Guideline for the management of a child aged 0-18 years with a decreased conscious level

Appendix A

Search strategies and evidence tables

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1. Definition of decreased conscious level in children

Clinical Questions:

(i) In children, which conscious level scores are associated with outcome?

Selection criteria
Criteria for choosing papers were drawn up before the search took place. Papers would be included if they specifically looked at the prediction of clinical outcome using a conscious level score in children. Prospective cohort studies or case-control studies would be included. Validation studies of clinical decision rules would be included if a conscious level score was one of the variables. Retrospective case series and derivation studies of clinical decision rules would not be included in the analysis, as the data collection and conclusions drawn could not be reliably free from error. Studies involving both children and adults were only included if the results for children could be analysed separately.

Search
A review of the Cochrane library, MEDLINE (1966-present), EMBASE (1980-present), CINAHL (1982-present), British Nursing Index (1985-present) and AMED (1985-present) was performed using the search terms below. A review of the references of the selected papers for further evidence was included in the search strategy and a hand search of five key journals in the field in the previous 12 months.

Search filter

#	Search terms	No. of articles
1	exp COMA/ or exp GLASGOW COMA SCALE/	30002
2	exp confusion/ or exp coma/ or exp coma, post-head injury/	36808
3	exp Glasgow Coma Scale/	6412
4	1 or 2 or 3	42600
5	exp adolescent/ or exp child/ or exp child, preschool/ or exp infant/ or exp infant, newborn/ or exp adolescent, hospitalized/ or exp child, hospitalized/	2815604
6	4 and 5	8994
7	prognos$.mp. [mp=ab, hw, ti, sh, it, tn, ot, dm, mf, rw]	490966
8	6 and 7	1480
9	from 8 keep 44, 127, 136, 176, 196, 212...	45
10	from 9 keep 1-4, 6-8, 11, 13-16, 20, 23-24	25

Results
A total of 45 abstracts were reviewed from 1480 titles. A total of 25 papers were selected for further review. The hand search of journals and references identified three other papers for further review. Seven papers were included in the final analysis.

Papers not included in the final analysis are listed in table 1.1.i
Papers included in the final analysis are listed in table 1.1.ii

Reference	**Reason for exclusion**
Berger (1)	Analysis of coma scale to outcome only analysed in 7 of the 37 prospectively identified cases.
Perez (2)	Retrospective case series and published in a foreign language.
Kornelisse (3)	Retrospective case series
Lieh-lai (4)	Retrospective case series
Suresh (5)	Retrospective case series
Pillai (6)	Retrospective case series
Bhutto (7)	Retrospective case series
Skarmeta (8)	Case-control study looking at prognostic indicators in bacterial meningitis in children including the Glasgow Coma Scale. Published in a foreign language, unable to translate.
Ong (9)	Retrospective case series used as a derivation set for a clinical decision rule
Mohanty (10)	Retrospective case series
Pfenninger (11)	Retrospective case series and published in a foreign language

Seshia (12)	Prospective cohort but used as derivation set of a clinical decision rule, without data on conscious level score and outcome being validated
Dean (13)	Retrospective case series
Sacco (14)	Prospective cohort study looking at GCS and outcome, but children below age of 10 years excluded and data from children aged 10-18 not analysed separately from adult data.
Seshia (15)	A four point coma scale is assessed on children in relation to outcome, with those children with the lowest level of consciousness on the scale having the worst outcome. Unable to tell if the data was collected prospectively or retrospectively.
Dhellemmes (16)	Retrospective case series
Duncan (17)	Retrospective case series used to compare outcomes against the GCS and Lovejoy scale
Raimondi (18)	Retrospective case series
Morray (19)	Retrospective case series
Hennes (20)	Retrospective case series
Lovejoy (21)	Retrospective case series used as a derivation set for a clinical decision rule
Grewal (22)	Retrospective case series used as a derivation set for a clinical decision rule
Castellanos-Ortega (23)	Retrospective cohort study using data to derive and validate a clinical decision rule. As the data was collected retrospectively for both derivation and validation sets, cases with poor records were excluded which may affect the overall results.

Table 1.1.i Papers excluded from the analysis of outcome associated with conscious level scores

Study	Methods	Participant definition	Length of follow-up	Outcomes	Results	Notes	Evidence level
Prabbha (24)	Prospective cohort study to assess modified GCS and other variables associated with short-term outcomes in paediatric non-traumatic coma	Children aged between 3 months and 12 years presenting to a tertiary referral hospital with coma (defined by the authors) of less than 7 days duration. Study period Oct 1998 to March 2000	72 hours. 100% of those recruited followed up.	Death within 72 hours of admission	270 children were included in the study. 100 patients died during follow up period. Of the parameters assessed, those significantly associated with mortality at 72 hours were total GCS, the individual components of the GCS, and brain stem responses.	If summing the GCS the total was less than 8 there was a relative risk of death within 72 hrs of 27:1. This population had a very high mortality rate and the spectrum of diagnoses was different to that seen in the UK but with significant overlap.	Prognosis 1b
Hannan (25)	Prospective cohort study to assess the AVPU scale and other variables associated with outcome in paediatric trauma	Children aged 0 to 12 years presenting with blunt trauma (defined by the authors) to the emergency departments 192 hospitals which contribute to the New York State Trauma Registry. Study period 1994 to 1995.	From hospital admission to discharge. 100% of those recruited followed up.	Death during hospital admission period	2923 children were included in the study. 54 patients died. Of the parameters assessed, those significantly associated with mortality during the hospital admission period were Being unresponsive on the AVPU scale, having a best motor response of <2 from the motor response of the GCS, and having an ICISS score <.50	Although this was part of a study to derive a clinical decision rule, the fact that being unresponsive on the AVPU scale was independent predictor of death (odds ratio of 5.6) meant the study could be included in the analysis. The study is not clear, however, whether the AVPU scale was taken at presentation or whether it is the lowest score during the child's time in the emergency department. It is unlikely that there is an association between outcome and the middle values on the AVPU scales which leads to the conclusion that the score of U is more useful than the other scores on the scale.	Prognosis 1b

