostic dilemmas

The differential diagnosis of decreased conscious level in children includes all known and unknown diseases in their severest form. The symptoms and signs of the more common causes often overlap, making clinical judgements difficult. For example, the ability to distinguish between raised intracranial pressure secondary to meningitis and raised intracranial pressure secondary to a metabolic condition can be impossible, even for the experienced clinician.

Due to the rarity of some of the diagnoses, the patient relies on the health professional thinking about the possible condition they are suffering from and performing the appropriate diagnostic tests. The health professional may never have seen that particular condition and often rare diagnoses are recognised late, sometimes too late(3).

The Emergency Departments and Paediatrics Assessment Units across the UK are staffed in the main by junior doctors with senior support(4). For health professionals with less experience, guidance on what to do when faced with a problem is essential to ensure appropriate investigations are sent and treatments initiated. Problem-based guidelines have been shown to reduce waiting times, reduce inappropriate tests and reduce costs in Emergency Departments(5). Up to this point in time, there has been no national problem-based guideline for children presenting with decreased conscious level.

Current practise in the United Kingdom

Due to the difficulties in diagnosing the conditions which present with non-traumatic coma in children, health professionals perform multiple tests and treat for several different causes initially, whilst waiting for the test results to narrow down the differential diagnosis list. Before this guideline was developed, there was no national guidance for which investigations to perform when admitting a child with reduced consciousness. Also, there were no evidence-based treatment guidelines to help the health professional deal with the problems or suspected diagnoses of the child with a reduced conscious level.

2. Aim of the guideline

The guideline aims to improve and standardise the assessment, investigation and treatment of the child presenting to hospital with a decreased conscious level. With the appropriate assessment and investigations, the risk of missing an important diagnosis will be reduced and potentially life-saving treatment can be initiated without delay.

The guideline also aims to highlight the need for early involvement of appropriate specialists, who can advise on the management of these complicated individual cases.

3. Scope

The scope of the guideline was finalised by the Guideline Development Group in February, 2004, after a period of consultation with the Stakeholder Groups.

Patient inclusion criteria

The guideline will be relevant to children aged 0-18 years, who have a decreased conscious level, and who are being reviewed in a hospital setting.

A reduced conscious level is defined as a modified Glasgow coma score of 14 or less (see Guideline Algorithm) or being responsive only to voice, pain or being unresponsive on the AVPU scale (see Guideline Algorithm).

Patient exclusion criteria

The guideline does not apply to pre-term infants on a neonatal intensive care unit or full term infants who have had a reduced conscious level from the moment of birth onwards.

The guideline does not apply to children with a previously diagnosed condition which is known to be the cause of the reduced conscious level. This group includes children with previously diagnosed epilepsy, children with a ventriculoperitoneal shunt, and children with a previously diagnosed metabolic condition with an agreed management plan for acute admissions.

The guideline does not apply to children who, on a day to day basis, score less than 15 on the Glasgow coma scale. Assessing an abnormal conscious level is very difficult when a child's level of consciousness is chronically less than the population norm. The differential diagnosis list is different for this group of patients and therefore many of the causes of decreased conscious level discussed in this guideline will not be relevant.

Limitations of the recommendations

The guideline covers the assessment and observations of children with reduced consciousness and the initial investigations to determine the underlying cause. The guidance covers the treatments for the causes of decreased consciousness, which are available within the first hours of admission to hospital,

The suspected diagnoses or problems for which guidance is given include:

Shock
Sepsis
Raised intracranial pressure
Bacterial meningitis
Herpes simplex encephalitis
Hypoglycaemia
Hyperammonaemia
Non-hyperglycaemic ketoacidosis
Prolonged convulsions
Post convulsion state
Hypertensive encephalopathy
Cause unknown.

Trauma, diabetic ketoacidosis, tuberculous meningitis and intracranial abscess are also covered in less detail. Users are referred to other guidelines or specialists available to assist with these conditions.

These suspected diagnoses or problems have been selected because they can be identified and treated within the first hours of presenting to a hospital. The list is not exhaustive but other causes of decreased conscious level in children require specific tests which may take longer than a few hours to organise and / or there is no beneficial therapy available for that cause.

The guideline does not cover further tests and treatments which may be performed on intensive care units or in other specialist units.

Guideline users

The guideline is aimed at junior doctors and nursing staff in Emergency Departments and Paediatric Assessment Units. More senior doctors may find the guideline a useful reference source also.

Clinical judgement

This guideline has been developed with careful consideration of the evidence available. Health professionals should use it when exercising their clinical judgement. The guidance does not, however, override the responsibility of health professionals to make decisions appropriate to the condition of the individual child, taking account of the views of the child and/or guardian.

4. Guideline methodology

A grant from the National Reye's Syndrome Foundation commissioned a clinical guideline for the management of children presenting with a decreased conscious level to hospital. The project began in November 2003.

i. Participants

Guideline Development Group

A Guideline Development Group was assembled for the project in November 2003. Potential members were ascertained from individual stakeholder groups. The members were then selected by personal invitation with an agreement on their part to contribute to the guideline development process over two years. The Guideline Development Group was chaired by Professor Terence Stephenson, a paediatrician who has had experienced of chairing guideline development groups in the past.

The 17 members of the group were drawn from a broad background, as the scope of the project required input from many specialities. Primary care professionals were represented on the group, as were lay parent representatives. These members ensured a patient-centred approach was taken throughout the development process.

Guideline Development Group meetings took place every 3 months with minutes kept for reference. None of the Guideline Development Group stated any conflict of interest during the development process.

Further details of the Guideline Development Group are provided in Appendix C.

Stakeholder Groups

Due to the breadth of the scope, input from a wide variety of specialities was required. These speciality groups and other stakeholders were invited to make comments throughout the guideline development process. Draft versions of the recommendations were reviewed before the final version was drawn up. Patient groups were represented as stakeholders in this project, and participated fully in the discussions.

Further details of the Stakeholder Groups are provided in Appendix D.

Delphi panel

A large multi-professional Delphi panel was convened for the Delphi Consensus process (see section 4 v). The results of this process helped form the recommendations and provided feedback on the guideline algorithm.

Further details of the Delphi panel are provided in Appendix B.

Funding

The guideline was developed with a grant from the National Reye's Syndrome Foundation UK (Registered charity no. 288064). The funding body was also one of the Stakeholder Groups and helped provide patient input for the guideline. The funding body did not influence the Guideline Development Group's decisions or the guideline recommendations other than through its role as a Stakeholder.

ii. Clinical Questions

After the scope had been drafted, a list of clinically relevant questions was drawn up which the guideline aimed to answer. The questions were based around themes of defining decreased conscious level, assessing children with a decreased conscious level, identifying the cause of the decreased conscious level and initial treatment strategies for the causes of decreased conscious level.

The list of clinical questions is provided below:

1. Definition of decreased conscious level in children

(i) In children, which conscious level scores are associated with outcome?
(ii) In children, which conscious level scores can be reliably used to identify decreased conscious level?

2. Observations to monitor and help manage children with a reduced conscious level

(i) In children with a reduced conscious level, which observations should be performed to assess their underlying diagnosis?
(ii) In children with a reduced conscious level, which observations should be performed to monitor their clinical status?

3. Assessment of capillary glucose in children with a decreased conscious level

In children with a reduced conscious level, how soon should a capillary (bedside) glucose measurement be performed?

4. Features in the history to help manage children with a reduced conscious level

In children with a reduced conscious level, which features in the history should be elicited to assess the underlying diagnosis?

5. Assessment of airway and airway protection in children with a reduced conscious level

(i) In children with a reduced conscious level, what is the incidence of airway obstruction either requiring manual support or intubation?
(ii) What are the indications for intubation in children with a reduced conscious level?

6. Assessment of breathing and oxygen requirements in children with reduced level of consciousness

(i) In children with a reduced conscious level, what is the incidence of respiratory depression or apnoea?
(ii) What are the indications for additional oxygen therapy in children with a reduced conscious level?

7. Identifying the causes of reduced level of consciousness in children

(i) What are the non-traumatic causes of reduced conscious level in children?
(ii) How frequently does trauma cause a reduced conscious level in children?

8. Investigating the causes of reduced conscious level in children

(i) Which investigations will screen for the causes of reduced conscious level in children?
(ii) For which causes of reduced conscious level in children should a lumbar puncture be performed?
(iii) What tests should be performed on a sample of cerebrospinal from a child with a reduced conscious level?
iv) Which clinical features in a child with a reduced conscious level should be considered as contraindications to performing a lumbar puncture?
(v) Can an intracranial scan (computed tomography [CT] scan, magnetic resonance imaging [MRI] scan or ultrasound scan) rule out raised intracranial pressure to allow for a lumbar puncture to be performed?
(vi) Can a computed tomography [CT] scan demonstrate raised intracranial pressure?
(vii) Can a computed tomography [CT] scan demonstrate an intracranial abscess?

9. Managing the causes of reduced level of consciousness in children

Which cause of reduced conscious level in children should be treated first to improve clinical outcome?

10. Circulatory shock

(i) What clinical features determine the presence of circulatory shock in a child with a reduced conscious level?
(ii) What are the causes of circulatory shock in children with a reduced conscious level?
(iii) What tests should be performed in the presence of circulatory shock in children with a reduced conscious level to determine the underlying diagnosis?
(iv) What monitoring should be initiated in the presence of circulatory shock in children with a reduced conscious level?
(v) What fluid therapy should be initiated in the presence of circulatory shock in children with a reduced conscious level?

(vi) How much fluid is required for the treatment of circulatory shock in children with a reduced conscious level?
(vii) When should intubation and ventilation be initiated for the treatment of circulatory shock in children with a reduced conscious level?
(viii) When should specific circulatory support (including vasopressor, inotropic and vasodilator treatments) be initiated for the treatment of circulatory shock in children with a reduced conscious level?

11. Sepsis

(i) What clinical features determine the presence of sepsis in a child with a reduced conscious level?
(ii) What investigations should be sent in a child with sepsis and a reduced conscious level to determine the cause and any predisposing factors?
(iii) Which antibiotics should be started in children with sepsis and reduced level of consciousness?

12. Trauma

This subject fell outside the scope of the guideline. No evidence searches were undertaken. Recommendations were based on Delphi consensus.

13. Metabolic illness

a) Hyperglycaemia

This subject fell outside the scope of the guideline. No evidence searches were undertaken. Recommendations were based on Delphi consensus.

b) Hypoglycaemia

(i) In children with a reduced conscious level, what level of hypoglycaemia is associated with a poor outcome in terms of mortality or long term neurological morbidity?
(ii) In children with a reduced conscious level and hypoglycaemia, what further investigations will diagnose the underlying cause?
(iii) In children with a reduced conscious level and hypoglycaemia, what treatment will improve their hypoglycaemia?

c) Hyperammonaemia

(i) In children with a reduced conscious level and hyperammonaemia, what plasma ammonia level should prompt treatment?
(ii) In children with a reduced conscious level and hyperammonaemia, what tests should be performed to diagnose the underlying cause?
(iii) In children with a reduced conscious level and hyperammonaemia, what treatments should be performed to reduce the plasma ammonia level?

d) Non-hyperglycaemic ketoacidosis

(i) In children with a reduced conscious level, what are the causes of non-hyperglycaemic ketoacidosis?
(ii) In children with a reduced conscious level and non-hyperglycaemic ketoacidosis, what screening tests should be performed to determine the underlying cause?

14. Intracranial infections

a) Bacterial meningitis

(i) In children with a reduced conscious level, what are the clinical signs of bacterial meningitis?
(ii) In children with a reduced conscious level, which rapid investigations help screen for or diagnose bacterial meningitis?
(iii) In children with a reduced conscious level and suspected bacterial meningitis, which antibiotics should be started?
(iv) In children with a reduced conscious level and suspected bacterial meningitis, does adjuvant treatment with steroids improve survival or neurological morbidity?

b) Herpes simplex encephalitis

(i) In children with a reduced conscious level, what are the clinical signs of herpes simplex encephalitis?
(ii) In children with a reduced conscious level, which investigations help screen for or diagnose herpes simplex encephalitis?
(iii) In children with a reduced conscious level and suspected herpes simplex encephalitis, is aciclovir an effective treatment?
(iv) In children with a reduced conscious level and suspected herpes simplex encephalitis, how long should aciclovir be continued for?

c) Intracranial abscess

(i) In children with a reduced conscious level, what are the clinical signs of an intracranial abscess?
(ii) In children with a reduced conscious level, which investigations help screen for or diagnose intracranial abscess?
(iii) In children with a reduced conscious level and suspected intracranial abscess, which treatments should be started?

d) Tuberculous (TB) meningitis

(i) In children with a reduced conscious level, what are the clinical signs of tuberculous (TB) meningitis?
(ii) In children with a reduced conscious level, which investigations help screen for or diagnose TB meningitis?

15. Raised intracranial pressure

(i) In children with a reduced conscious level, what are the clinical signs of raised intracranial pressure?

(ii) In children with a reduced conscious level and raised intracranial pressure, what tests should be performed to determine the level of raised intracranial pressure?
(iii) In children with a reduced conscious level and raised intracranial pressure, what tests should be performed to determine the underlying cause of raised intracranial pressure?
(iv) In children with a reduced conscious level and raised intracranial pressure, what head position should be maintained to reduce the raised intracranial pressure?
(v) In children with a reduced conscious level and raised intracranial pressure, what maintenance fluid strategy should be used?
(vi) In children with a reduced conscious level and raised intracranial pressure, what are the indications for mannitol or hypertonic saline?
(vii) In children with a reduced conscious level and raised intracranial pressure, what are the indications for sedation and ventilation?
(viii) In children with a reduced conscious level and raised intracranial pressure, what are the indications for paralysing agents?
(ix) In children with non-traumatic reduced conscious level and raised intracranial pressure, what are the indications for invasive intracranial pressure monitoring?

16. Hypertensive encephalopathy

(i) In children with a reduced conscious level, what are the clinical signs of hypertensive encephalopathy?
(ii) In children with a reduced conscious level and hypertension, what investigation screen for or diagnose the causes of hypertensive encephalopathy?
(iii) In children with a reduced conscious level and hypertension, what treatments should be started to reduce morbidity associated with hypertensive encephalopathy?

17. Prolonged convulsion

(i) In children with a reduced conscious level, what is the neurological outcome after a prolonged convulsion?
(ii) In children with a reduced conscious level and a prolonged convulsion, what tests screen for or diagnose the underlying treatable causes?
(iii) In children with a reduced conscious level and a prolonged convulsion, what treatment is required to stop the convulsion?
(iv) In children with a reduced conscious level and a prolonged convulsion secondary to hyponatraemia, what treatment is required to stop the convulsion?
(v) In children with a reduced conscious level and a prolonged convulsion secondary to hypocalcaemia, what treatment is required to stop the convulsion?
(vi) In children with a reduced conscious level and a prolonged convulsion secondary to hypomagnesaemia, what treatment is required to stop the convulsion?

18. Post convulsion state

(i) In children after a convulsion, what is the incidence of a reduced conscious level (post convulsion state)?
(ii) In children after a convulsion, what is the duration of a reduced conscious level (post convulsion state)?
(iii) In children after a convulsion, what tests should be performed to determine the underlying cause of the convulsion?
(iv) In children after a convulsion, what treatment is required?

19. No clinical clues to the cause

(i) In children with a reduced conscious level and no clinical clues to the cause, what tests should be performed to determine the diagnosis?
(ii) In children with a reduced conscious level and no clinical clues to the cause, what treatments should be started empirically to improve the long term neurological prognosis?

20. Good practice points

This subject was based on patient / parent testimonies and Delphi consensus. No evidence searches were undertaken.

21. Peri-arrest management

This subject fell outside the scope of the guideline. No evidence searches were undertaken. Recommendations were based on Delphi consensus.

iii. Evidence Search

The medical literature was searched to find papers to help answer the clinical questions. The electronic databases reviewed were:

The Cochrane Library	
Medline	(1966 – present)
Embase	(1980 – present)
CINAHL	(1982 – present)
British Nursing Index	(1985 – present)
AMED	(1985 – present)

A hand search of five peer-reviewed journals relevant to the topic of decreased conscious level in children was performed for the previous 12 months. This was to ensure that an important article, which had been recently published but not yet indexed in the electronic databases, was not missed. The journals were:

Acta Paediatrica
Journal of Pediatrics
Journal of Neurology, Neurosurgery & Psychiatry
Neurology
Pediatrics

The references of all the selected papers were reviewed and those relevant to the clinical question were also retrieved.

Criteria for selecting papers were drawn up before the searches took place. Papers were selected for review by a clinical research fellow trained in evidence-based medicine and electronic literature searching.

All the searches were performed between March 2004 and July 2005. Further details of the electronic search strategies are provided in Appendix A.

iv. Evidence Appraisal

The selected papers were reviewed by a clinical research fellow trained in evidence appraisal. Each selected paper was summarised and entered into an evidence table. The papers were appraised on their methodological quality with the aid of the critical appraisal checklists developed by the Scottish Intercollegiate Guideline Network(6).

Each paper was given a level of evidence according to the criteria developed by the Oxford Centre for Evidence-Based Medicine(7). These criteria are reproduced with permission in Table 1, with the grading system in Table 2 and accompanying notes in Table 3.

Level	Therapy/Prevention, Aetiology/Harm	Prognosis	Diagnosis	Differential diagnosis/symptom prevalence study	Economic and decision analyses
1a	SR (with homogeneity*) of RCTs	SR (with homogeneity*) of inception cohort studies; CDR† validated in different populations	SR (with homogeneity*) of Level 1 diagnostic studies; CDR† with 1b studies from different clinical centres	SR (with homogeneity*) of prospective cohort studies	SR (with homogeneity*) of Level 1 economic studies
1b	Individual RCT (with narrow Confidence Interval‡)	Individual inception cohort study with > 80% follow-up; CDR† validated in a single population	Validating** cohort study with good††† reference standards; or CDR† tested within one clinical centre	Prospective cohort study with good follow-up****	Analysis based on clinically sensible costs or alternatives; systematic review(s) of the evidence; and including multi-way sensitivity analyses
1c	All or none§	All or none case-series	Absolute SpPins and SnNouts††	All or none case-series	Absolute better-value or worse-value analyses ††††
2a	SR (with homogeneity*) of cohort studies	SR (with homogeneity*) of either retrospective cohort studies or untreated control groups in RCTs	SR (with homogeneity*) of Level >2 diagnostic studies	SR (with homogeneity*) of 2b and better studies	SR (with homogeneity*) of Level >2 economic studies
2b	Individual cohort study (including low quality RCT; e.g., <80% follow-up)	Retrospective cohort study or follow-up of untreated control patients in an RCT; Derivation of CDR† or validated on split-sample§§§ only	Exploratory** cohort study with good†††reference standards; CDR† after derivation, or validated only on split-sample§§§ or databases	Retrospective cohort study, or poor follow-up	Analysis based on clinically sensible costs or alternatives; limited review(s) of the evidence, or single studies; and including multi-way sensitivity analyses
2c	"Outcomes" Research; Ecological studies	"Outcomes" Research		Ecological studies	Audit or outcomes research
3a	SR (with homogeneity*) of case-control studies		SR (with homogeneity*) of 3b and better studies	SR (with homogeneity*) of 3b and better studies	SR (with homogeneity*) of 3b and better studies
3b	Individual Case-Control Study		Non-consecutive study; or without consistently applied reference standards	Non-consecutive cohort study, or very limited population	Analysis based on limited alternatives or costs, poor quality estimates of data, but including sensitivity analyses incorporating clinically sensible variations.
4	Case-series (and poor quality cohort and case-control studies§§)	Case-series (and poor quality prognostic cohort studies***)	Case-control study, poor or non-independent reference standard	Case-series or superseded reference standards	Analysis with no sensitivity analysis
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on economic theory or "first principles"

Table 1. Oxford Centre for Evidence-based Medicine Levels of Evidence

Grade	Criteria
A	consistent level 1 studies
B	consistent level 2 or 3 studies ***or*** extrapolations from level 1 studies
C	level 4 studies ***or*** extrapolations from level 2 or 3 studies
D	level 5 evidence ***or*** troublingly inconsistent or inconclusive studies of any level

"Extrapolations" are where data is used in a situation which has potentially clinically important differences than the original study situation.

Table 2. Oxford Centre for Evidence-based Medicine Levels of Evidence Grading of Recommendations

Notes

Users can add a minus-sign "-" to denote the level of that fails to provide a conclusive answer because of:
· EITHER a single result with a wide Confidence Interval (such that, for example, an ARR in an RCT is not statistically significant but whose confidence intervals fail to exclude clinically important benefit or harm)
· OR a Systematic Review with troublesome (and statistically significant) heterogeneity.
· Such evidence is inconclusive, and therefore can only generate Grade D recommendations.

*	By homogeneity we mean a systematic review that is free of worrisome variations (heterogeneity) in the directions and degrees of results between individual studies. Not all systematic reviews with statistically significant heterogeneity need be worrisome, and not all worrisome heterogeneity need be statistically significant. As noted above, studies displaying worrisome heterogeneity should be tagged with a "-" at the end of their designated level.
†	Clinical Decision Rule. (These are algorithms or scoring systems which lead to a prognostic estimation or a diagnostic category.)
‡	See note #2 for advice on how to understand, rate and use trials or other studies with wide confidence intervals.
§	Met when all patients died before the Rx became available, but some now survive on it; or when some patients died before the Rx became available, but none now die on it.
§§	By poor quality cohort study we mean one that failed to clearly define comparison groups and/or failed to measure exposures and outcomes in the same (preferably blinded), objective way in both exposed and non-exposed individuals and/or failed to identify or appropriately control known confounders and/or failed to carry out a sufficiently long and complete follow-up of patients. By poor quality case-control study we mean one that failed to clearly define comparison groups and/or failed to measure exposures and outcomes in the same (preferably blinded), objective way in both cases and controls and/or failed to identify or appropriately control known confounders.
§§§	Split-sample validation is achieved by collecting all the information in a single tranche, then artificially dividing this into "derivation" and "validation" samples.
††	An "Absolute SpPin" is a diagnostic finding whose Specificity is so high that a Positive result rules-in the diagnosis. An "Absolute SnNout" is a diagnostic finding whose Sensitivity is so high that a Negative result rules-out the diagnosis.
‡‡	Good, better, bad and worse refer to the comparisons between treatments in terms of their clinical risks and benefits.
†††	Good reference standards are independent of the test, and applied blindly or objectively to applied to all patients. Poor reference standards are haphazardly applied, but still independent of the test. Use of a non-independent reference standard (where the 'test' is included in the 'reference', or where the 'testing' affects the 'reference') implies a level 4 study.
††††	Better-value treatments are clearly as good but cheaper, or better at the same or reduced cost. Worse-value treatments are as good and more expensive, or worse and the equally or more expensive.
**	Validating studies test the quality of a specific diagnostic test, based on prior evidence. An exploratory study collects information and trawls the data (e.g. using a regression analysis) to find which factors are 'significant'.
***	By poor quality prognostic cohort study we mean one in which sampling was biased in favour of patients who already had the target outcome, or the measurement of outcomes was accomplished in <80% of study patients, or outcomes were determined in an unblinded, non-objective way, or there was no correction for confounding factors.
****	Good follow-up in a differential diagnosis study is >80%, with adequate time for alternative diagnoses to emerge (eg 1-6 months acute, 1 - 5 years chronic)

Table 3. Accompanying notes for the Oxford Centre for Evidence-based Medicine Levels of Evidence

A number of the papers, which contributed to the Grade A and B recommendations, were appraised by a second member of the Guideline Development Group to ensure validity of the appraisal methodology.

Further details of the evidence appraisal with the evidence tables are provided in Appendix A.

v. Delphi Consensus Process

Problem-based guidelines are often challenged with the limited availability of peer-reviewed evidence. This is because most clinical research is based around specific diagnoses rather than presenting problems. When there is no published evidence found, a consensus recommendation can be made to make the guideline algorithm comprehensive and coherent.

One formal method of producing consensus statements in guideline development is the Delphi consensus process(8). The Delphi consensus process can be described briefly as an anonymous iterative method of producing statements, which are statistically agreed or disagreed with by a panel of experts. The process has been summarised in diagrammatic form in Figure 1.

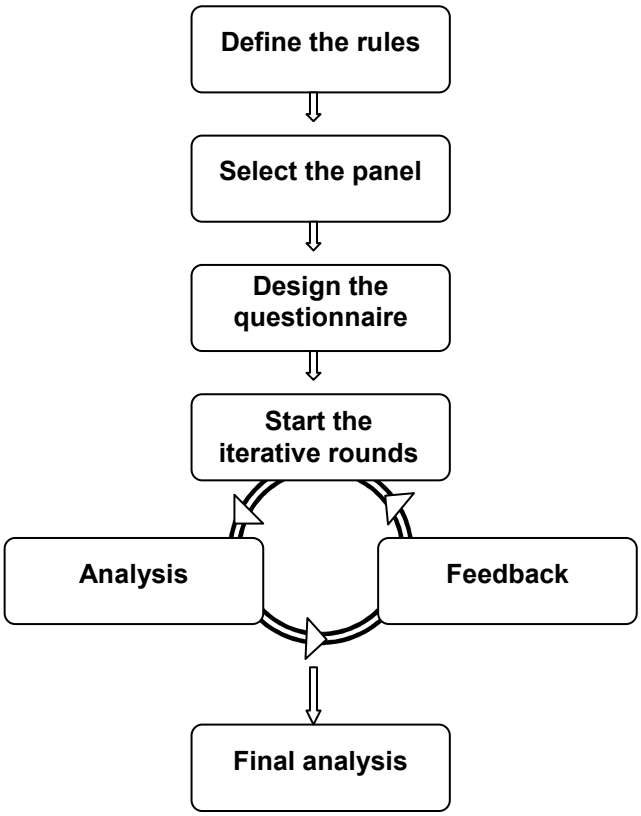

Figure 1. Summary of performing a Delphi process

In the Delphi consensus process performed as part of this guideline, the defining rules were as follows:

1. The panel must be multidisciplinary and include patient / parent representatives.
2. The panel should be reasonably large (i.e. 30 – 50 participants) and at least 7 panellists must respond to each statement.
3. A nine-point Likert scale will be used for panellists to provide their responses to statements.
4. A "Don't know" option will be provided for panellists to select for a statement regarding a field of medicine in which they have no experience.
5. "Consensus agrees" will be defined as 75% of panellists selecting 7, 8 or 9 on the Likert scale for a statement.
6. "Consensus disagrees" will be defined as 75% of panellists selecting 1, 2 or 3 on the Likert scale for a statement.
7. Those answering "Don't know" will not be included in the statistical analysis of consensus.
8. There will be no literature sent out to participants as any evidence sent out could bias the responses.
9. Feedback will be provided by the statistical analysis of the group's responses and by the comments from the group anonymised.
10. There will be three rounds in total.
11. Any statements which fail to reach consensus will be made explicit in the final guideline.

A total of 39 panellists participated in forming over 100 statements. These statements were used to form the recommendations in areas where there was limited published evidence.

The details of the rounds and statements are provided in Appendix B.

vi. Economic Evaluation

Evidence searches and appraisal

Economic evidence was included whenever it was available. Specific searches were performed to look for economic data regarding the core investigations recommended by the guideline. The economic search strategy was based on the work by the NHS Centre for Reviews and Dissemination for the National Institute for Clinical Excellence(9). As well as the electronic databases used for clinical trials, the economic databases of the NHS Health Technology Assessment Programme and the NHS Economic Evaluation Database were also searched.

No economic evaluations were found for the topic of using the core investigations as the initial screening tests in the guideline target population.

Economic modelling

One of the key recommendations made in the guideline is to perform the core investigations in a child with decreased consciousness. Current practice of investigating this group of patients varies widely between professionals. Performing a cost-effectiveness analysis was beyond the scope of the guideline.

A cost-comparison analysis of performing the core investigations in children with a decreased conscious level compared with the sorts of tests performed currently on these patients has been performed (see Figure 2). As the number of children to whom the guideline will apply is small, the changes in investigation practices will not require the establishment of a new laboratory service. Therefore, the analysis has used the marginal costs of the laboratory consumables (blood bottles, reagents and other consumables). The costs incurred by equipment purchase, phlebotomy, staffing and other laboratory overheads have not been included as these are also incurred by current practice.

The data of laboratory consumable costs have been provided by a teaching hospital laboratory (Queen's Medical Centre, Nottingham(10)) and therefore may represent an underestimate for smaller units.

Recommended Core Investigations	*Estimated Current Investigations*	*Extra cost (£)*
capillary glucose	capillary glucose	0
blood gas (arterial or capillary or venous)	blood gas (arterial or capillary or venous)	0
urinalysis (dipstick at bedside)	urinalysis (dipstick at bedside)	0
laboratory blood glucose		0.22
urea and electrolytes	urea and electrolytes	0
liver function tests		0.15
plasma ammonia		0.29
full blood count and film	full blood count and film	0
blood culture	blood culture	0
1-2ml of plasma (separated, frozen and saved for later analysis if required)		0.09
1 - 2 ml of plain serum (frozen and saved for later analysis if required)		0.09
10ml of urine (saved for later analysis)		0.07
	Total	***£1.01***

Figure 2. Cost-comparison of the incurred marginal costs associated with sending the recommended core investigations

From this basic cost-comparison study, an extra £1.01 would be needed to investigate each child presenting with a decreased level of consciousness. However, as individual laboratories use different consumables and have different purchasing agreements, this is a very rough estimate.

A cost-comparison analysis is not the gold standard economic evaluation for an evidence-based guideline(11). A cost-effectiveness analysis of this issue has been proposed as a research question.

vii. Good Practice Points

Good practice points are recommendations about important issues which are highlighted by the guideline, but for which there is not, nor is there likely to be, any research evidence(12). This typically involves issues of communication and documentation.

The Guideline Development Group used patient testimonies and the Delphi consensus process to form the Good Practice Points.

Further details of the Delphi consensus process are provided in Appendix B and details of the patient testimonies are provided in Appendix E.

viii. Recommendation Formation

At the Guideline Development Group meetings, recommendations were agreed upon using the evidence tables or the Delphi consensus results if no evidence was available. Any disagreements on the wording of the recommendations within the group, which could not be settled by discussion, were settled by consultation with Stakeholder Groups. After a period of consultation with the Stakeholder groups, the Guideline Development Group reassessed the recommendations based on the comments received.

The final recommendations were translated into an algorithm for easy use on a Paediatric Assessment Unit or in the Emergency Department setting.

Further details of the Guideline Development Group discussions are provided in Appendix C.

ix. Review Process

The draft guideline was reviewed by all the Stakeholder Groups in August 2005. A public open day was held in October 2005. This event was nationally advertised by the Royal College of Paediatrics and Child Health, and personal invitations were sent to the Stakeholder Groups, the Delphi panellists and end-user groups. The open day provided a forum for the Stakeholders, parents and end-users of the guideline to discuss the recommendations. Any potential barriers to the implementation of the recommendations were identified at this meeting. The final recommendations were signed off by the Guideline Development Group after this meeting.

A formal appraisal process for the guideline will take place using the AGREE instrument criteria(13). The external bodies identified to appraise the guideline include:

The Royal College of Paediatrics and Child Health
The British Association for Accident and Emergency Medicine

5. Guideline Recommendations with Explanations

The guideline recommendations cover a wide variety of conditions. There are 134 recommendations in total, with 10 grade A and 10 grade B recommendations. The recommendations which could not be agreed upon by the Delphi panel have been underlined. These will need to be discussed locally during the implementation process.

The recommendations are broken down into subject headings. They have been translated into a quick reference algorithm provided in the next section.

Index of recommendations

1. Definition

- **Children presenting to hospital have a reduced conscious level if they score less than 15 on the modified Glasgow coma score (GCS) or they are only responsive to voice, pain or are unresponsive on the AVPU score.**

Strength of evidence	5
Recommendation grade	D
Consensus achieved	89% for GCS, 77% for AVPU (round 1)

Rationale

Conscious level is a continuous physiological variable. It is not a diagnosis in itself. Therefore, there is no gold standard test against which to compare conscious level scoring systems. There are many different scoring systems described in the literature(14-20). A way of determining whether one scoring system is superior to another would be to compare the scale with the prognosis of the patient. If the prognosis of the patient is better predicted using one score compared to another, then that score should be used in preference. There are several prospective studies (20-26) which have linked the various scoring systems to outcome (evidence level 1b prognosis). However, these studies have found that the scoring systems are predictors of outcome only at the extremely low end of the conscious level spectrum e.g. scoring "U" on the AVPU scale or scoring 1 for best motor response from the GCS.

The decision to use one score over another also rests on reliability. There have been studies performed(18, 19, 23, 27-29) to determine the interobserver variability of GCS and AVPU and other scoring systems (evidence level 2b diagnosis). These studies suggest that the fewer items to observe the better the reliability. However, if there are only a few categories to choose from the scale will be less able to detect small changes in conscious level.

The literature available does not provide enough evidence to suggest using one scale over another. The guideline development group (GDG) proposed that both the GCS and the AVPU scale can be used to recognise reduced consciousness and therefore define the patient group whom the guideline is developed for. The Delphi panel agreed with using the modified GCS (89%) and AVPU (77%) for recognition of a decreased conscious level in a child.

- **Attempts to fully rouse a sleeping child should be made before recording the assessment of conscious level**

Strength of evidence	5
Recommendation grade	D
Consensus achieved	96% (round 3)

Rationale

The original Glasgow Coma Scale(14) recorded the best response achieved during the assessment. The Delphi panel and Stakeholders commented that sleeping children could be interpreted as having a pathologically reduced conscious level if efforts were not made to rouse the child. This recommendation reminds practitioners to record the best response during the assessment of conscious level.