Molyneux (26)	Prospective cohort study to assess the "Blantyre scale" of coma and other variables associated with outcome in children with cerebral malaria	Children aged 0 to 10 years presenting with a Blantyre coma score of 4/5 or less and with a definitive diagnosis of cerebral malaria (defined in the paper) Study period January 1987 to June 1988	From hospital admission to one month after hospital discharge. 100% of recruited patients were	Death during the follow up period or neurological sequelae. Neurological sequelae reported were hemiparesis, inability to walk due to hypotonia, generalized spasticity of the limbs, cerebellar ataxia and persistent extrapyramidal tremor.	131 patients were included in the study. 20 patients died, and a further 12 had neurological sequelae. Of the parameters assessed profound coma scoring 0/5 on the Blantyre scale, hypoglycaemia, convulsions in hospital, and age were all significantly associated with death or neurological sequelae.	The study found an association with the Blantyre scale and outcome in cerebral malaria. The relationship is observed at the extreme end of the coma scale. It is unlikely that there is an association between outcome and the middle values on the Blantyre scale, which leads to the conclusion that the score of zero is more useful than the other scores on the scale. The transferability of the findings of outcome by using this scale to other more common causes of coma in the UK is undetermined.	Prognosis 1b
Simpson (27)	Prospective cohort study to assess the Adelaide Coma Scale with outcome in children with head injuries.	Children aged from birth to 71 months presenting with head injury. Study period not stated but data collection for two years.	1 month follow up in clinic, telephone interview or correspond-ence. A six month Griffiths score was performed in those with sequelae. 3 patients not traced (5%).	Outcomes were "good", "suspect" or "poor". These definitions are poorly defined in the text.	60 children were studied with 3 lost to follow up. The author state that outcome is related to the Adelaide coma score at 6 hours following admission, although no statistical analysis is performed on the figures.	Although this was a prospective study many children were not recruited with minor head injuries. There is no statistical analysis of the data so conclusions cannot be drawn on whether there really is a relationship between outcome and coma score.	Prognosis 4
Newton (28)	Prospective cohort study to assess the Adelaide coma scale and the	Children aged 7 months and older presenting with a Blantyre score of	Not stated	Death in hospital or severe neurological	240 children were included in the study. 38 patients died and 39 had severe neurological sequelae. The	There is limited information provided on the age of the children and length of follow up to	Prognosis 1b

	Blantyre coma scale at admission with outcome in children with cerebral malaria. A deterioration in the either scale was assessed against death within 6 hours of the second assessment.	less than 5/5 for more than one hour, with a diagnosis of severe malaria (defined in the paper) and who survived for more than 12 hours from admission. Study period 1898 to 1991		sequelae (defined as hemiparesis, cortical blindness, or quadra-paresis)	Blantyre coma scale (BCS) on admission demonstrated a statistically significant linear trend with poor outcome. The summated Adelaide coma scale (ACS) showed a statistically significant linear trend for poor outcome as well as for severe neurological sequelae. A deterioration in ACS was a better predictor of death within 6 hours than the BCS although no statistical analysis is provided.	determine severe neurological sequelae. During the statistical analysis of the ACS rather than maintaining the 14 points (i.e. 3, 4, 5, etc.) they were reduced to 6 bands of scores (i.e. 3-4, 5-6, 7-8, etc). This may have implications to how the score should be used in the field for outcome prediction. The transferability of the findings of outcome by using this scale to other more common causes of coma in the UK is undetermined.	
Awasthi (29)	Prospective cohort study to assess the modified Glasgow coma score (MGCS) in the first 24 hrs with mortality in children with acute intracranial infections in a referral hospital in India.	Children (aged 1 month to 12 years) with symptoms of acute intracranial infections (fever, headache or irritability, with or without vomiting and reduced consciousness or first seizure) admitted to a teaching hospital in India. Patients were excluded if they were found later not to have intracranial infection, those not having had a MGCS performed within 24 hrs and	Discharge from hospital.	Death before discharge from hospital.	256 children were identified, 26 were excluded (2 no infection; 2 no MGCS in 24hrs; 22 self-discharged). 42% had pyogenic meningitis; 37 % had TB meningitis; and 21% had meningo-encephalitis. Mortality rate was 19%. A MGCS in the first 24 hrs from admission <5 decreased the likelihood of survival by 0.52, while a MGCS of >10 increased the likelihood of survival by 5.52 times from pre-test odds. Having a MGCS between 5 and 10 did not significantly affect the post-test odds.	Study used MGCS in first 24 hrs not at admission.	Prognosis 1b