- **For assessing changes in conscious level the modified Glasgow coma score should be used.**

Strength of evidence	5
Recommendation grade	D
Consensus achieved	81% (round 1)

Rationale

There has been one study to assess the trend in paediatric conscious level scoring with outcome(20). The Adelaide coma scale (which is a modification of the GCS) performed better at predicting outcome with changes in conscious level than a scale using fewer categories of conscious level (evidence 1b). The Adelaide coma score like the other scores of conscious level has only fair inter-observer reliability(27) and it is not well established in UK practice. Therefore, the modified GCS(16, 19) was recommended by the Delphi consensus panel to detect changes in conscious level.

2. Observations

- **Children with a reduced conscious level should have the following observations recorded at presentation:**
  heart rate
  respiratory rate
  oxygen saturation level
  blood pressure
  temperature

Strength of evidence	5
Recommendation grade	D
Consensus achieved	100% (round 3)

- **Children with a reduced conscious level should have the following observations recorded at least every hour until the observations and clinical state are stable:**
  heart rate
  respiratory rate
  oxygen saturation level
  blood pressure

Strength of evidence	5
Recommendation grade	D
Consensus achieved	84% (round 3)

- **Children with a reduced conscious level should have the following monitored continuously from presentation until the monitoring and clinical state are stable:**
  heart rate
  oxygen saturation level
  continuous cardiac monitoring (ECG leads monitoring rhythm)

Strength of evidence	5
Recommendation grade	D
Consensus achieved	91% (round 3)

- **Changes in conscious level should be observed by recording a modified Glasgow coma score every 15 minutes if GCS less than or equal to 12, or every hour if greater than 12**

Strength of evidence	5
Recommendation grade	D
Consensus achieved	78% (round 1)

Rationale

A list of causes of or problems causing reduced conscious level was devised by the GDG and agreed by the Delphi panel. This list included all the causes / problems which could be identified and treated in the first hours of admission. It was based on a literature search of the aetiology of reduced conscious level in children (see Recommendations 10-19 and Search strategy 7). From this list a search for validated guidelines or studies validating the observations which are suggestive of each of the causes / problems was undertaken.

There are no validated guidelines and only one clinical diagnostic decision rule (level 2b diagnosis) to recommend which observations are useful in determining the diagnosis(30). As the clinical diagnostic decision rule is validated only for children with bacterial meningitis, other observations may be important for children with other causes of reduced conscious level. There is no evidence available to guide on how frequently observations should be performed to monitor children with a reduced conscious level.

The Delphi consensus panel agreed the recommendations above.

3. Capillary glucose test

- **Children with a reduced conscious level should have a capillary glucose tested within 15 minutes of presentation.**

Strength of evidence	5
Recommendation grade	D
Consensus achieved	91% (round 1)

Rationale

There are prognostic studies(20, 31-33) which relate hypoglycaemia to a poor outcome (level 1b prognosis). However, there are other studies(34, 35) which found no difference in outcome if a patient was hypoglycaemic or normoglycaemic (level 1b prognosis). None of the studies specifically addressed length of time of hypoglycaemia. The GDG proposed that hypoglycaemia should be avoided in children with reduced conscious level and be recognised as soon as possible from admission to hospital. A prospective audit of hypoglycaemic children attending an emergency department in the USA found the mean time to perform a capillary glucose test was 11 minutes(36). The Delphi panel agreed that up to 15 minutes from admission was an appropriate time frame for the recognition of hypoglycaemia.

4. History of illness

- **In children with a reduced conscious level, the following features should be elicited from the history:**
  - **vomiting before or at presentation**
  - **headache before or at presentation**
  - **fever before or at presentation**
  - **convulsions before or at presentation**
  - **alternating periods of consciousness**
  - **trauma**
  - **ingestion of medications or recreational drugs**
  - **presence of any medications in the child's home**
  - **any previous infant deaths in the family**
  - **length of symptoms**

Strength of evidence 5
Recommendation grade D
Consensus achieved 91%; 97%; 100%; 100%; 100%; 100% 100%; 89%; 85%; 97% respectively for each feature (round 1)

Rationale

A list of causes of or problems causing reduced conscious level was devised by the GDG and agreed by the Delphi panel. This list included all the causes / problems which could be identified and treated in the first hours of admission. It was based on a literature search of the aetiology of reduced conscious level in children (see Recommendations 10-19 and Search strategy 7). From this list, a search for validated guidelines or studies validating the signs and symptoms which are suggestive of each of the causes / problems was undertaken.

There are no validated guidelines and only one clinical diagnostic decision rule (level 2b diagnosis) to recommend which features in the history are useful in determining the diagnosis(30). As the clinical diagnostic decision rule is only for children with bacterial meningitis, other history features may be important for children with other causes of reduced conscious level.

The Delphi consensus panel agreed the history features above.

- **Non-accidental injury or other child protection issues may be behind the cause of reduced consciousness in children.**

Strength of evidence 5
Recommendation grade D
Consensus achieved 100% (round 1)

Rationale

The need to remind those working with children presenting with reduced conscious level to consider child protection issues was felt to be important by the GDG and agreed by the Delphi panel.

5. Airway assessment and protection

- **Children with a reduced conscious level are at risk of airway obstruction.**

Strength of evidence 5
Recommendation grade D
Consensus achieved 100% (round 1)

Rationale

No studies were found investigating decreased conscious level and risk of airway obstruction in children. A study in adults(37) found there was little relationship between the cough reflex being absent and the GCS. The Delphi panel agreed that there is an increased risk of airway obstruction in children with reduced conscious level.

Intubation

- **Children with a reduced conscious level should be considered for intubation if:**
    - **their airway obstructs when it is not supported**
    - **their airway is compromised by vomiting**
    - **their respiratory rate is inadequate for oxygenation or ventilation**
    - **their oxygen saturations are less than 92% despite high flow oxygen therapy and airway opening manoeuvres**
    - **they have signs of shock despite resuscitating with fluid boluses totalling 40 ml / kg or more**
    - **they look exhausted**
    - **their Glasgow coma score is 8 or less**
    - **their Glasgow coma scale is deteriorating**
    - **they have signs of raised intracranial pressure**

Strength of evidence	5
Recommendation grade	D
Consensus achieved	93% (round 2); 92% (round 2); 96% (round 2); 83% (round 3); 92% (round 3); 81% (round 2); 96% (round 2); 96% (round 2); 92% (round 2) respectively

Rationale

There are no studies validating the use of intubation guidelines in children. There are several prospective cohort studies(38-40) which describe the indications for intubating children (level 2b aetiology). There is a prospective cohort study(41) which demonstrates that intubation improves the chance of survival after cardiac arrest (level 1b prognosis), but this is based in an out-of-hospital setting. A randomised controlled trial(42) to determine the benefits of intubating children requiring respiratory support compared to the bag-valve-mask technique demonstrated that bag-valve-mask respiratory support led to better outcomes in the patients than if they were intubated at the scene (level 1b therapy). These out-of-hospital trials and in hospital trials describe the difficulties of intubation and that outcome may be worse if intubation is performed inappropriately.

The Delphi panel recognised that intubating a child should be considered in the circumstances listed above. However, intubation should be discussed with the relevant senior clinicians involved in the case and the anaesthetist performing the procedure to ensure that other airway manoeuvres are not more appropriate.

6. Breathing assessment

- **Children with a reduced conscious level are at risk of respiratory depression**

Strength of evidence	5
Recommendation grade	D
Consensus achieved	100% (round 3)

Rationale

There are no population studies to assess the rates of respiratory depression in children. A series of paediatric near drowning cases with GCS levels of 3 or 4 were found to be apnoeic 50% of the time(43). The presence of apnoea is part of the test for brain death in children(44-47). The Delphi panel agreed that there is an increased risk of respiratory depression in children with a reduced level of consciousness.

- **Children with a reduced conscious level should be treated with high flow oxygen if their oxygen saturations are less than 95%.**

Strength of evidence	5
Recommendation grade	D
Consensus achieved	77% (round 1)

Rationale

Oxygen saturations measured by pulse oximetry in childhood populations are normally greater than 95% in air(48). However, this value can be affected by position(49), activity (e.g. feeding and sleeping)(50), and altitude(51) in healthy children. Children do have brief spells of much lower oxygen saturations(48, 52), and pulse oximetry may be less accurate at detecting hypoxaemia in children with haemoglobinopathies(53-55), where the oxygen-haemoglobin dissociation curve is shifted to the right.

There are no randomised controlled trials of oxygen therapy verses no oxygen therapy as one would expect for ethical considerations. There are a number of prognostic studies looking at outcomes in children with hypoxaemia(55-63). Of the high quality studies, a systematic review(64) found that children exposed to hypoxia had a worse prognosis in terms of development, behaviour and academic achievement (level 2a- prognosis). Two prospective cohort studies in Africa(57, 63) found an increased mortality rate in children with hypoxia (defined as an oxygen saturation of <90%(63) or <92%(57)) related to lower respiratory tract infections than children without hypoxia (RR 4.6; 95% confidence intervals 2.2-9.6) (level 1b prognosis).

All the studies assessed different populations, which makes transferring the conclusions from the study population to the population of children with a decreased conscious level difficult. The Delphi panel agreed that children with a decreased conscious level should be treated with oxygen especially if the pulse oximeter reading was less than 95% (the lower limit of normal in most healthy children at sea level).

7. Identifying the causes of reduced conscious level in children

- **The causes of reduced conscious level in children which can be suspected and treatment initiated within the first hour after presentation include:**
  shock (hypovolaemic, distributive and cardiogenic)
  sepsis
  trauma*
  metabolic diseases
  intracranial infection
  raised intracranial pressure
  convulsions
  hypertension[+]

Strength of evidence	1b Differential diagnosis *2b Symptom prevalence [+]5
Recommendation grade	B *B [+]D
Consensus achieved	[+]Guideline development group

Rationale

There is a population-based prospective study from the UK(2) which identified all children presenting with coma across a region (level 1b differential diagnosis). The differential diagnosis of this population of children included infection, intoxication, epilepsy, metabolic diseases, unknown causes, non-communicating hydrocephalus, and complications of surgery. Trauma was specifically excluded from this study, but a population-based prospective study of children suffering trauma(65) found that 7% of children had a reduced conscious level (level 2b symptom prevalence).

The Delphi panel helped to extrapolate this evidence for the population covered by the guideline and for those conditions which there is a treatment available within the first hour from presentation to hospital. The metabolic diseases are further divided into hyperglycaemia, hypoglycaemia, hyperammonaemia and non-hyperglycaemic ketoacidosis. The intracranial infections are further divided into bacterial meningitis, herpes simplex encephalitis, tuberculous meningitis and intracranial abscess.

Hypertension, which may indicate a rare condition hypertensive encephalopathy, was added to the list by the guideline development group after consultation with stakeholder groups (grade D recommendation).

- **Some children will be recovering from a previous convulsion (post-convulsion state).**

Strength of evidence	5
Recommendation grade	D
Consensus achieved	84% (round 1)

Rationale

In a population-based prospective study from the UK(2) which identified all children presenting with coma across a region, 9% of cases were suffering with epilepsy (level 1b differential diagnosis). However, the proportion of those who were actively convulsing compared with those who were in a post-convulsion state was not stated. The Delphi panel agreed that post-convulsion state is a cause of reduced conscious level in children which can be recognised in the first hour of presentation.

- **There may be a group of children with reduced conscious level who have no specific clinical features to aid diagnosis within the first hour of initial presentation.**

Strength of evidence	1b Differential diagnosis
Recommendation grade	A

Rationale

In a population-based prospective study from the UK(2) which identified all children presenting with coma across a region, 14% of cases remained undiagnosed after hospital discharge or post mortem examination (level 1b differential diagnosis).

8. Investigating the causes of reduced conscious level in children

Core investigations

- **All children with reduced conscious level (except those patients within one hour post convulsion, who are clinically stable and have a normal capillary glucose, and those patients involved in trauma not related to a medical collapse) should be investigated with the following tests at presentation:**
    - **capillary glucose**
    - **blood gas (arterial or capillary or venous – pH, pCO_2, HCO_3^-)**
    - **urinalysis (dipstick at bedside) for ketones, glucose, protein, nitrites and leucocytes**
    - **laboratory blood glucose**
    - **urea and electrolytes (Na, K, Cr)**
    - **liver function tests (aspartate transaminase or alanine transaminase, alkaline phosphatase, albumin or protein)**
    - **plasma ammonia (taken from a venous or arterial sample)**
    - **full blood count and film (haemoglobin, white cell count and differential, and platelet count)**
    - **blood culture**
    - **1-2ml of plasma to be separated, frozen and saved for later analysis if required**
    - **1 - 2 ml of plain serum to be saved for later analysis if required**
    - **10ml of urine to be saved for later analysis**

Strength of evidence	5
Recommendation grade	D
Consensus achieved	100%(round 1); 94%(round 1); 81%(round 1); 83%(round 1); 77% and 97%(round 1); 75%(round 1); 81%(round 2); 91%(round 1); 88%(round 1); 77%(round 1); 75%(round 1); 80%(round 1) respectively

Rationale

There are no studies validating the investigation or screening of reduced conscious level in children. Several of the causes of reduced conscious level in children are clinically recognised (shock(66), trauma, raised intracranial pressure(67-69), hypertension, prolonged convulsion, post-convulsion state). These clinically recognised problems however may require further investigating to determine the exact cause (e.g. CT scan to determine the cause of raised intracranial pressure(70), plasma sodium to ensure the cause of prolonged convulsion is not secondary to hyponatraemia; four-limb blood pressure to screen for coarctation of the aorta in a hypertensive patient). Some diagnoses are generally clinical but may be enhanced by laboratory tests, e.g. sepsis can be confirmed by a positive culture result but the suspicion of sepsis may be raised by the white blood cell count(66); a drug ingestion may be suspected by the history but will be confirmed by drug levels in the blood or urine. Finally, some causes are only detected with laboratory investigations e.g. hypoglycaemia, hyperglycaemia, hyperammonaemia, and acidosis(71).

As there are an enormous number of possible causes of reduced conscious level in children a balance has to be struck between performing every test available and performing enough tests to pick up the important causes. The list of investigations to be taken at the

presentation of all children* with a reduced conscious level was drawn up by the Delphi panel to identify all the immediately treatable problems (e.g. sepsis, hypoglycaemia, hyperammonaemia) and take the samples which could diagnose the cause at a later stage if it were not initially obvious (e.g. saved plasma samples for metabolic tests; saved urine samples for drug / metabolic tests). The total volume of blood required to perform the core investigations is 4.6ml, which is not unreasonable in most age groups of children. It was assumed by the guideline development group that in most cases of reduced conscious level the following tests were already being performed: full blood count, urea and electrolytes, capillary glucose, blood culture, urinalysis at the bedside. The addition of a laboratory glucose, plasma ammonia, saved plasma, and saved serum to this list would widen the initial diagnostic net without incurring excessive costs to the patient or healthcare system. A search for economic evidence of benefit for any of the core investigations revealed no relevant papers.

*It was agreed that those children who had had a convulsion and in whom a watch and wait policy was appropriate should not undergo the core investigations if their capillary glucose was normal. Similarly, a child who had suffered trauma need not undergo the core investigations, unless the cause of the trauma was due to a medical illness (e.g. loss of consciousness led to a fall rather than a fall led to loss of consciousness).

- **As a non-sterile urine sample is required for the core investigations, a technique for collecting urine should be in place as soon as the patient has had monitors attached, e.g. urine bag, clean catch collecting device, catheter**

Strength of evidence	5
Recommendation grade	D
Consensus achieved	84% (round 1)

Rationale

The Delphi panel agreed that a non-sterile urine sample is required for a number of the core investigations and that collecting this sample should begin as soon as possible. The original Delphi statement, "As a non-sterile urine sample is required for many of the tests, a urine bag should be in situ as soon as the patient has had monitors attached", was adapted by stakeholder comments because pubertal children would not tolerate urine bags.

Lumbar puncture

- **A lumbar puncture should be performed, when no acute contraindications exist, if the clinical working diagnosis is:**
  - **Sepsis / Bacterial meningitis**
  - **Herpes simplex encephalitis***
  - **Tuberculous meningitis***
  - **Cause unknown**

Strength of evidence	5 *1b Diagnosis
Recommendation grade	D *B
Consensus achieved	77% / 96%; 96%; 92%; and 86% respectively (round 2)

Rationale

A lumbar puncture is an invasive test to obtain a cerebrospinal fluid (CSF) sample. A CSF sample is required to perform the gold standard tests of culture and / or polymerase chain reaction (PCR) to diagnose bacterial meningitis. There are many papers in the literature stating that a CSF sample is required to perform these gold standard tests. However, the definition of a gold standard is a consensus-based process, therefore the recommendation to perform a lumbar puncture when either sepsis or bacterial meningitis is the clinical working diagnosis is based on consensus from the Delphi panel.

A CSF sample is required to perform herpes simplex virus (HSV) PCR and / or detect intrathecal production of HSV-specific IgG antibodies to diagnose herpes simplex encephalitis (HSE). There is good consistent evidence(72-75) which shows that detecting HSV DNA by PCR is highly sensitive and specific when compared to the gold standard tests of either viral detection in brain tissue or intrathecal production of HSV-specific antibodies (level 1b-3c). Brain biopsy was the gold standard method for diagnosing HSE up to the 1980s. As PCR of CSF is a less invasive test and has been demonstrated to be highly sensitive and specific, the recommendation to collect a CSF sample by lumbar puncture for suspected HSE is evidence based (extrapolated from level 1 studies / consistent with level 2 or 3 studies).

A CSF sample is required to perform Mycobacterium tuberculous PCR to help diagnose tuberculous meningitis (TBM). The gold standard for diagnosing TBM can be defined as a combination of clinical features and responding to treatment. One diagnostic test study(76) blindly applied this gold standard to patients with suspected TBM and assessed the accuracy of TB PCR (Diagnosis level 1b). The sensitivity of PCR was only 48% but the specificity was 100%. The performance of TB PCR against other tests such as CSF microscopy or culture was superior(76). As PCR of CSF is a more rapid test than CSF culture and less invasive than waiting for a response to anti-tuberculous treatment (with its many side effects), the recommendation to collect a sample of CSF for suspected TB meningitis is evidence based (extrapolated from level 1 studies).

- **Cerebrospinal fluid should be analysed initially for**
  - **Microscopy***
  - **Gram staining**
  - **Culture and sensitivity**
  - **Glucose***
  - **Protein**
  - **PCR for herpes simplex^{+} and other viruses**

Strength of evidence	5 *2b Diagnosis $^{+}$1b Diagnosis
Recommendation grade	D *B/$^{+}$B
Consensus achieved	100%; 100%; 100%; 96%; 93%; and 84% respectively (round 1)

Rationale

Cerebrospinal fluid (CSF) can be analysed with a number of different tests. The list above was agreed by the guideline development group and Delphi panel as the list of tests to be sent in all cases. In some circumstances further tests may be required (e.g. PCR for tuberculosis) but these should not be sent on all cases.

The gold standard test for bacterial infections in the CSF is stated in numerous articles as the culture of CSF(30, 77-79). The microscopy has been shown in a validation study(30) of

a clinical decision rule to help accurately diagnose children with bacterial meningitis when combined with a clinical scoring system (level 2b Diagnosis). The use of the CSF glucose to blood glucose ratio was also incorporated in this decision rule, which had a specificity of 79% and a sensitivity of 100%(30).

The gold standard for herpes simplex encephalitis had in the past been considered to be brain biopsy. Polymerase chain reaction for herpes simplex encephalitis is now the standard for early diagnosis and was proved to be as accurate as brain biopsy in comparative studies(72, 73) (level 1b Diagnosis).

The Delphi panel agreed that these and the other tests should be sent on cerebrospinal fluid samples.

- **However, a lumbar puncture should be deferred or not performed as part of the initial acute management in a child who has:**
  - **a Glasgow coma score of less than or equal to 8**
  - **a deteriorating Glasgow coma score**
  - **focal neurological signs**
  - **had a seizure lasting more than 10 minutes and has a GCS less than or equal to 12**
  - **shock**
  - **clinical evidence of systemic meningococcal disease**
  - **papillary dilation (unilateral or bilateral)**
  - **papillary reaction to light impaired or lost**
  - **bradycardia (heart rate less than 60 beats per minute)**
  - **hypertension (mean blood pressure above 95th centile for age)**
  - **abnormal breathing pattern**
  - **an abnormal doll's eyes response (an abnormal response is random movement or no movement relative to the eye socket on turning the head to the left or right, or no upward gaze on flexing the neck)**
  - **an abnormal posture**
  - **signs of raised intracranial pressure**

Strength of evidence	5
Recommendation grade	D
Consensus achieved	88% (round 2) ; 84% (round 1); 84%(round 1); 76%(round 2); 81%(round 1); 80%(round 1); 86% (round 1); 93%(round 1); 90%(round 1); 85%(round 1); 83%(round 1); 100%(round 1); 86%(round 1); and 100%(round 1) respectively

Rationale

There are several studies, which examine the risk factors associated with death in children who have had a lumbar puncture performed to diagnose meningitis or cerebral malaria(68, 69, 80). Unfortunately none of these studies provide the data in a form which can assess the risk of performing a lumbar puncture itself. Instead, the studies focus on the clinical signs associated with severity of illness in these children. Using these criteria and other quoted contraindications to performing a lumbar puncture(81), the Delphi panel agreed that in the presence of the above clinical signs a lumbar puncture should be deferred.

It is worth noting that a number of the panellists would have performed a lumbar puncture in the presence of these signs, if other test results were available or if the child had been clinically stable for some time. Therefore, the signs above are not absolute contraindications. However, a lumbar puncture should not be performed in the acute situation before further evidence of it being safe to proceed has been obtained.

- **A normal CT scan does not exclude acute raised intracranial pressure* and should not influence the decision to perform a lumbar puncture if other contraindications are present.**

Strength of evidence	*1b diagnosis 5
Recommendation grade	*A D
Consensus achieved	81% (round 1)

Rationale

A number of studies have looked at the relationship between raised intracranial pressure and appearances on intracranial scans, whether that be computed tomography (CT)(69, 82-87), magnetic resonance imaging (MRI)(88) or ultrasound. One blinded diagnostic study assessing CT against the gold standard of intracranial pressure monitoring equipment(89), which found that overall the sensitivity of CT to detect raised intracranial pressure was 84%, with a specificity of 44% (level 1b diagnosis). Therefore, in 16% of cases with raised intracranial pressure, the CT scan will not demonstrate this.

A normal CT may help with the decision to perform a lumbar puncture, but the Delphi panel agreed that to rely on CT alone in the face of other signs, which suggest delaying a lumbar puncture, was not advisable.

- **The decision to perform a lumbar puncture in a child with a reduced conscious level should be made by an experienced paediatrician, who has examined the child.**

Strength of evidence	5
Recommendation grade	D
Consensus achieved	94% (round 1)

Rationale

The Delphi panel agreed that experienced clinicians should make the decision to perform a lumbar puncture in a child with reduced level of consciousness. The definition of "experienced paediatrician" will be left to the individual centres when the guideline is implemented. This definition may include consultant paediatricians, middle grade trainee paediatricians, emergency department clinicians with experience of paediatrics etc.

Cranial imaging

- **A cranial CT scan should be considered when the patient is stable if the working diagnosis is:**
  - **Raised intracranial pressure***
  - **Intracranial abscess**
  - **Cause unknown**

Strength of evidence	*1b Diagnosis 5
Recommendation grade	*A D
Consensus achieved	100% (round 2); and 97% (round 2) respectively

Rationale

A CT scan can demonstrate raised intracranial pressure. A study of CT scanning blindly compared to intracranial pressure monitoring(89) showed that if the intracranial pressure is greater than 25 mmHg then the sensitivity of the CT scan was 97.7% and specificity 60.6% (1b diagnosis). A CT scan can detect the underlying cause of the raised intracranial pressure in some circumstances also.

Although there are many studies reporting CT as a useful test for an intracranial abscess(90-92), none of them blindly compared CT to a gold standard of aspiration of the abscess in children. The Delphi panel agreed that if an intracranial abscess was suspected clinically then a CT scan was indicated.

There are no validated guidelines for the child with a reduced conscious level or for performing CT scans. The Delphi panel agreed that in the case of a child with an unknown cause for the reduced conscious level a CT scan was indicated.

It is worth noting that the technical details of the scan should be determined by the radiologist performing the scan.

9. Managing the causes of reduced conscious level in children

- **In children with reduced consciousness, concurrent management strategies need to be started to treat the potential different causes, whilst waiting for test results to confirm the most likely diagnosis.**

Strength of evidence	5
Recommendation grade	D
Consensus achieved	91% (round 1)

Rationale

There are no studies validating the treatment of reduced conscious level in children, therefore there is no evidence that prioritising the treatment of one suspected cause over another will improve outcomes. The Delphi panel agreed that treating all the likely causes concurrently at the beginning of the clinical course was the best management strategy.

10. Shock

Recognition

- **Circulatory shock can be recognised clinically if one or more of the following signs are present in a child with reduced conscious level:**
  - **Capillary refill time > 2 seconds**
  - **Mottled cool extremities**
  - **Diminished peripheral pulses**
  - **Systolic blood pressure is less than 5th percentile for age**
  - **Decreased urine output <1ml/kg/hour**

Strength of evidence	5
Recommendation grade	D
Consensus achieved	87% (round 1)

Rationale

Circulatory shock is a clinical definition and there are no gold standard diagnostic tests to determine its presence or absence. There are a number of guidelines available which have defined shock in children(66, 81, 93, 94), but none of them have been validated to demonstrate improvements in outcome. A number of randomised controlled trials have used various definitions of shock as entry criteria for randomisation(95-98). None of these trials has demonstrated a clinically relevant benefit of the study treatment. Therefore the clinical definition of circulatory shock, which will lead to initiating treatment, is based on consensus.

The Delphi panel agreed that the following criteria in the presence of reduced conscious level corresponded to circulatory shock.

- **If shock is present in a child with reduced consciousness, look for signs of:**
  sepsis
  trauma (blood loss, tension pneumothorax, cardiac tamponade)
  anaphylaxis (urticarial rash, wheeze, stridor, swollen lips/tongue)
  heart failure (enlarged liver, peripheral oedema, distended neck veins, heart murmur)

Strength of evidence	5
Recommendation grade	D
Consensus achieved	100%; 100%; 100%; and 94% respectively (round 1)

Rationale

There are no studies specifically looking at the epidemiology of circulatory shock in children. The list of causes to look out for was drawn up in agreement with the Delphi panel.

- **Shock in a child with a reduced conscious level is not a diagnosis in itself and so the core investigations should be requested to determine the cause.**

Strength of evidence	5
Recommendation grade	D
Consensus achieved	91% (round 1)

Rationale

There are no guideline validation studies to determine which tests to perform in children with circulatory shock. The core investigations listed in Recommendation 8 were agreed upon by the Delphi panel.

Treatment

- **If shock is present in a child with a reduced conscious level, a fluid bolus of 20 ml per kg of either crystalloid or colloid should be given.**

Strength of evidence	1b Therapy
Recommendation grade	A

Rationale

There have been several systematic reviews on the topic of fluid administration in critical illness(99, 100) and shock(100, 101). They all conclude that there is no difference between crystalloid and colloid solutions. However, all of these reviews have included heterogeneous study populations and none of these have focussed on paediatric shock. There are three randomised controlled trials assessing the comparing the benefit of using colloid or

crystalloid for the treatment of septic shock(95-97). All three studies use an initial fluid bolus of 20 ml/kg (which is approximately 25% of a child's circulating volume), and all three found very little difference in important outcomes between the different fluid types used (level 1b). The studies were not powered to demonstrate equivalence of treatment effect. Therefore there may be small benefits in using one type of fluid over the other which was not demonstrated by these studies. Until a larger study is performed, the recommendation that either fluid could be used is based on the best available evidence. There are no studies looking at different fluid volumes given for treatment of shock in children.

- **The response to a fluid bolus should be monitored by heart rate, capillary refill time, urine output and level of consciousness.**

Strength of evidence	5
Recommendation grade	D
Consensus achieved	96% (round 1)

Rationale

Circulatory shock is a clinical definition and there are no gold standard diagnostic tests to determine its presence or absence. There are a number of guidelines available which have defined shock in children(66, 81, 93, 94), but none of them have been validated to demonstrate improvements in outcome. The randomised controlled trials of fluid therapy in shock have used various clinical markers of good response to fluid therapy (95-97). None of these trials has demonstrated a benefit of the study treatments, therefore the definition of resolution or improvement of circulatory shock is based on consensus.

The Delphi panel agreed that the following criteria should be assessed to determine if circulatory shock is resolving.

- **A positive response to a fluid bolus can be defined as a reduction in tachycardia, a reduction in a prolonged capillary refill time, an increase in urine output and an improvement in the level of consciousness.**

Strength of evidence	5
Recommendation grade	D
Consensus achieved	96% (round 1)

Rationale

The Delphi panel agreed that the following findings should be used to determine if circulatory shock is resolving.

- **Further fluid therapy should be guided by clinical response.**

Strength of evidence	5
Recommendation grade	D
Consensus achieved	90% (round 1)

Rationale

The Delphi panel agreed that the decision to infuse further fluid therapy should be based on individual patient response to initial fluid therapy. There are no validated clinical guidelines or trials in non-invasive or invasive monitoring techniques of children with shock. The Delphi panel commented that invasive monitoring of blood pressure, central venous pressure and plasma lactate would be helpful in some cases.

- **Fluid boluses of up to and over 60 ml per kg may be required, guided by clinical response.**

Strength of evidence	1b Therapy / 2b Prognosis
Recommendation grade	B

Rationale

There are no studies to determine the optimal volume of fluid which is needed to reverse circulatory shock in children. There are randomized control trials(95-97) to determine which type of fluid is optimal in the reversal of circulatory shock in children (level 1b therapy). There is a prognostic paper(102) which described the median fluid volumes used in patients with shock (level 2b prognosis). These trails report that in some cases children required over 60ml/kg of fluid as boluses to reverse shock.

- **If more than 40 ml per kg has been given, intubation and ventilation should be considered to prevent uncontrolled pulmonary oedema developing**

Strength of evidence	5
Recommendation grade	D
Consensus achieved	78% (round 2)

Rationale

There are no studies reporting optimum strategies for intubation and ventilation. The Delphi panel agreed that respiratory support should be considered in children with circulatory shock after 40ml/kg of fluid has been given.

- **If more than 40 ml per kg has been given with little clinical response, drug treatment to support the circulation should be considered.**

Strength of evidence	5
Recommendation grade	D
Consensus achieved	88% (round 2)

Rationale

There are no studies reporting optimum initial strategies for circulatory support. There is one randomised controlled trial looking at the benefits of adding milrinone (a vasodilating drug) to inotropic treatment already started(98) (level 1b therapy) and several unvalidated guidelines which advocate the use of inotropic or vasopressor treatments early in the course of shock, especially if related to sepsis(66, 93, 103) (level 5 therapy). The Delphi panel agreed that specific circulatory support should be considered in children with circulatory shock after 40ml/kg of fluid has been given. (Note: the term “inotropic agent” is often used loosely including vasopressor agents such as dopamine and phenylephrine under its umbrella. In view of this the term “drug treatment to support the circulation” was preferred).

Ongoing management

- **Children with a reduced conscious level and shock which has been unresponsive to 40 ml per kg should be monitored on an intensive care or high dependency unit.**

Strength of evidence	5
Recommendation grade	D
Consensus achieved	100% (round 2)

Rationale

The Delphi panel agreed that children with shock unresponsive to fluid should be monitored closely.

11. Sepsis

Recognition

- **Sepsis can be defined as the systemic response to infection.**

Strength of evidence	5
Recommendation grade	D
Consensus achieved	84% (round 1)

Rationale

The definition of "sepsis" has been considered by various groups. This definition was produced by a consensus method in America(104). The Delphi panel for this guideline agreed with this definition of sepsis.

- **In a child with a reduced conscious level, sepsis should be suspected and treated if two or more of the following four are present:**
  - **a body temperature of >38 C or <35.5 C or history of fever at home**
  - **tachycardia**
  - **tachypnoea**
  - **a change in white cell count to >15000 cu mm or <5000 cu mm**

  or if there is a non-blanching petechial or purpuric skin rash*

Strength of evidence	1b Diagnosis *2b Diagnosis
Recommendation grade	C *B

Rationale

Several studies of infants and young children with fever have been performed to determine if there are any signs which indicate whether the child will have a serious bacterial infection grown on culture(105-109) (level 1b diagnosis), (110-113)(level 2b diagnosis). A systematic review(114) demonstrated that being classed as "low risk" on one scoring system (the Rochester criteria: appearing well, being previously healthy, no focal infection detected, white blood cell [WBC] count 5-15000/mm^3, <10 WBC in urine; <5 WBC per high-powered field microscopy of stool if diarrhoea) had a 99.3% negative predictive value for bacteraemia or meningitis (level 1a- diagnosis). Other scoring systems have also been derived and validated in a number of studies, and have included a lower limit of temperature(115), and tachypnoea(115) in the scoring system (level 4). Another study used signs of shock(116) in the decision rule (level 4). Some studies used the above criteria as the gold standard for sepsis (which was originally devised by consensus(104)). All these studies looked at young and "well" infants, whereas the guideline refers to children who have a reduced conscious level. The recommendation has been extrapolated from these studies and given a grade C.