		those who discharged within one week against medical advice. Study period from Oct 1995 to Sept 1996.					
Chaturvedi (30)	Prospective cohort study to assess the modified Glasgow coma scale (MGCS) at admission with mortality in febrile children presenting to a hospital in India.	Children (ages not defined) presenting with fever and unconsciousness (not defined) to paediatric ward in Indian hospital. Study period Jan 1997 to December 1998	Discharge from hospital.	Death before discharge from hospital.	48 children were included in the two year period. The causes of fever and reduced conscious level were viral encephalitis (50%); cerebral malaria (12%); pyogenic meningitis (8%); TB meningitis (6%). Mortality was 30%. The mean MGCS at admission in survivors (>10) was higher than those who died (<5). A Receiver-operator curve could be constructed from the results as data are also presented for MGCS 5-7 and MGCS 8-10.	The MGCS can predict death in patients with a low score in this population with a high mortality rate 30%. There is no definition of unconsciousness to assess how the patients were included or excluded from the cohort.	Prognosis 4

Table 1.1.ii Papers included in the analysis of outcome associated with conscious level scores

1. Recognition of reduced conscious level in children

Clinical Questions:

(ii) In children, which conscious level scores can be reliably used to identify decreased conscious level?

Selection criteria
Criteria for choosing papers were drawn up before the search took place. Papers would be included if they specifically looked at the inter-observer and / or intra-observer reliability of performing a conscious level score in children. Studies involving both children and adults were only included if the results for children could be analysed separately

Search
A review of the Cochrane library, MEDLINE (1966-present), EMBASE (1980-present), CINAHL (1982-present), British Nursing Index (1985-present) and AMED (1985-present) was performed using the search terms below. A review of the references of the selected papers for further evidence was included in the search strategy and a hand search of five key journals in the field in the previous 12 months.

#	Search terms	No. of articles
1	exp COMA/ or exp GLASGOW COMA SCALE/	30002
2	exp confusion/ or exp coma/ or exp coma, post-head injury/	36808
3	exp Glasgow Coma Scale/	6412
4	1 or 2 or 3	42600
5	exp adolescent/ or exp child/ or exp child, preschool/ or exp infant/ or exp infant, newborn/ or exp adolescent, hospitalized/ or exp child, hospitalized/	2815604
6	4 and 5	8994
7	interobserver.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	9901
8	inter-observer.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	2547
9	intraobserver.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	4112
10	intra-observer.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1491
11	or/7-10	14022
12	variability.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	174299
13	reliability.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	130132
14	12 or 13	299319
15	11 and 14	7482
16	6 and 15	32
17	from 16 keep 1, 4, 10, 12-17, 32	10

Results
A total of 10 abstracts were reviewed from 32 titles. A total of 5 papers were selected for further review. The hand search of journals and references identified four papers for further review.
Six papers were included in the final analysis.

Papers not included in the final analysis are listed in table 1.2.i
Papers included in the final analysis are listed in table 1.2.ii

Reference	**Reason for exclusion**
McNarry (31)	AVPU and ACDU scales assessed for inter-observer reliability in children aged over 5 and adult. Data for children not analysed separately and number of children included not stated
Warren (32)	Data reported previously in Tatman 1997(33)
Seshia (34)	Data reported previously in Yager 1990(35)

Table 1.2.i Papers excluded from the analysis of reliability of conscious level scores

Study	Methods	Patients	Observers	Results	Comment	Evidence level
Newton (36)	Three measures of consciousness (the Adelaide coma scale, the Jacobi scale and the 0-IV scale) were assessed in children with reduced conscious level. Two observers were trained in assessment methods. They recorded the results of patient assessments within an hour of each other. They were blinded to the results of the assessment of the other observer. Disagreement rates, the kappa statistic and the weighted kappa were used to analyse the results.	19 children (aged 15 months to 6 years) admitted to a hospital in Kenya with impaired consciousness secondary to non-traumatic causes. None were ventilated. Study period 1991	2 experienced paediatric neurologists	The 0-IV scale had a “fair” level of agreement, which was better than the summed Adelaide or summed Jacobi scale.	Small number of observations makes firm conclusions about the interobserver reliability difficult. The fact that the patients were reviewed at different times may explain some of the variability.	This type of study does not fit into a simple scale of evidence. It has been assigned Diagnosis 2b.
Yager (35)	Six measures of consciousness (the Glasgow coma scale, the Adelaide coma scale, the Children’s coma scale, the Children’s Orthopedic and Medical Center scale, the Jacobi scale and the 0-IV scale) were assessed in children with reduced conscious level. Two observers were not trained in the assessment methods. They recorded the results of patient assessments within half an hour of each other. They were blinded to the results of the assessment of the other observer. Disagreement rates, the kappa statistic and the weighted kappa were used to analyse the results.	15 children (aged 2 months to 17 years) admitted to a hospital in Canada with impaired consciousness secondary to traumatic causes (n=4) and non-traumatic causes (n=11). All patients were intubated at the time of assessment. Study period September 1986 to December 1987.	2 experienced paediatric neurologists	The 0-IV scale and the Adelaide scale had the highest inter-observer reliability, but there was still a reasonable level of disagreement in the verbal component of the Adelaide scale.	All the patients were intubated making an assessment of verbal responses difficult as the scales being assessed do not account for intubation. The two observers had not been trained together in how to use the scales which may have increased the inter-observer variability.	This type of study does not fit into a simple scale of evidence. It has been assigned Diagnosis 2b.
Newton (28)	Two measures of consciousness (the Blantyre coma scale and the Adelaide coma scale) were assessed in children with reduced conscious level. Two or three observers were trained in	17 children (aged 7 months and older) admitted to a hospital in Kenya with impaired consciousness for	3 experienced paediatricians trained in the conscious level assessments used.	The summated Blantyre coma scale (BCS) had the highest inter-observer reliability but if the Adelaide	The lower the number of points on a scale the better the inter-observer reliability. Banding the ACS (i.e. bands	This type of study does not fit into a simple scale of evidence. It has been assigned Diagnosis 2b.