Studies looking at children with petechiae (pin-point bleeding under the skin <2mm in diameter)(117, 118) or purpura(118) have shown that being described as "ill" has a sensitivity of between 79-100% with a specificity of 81-88% (level 2b diagnosis). Being lethargic was a criteria for being assessed as "ill", which is consistent with a child with a reduced conscious level. Children with a petechial or purpuric rash and reduced conscious level should be treated for sepsis (grade B).

- **A child with a reduced conscious level and suspected sepsis could have another underlying diagnosis and should have the core investigations requested.**

Strength of evidence	5
Recommendation grade	D
Consensus achieved	94% (round 1)

Rationale

The Delphi panel agreed that infections could be the only cause of the reduced conscious level but may also precipitate other illnesses (e.g. diabetic ketoacidosis, hypoglycaemia). The panel agreed that the core investigations should be performed to rule out other causes of reduced conscious level.

- **A child with a clinical diagnosis of sepsis should be considered for the following additional investigations:**
  - **chest X-ray**
  - **throat swab**
  - **urine culture, if urinalysis positive for leucocytes and / or nitrites**
  - **lumbar puncture**
  - **PCR from blood for meningococcus and pneumococcus**
  - **Coagulation studies (activated partial thromboplastin time, prothrombin time, fibrinogen, fibrinogen degradation products) if clotting abnormality suspected**
  - **skin swab, if areas of inflammation are present**
  - **joint aspiration, if signs of septic arthritis are present**
  - **a thick and thin film for malarial parasites if foreign travel to endemic area**
  - **intracranial imaging, if no other source of infection determined**

Strength of evidence	5
Recommendation grade	D
Consensus achieved	90% (round 2); 86% (round 2); 100% (round 2); 78% (round 2); 100% (round 2); 92% (round 3); 89% (round 2); 96% (round 2); 100% (round 2); and 90% (round 2) respectively

Rationale

There are no validation studies of guidelines for children with sepsis which determine which samples to send. A blood culture, urine culture and culture of cerebrospinal fluid are all gold standard tests. The list of tests above was agreed upon by the Delphi panel to be considered, depending upon the clinical findings of the individual child.

Treatment

- **In a child with a reduced conscious level and suspected sepsis, broad spectrum antibiotics should be started intravenously after appropriate cultures have been taken.**

Strength of evidence	5
Recommendation grade	D
Consensus achieved	91% (round 1)

Rationale

There are a few studies(119-121) comparing different antibiotics for bacteraemia and sepsis (level 1b therapy). However, none of these studies showed a clear benefit of one form of treatment over another. The resistance pattern of infections causing sepsis will depend on location. Therefore, the Delphi panel agreed that the antibiotics to start should be broad spectrum, but that the precise antimicrobial agent should be decided locally.

- **In a child with a reduced conscious level and suspected sepsis, microbiological advice should be sought for second line antibiotics if there is a poor response to treatment.**

Strength of evidence	5
Recommendation grade	D
Consensus achieved	85% (round 1)

Rationale

The Delphi panel agreed that if second line antibiotics are required then a microbiologist should be consulted.

- **A child with a reduced conscious level and suspected sepsis should be reviewed by an experienced paediatrician within the first hour of presentation.**

Strength of evidence	5
Recommendation grade	D
Consensus achieved	94% (round 1)

Rationale

The Delphi panel agreed that an experienced paediatrician should be involved in the management of a septic child as early as possible. The definition of "experienced paediatrician" will be left to the individual centres when the guideline is implemented. This definition may include consultant paediatricians, middle grade trainee paediatricians, emergency department clinicians with experience of paediatrics etc.

12. Trauma

Recognition

- **In a child with reduced conscious level, evidence of trauma should be elicited from the history and examination.**

Strength of evidence	5
Recommendation grade	D
Consensus achieved	100% (round 1)

Rationale

Traumatic causes of reduced level of consciousness in children were determined to be outside the scope of the guideline. However, for completeness the Delphi panel agreed that identifying injury should be part of the evaluation of the child with reduced consciousness.

Investigations

- **In a child with reduced consciousness and evidence of trauma from a collapse, the core investigations should be requested to detect an underlying medical cause in the child.**

Strength of evidence	5
Recommendation grade	D
Consensus achieved	87% (round 1)

Rationale

The Delphi panel agreed that trauma could be secondary to a medical condition (e.g. the child became unconscious and fell out of a tree). Therefore the core investigations would be appropriate to perform in these cases.

Treatment

- **A child with reduced conscious level and evidence of trauma should be further managed according to Advanced Paediatric Life Support and the NICE Head injury guidelines.**

Strength of evidence	5
Recommendation grade	D
Consensus achieved	79% (round 1)

Rationale

The Delphi panel agreed following these guidelines would be an appropriate step to take after the patient has left the scope of this guideline.

13. Metabolic illness

a) Hyperglycaemia

- **Diabetic ketoacidosis can be diagnosed if all three of the following are present in a child with reduced consciousness:**
  A capillary or venous blood glucose of 11.0 mmol/l or more
  A capillary or venous blood pH of less than 7.3
  Ketones in the urine

Strength of evidence	5
Recommendation grade	D
Consensus achieved	84% (round 1)

Rationale

Diabetic ketoacidosis recognition and management fell outside the scope of the guideline. However, for completeness the Delphi panel agreed to the above definition of diabetic ketoacidosis in a child with a reduced conscious level.

- **If diabetic ketoacidosis is diagnosed, then follow the NICE guidelines on the management of type 1 diabetes**

Strength of evidence	5
Recommendation grade	D
Consensus achieved	96% (round 1)

Rationale

The Delphi panel agreed that children with diabetic ketoacidosis should be managed using an evidence-based guideline.

13. Metabolic illness

b) Hypoglycaemia

Recognition

- **In children with a reduced conscious level, a capillary glucose level of < 2.6 mmol/l is low and should be investigated further and corrected (see Metabolic illness "Hypoglycaemia").**

Strength of evidence	5
Recommendation grade	D
Consensus achieved	97% (round 2)

- **In children with a reduced conscious level, a capillary glucose of 2.6–3.5 mmol/l is borderline low and the result of the laboratory glucose (requested with the core investigations) should be reviewed urgently**.

Strength of evidence	5
Recommendation grade	D
Consensus achieved	93% (round 3)

Rationale

There are prognostic studies(20, 31-33) which relate hypoglycaemia to a poor outcome (level 1b prognosis). However, there are other studies(34, 35) which found no difference in outcome if a patient was hypoglycaemic or normoglycaemic (level 1b prognosis). The studies were heterogeneous in terms of the cause of the hypoglycaemia. The cause of the hypoglycaemia may be important in relation to determining outcome (e.g. diabetic children who become hypoglycaemic seem to be less likely to suffer neurological sequelae than patients with cerebral malaria). The level of hypoglycaemia in the studies ranged from 1.1mmol/l blood glucose(34) to 2.2mmol/l(20, 31, 32). The GDG proposed that although there is conflicting evidence about the importance of hypoglycaemia and outcome, it is important that the unquantifiable risk of hypoglycaemia be avoided.

The Delphi panel was given a range of options to determine the level of hypoglycaemia at which investigation and treatment should be initiated. The Delphi panel agreed with a capillary glucose level of <2.6mmol/l should definitely be investigated and treated. As there are concerns with regards to the accuracy of capillary glucose monitoring devices in the low range, the Delphi panel agreed that a borderline capillary glucose does not necessarily need investigating or treating unless the laboratory glucose result comes back as <2.6mmol/l (see also Recommendation 13b).

Investigation

- **A child with a reduced conscious level and a laboratory glucose of < 2.6 mmol/l should have the following tests requested from the saved samples, which were taken with the core investigations:**
  plasma lactate
  plasma insulin
  plasma cortisol
  plasma growth hormone
  plasma free fatty acids
  plasma beta-hydroxybutyrate
  acyl-carnitine profile (on Guthrie card or from stored frozen plasma)
  urine organic acids

Strength of evidence	5
Recommendation grade	D
Consensus achieved	90%; 89%; 92%; 78%; 81%; 91%; 75%; and 85% respectively (round 1)

Rationale

Although there are several guidelines for the investigation and management of hypoglycaemia(122-125), none have been validated. The causes of hypoglycaemia in children not receiving exogenous insulin include severe sepsis, endogenous insulin excess, disorders of hormone production (e.g. Addison's disease, growth hormone deficiency or congenital adrenal hyperplasia), disorders of fatty acid oxidation (e.g. medium chain acyl CoA dehydrogenase deficiency), organic acidurias / acidaemias and glycogen storage disorders.

The Delphi panel agreed that, along with the results of the core investigations, further tests should be sent to screen for the causes of hypoglycaemia. These extra tests can be sent from the saved samples taken with the core investigations at the time of the hypoglycaemic episode. This way only one list of tests needs to be considered during resuscitation of the hypoglycaemic child – the core investigations – and the correct samples are available for further testing after the child has been treated.

- **(The investigation and treatment of children with a reduced conscious level and a blood glucose between 2.6 to 3.5 mmol/l needs to be agreed at a local level)**

Rationale

The Delphi panel could not reach agreement on how to manage patients with a borderline blood glucose level. Some would not investigate and treat a blood glucose of between 2.6 and 3.5mmol/l, while others would fully investigate and treat at this level. Before implementation of the guideline, a discussion should take place locally to decide how to manage this group of patients.

Treatment

- **The emergency treatment of hypoglycaemia in a child 4 weeks old or less is an intravenous bolus of 2ml/kg of 10% dextrose**

- **The emergency treatment of hypoglycaemia in a child more than 4 weeks old is an intravenous bolus of 5ml/kg of 10% dextrose.**

Strength of evidence	5
Recommendation grade	D
Consensus achieved	90% and 88% respectively (round 2)

Rationale

There are three studies looking at the emergency treatment of hypoglycaemia in children(126-128), but these all relate to treatments for hypoglycaemia in insulin dependent diabetes mellitus (IDDM). Unfortunately the treatments for hypoglycaemia in IDDM (e.g. glucagons) may not work in hypoglycaemia due to other causes (e.g. medium chain acyl coA dehydrogenase deficiency). Dextrose is the first line treatment for hypoglycaemia when the cause is unknown. The concentration of dextrose used in paediatric management of hypoglycaemia is usually 10%. There is one adult trial of 10% versus 50% dextrose(129), which found no difference in time for resolution of hypoglycaemia, however no children were involved in the trial.

The Delphi panel agreed that a bolus of 10% dextrose should be given, 2ml/kg for neonates and 5ml/kg for older infants. The reason behind the different volumes for the different age groups is that in the neonatal period hyperinsulinism may be the underlying cause. By increasing the blood glucose by too much may lead to a rebound secretion of insulin leading to a worsening of the hypoglycaemia.

- **An infusion of 10% dextrose solution should be administered to maintain the blood glucose between 4 and 7 mmol/l**

Strength of evidence	5
Recommendation grade	D
Consensus achieved	88 (round 1)

Rationale

The Delphi panel agreed that once the hypoglycaemia has been corrected the child's blood glucose should be maintained in the normal range.

- **Hypoglycaemia is not a diagnosis in itself, therefore urgent support from an endocrinologist and metabolic medicine physician should be obtained to determine the subsequent management**

Strength of evidence	5
Recommendation grade	D
Consensus achieved	77% (round 1)

Rationale

The underlying cause of hypoglycaemia may not be obvious. The further management of these cases requires expert help.

13. Metabolic illness

c) Hyperammonaemia

Recognition

- **A plasma ammonia level of 200 micromol/l is significantly raised and needs actively treating**

Strength of evidence	4 Prognosis
Recommendation grade	D
Consensus achieved	85% (round 1)

Rationale

There are several studies looking at the prognosis of children with a variety of conditions which cause a rise in the plasma ammonia level(130-135). They all agree that the plasma concentration of ammonia is related to outcome, i.e. the higher the peak or the longer the level remains high the worse the prognosis (level 4 prognosis). The level of peak plasma ammonia at which prognosis deteriorates is between 180 micromol/l and 350 micromol/l according to a couple of these studies(132, 133).

The Delphi panel agreed that a level of 200 micromol/l should be taken as the cut-off level for action.

- **As soon as a plasma ammonia level of 200 micromol/l or above is detected, contact the nearest metabolic medicine centre for advice**

Strength of evidence	5
Recommendation grade	D
Consensus achieved	96% (round 1)

Rationale

The Delphi panel agreed that it is important to get advice as soon as possible in this situation.

Investigation

- **A child with a reduced conscious level and a plasma ammonia level of >200 micromol/l, should have the following tests requested from the saved samples, which were taken with the core investigations:**
  plasma amino acids profile
  urinary amino acids profile
  urinary organic acids profile
  urinary orotic acid
  Coagulation studies* – activated partial thromboplastin time, prothrombin time, fibrinogen, fibrinogen degredation products

Strength of evidence	3a Diagnosis *5
Recommendation grade	C *D
Consensus achieved	*96% (round 1)

Rationale

There is one study(136) which defined the differential diagnosis of hyperammonaemia. From this study, the causes of hyperammonaemia in children included hepatic failure, organic acidurias, urea-cycle enzyme defects, amino acid transport defects and Reye's syndrome (evidence level 4 differential diagnosis).
Other causes included sodium valproate use, neonatal encephalopathy, convulsions and unknown causes.

Population screening programmes(137-139) conclude that:
a) detection of organic acidopathies can be achieved with tandem mass spectroscopy of blood or urine
b) detection of urea cycle defects can be achieved with urinary measurements of orotic acid and citrilline or tandem mass spectroscopy
c) detection of aminoacidopathies can be achieved with plasma chromatograms of amino acids or tandem mass spectroscopy or dried blood spot leucine (level 3a Diagnosis).

From the list of possible causes of hyperammonaemia, the Delphi panel agreed that once the plasma ammonia result was known, the further tests listed above should be requested from the saved plasma and urine samples (taken as part of the core investigations), and in the case of coagulation studies be performed on the child.

Treatment

- **A plasma ammonia level of 200 micromol/l needs actively reducing by starting a sodium benzoate infusion**
  - **Sodium benzoate should be given with a loading dose of 250 mg/kg (diluted in 15ml/kg of 10% dextrose) over 90 minutes**
  - **After the loading dose, a further infusion of sodium benzoate 250 mg/kg (diluted in 15ml/kg of 10% dextrose) should be administered over 24 hours**

Strength of evidence	2b Therapy
Recommendation grade	C

Rationale

There are a number of studies reporting the use of sodium benzoate for hyperammonaemia in children usually with an inborn error of urea synthesis(140-145). One prospective cohort(141) study reported a significant reduction in plasma ammonia in 61 out of 64 episodes using sodium benzoate if the plasma ammonia was over 200micromol/l (level 2b therapy). The survival and neurological outcome of children in this study was better than previously reported cases. The dose of sodium benzoate was 250mg/kg bolus followed by 250mg/kg over the next 24 hours. Sodium benzoate alone or with arginine did not help in cases where the plasma ammonia was nearer to 500micromol/l (n=3).

- **If the plasma ammonia remains between 200 and 500mmol/l and has not improved with the sodium benzoate infusion after 6 hours, the child should be considered for emergency haemodialysis.**

- **A plasma ammonia level above 500 micromol/l requires emergency haemodialysis and transfer should be arranged urgently, whilst starting the ammonia reducing treatments available locally**

Strength of evidence	5
Recommendation grade	D
Consensus achieved	90% (round 2); and 95% (round 1) respectively

Rationale

There are a number of studies which report the use of dialysis in the successful reduction of plasma ammonia in children with urea cycle disorders (131, 132, 140, 142-144, 146) and Reye's syndrome(132). All of these studies are case series (level 4 therapy). Long term outcome is no different between haemodialysis modalities and peritoneal dialysis, however, haemodialysis reduces the ammonia and other metabolites more rapidly. This is backed up by case reports where multiple treatments have been used sequentially in individuals(147-151). In none of the studies was a cut-off point for plasma ammonia reported as an indication for starting dialysis.

The Delphi panel agreed that the indications for arranging dialysis should be a raised ammonia not responding to sodium benzoate, or a raised ammonia above 500micromol/l at presentation. Haemodialysis was agreed to be the modality of choice but this would need to be decided by the unit accepting the patient for dialysis.

13. Metabolic illness

d) Non-hyperglycaemic ketoacidosis

- **Non-hyperglycaemic ketoacidosis is present in a child with a reduced conscious level, a normal or low capillary/blood glucose, a capillary/venous pH < 7.3 and ketones in the urine**

Strength of evidence	5
Recommendation grade	D
Consensus achieved	75% (round 1)

Rationale

There are some inherited conditions which present with acute encephalopathy but do not present with hypoglycaemia or hyperammonaemia. There are no population studies to

determine the differential diagnosis in children with non-hyperglycaemic ketoacidosis, but expert opinions agree that the list includes organic acidopathies, amino acidopathies (especially branch chain amino acid disorders), fatty acid oxidation defects, mitochondrial electron transport chain defects and sometimes urea cycle enzyme defects. The differential diagnosis can also include acquired causes such as circulatory shock, however the level of ketones present in the urine will be variable in these cases.