	assessment methods. They recorded the results of patient assessments within an hour of each other. They were blinded to the results of the assessment of the other observer. The proportion of agreement, disagreement rates, and the concordance rate were used to analyse the results.	more than one hour. All patients had severe malaria and none were intubated. 12 children had repeated conscious level assessments during the period of admission. Study period June 1990 to December 1990		coma scale (ACS) was banded into 6 bands (the same number as the BCS) then there was similar inter-observer reliability between the two scales.	3-4, 5-6, 7-8 etc) may be beneficial in improving the reliability of a scale which originally has 11 points, however information may be lost about changes in conscious level.	
Tatman (33)	Two measures of consciousness (the James adaptation of the Glasgow coma score and the grimace score incorporated into the GCS) were assessed in children with reduced conscious level. If the child was intubated the grimace score was recorded, if not intubated the verbal component of the JGCS was recorded. Two observers, the child's nurse and a trained investigator, recorded the results of patient assessments within 15 minutes of each other. They were blinded to the results of the assessment of the other observer. The kappa and weighted kappa were used to measure agreement between the observers.	104 sets of observations were made on 73 children (aged 1 day to 16 years) in a paediatric intensive care unit. Study period not stated.	41 observers were included. 38 nurses were paired with one of three trained investigators (paediatric neurologists or a paediatric intensivist).	There was moderate to good interobserver reliability for the components of the JGCS. The grimace score was more reliable than the verbal score of the JGCS. The motor component was the least reliable but still moderate agreement. Summation of the components of the JGCS was less reliable than the separate components.	The use of large numbers of observers is similar to real life experience and suggests that the JGCS is a moderately reliable tool across the range of experiences of staff. The grimace score was reliable for intubated children.	This type of study does not fit into a simple scale of evidence. It has been assigned Diagnosis 2b.
Barrett-Goode (37)	The interobserver reliability of the Adelaide coma score was assessed by filming children undergoing the assessment by an experienced nurse. Other nurses from the neurosurgical unit recorded the Adelaide coma score after watching the video	10 children (aged 11 months to 13 years) were filmed. All children were admitted on the paediatric neurosurgical unit at a UK hospital.	46 nurses of varying experience scored the video assessments.	There was only moderate agreement in any of the components of the Adelaide coma score. Summation of the ACS led to poor agreement of	Filming the child being assessed allowed a consistent assessment as the child's conscious level would be stable between observers. However, this	This type of study does not fit into a simple scale of evidence. It has been assigned Diagnosis 2b.

	assessment. They were blinded to the scores recorded by the other nurses. The proportion of agreement, the disagreement rate and the kappa statistic were used to measure agreement between the observers.	Study period not stated.		scoring.	method may make interpretation of the assessment difficult. There was disagreement amongst the nurses how to score children with delayed development.	
Reilly (38)	The interobserver reliability of the Adelaide coma score was assessed by filming children undergoing the assessment by an experienced doctor. Nurses and doctors from a children's hospital recorded the Adelaide coma score after watching the video assessment. They were blinded to the scores recorded by the other nurses. The disagreement rate was used to measure agreement between the observers.	15 children (aged 12 days to 13 years) were filmed. All children were admitted to an Australian hospital with a variety of medical or surgical conditions. A subset of the videos were used to determine if training of the nursing staff improved the interobserver reliability. Study period not stated.	Up to 23 observers were used to determine the disagreement rate.	There was an unacceptable level of disagreement in the fields of eye opening and best motor response. Even with training the best motor response continued to have an unacceptable level of disagreement between staff.	Filming the child being assessed allowed a consistent assessment as the child's conscious level would be stable between observers. However, this method may make interpretation of the assessment difficult.	This type of study does not fit into a simple scale of evidence. It has been assigned Diagnosis 2b.

Table 1.2.ii Papers included in the analysis of reliability of conscious level scores

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

Clinical Questions:

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

Selection criteria
Criteria for choosing papers were drawn up before the search took place. Papers would be included if they were validated clinical diagnostic decision rules or validation studies of guidelines for children with reduced conscious level or causes of reduced conscious level which had improved the outcome of children with reduced consciousness. Derivation studies of clinical diagnostic decision rules would not be included in the analysis. Studies involving both children and adults were only included if the results for children could be analysed separately.

Search
A review of the Cochrane library, MEDLINE (1966-present), EMBASE (1980-present), CINAHL (1982-present), British Nursing Index (1985-present) and AMED (1985-present) was performed using the search terms below. A review of the references of the selected papers for further evidence was included in the search strategy and a hand search of five key journals in the field in the previous 12 months.

Search filters

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	956588
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1465344
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1670568
4	1 or 2 or 3	2874741
5	"clinical decision rule".mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	157
6	"diagnostic decision".mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	729
7	“decision rule”.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	764
8	5 or 6 or 7	1446
9	4 and 8	203

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	956588
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1465344
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1670568
4	1 or 2 or 3	2874741
5	exp COMA/ or exp GLASGOW COMA SCALE/	30780
6	exp confusion/ or exp coma/ or exp coma, post-head injury/	37862
7	exp Glasgow Coma Scale/	6836
8	5 or 6 or 7	44035
9	guideline$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	223821
10	validat$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	168454
11	9 or 10	386657
12	4 and 8 and 11	354

Results
A total of 20 abstracts were reviewed from 478 titles. A total of 3 papers were selected for further review. The hand search of journals and references identified no other papers for further review. One paper was included in the final analysis.

Papers excluded from the final analysis are listed in table 2.1.i
Papers included in the final analysis are listed in table 2.1.ii

Reference	Reason for exclusion
Nigrovic (39)	Retrospective data collection used for validation set. The inclusion of several CSF findings and only a few clinical findings in the rule.
Oostenbrink (40)	Further up-dated validation of same clinical diagnostic decision rule is provided in the included paper Oostenbrink 2004

Table 2.1.i Papers excluded from the analysis observations to be performed to aid diagnosis of the cause of reduced conscious level in children

Study	Methods	Participants	Diagnostic dilemma	Blinded comparison	Gold standard tested	Results	Notes	Evidence level
Oostenbrink (41)	Validation study of a clinical diagnostic decision rule to determine the accuracy of a clinical test to detect bacterial meningitis in children.	Children (aged 1 month to 15 years) presenting to 4 centres in Holland with neck stiffness. Study period Nov 1999 to May 2001.	Did the children with neck stiffness have bacterial meningitis?	The clinical decision rule was applied to them along with the gold standard of lumbar puncture (or follow-up to one week if no LP or antibiotics – i.e. no clinical deterioration in one week without treatment ruled out the diagnosis bacterial meningitis).	Gold standard: CSF culture or no clinical deterioration without treatment within one week of presenting (if no lumbar puncture performed). Comparison test:Clinical decision rule previously derived. (The rule included the following clinical features: duration of main complaint; vomiting; meningeal irritation; cyanosis; petechiae or ecchymoses; disturbed consciousness; serum CRP).	Children with score of less than 8.5 never had bacterial meningitis, while children with a score of more than 20 always had bacterial meningitis. Sensitivity of the test set at 100% with a specificity of 60%.	The clinical signs and symptoms can be used for the diagnosis of bacterial meningitis. Bacterial meningitis is only one of several diagnoses which children who present with reduced conscious level have. During the study they reduced the cut-off value from 9.5 to 8.5 and did not re-validate prospectively. Therefore this is really a derivation study.	Diagnosis 2b

Table 2.1.ii Papers included in the analysis observations to be performed to aid diagnosis of the cause of reduced conscious level in children

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

Clinical Questions:

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

Selection criteria
Criteria for choosing papers were drawn up before the search took place. Papers would be included if they were validation studies of guidelines for children with reduced conscious level or causes of reduced conscious level which had improved the outcome of children with reduced consciousness. Studies involving both children and adults were only included if the results for children could be analysed separately

Search
A review of the Cochrane library, MEDLINE (1966-present), EMBASE (1980-present), CINAHL (1982-present), British Nursing Index (1985-present) and AMED (1985-present) was performed using the search terms below. A review of the references of the selected papers for further evidence was included in the search strategy and a hand search of five key journals in the field in the previous 12 months.

Search filter

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3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1670568
4	1 or 2 or 3	2874741
5	exp COMA/ or exp GLASGOW COMA SCALE/	30780
6	exp confusion/ or exp coma/ or exp coma, post-head injury/	37862
7	exp Glasgow Coma Scale/	6836
8	5 or 6 or 7	44035
9	guideline$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	223821
10	validat$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	168454
11	9 or 10	386657
12	4 and 8 and 11	354

Results
A total of 15 abstracts were reviewed from 354 titles. No papers were selected for further review. The hand search of journals and references identified no other papers for further review.