- **A child with a reduced conscious level and non-hyperglycaemic ketoacidosis, should have the following tests requested from the saved samples, which were taken with the core investigations:**
  - **plasma lactate***
  - **plasma amino acids**
  - **urinary amino acids profile**
  - **urinary organic acids profile**

Strength of evidence	3a Diagnosis *5
Recommendation grade	C *D
Consensus achieved	*89% (round 1)

Rationale

The evidence from population screening programmes(137-139) concludes that:

a) detection of urea cycle defects can be achieved with urinary measurements of orotic acid and citrilline or tandem mass spectroscopy

b) detection of aminoacidopathies can be achieved with plasma chromatograms of amino acids or tandem mass spectroscopy or dried blood spot leucine

c) detection of organic acidopathies can be achieved with tandem mass spectroscopy of blood or urine

d) fatty acid oxidation defects can be by analysis of octanocarnitine by tandem mass spectroscopy (level 3a Diagnosis).

Plasma lactate rises in some of the conditions above, but it is especially seen in disorders of the respiratory electron transport chain. The Delphi panel agreed that, although there is no specific treatment for respiratory electron transport chain defects, it is useful to know the lactate in acidotic children to aid the diagnosis.

- **For any child with non-hyperglycaemic ketoacidosis, advice should be obtained urgently from the nearest metabolic medicine unit**

Strength of evidence	5
Recommendation grade	D
Consensus achieved	75% (round 1)

Rationale

There are no rigorous trials to determine the best options in this field. Therefore expert advice is required to recommend the most appropriate diagnostic strategy and treatment in individual cases.

- **If lactate levels rise above 15 mmol/l obtain urgent advice from the nearest metabolic medicine unit**

Strength of evidence	5
Recommendation grade	D
Consensus achieved	91% (round 1)

Rationale

Lactic acidosis is seen in a number of conditions which can broadly be divided into an imbalance between oxygen supply and oxygen demand (type A) and cellular metabolic defects (type B) (152) The normal range for plasma lactate is often quoted as up to 2 mmol/l. There is one paper which looked at the differential diagnosis of chronic lactic acidosis(153) but none have reviewed acute hyperlactaemia.

The Delphi panel agreed that advice regarding any specific therapy (such as dichloroacetate) should be given on a case by case basis from a metabolic specialist.

- **Children with non-hyperglycaemic ketoacidosis are at risk of raised intracranial pressure, therefore careful monitoring is required with fluid balance.**

Strength of evidence	5
Recommendation grade	D
Consensus achieved	81% (round 1)

Rationale

There are no studies determining the link between non-hyperglycaemic ketoacidosis and raised intracranial pressure. However anecdotal and case reports provide evidence that raised intracranial pressure develops if aggressive fluid management strategies are implemented. This is often the case as high volumes of 10% dextrose are used to switch catabolism off in the cases caused by inborn errors of metabolism.

The Delphi panel agreed that careful management of fluid balance is required in these cases.

- **A child with non-hyperglycaemic ketoacidosis will need nutrition restarted early to prevent further catabolism**

Strength of evidence	5
Recommendation grade	D
Consensus achieved	92% (round 1)

Rationale

Non-hyperglycaemic ketoacidosis is a sign that the patient is in a catabolic state. There are no validated guidelines or studies reviewing the management of children in a catabolic state caused by metabolic or other conditions. The Delphi panel agreed that reversing catabolism requires close consideration to nutrition. A dextrose infusion is the first option, but protein will be required in the first 24-48 hours after admission to hospital.

14. Intracranial infections

a) Bacterial meningitis

Recognition

- **Bacterial meningitis should be suspected in children with neck pain / stiffness who score 8.5 or more in the following clinical decision rule:**

Instructions	Symptom/sign	Score
Sum the scores of the symptoms/signs present. If the total is 8.5 or more then the chances of having bacterial meningitis is high.	**If GCS < 9**	**= 8**
	Neck stiffness present	**= 7.5**
	Duration of symptoms	**= 1 /each 24 hrs**
	Vomiting	**= 2**
	Cyanosis	**= 6.5**
	Petechiae	**= 4**
	Serum CRP	**= CRP value (mg/l) divided by 100**

Strength of evidence 2b Diagnosis
Recommendation grade C

Rationale

Diagnosing bacterial meningitis clinically is not always straightforward. There have been several studies looking at the prevalence of various symptoms and signs associated with bacterial meningitis (154-158), but many have not been prospectively validated in a new group of children. There is one clinical diagnostic decision rule(30) which predicts the need to perform a lumbar puncture in children with neck stiffness (level 2b diagnosis). The study was designed to ensure that all children with bacterial meningitis (diagnosed on positive CSF culture) were identified and that lumbar punctures were not being performed unnecessarily on children who did not have bacterial meningitis. The rule can therefore be used to decide whom to lumbar puncture. It can be extrapolated from this rule that in the case of children with a reduced conscious level those that reach the threshold to perform a lumbar puncture should be treated as having bacterial meningitis until proven otherwise. A lumbar puncture may be contraindicated in this group of children initially and therefore to delay treatment until a lumbar puncture has been performed may lead to a worse outcome for the child.

- **Children with bacterial meningitis do not always present with neck stiffness.**

Strength of evidence 2b Differential diagnosis
Recommendation grade B

Rationale

There are several studies which look at the symptoms and signs of bacterial meningitis in children(154-158). The majority of these studies are case series which determined the incidence of neck stiffness in cases of bacterial meningitis to be between 13% and 29% for infants less than 6 months old and up to 96% for children aged up to 4 years (level 4 differential diagnosis). There is one retrospective cohort study(155) which determined the incidence of neck stiffness in children with bacterial meningitis and the incidence of bacterial meningitis in children with neck stiffness. Neck stiffness was present in 32% of children less than a year of age and in only 45% of children over 1 year (level 2b differential diagnosis).

There are clearly many children with bacterial meningitis who present without neck stiffness. This seems more likely the younger the child.

- **Children with reduced conscious level but no neck stiffness should be suspected of having bacterial meningitis clinically if they have fever and two of the following:**
    - **rash**
    - **irritability**
    - **bulging fontanelle**

Strength of evidence	5
Recommendation grade	D
Consensus achieved	75% (round 3)

Rationale

There are no validated clinical diagnostic decision rules for children without neck stiffness to determine clinically which children have bacterial meningitis. The Delphi panel were given a number of options and agreed to the statement above.

- **A child with a reduced conscious level and suspected bacterial meningitis should have the core investigations requested and should have a lumbar puncture if no acute contraindications exist**

Strength of evidence	5
Recommendation grade	D
Consensus achieved	96% (round 2)

Rationale

The gold standard test for bacterial meningitis is a positive culture from a cerebrospinal fluid sample (level 5 diagnosis). The Delphi panel agreed that the core investigations should be performed to ensure that the other differential diagnoses are not missed.

Treatment

- **If bacterial meningitis is suspected, dexamethasone 0.15 mg / kg should be administered before or with the first dose of antibiotics**

Strength of evidence	1a
Recommendation grade	A

Rationale

There have been four high quality meta-analyses looking at the effects of steroid treatment with antibiotics for bacterial meningitis(159-162). There is sound evidence that treating with steroids reduces profound hearing loss if the causative organism is Haemophilus influenza type B (HIB). In areas where HIB vaccination programmes are established, the incidence of HIB meningitis has dramatically reduced. The effect of steroids on profound hearing with other types of bacterial meningitis (e.g. meningococcal meningitis) is less well established.

The Cochrane meta-analysis(161) demonstrated that the effect of steroids to reduce profound hearing loss was still evident in cases of meningococcal or Streptococcal meningitis.

The number of children needed to treat (NNT) was 20 with non-HIB meningitis to reduce one case of profound hearing loss. The NNT with steroids to reduce one death was 250.

The side effect profile of steroids has been questioned in infective processes. However, even in severe sepsis steroids may be beneficial to the patient and are sometimes used to boost blood pressure (66). Therefore, in the case of suspected meningitis the benefits outweigh the risks, even if the diagnosis turns out to be something else eventually.

- **If bacterial meningitis is suspected, broad spectrum antibiotics should be started without waiting for a lumbar puncture to be performed if it is contraindicated**

Strength of evidence	1a Therapy
Recommendation grade	A

Rationale

There have been several studies to determine if one antibiotic regime is better than any other for bacterial meningitis. A systematic review of the topic(163) demonstrated that no single regime significantly improved outcome over any other regime (level 1a therapy). There were no studies using placebo as the comparison. The studies were homogenous and the meta-analysis confidence intervals were small for the outcomes of both death and profound hearing loss. The choice of antibiotic will be based on local resistance patterns and departmental preference.

- **If bacterial meningitis is suspected, broad spectrum antibiotics should be continued until further advice is available from microbiology**

Strength of evidence	5
Recommendation grade	D
Consensus achieved	96% (round 1)

Rationale

As the type of antibiotic used will be different from one department to the next, there are no applicable studies for this question. The Delphi panel agreed that the decision to stop antibiotics should be made with the microbiology tests results available and the clinical picture.

14. Intracranial infections

b) Herpes simplex encephalitis (HSE)

Recognition

- **HSE should be suspected clinically in a child with reduced conscious level if one or more of the following 4:**
  - **the child has focal neurological signs**
  - **the child has had a fluctuating conscious level for 6 hours or more**
  - **the child has or has been in contact with herpetic lesions**
  - **the child has no obvious clinical signs pointing towards the cause**

Strength of evidence	5
Recommendation grade	D
Consensus achieved	84% (round 3); 79% (round 3); 84% (round 2) and 81% (round 1) respectively

Rationale

There are no validated clinical diagnostic decision rules to help identify children with herpes simplex encephalitis from those with bacterial meningitis or other causes of reduced conscious level. Several neurologists commented that HSE is a diagnosis of exclusion. The Delphi panel were given several options to decide whom to give intravenous aciclovir to in the acute situation. As well as being a diagnosis of exclusion ("no obvious signs pointing towards the cause") the Delphi panel agreed to some inclusion criteria as well.

There has been debate amongst the virologist stakeholders about the relevance of contact with herpetic lesions, as this is rarely the route of transmission for the primary infection of HSE. However, the guideline developers felt that, in the situation of a child with reduced consciousness and the knowledge that there had been contact with herpetic lesions (i.e. cold sores), it would be reasonable to treat with aciclovir on that basis alone.

- **The clinical suspicion of herpes simplex encephalitis can be strengthened by:**
  - **a magnetic resonance image scan with non-specific features of herpes simplex encephalitis**
  - **an abnormal EEG with non-specific features of herpes simplex encephalitis**
  - **a positive CSF result for herpes simplex virus DNA in PCR of CSF***

Strength of evidence	5 *1b Diagnosis
Recommendation grade	D *A
Consensus achieved	91% (round 1)

Rationale

Magnetic resonance imaging cannot precisely diagnose HSE. A normal MRI will be reassuring but abnormal findings are not specific enough to rule out other diagnoses(164). Similarly electroencephalogram (EEG) features of HSE are not specific enough to rule out other diagnoses, but a normal EEG would be reassuring(164).

The gold standard for herpes simplex encephalitis had in the past been considered to be brain biopsy. As PCR of CSF is a less invasive test and has been demonstrated to be highly sensitive and specific this is now the standard for early diagnosis and was proved to be as accurate as brain biopsy in comparative studies(72, 73) (level 1b Diagnosis). It is not 100% accurate as some laboratories have found false positive results through cross-contamination and false negative results if the sample is taken several days after initial treatment was started.

Treatment:

- **If HSE is suspected clinically then intravenous aciclovir 10mg / kg (or 500mg/m^2 if aged 3 months to 12 years) three times a day should be administered, without waiting to perform a lumbar puncture.**

Strength of evidence	1b Therapy
Recommendation grade	A

Rationale

Aciclovir is a well established treatment for herpes simplex encephalitis. There are two linked studies which prove its worth. The first(165) investigated vidaribine (an early anti-viral treatment) against placebo in children and adults. In the placebo arm 70% of patients died (this high figure is consistent with other survival data at the time), whereas only 28% of patients died in the treatment arm. A second study(166) compared vidaribine with acyclovir. This study found that risk of dying from HSE was almost halved by using aciclovir compared to vidaribine (RR = 0.4). Vidaribine is better that placebo and aciclovir is better than vidaribine for the treatment of HSE. If the fatality rate of untreated HSE is still 70% then the NNT with aciclovir to reduce one death is 2.

- **If HSE is confirmed or highly suspected then intravenous aciclovir should continue for 14 days**

Strength of evidence	5
Recommendation grade	D
Consensus achieved	80% (round 1)

Rationale

There are no comparative studies comparing length of course of aciclovir with outcome. The randomised controlled trials(165-167) used a 10 day course. Various case reports have suggested relapses after a 10 day course. There are studies to determine the length of time to clear herpes simplex viral DNA from CSF, which conclude that there is still DNA detectable after 14 days in a large proportion of patients (168). However, there are no studies which show whether patients with detectable HSV DNA at two weeks relapse more frequently than those who do not have residual DNA.

The Delphi panel agreed that 14 days of intravenous aciclovir was recommended, but note that longer courses may be necessary in some individuals.

- **Intravenous acyclovir can be stopped before 14 days of treatment if there is no ongoing clinical suspicion of herpes simplex encephalitis**

Strength of evidence	5
Recommendation grade	D
Consensus achieved	79% (round 2)

Rationale

The likelihood of the diagnosis being HSE in as child with decreased consciousness may reduce significantly as other test results are reviewed. As there is no rapid diagnostic test which can rule out HSE, the Delphi panel agreed that if the clinical suspicion had diminished then aciclovir could be stopped.

14. Intracranial infections

c) Intracranial abscess

Recognition

- **An intracranial abscess should be suspected in a child with a reduced conscious level if:**
  - **there are focal neurological signs +/- clinical signs of sepsis**
  - **there are signs of raised intracranial pressure**

Strength of evidence	5
Recommendation grade	D
Consensus achieved	88% and 81% (round 2) respectively

Rationale

There are no diagnostic decision rules to aid the diagnosis of an intracranial abscess clinically. The gold standard test to diagnose an intracranial abscess is neuroimaging (usually CT initially with MRI being employed in specific cases). The Delphi panel agreed that in the presence of focal neurological signs or signs of raised intracranial pressure then a CT should be performed to rule in or out an intracranial abscess.

- **An intracranial abscess can be diagnosed from the results of cranial imaging.**

Strength of evidence	5
Recommendation grade	D
Consensus achieved	90% (round 1)

Rationale

Cranial imaging is the now the gold standard investigation for a suspected intracranial abscess. Although there are many studies reporting CT as a useful test for an intracranial abscess(90-92), none of them blindly compared CT to a gold standard of aspiration of the abscess, autopsy or intraoperative findings in children. The determination that cranial imaging is the gold standard is therefore based on expert opinion.

Treatment:

- **If an intracranial abscess is diagnosed, broad spectrum antibiotics should be administered after blood cultures have been taken**

Strength of evidence	5
Recommendation grade	D
Consensus achieved	93% (round 1)

Rationale

There are no validated guidelines for the management of intracranial abscesses. The majority are caused by bacterial infections(169). It is important to identify the causative agent so that antibiotic therapy can be tailored. However, because of the location of the abscess, antibiotics penetrate the abscess poorly and therefore are often insufficient to treat the abscess in isolation. The Delphi panel agreed that broad spectrum antibiotics should be started early but the choice should be determined by local resistance patterns and departmental preference.

- **If an intracranial abscess is diagnosed, advice from a paediatric neurosurgeon should be obtained urgently**

Strength of evidence	5
Recommendation grade	D
Consensus achieved	100% (round 1)

Rationale

There are no validated guidelines for the management of intracranial abscesses. As the majority of abscesses will be managed by a neurosurgical team (either for active drainage/aspiration or for close observation), the Delphi panel agreed that they need to be involved as soon as the suspected diagnosis is confirmed by cranial imaging, or sooner if imaging is unavailable locally.

14. Intracranial infections

d) Tuberculous meningitis

Recognition

- **Tuberculous meningitis should be suspected in a child with reduced conscious level if**
  - **there are clinical features of meningitis**
  - **there has been contact with a case of pulmonary tuberculosis**

Strength of evidence	5
Recommendation grade	D
Consensus achieved	78% and 96% (round 2)

Rationale

There is a validated clinical decision rule to diagnose TB meningitis(77). However, the population on which it was validated was different from the UK population in terms of length before presentation and TB prevalence. Also, the signs it relied upon included optic atrophy on fundoscopy. This sign would have very poor inter-observer reliability amongst doctors in training, making the rule difficult to validate for all levels of experience.

The Delphi panel agreed that TB meningitis should be suspected, but not treated until further information was available, if the child had signs of meningitis or had been in contact with TB.

- **A child with a reduced conscious level and suspected tuberculous meningitis should have the core investigations requested and should have a lumbar puncture* if no acute contraindications exist**

Strength of evidence	5 *1b Diagnosis
Recommendation grade	D *B
Consensus achieved	75%-100% (rounds 1 and 2) for individual core investigations

Rationale

The decision to perform the core investigations for all causes of reduced conscious level has been discussed in section 7. This decision is based on the agreement of the Delphi panel.

A CSF sample is required to perform Mycobacterium tuberculous PCR to help diagnose tuberculous meningitis (TBM). The gold standard for diagnosing TBM can be defined as a combination of clinical features and responding to treatment. One diagnostic test study(76) blindly applied this gold standard to patients with suspected TBM and assessed the accuracy of TB PCR (Diagnosis level 1b). The sensitivity of PCR was only 48% but the specificity was 100%. The performance of TB PCR against other tests such as CSF microscopy or culture was superior(76). As PCR of CSF is a more rapid test than CSF culture and less invasive than waiting for a response to anti-tuberculous treatment (with its many side effects), the recommendation to collect a sample of CSF for suspected TB meningitis is evidence based (extrapolated from level 1 studies).

- **If the microscopy of a cerebrospinal fluid sample is abnormal seek urgent advice from the microbiology department**

Strength of evidence	5
Recommendation grade	D
Consensus achieved	81% (round 1)

Rationale

There are no validated guidelines for the management of TB meningitis. The World Health Organization has produced guidelines for TB meningitis in children but these are not validated. There can be overlap between the microscopy findings for pyogenic meningitis and TB meningitis(77). Acid fast bacilli may not be detected in all cases of TB meningitis and TB culture results take over 6 weeks to be conclusive and can often be falsely negative(76, 77).

The Delphi panel agreed that if the CSF sample is abnormal advice from the microbiology department should be sought to help with further management. This will be especially helpful if the CSF culture is negative and the clinical course of the child is not as expected.

- **Tuberculous (TB) meningitis can be diagnosed quickly from a cerebrospinal fluid sample by a positive PCR for TB DNA.**

Strength of evidence	1b Diagnosis
Recommendation grade	A

Rationale

The gold standard for diagnosing TBM can be defined as a combination of clinical features and responding to treatment. One diagnostic test study(76) blindly applied this gold standard to patients with suspected TBM and assessed the accuracy of TB PCR (Diagnosis level 1b). The sensitivity of PCR was only 48% but the specificity was 100%. The performance of TB PCR against other tests such as CSF microscopy or culture was superior(76). As PCR of CSF is a more rapid test than CSF culture and less invasive than waiting for a response to anti-tuberculous treatment (with its many side effects), it is recommended that this is the investigation of choice where available. The decision to send a CSF sample for this test should be discussed with the microbiology department on an individual case basis.

15. Raised intracranial pressure

Recognition

- **Raised intracranial pressure can be suspected clinically by the presence of 2 or more of the following 5 signs:**
  - **Reduced conscious level (being Unrousable or GCS < 9)**
  - **Abnormal pattern of respiration (hyperventilation, irregular ventilation or apnoeas)**
  - **Abnormal pupils (unilateral or bilateral dilated pupils or unreactive pupils)**
  - **Abnormal posture (decorticate or decerebrate posture or complete flaccidity)**
  - **Abnormal doll's eye (oculocephalic) response or caloric (oculovestibular) response**

  or papilloedema is detected*

Strength of evidence	5/*5
Recommendation grade	D/*D
Consensus achieved	83% (round 1) / *Guideline development group

Rationale

There are reports of the signs of raised intracranial pressure in children(68, 69, 80, 170), but there are no validated, or even derivations, of a clinical diagnostic decision rule. The Delphi panel agreed on the above criteria for recognising raised intracranial pressure clinically. These were based on the studies which used them as inclusion criteria(68, 69, 80), which in turn were based on the long standing criteria described by Plum and Poysner(67). The Delphi panel agreed that raised intracranial pressure should be clinically suspected and acted upon if the above features are present. The guideline development group added "papilloedema" to the list after discussions with stakeholders.

Investigations

- **A child with a reduced conscious level and suspected raised intracranial pressure should have the core investigations requested and should be considered for a cranial CT scan* when the patient is stable.**

Strength of evidence	5 / *1b Diagnosis
Recommendation grade	D / *A
Consensus achieved	75%-100% (rounds 1 and 2) for individual core investigations

Rationale

Raised intracranial pressure is not a diagnosis in itself, but is the effect of another underlying problem. The core investigations were agreed by the Delphi panel to be requested on all children with a decreased level of consciousness (see Statement 8). A CT scan can demonstrate raised intracranial pressure. A study of CT scanning blindly compared to intracranial pressure monitoring(89) showed that if the intracranial pressure is greater than 25 mmHg then the sensitivity of the CT scan was 97.7% and specificity 60.6% (1b diagnosis). A CT scan can detect the underlying cause of the raised intracranial pressure in some circumstances also.

It is worth noting that the technical details of the scan should be determined by the radiologist performing the scan.

- **Ensure the results of all the investigations performed are reviewed and consider further tests (see "Cause unknown") if the cause of the raised intracranial pressure is not diagnosed.**

Strength of evidence	5
Recommendation grade	D
Consensus achieved	100% (round 1)

Rationale

The Delphi panel agreed that the cause of the raised intracranial pressure should be investigated further if the core investigations and cranial CT scan did not help with the diagnosis.

Treatment

- **Children with a clinical diagnosis of raised intracranial pressure should have the following treatments to prevent coning:**
  - **Position the patient's head in the midline**
  - **Angle the patient head up at 20 degrees above the horizontal**
  - **Avoid inserting central venous lines placement in the neck^{+}**
  - **Sedate, intubate and ventilate the patient to maintain the $PaCO_2$ between 4.0 and 4.5 kPa**
  - **Maintenance fluids should not be hypotonic***

  (The rate of maintenance fluids needs to be agreed at a local level)
  (The decision to give and the dose of mannitol or hypertonic saline needs to be agreed at a local level)

Strength of evidence	5/$^{+}$5 *1b Therapy
Recommendation grade	D/$^{+}$D *B
Consensus achieved	86% (round 1); 88% (round 1): $^{+}$Guideline development group; 100% (round 2) respectively

Rationale

The initial management of children with raised intracranial pressure involves the above measures. There is limited evidence to support these therapies and are based on consensus practice. Maintenance fluids have been studied in the presence of raised intracranial pressure due to head injury in children(171). In this randomised controlled trial, the use of hypertonic saline (1.8% saline) reduced the length of stay on intensive care and reduced the number of other interventions required to manage raised intracranial pressure (level 1b Therapy).

The Delphi panel agreed to the other treatments for raised intracranial pressure, except no consensus was found in three areas: the rate of maintenance fluid; the indications for mannitol or hypertonic saline; or the indications for invasively monitoring intracranial pressure. The finding of limited agreement in these areas is not surprising and is backed up by a study from the UK surveying intensive care unit guidelines for the management of raised intracranial pressure(172). During the guideline implementation phase, individual centres will need to discuss these points and reach agreement on local practice preferences.

Monitoring

- **Arrange for patient transfer to a paediatric intensive care unit.**

Strength of evidence	5
Recommendation grade	D
Consensus achieved	93% (round 1)

Rationale

The Delphi panel agreed that a paediatric intensive care unit would be the appropriate place to monitor and manage children with raised intracranial pressure. It should be noted that the Delphi panel did not reach consensus the indications for invasive intracranial pressure monitoring in children with clinically raised intracranial pressure. Each case therefore needs to be assessed individually for intracranial pressure monitoring.

16. Hypertensive encephalopathy

Recognition

- **In a child with a decreased level of consciousness, hypertension is defined as the systolic blood pressure >95th centile for age on two separate readings.**

Strength of evidence	5
Recommendation grade	D
Consensus achieved	Guideline development group

Rationale

There is a published guideline on the management of hypertension in children and adolescents (173), however this has not been validated. The guideline development group in discussion with stakeholders agreed that the definition of hypertension should be >95th centile for age repeated for accuracy. Often children who have hypertensive encephalopathy have a blood pressure significantly higher than this centile.

Investigations

- **In children with hypertension and a decreased conscious level, look for:**
  - **signs of raised intracranial pressure,**
  - **papilloedema,**
  - **and check a four limb blood pressure**

Strength of evidence	5
Recommendation grade	D
Consensus achieved	Guideline development group

Rationale

Hypertension may be caused by raised intracranial pressure, in which case a reduction in BP may lead to a clinical deterioration due to the concomitant fall in cerebral perfusion pressure. However, if the cause of the decreased conscious level is hypertension itself then it is important to reduce this in a controlled way. Therefore, distinguishing between hypertensive encephalopathy and hypertension secondary to raised intracranial pressure is crucial to making the correct management decisions. Hypertensive encephalopathy is often caused by a renal problem and the high blood pressure has been present for some time. This is

not usually the case with raised intracranial pressure, as the raised blood pressure is often a transient phenomenon responding to changes in cerebral perfusion pressure.

There are no validated clinical decision rules for either raised intracranial pressure or hypertensive encephalopathy. The guideline development group in discussion with stakeholders agreed that trying to differentiate raised intracranial pressure from hypertensive encephalopathy was an important part of the management of these cases.

- **Ensure the results of the core investigations are reviewed, especially the urinalysis for blood and protein, and the plasma levels of creatinine and urea.**

Strength of evidence	5
Recommendation grade	D
Consensus achieved	Guideline development group

Rationale

As hypertensive encephalopathy is often caused by an acute or chronic renal problem, the guideline development group in discussion with stakeholders agreed that reviewing the screening tests of renal function may help differentiate hypertensive encephalopathy from raised intracranial pressure.

Treatment

- **In a child with hypertension and no other cause for reduced conscious level, seek urgent help from a paediatric nephrologist or intensivist.**

Strength of evidence	5
Recommendation grade	D
Consensus achieved	Guideline development group

Rationale

There are no randomised controlled trials for the treatment of hypertensive encephalopathy and therefore treatments vary according to experience. A published guideline for treating hypertension in children states that "severe, symptomatic hypertension should be treated with intravenous drugs"(173). The decision to treat should be made with the involvement of a nephrologists or intensivist with experience of hypertensive encephalopathy.

17. Prolonged convulsion

- **A convulsion needs treating if it has not stopped after 10 minutes.**

Strength of evidence	5
Recommendation grade	D
Consensus achieved	91% (round 1)

Rationale

There are no randomised trials of waiting to treat convulsions after a specific length of time from it starting. A systematic review(174) of prospective cohort studies and case-control studies in adults and children found the mortality of patients suffering convulsions to be significantly higher than the general population (level 1a- prognosis). However, many of the included studies also found that status epilepticus secondary to idiopathic epilepsy is not associated with significantly higher mortality(175-178). Therefore the underlying cause of the epilepsy or seizure may be more important than the seizure in terms of mortality.

There is one prospective cohort study(179) which looked at the duration of a seizure on outcome in children (level 1b prognosis). This found that neurological outcome was not dependent upon the duration of the convulsion but on the underlying cause. The duration of seizure in this cohort (excluding children whose convulsion lasted less than 5 minutes) was on average 42 minutes. There were no deaths in this group (n=186 children and 279 convulsions) and very few long term neurological deficits (n=3). The long term effects were seen after convulsions lasting less than 40 minutes and were related to the underlying cause rather than the length of convulsion.

Although there is no strong evidence that a convulsion lasting 5 minutes or 10 minutes or 15 minutes has a poor prognosis, a prolonged convulsion is not desirable. The Delphi panel agreed that a convulsion needs to be actively treated if it has not spontaneously stopped by 10 minutes. Some would advocate treating after 5 minutes.

- **The treatment of a prolonged convulsion (i.e. lasting longer than 10 minutes) should follow the A.P.L.S. guidance (Advanced Paediatric Life Support).**

Strength of evidence	5
Recommendation grade	D
Consensus achieved	100% (round 1)

Rationale

There are no validated guidelines for the acute treatment of a convulsion. Developing an evidence-based guideline in this area was outside the scope of this guideline. The A.P.L.S. guidelines for managing a convulsing child(81) are widely used. They are based on the consensus guidelines produced by the Status Epilepticus Working Party(6). The Delphi panel agreed to use these recommendations.

- **If the convulsion is prolonged (i.e. lasting longer than 10 minutes) and the child is not known to have epilepsy, then the core investigations should be sent at presentation.**

Strength of evidence	5
Recommendation grade	D
Consensus achieved	87% (round 1)

Rationale

There are no validated guidelines for the management of prolonged convulsions and which tests to send. The Delphi panel agreed that the core investigations should be sent in children without a known epilepsy syndrome.

- **If the convulsion is prolonged (i.e. lasting longer than 10 minutes) and the child is under a year old, then plasma calcium and magnesium should be requested as well as the *core investigations at presentation.**

Strength of evidence	1b Symptom prevalence *5
Recommendation grade	B
Consensus achieved	*75%-100% (rounds 1 and 2) for individual core investigations

Rationale

There are no validated guidelines for the management of prolonged convulsions. There are studies which have looked at the yield of performing “routine” blood investigations

in children whose convulsion has stopped and they found very few positive results(180-182). However, this may not apply to children whose convulsion is prolonged and did not look specifically at children under a year of age. There is one cohort study (183) and one case series(184), which specifically determined the incidence of hypocalcaemia and hypomagnesaemia in infants less than 4 weeks old with seizures (level 1b / 4 Symptom prevalence). 84% of breast fed infants who suffered a convulsion during days 5 to 8 of life had hypocalcaemia and 46% hypomagnesaemia(183). 12% of infants (aged up to 28 days of life) who suffered a convulsion had a plasma calcium of less than 1.9 mmol/l and the convulsion stopped upon administration of calcium. It is therefore reasonable to check the calcium and magnesium in this group of convulsing children.

- **If the plasma sodium is less than 115 mmol/l and the convulsion is ongoing despite anticonvulsant treatment, an infusion of 5ml/kg of 3% saline should be given over one hour**

Strength of evidence	5
Recommendation grade	D
Consensus achieved	86% (round 2)

Rationale

Hyponatraemia is a recognised cause of prolonged convulsions in children, although there are no studies to determine the incidence. There are no randomised controlled trials of treatment for hyponatraemia in the context of a child convulsing. There is one case series of treating hyponatraemic seizures with 3% saline with beneficial results(185). The Delphi panel agreed that in the case of severe hyponatraemia, hypertonic saline should be infused.

- **If the ionized calcium is less than 0.75 mmol/l or plasma calcium is less than 1.7 mmol/l and the convulsion is ongoing, an infusion of 0.3ml/kg of 10% calcium gluconate should be given over 5 minutes**

Strength of evidence	5
Recommendation grade	D
Consensus achieved	95% and 81% respectively (round 1)

Rationale

There are no randomised controlled trials of intravenous calcium gluconate for hypocalcaemic convulsions in young children. There is one randomised controlled trail(186) of oral calcium supplements versus oral phenobarbitone versus intramuscular magnesium sulphate for the treatment of hypocalcaemic convulsions in infancy. This demonstrated that intramuscular magnesium was the most successful treatment at reducing the number of convulsions at 48 hours(level 2b therapy). However in this study all the infants were also hypomagnesaemic.

In view of the different treatment modalities (intravenous calcium gluconate versus oral route) the Delphi panel agreed that if there were ongoing convulsions in hypocalcaemic children then intravenous calcium supplementation should be prescribed.

- **If the plasma magnesium is less than 0.65 mmol/l and the convulsion is ongoing, an infusion of magnesium sulphate 50mg/kg should be given over one hour.**

Strength of evidence	2b
Recommendation grade	C

Rationale

There is one randomised controlled trial of intramuscular magnesium sulphate versus oral phenytoin versus oral calcium supplements for the treatment of hypocalcaemic (plasma calcium <1.5mmol/l) and hypomagnesaemic (plasma magnesium <0.6mmol/l) convulsions in infancy(186). This study demonstrated that in 104 infants intramuscular magnesium sulphate was more effective than the other treatments (level 2b therapy).

The intravenous route is now the preferred route (if available) for administration of any anticonvulsant in the acute situation. The comparison of oral calcium or phenytoin against a systemic treatment may have over estimated the treatment effect of intramuscular magnesium. Intravenous magnesium sulphate has been shown to be effective in other convulsion conditions (e.g. eclampsia(187, 188)). The Delphi panel agreed that it is reasonable to recommend intravenous magnesium sulphate as a treatment for hypomagnesaemia in this population of convulsing children.

18. Post-convulsion state

- **After a convulsion has stopped, a child will often have a period of reduced consciousness, the "post-convulsion state"**

Strength of evidence	5
Recommendation grade	D
Consensus achieved	97% (round 1)

Rationale

There are no population studies to determine how many children have a period of reduced conscious level after a convulsion (be that an epileptic seizure or convulsion due to another cause). However, it is a well observed phenomenon and the Delphi panel agreed.