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

Clinical Questions:

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

Selection criteria
Criteria for choosing papers were drawn up before the search took place. Papers would be included if they were validating studies of guidelines for the management of hypoglycaemia in children, or if they were prospective cohort studies determining the prognosis of children who had hypoglycaemia for a known duration or case-control studies of children with poor outcome to determine if length of hypoglycaemia was a factor. Studies were excluded if they were retrospective cohort studies. Studies involving both children and adults were only included if the results for children could be analysed separately.

Search
A review of the Cochrane library, MEDLINE (1966-present), EMBASE (1980-present), CINAHL (1982-present), British Nursing Index (1985-present) and AMED (1985-present) was performed using the search terms below. A review of the references of the selected papers for further evidence was included in the search strategy and a hand search of five key journals in the field in the previous 12 months.

Search filters

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	936486
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1412651
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1611164
4	1 or 2 or 3	2784039
5	prognos$.mp. [mp=ab, hw, ti, sh, it, tn, ot, dm, mf, rw]	490966
6	risk$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1410795
7	group$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	2613071
8	cohort studies.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	60608
9	cohort$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	186555
10	or/5-9	4096978
11	hypoglycaemi$.mp. [mp=ab, hw, ti, sh, it, tn, ot, dm, mf, rw]	12039
12	hypoglycemi$.mp. [mp=ab, hw, ti, sh, it, tn, ot, dm, mf, rw]	57001
13	11 or 12	62118
14	4 and 10 and 13	2645

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	936486
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1412651
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1611164
4	1 or 2 or 3	2784039
5	guideline$.mp. [mp=ab, hw, ti, sh, it, tn, ot, dm, mf, rw]	155070
6	hypoglycaemi$.mp. [mp=ab, hw, ti, sh, it, tn, ot, dm, mf, rw]	12039
7	hypoglycemi$.mp. [mp=ab, hw, ti, sh, it, tn, ot, dm, mf, rw]	57001
8	6 or 7	62118
9	4 and 5 and 8	120

Results
A total of 37 abstracts were reviewed from 2765 titles. A total of 9 papers were selected for further review. The hand search of journals and references identified two other paper for further review. 9 papers were included in the final analysis.

Papers excluded from the final analysis are listed in table 3.1.i
Papers included in the final analysis are listed in table 3.1.ii

Reference	Reason for exclusion
Nordfelt (42)	Cost analysis rather than clinical outcome based study
Pildes (43)	Prospective study of preterm infants only, who are excluded in the scope of the guideline.

Table 3.1.i Papers excluded from the analysis of outcome associated with length of time of hypoglycaemia

Study	Methods	Participant definition	Length of follow-up	Outcomes	Results	Notes	Evidence level
Krishna (44)	Prospective cohort study to assess the relative risk of dying if the patient has malaria and is hypoglycaemic (<2.2mmol/l) at admission. Data taken from an RCT of treatments for malaria.	Children (aged 18 months to 12 years) with severe falciparum malaria presenting to a hospital in The Gambia. Study period between 1988 and 1989.	Duration of hospital admission. 100% of those recruited followed up.	Death during period of hospital admission.	115 children were enrolled in the study. 21 (18%) children died. Being hypoglycaemic (<2.2mmol/l) at admission was an independent indicator of outcome. The relative risk of death was 6.8 (95%CI 3.5-13.4)	Numbers in tables don't add up to what is written results. Primary analysis based on lactate levels not glucose levels. Analysis not limited to one treatment arm of RCT, therefore results may be affected by different treatments.	Prognosis 4
Bondi (45)	Prospective cohort study to assess the sequelae of cerebral malaria and determine any prognostic factors relating to poor outcome at admission.	Children (mean age 5.2 years – range not stated) with cerebral malaria presenting to a hospital in Nigeria. Study period March 1987 to October 1988.	Surviving children were followed up for a minimum of 12 months. 100% children followed up or included in the analysis.	Death or neurological sequelae (these ranged from hearing loss to cortical blindness to quadriplegia)	78 children were enrolled in the study. 16 children (20%) died and 11 (17.7%) had neurological sequelae. Being hypoglycaemic (<2.2mmol/l), having severe seizures and a longer period of unconsciousness was related to a poor outcome.	Treatments given differed in only 6 patients due to chloroquine-resistance. It is difficult to determine causation from this paper.	Prognosis 1b
Molyneux (26)	Prospective cohort study to assess the sequelae of cerebral malaria and determine any prognostic factors relating to poor outcome at admission	Children (aged 7 months to 10 years) with cerebral malaria presenting to a hospital in Malawi. Definition of suspected cerebral malaria clear and exclusions noted. Study period January 1987 to June 1988.	Surviving patients were reviewed one month after hospital discharge. 100% of children included in the analysis.	Death or neurological sequelae (including hemiparesis, ataxias and inability to walk) at one month after hospital discharge.	131 children were enrolled. 99 made a full recovery, 12 (9%) had neurological sequelae, and 20 (15%) died. Being hypoglycaemic (<2.2mmol/l) on admission was associated with a poor outcome. No p values stated.	Treatments were the same for all patients. This finding was part of a derivation set of prognostic indicators at admission for cerebral malaria. Part of the group are also included in Taylor (1988).	Prognosis 1b
Taylor (46)	Prospective cohort study to assess the prognostic value of	Children (aged 7 months to 8 years) with cerebral	Surviving patients were followed up to	Death or neurological sequelae	95 children were enrolled.19 were hypoglycaemic	Treatments were the same for both the hypoglycaemic and	Prognosis 1b

	admission hypoglycaemia on the sequelae of cerebral malaria.	malaria presenting to a hospital in Malawi. Definition of suspected cerebral malaria clear and exclusions noted. Study period December 1986 to June 1987.	hospital discharge. 100% of children followed up.	(including hemiparesis, ataxias and inability to walk) at hospital discharge.	(<2.2mmol/l). Being hypoglycaemic significantly increased the chance of death (RR = 9.3) or neurological sequelae (RR = 4). (Comparing the risk in the groups the p values were highly significant)	normoglycaemic groups.	
Haworth (47)	Prospective cohort study to assess the prognosis of infants born to diabetic mothers with relation to the infants' blood glucose level in the first 3 days of life.	Infants born to diabetic mothers in a US hospital between August 1967 and 1971.	Patients were assessed up to the age of 3 years. A standardised develop-mental examination was performed on each child without the knowledge of their blood glucose at birth.	Neurological sequelae including a) develop-mental retardation b) major CNS abnormality c) delay in one field of development alone.	37 infants were followed up. 25 infants were hypoglycaemic (<1.11 mmol/l if low birth weight infant; <1.67mmol/l if normal birthweight infant). Being hypoglycaemic was not related to a poor outcome.		Prognosis 1b
Koivisto (48)	Prospective cohort study of newborn infants treated for hypoglycaemia to assess outcome. The hypoglycaemic group was divided into "symptomatic – convulsive", "symptomatic – non-convulsive" and asymptomatic". A control group of non-hypoglycaemic patients was also followed.	Infants with hypoglycaemia (<1.67mmol/l) born between 1967 and 1969 in a hospital in Finland. Infants were excluded if they had co-existing asphyxia, respiratory distress syndrome, infectious disease, haemolytic disease, cerebral haemorrhage or congenital anomaly.	Patients were followed up to between 1 and 4 years of age. Examination included develop-mental assessment and visual acuity. % followed up not reported – but the figures suggest 100%.	Neurological development at 12-48 months (graded normal, doubtful, or pathological).	151 children were included in the hypoglycaemic groups (181 excluded) with 56 in the control group. 8 in the convulsive group, 77 in the symptomatic – non-convulsive group and 66 in the asymptomatic group. The main finding was a significant difference between the convulsive group and controls in terms of neurological outcome. If the symptomatic infants were grouped together	A number of infants included were preterm infants. These infants are excluded from the guideline in the scope.	Prognosis 1b

					then they also had a significantly worse outcome than the controls. The asymptomatic group had a wide range of hypoglycaemia but this did not affect the outcome.		
Fluge (49)	Prospective cohort study of hypoglycaemic infants categorised according to severity to assess prognosis. The categories were asymptomatic, symptomatic transient and secondary hypoglycaemia.	Infants with hypoglycaemia (level not defined). Study period 3 years 1967-1969.	Patients were followed up at about 3 years of age. 81% followed up.	Neurological sequelae including develop-mental delay, hearing, vision and behaviour. Children who died in the neonatal period or later were not included in the analysis.	20 patients died. of the 37 patients assessed a description of the abnormalities is provided but no statistical analysis of the findings.	No control group and no comparison within groups provided. 19% loss to follow up and 30% patient not included in analysis because they died.	Prognosis 4
Rovet (50)	Prospective cohort study of diabetic children and controls to assess cognitive function in relation to hypoglycaemic episodes and seizures.	Children with diabetes diagnosed in early childhood selected from previous studies of diabetic outcomes. Control group age and sex matched with subjects – they were not assessed longitudinally. Study period not reported.	Standard cognitive function measures assessed at 1, 3 and 7 years post diagnosis. % followed up not reported – but the figures suggest 100%.	Cognitive function including IQ, verbal IQ, vocabulary and digit span / sentence, achievement tests.	16 children were included in the cohort with a control matched for age, sex and socio-economic background. Those children who suffered hypoglycaemic (level not defined) seizures had a significant decline in verbal IQ compared to controls. No visuospatial skills were lost.	Very small numbers and highly selective cohort. No confirmation of hypoglycaemia definition.	Prognosis 4
Wysocki (51)	Prospective cohort study of children with type 1 diabetes being treated with 2 types of insulin therapy to	Children (aged 5-15) were enrolled in a trial of intensive vs. usual insulin therapy. Diaries of severe	Follow up was for 18 months following enrolment into the trial.	The Das-Naglieri cognitive assessment system measured in all	142 children were enrolled (72 into intensive regime). 111 episodes of severe hypoglycaemia (defined as coma or seizures with a low	No difference found in severe hypoglycaemic episodes between the two treatment groups and the treatment differed only in its	Prognosis 1b

	determine the affect of severe hypoglycaemia on cognitive outcomes. The study was undertaken in 2 centres in the US.	hypoglycaemic events were kept by all participants. Study period not reported.		participants at baseline, 9 months and 18 months after enrolment.	glucose or the need for intravenous glucagons/dextrose) were recorded. The population of patients who suffered severe hypoglycaemia did not have a statistically significant reduction in their cognitive function when compared to those who did not suffer hypoglycaemia.	intensity not in the insulin type. Therefore, the fact that the cohort was made up of two groups is unlikely to have had a major effect on outcome. No clear value of hypoglycaemia reported in the study.	