- **The post convulsion state will last for less than one hour in the majority of children**

Strength of evidence	5
Recommendation grade	D
Consensus achieved	75% (round 1)

Rationale

There are no population studies to determine how long a period of reduced conscious level lasts for after a convulsion. The Delphi panel agreed that most children have a decreased conscious level for less than an hour.

- **During the first hour of the post-convulsion state, a detailed history and examination should be performed**

Strength of evidence	2c Therapy
Recommendation grade	C

Rationale

There is a validated evidence-based guideline for the management of the child post-seizure(5). When implemented the guideline reduced the number of unnecessary invasive tests and reduced the number of children admitted to hospital, without increasing the number of adverse events (e.g. returning to hospital with the same complaint). The guideline

recommends a detailed history and examination as part of the management strategy (level 2c ["Outcomes" research] Therapy).

- **During the first hour of the post-convulsion state, it may be appropriate to closely observe a child, whose capillary glucose is normal, without performing any further tests or treatments**

Strength of evidence	5
Recommendation grade	D
Consensus achieved	92% (round 2)

Rationale

The validated guideline on post-seizure management recommends that no tests need to be performed routinely(5), unless findings in the history or examination suggest otherwise (level 2c). The Delphi panel agreed that in the post-convulsion state many children need to be observed without any other investigations, as long as the capillary glucose has been checked as normal.

- **After the first hour of the post-convulsion state, if the child has not recovered normal consciousness the core investigations should be performed**

Strength of evidence	5
Recommendation grade	D
Consensus achieved	81% (round 1)

Rationale

There are no population studies to determine how long the period of reduced consciousness lasts for after a convulsion. It was agreed by the Delphi panel that after an hour of observation, if a child had not recovered to normal consciousness (i.e. a GCS of 15) then the core investigations should be performed. If a child has had a prolonged convulsion and been given anti-convulsant medication, then this will affect the length of any post-ictal phase.

19. No clinical clues to the cause

Investigations

- **The following additional tests should be requested if, after reviewing the core investigations' results, the cause of a child's reduced conscious level remains unknown:**
  - **CT scan**
  - **a lumbar puncture (if no acute contraindications exist)**
  - **urine toxicology screen**
  - **urine organic and *amino acids**
  - **plasma lactate**

Strength of evidence	5
Recommendation grade	D/*D
Consensus achieved	96% (round 3) / *Guideline Development Group

Rationale

This is the group of children which causes significant concern and confusion for hospital practitioners about what investigations to send and what treatments to start. However, there are no validated guidelines for children with an unknown cause for their reduced level of consciousness. The causes of reduced conscious level in children have been studied on a population basis(2) but it is uncertain how many of these diagnoses would have been clinically obvious at presentation.

The Delphi panel was asked to determine what they would do in the situation of a child with a reduced level of consciousness. They agreed that the core investigations should be sent initially. If after reviewing these screening tests no further clues emerged (e.g. hyperammonaemia or hyponatraemia), then the list of additional tests should be requested. Some of these tests can be requested from the saved samples taken with the core investigations.

The guideline development group, after consultation with stakeholders, added the urine amino acids to this group of tests rather than the next group of tests below. The reason being that although the yield of amino acidurias will be less than that of organic acidurias, the interpretation of the organic acid profile is helped by a knowledge of the amino acid profile. Therefore, in everyday laboratory practice the two tests need to be looked at together not separately.

- **In a child with a reduced conscious level with an unknown cause after reviewing the core investigations, CT scan and initial CSF results, the following tests should be considered:**
    - **an EEG, organised as soon as possible, to exclude non-convulsive status epilepticus**
    - **acyl-carnitine profile (on Guthrie card or from stored frozen plasma) and *plasma amino acids**
    - **ESR and autoimmune screen, to exclude cerebral vasculitis**
    - **Thyroid function test and thyroid antibodies, to exclude Hashimoto's encephalitis**

Strength of evidence	5
Recommendation grade	D/*D
Consensus achieved	100%; 91%; 95%; 86% and 86% round 3 respectively *Guideline development group

Rationale

The Delphi panel agreed that if no further information was added by the CT scan (e.g. cerebral abscess or cerebral oedema) or the CSF microscopy (e.g. possible encephalitic or meningitic process) then the following tests should be arranged. Again some of these tests can be requested from the saved samples taken as part of the core investigations.

The guideline development group after consultation with stakeholders added plasma amino acids to this list. This test can provide a positive result even if the urine metabolic tests are negative.

Treatment

- **A child with a reduced consciousness and no obvious clinical signs pointing towards the cause should have supportive treatments implemented to protect their airway, breathing and circulation.**

Strength of evidence	5
Recommendation grade	D
Consensus achieved	96% (round 1)

Rationale

The Delphi panel agreed that supportive treatments were essential to maintain vital organ perfusion and oxygenation.

- **A child with a reduced consciousness and no obvious clinical signs pointing towards the cause should be started on broad spectrum antibiotics and intravenous aciclovir**

Strength of evidence	5
Recommendation grade	D
Consensus achieved	90% and 81% round 1 respectively

Rationale

The Delphi panel agreed that in the face of the unknown the benefits of treating a potential infective cause (e.g. bacterial meningitis or herpes simplex encephalitis) outweigh the side effects of such treatment. Such treatment can be stopped once it becomes clear that the cause is no longer an infective process.

- **If there is no obvious cause for the child's reduced conscious level discuss the case with a paediatric neurologist within 6 hours of admission**

Strength of evidence	5
Recommendation grade	D
Consensus achieved	78% (round 1)

Rationale

The Delphi panel agreed that a paediatric neurologist should be consulted to assist with further management in these cases. Six hours was felt to be a reasonable time period for some investigation results to be at hand, and to access a neurologist if the child has not presented to a centre with a neurology service.

20. Good practice points

- **During resuscitation and initial management of a child with a reduced conscious level, the parents / guardians should be allowed to stay with the child if they wish**

Recommendation grade Good practice point
Consensus achieved 88% (round 1)

Rationale

Testimonies were sought from parents of children who had had an acute illness which resulted in reduced consciousness. The responses received from parents were positive about the experiences when they had been able to stay with their child. The Delphi panel which included patient/parent representation agreed that with enough staff support parents should be allowed to stay with their child.

- **During resuscitation and initial management of a child with a reduced conscious level, the parents / guardians should be kept informed of the possible underlying diagnoses and treatments required**

Recommendation grade Good practice point
Consensus achieved 91% (round 1)

Rationale

Testimonies were sought from parents of children who had had an acute illness which resulted in reduced consciousness. The responses received from parents were positive about the experiences when they had been kept informed of the management of their child's illness. The Delphi panel which included patient/parent representation agreed that parents should be kept informed and the information given should be tailored to each individual case.

- **During resuscitation and initial management of a child with a reduced conscious level, the parents / guardians should be kept informed of the possible prognosis of their child if it is known**

Recommendation grade Good practice point
Consensus achieved 88% (round 1)

Rationale

Testimonies were sought from parents of children who had had an acute illness which resulted in reduced consciousness. The responses received from parents were positive about the experiences when they had been kept informed of the seriousness of their child's condition. The Delphi panel which included patient/parent representation agreed that with parents should be kept informed of their child's prognosis on a case by case basis.

21. Peri-arrest management

Investigations taken at the resuscitation

- **If a child with a decreased conscious level deteriorates rapidly or dies suddenly, a urine sample should be collected by catheter or suprapubic aspiration (if not already collected)**

Strength of evidence	5
Recommendation grade	D
Consensus achieved	94% (round 1)

Rationale

The Delphi panel agreed that a sample of urine would provide vital clues to the diagnosis. The sample could be sent for microbiology investigations, metabolic investigations, toxicology investigations or stored for later analysis.

- **If a child with a decreased conscious level deteriorates rapidly or dies suddenly, a blood sample should be collected from a large vein or artery (if not already obtained)**

Strength of evidence	5
Recommendation grade	D
Consensus achieved	Guideline development group

Rationale

If no blood has been obtained then it would be preferable to take a fresh sample. This sample could be sent for metabolic investigations, toxicology investigations, microbiological investigations, chromosomal investigations or stored for later analysis.

- **If a child with a decreased conscious level dies without a diagnosis being made, the coroner needs to be informed and a post mortem examination should be performed by a paediatric pathologist within 24 hours of death**

Strength of evidence	5
Recommendation grade	D
Consensus achieved	97% (round 1)

Rationale

If a cause of death has not been firmly established then there is a statutory obligation to inform the coroner. The Delphi panel agreed that a post mortem examination should be carried out to help determine the cause. Some samples (e.g. skin fibroblasts) may deteriorate with time, therefore a post mortem should be carried out with as little delay as possible. Consent for the post mortem and/or retention of organs or tissues for use afterwards will need to be obtained from the family as per the Department of Health's best practice guideline (189).

Investigations taken at post mortem

- **If a child with a decreased conscious level dies without a diagnosis being made, a pathologist should perform the following:**

At the time of post mortem:	After the post mortem:
▪ **Full skeletal survey including skull X-ray, X-rays to be reported by a radiologist with expertise in NAI**	
▪ **Snap freeze a small sample (about 1cc) of heart, kidney, liver and muscle in liquid nitrogen**	▪ **Perform an oil red O stain on frozen sections of heart, kidney, liver, and muscle and examine for microvesicular fat**
▪ **Take samples of blood and bile on "Guthrie" cards**	▪ **Blood and bile to Chemical Pathology for mass spectrometry for acylcarnitine and fatty acid oxidation**
▪ **Take a sample of skin in tissue culture medium**	▪ **Skin to culture fibroblasts and storage in liquid nitrogen for enzymes and/or DNA analysis**
▪ **Take a sample of urine from the bladder or renal pelvis**	▪ **Urine to Chemical pathology for amino, organic and orotic acid assay, and toxicology**
▪ **Take specimens for virology and microbiology**	▪ **Document virology and microbiology results**
▪ **Take standard samples of all organs for histology**	▪ **Report on paraffin sections of samples for histology**
▪ **Retain the brain for neuropathological examination**	▪ **Neuropathological examination of the brain after a week and samples taken for microscopy. (The brain can then be returned to the body in time for the funeral).**

Strength of evidence 5
Recommendation grade D
Consensus achieved 93% (round 1)

Rationale

Determining the cause of death is important for parents understanding and may be life saving for siblings if a genetic diagnosis is made. The samples recommended above will provided the best chance of determining the cause of death. These recommendations are in agreement with the guidelines drawn up for post mortem examination in sudden unexplained death in infancy (SUDI)(190), however, this guideline covers a broader age range and potentially a different population of patients. Once again consent will be needed for retention of organs or tissues such as the brain for neuropathological examination.

6. Guideline Algorithm

A twelve page algorithm has been developed for use in Emergency Departments and Paediatric Assessment units. A colour version of the algorithm accompanies this technical document.

Two important features of using the algorithm need to be stressed during the implementation phase:

1) If a decision is taken to investigate a child with reduced conscious level, then request all the core investigations at the earlier opportunity. Once this set of blood and urine tests has been sent, all the diagnoses can be recognised from the results of these tests.

2) Review all the possible causes of reduced conscious level concurrently rather than sequentially. No individual cause is more important than another and several may coexist in the same child.

7. Implementation Strategy

A guideline needs to be actively implemented. The Guideline Development Group has developed a number of strategies to improve the use of the guideline which will be initiated after the external evaluation process is complete.

Dissemination

The guideline algorithm will be distributed to every Emergency Department and Paediatric Unit in the UK.

The guideline will be publicised in journals (current planned commissioned articles for "Archives of Disease in Childhood", "Current Paediatrics" and "Annals of Clinical Biochemistry") and at conferences across the UK (including The British Paediatric Neurology Association, 2006 meeting).

The guideline will be available on-line at www.nottingham.ac.uk/paediatric-guideline and a hand-held computer version will be freely accessible. Other versions of the guideline include a Guideline Recommendations Summary.

Education

An electronic education pack will be sent out with the guideline algorithm to all Emergency Departments and Paediatric Units. This will include an interactive presentation on how to use the guideline, how to implement the guideline and how to audit the guideline.

There will also be training modules for junior doctors on managing raised intracranial pressure and managing metabolic diseases acutely. This "added value" aspect of the guideline will help improve its use.

Local Facilitators

Several local facilitators will be approached to take the lead in implementing the guideline in their local departments. As a large number of different professionals from across the UK have been involved in the guideline development, these key figures already have ownership of the guideline. Therefore, all the many Delphi panellists and stakeholder leads will be encouraged to take on this role of local facilitator.

If possible, the local facilitators will be able to disseminate their experiences of using the guideline to other units in their area through regional meetings. Through this word of mouth approach the guideline will hopefully be implemented across the entire UK.

Parents

Parents will also play a key role in helping to establish the use of the guideline. A Parent Information Leaflet has been developed to empower parents to ask questions about the care their child receives. This will encourage the medical and nursing staff to ensure they are following best practice guidelines.

Further details of the Parent Information Leaflet are provided in Appendix F.

Audit

Audit not only helps to improve established practice, but will also help to implement changes in practice. Due to the Hawthorne effect(191) the use of the guideline will improve during the period of an audit cycle.

8. Audit

Audit is a tool to measure performance and set and improve standards. The Guideline Development Group has considered a number of practice points which are key in improving standards. These audit criteria are listed in Table 4. The audit criteria were selected as they were readily measurable, important markers of using the guideline, some are based on the level 1a evidence, and investigate areas where current performance can be improved.

To help audit the guideline once it has been implemented, the audit criteria and a care pathway available will be for use. The care pathway embeds the guideline recommendations into the routine clinical admission documentation, so that during the initial clerking of the child the doctor will be reminded of the best practice points. The care pathway also encourages recording the key information required for the audit. Therefore during the data collection phase of the audit, missing information will be infrequent.

As part of the implementation process, a national audit of the guideline is planned. This will allow comparisons of performance from one unit to another and help establish the standards for future audit cycles.

Further details of the care pathway are provided in Appendix G.

Criterion	Exception	Definition of terms
Percentage of children with a reduced conscious level having a plasma ammonia sent	Children within one hour post convulsion. Children with trauma not related to a medical collapse.	Plasma ammonia result should be available in the notes or on the hospital results system
Percentage of children with a reduced conscious level having a sample of urine sent to clinical pathology to be saved for later use	Children within one hour post convulsion. Children with trauma not related to a medical collapse	Saved urine sample sent should be documented in the notes or on the hospital results system
Percentage of children with a reduced conscious level who have their respiratory rate from admission documented in the notes		
Percentage of children with a reduced conscious level who have their blood pressure from admission documented in the notes		
Percentage of children with a reduced conscious level who have their GCS from admission documented in the notes		
Percentage of children with suspected bacterial meningitis that were treated with intravenous dexamethasone before or with the first dose of antibiotics.		Suspected bacterial meningitis is defined by a score of 8.5 or more using the clinical diagnostic decision rule below if the child has neck stiffness: Symptom/sign Score If GCS < 9 = 8 Neck stiffness present = 7.5 Duration of symptoms = 1 /each 24 hrs Vomiting = 2 Cyanosis = 6.5 Petechiae = 4 Serum CRP = CRP value (g/dl) divided by 100 or if the child does not have neck stiffness but has fever and two or more of the following: rash irritability bulging fontanelle

Table 4. Audit criteria recommended for measuring implementation of the guideline

9. Research Points

Part of the role of clinical guidelines is to highlight areas for future research. This should aid prioritisation of research resources. During the evidence searching and appraisal, several key areas were identified where there is no trial data.

Clinical diagnostic studies

A better understanding of the presenting features of several of the conditions featured in the guideline would help improve clinical diagnostic accuracy.

Research is therefore required in the following areas:

> Developing a clinical diagnostic decision rule for herpes simplex encephalitis
> Developing a clinical diagnostic decision rule for raised intracranial pressure

Therapy studies

There is debate about the length of treatment for herpes simplex encephalitis with aciclovir and when it is safe to stop.

Research is therefore required in the following area:

> A comparison trial of aciclovir treatment strategies for herpes simplex encephalitis in children

Economic evaluation studies

There is limited economic data available to help form "cost-conscious" recommendations. The extra cost of performing the core investigations compared to estimated current practice seems low, but a cost-comparison study will not provide the detailed analysis required to ensure that guideline implementation is cost-effective.

Research is therefore required in the following area:

> A cost-effectiveness analysis of using the core investigations compared to using current practice investigations in this target population.

10. Update Process

The guideline recommendations will need to be reviewed after a maximum of two years. At that point the results of a search for new evidence (limited to the last two years) and any feedback from implementation studies and audit results will need to be incorporated.

The Guideline Development Group will meet again in 2007 to discuss the updating process before the deadline of January 2008.

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