Table 3.1.ii Papers included in the analysis of outcome associated with length of time of hypoglycaemia.

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

Clinical Question:

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

Selection criteria
Criteria for choosing papers were drawn up before the search took place. Papers would be included if they were validated clinical diagnostic decision rules or validation studies of guidelines for children with reduced conscious level or causes of reduced conscious level which had improved the outcome of children with reduced consciousness. Derivation studies of clinical diagnostic decision rules would not be included in the analysis. Studies involving both children and adults were only included if the results for children could be analysed separately

Search
A review of the Cochrane library, MEDLINE (1966-present), EMBASE (1980-present), CINAHL (1982-present), British Nursing Index (1985-present) and AMED (1985-present) was performed using the search terms below. A review of the references of the selected papers for further evidence was included in the search strategy and a hand search of five key journals in the field in the previous 12 months.

Search filters

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	956588
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1465344
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1670568
4	1 or 2 or 3	2874741
5	"clinical decision rule".mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	157
6	"diagnostic decision".mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	729
7	“decision rule”.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	764
8	5 or 6 or 7	1446
9	4 and 8	203

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	956588
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1465344
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1670568
4	1 or 2 or 3	2874741
5	exp COMA/ or exp GLASGOW COMA SCALE/	30780
6	exp confusion/ or exp coma/ or exp coma, post-head injury/	37862
7	exp Glasgow Coma Scale/	6836
8	5 or 6 or 7	44035
9	guideline$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	223821
10	validat$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	168454
11	9 or 10	386657
12	4 and 8 and 11	354

Results
A total of 20 abstracts were reviewed from 557 titles. A total of 3 papers were selected for further review. The hand search of journals and references identified no other papers for further review. One paper was included in the final analysis.

Papers excluded from the final analysis are listed in table 4.1.i
Papers included in the final analysis are listed in table 4.1.ii

Reference	Reason for exclusion
Nigrovic (39)	Retrospective data collection used for validation set. The inclusion of several CSF findings and only a few clinical findings in the rule.
Oostenbrink (40)	Further up-dated validation of same clinical diagnostic decision rule is provided in the included paper Oostenbrink 2004

Table 4.1.i Papers excluded from the analysis of history features to aid diagnosis of the cause of reduced conscious level in children

Study	Methods	Participants	Diagnostic dilemma	Blinded comparison	Gold standard tested	Results	Notes	Evidence level
Oostenbrink (41)	Validation study of a clinical diagnostic decision rule to determine the accuracy of a clinical test to detect bacterial meningitis in children.	Children (aged 1 month to 15 years) presenting to 4 centres in Holland with neck stiffness. Study period Nov 1999 to May 2001.	Did the children with neck stiffness have bacterial meningitis?	The clinical decision rule was applied to them along with the gold standard of lumbar puncture (or follow-up to one week if no LP or antibiotics – i.e. no clinical deterioration in one week without treatment ruled out the diagnosis bacterial meningitis).	Gold standard: CSF culture or no clinical deterioration without treatment within one week of presenting (if no lumbar puncture performed). Comparison test:Clinical decision rule previously derived. (The rule included the following clinical features: duration of main complaint; vomiting; meningeal irritation; cyanosis; petechiae or ecchymoses; disturbed consciousness; serum CRP).	Children with score of less than 8.5 never had bacterial meningitis, while children with a score of more than 20 always had bacterial meningitis. Sensitivity of the test set at 100% with a specificity of 60%.	The clinical signs and symptoms can be used for the diagnosis of bacterial meningitis. Bacterial meningitis is only one of several diagnoses which children who present with reduced conscious level have. During the study they reduced the cut-off value from 9.5 to 8.5 and did not re-validate prospectively. Therefore this is really a derivation study.	Diagnosis 2b

Table 4.1.ii Papers included in the analysis of history features to aid diagnosis of the cause of reduced conscious level in children

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

Clinical Questions:

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

Selection criteria
Criteria for choosing papers were drawn up before the search took place. Papers would be included if they were prospective cohort studies of children with reduced conscious level of any cause reporting the rates of intubation or airway compromise, or prospective cohort studies indicating the reasons for intubation children with reduced conscious level. Studies were excluded if they were retrospective cohort studies or case-control studies (as the incidence could not be accurately calculated using these methods). Studies involving both children and adults were only included if the results for children could be analysed separately.

Search
A review of the Cochrane library, MEDLINE (1966-present), EMBASE (1980-present), CINAHL (1982-present), British Nursing Index (1985-present) and AMED (1985-present) was performed using the search terms below. A review of the references of the selected papers for further evidence was included in the search strategy and a hand search of five key journals in the field in the previous 12 months.

Search filters

#	Search terms	No. of articles
1	exp COMA/ or exp GLASGOW COMA SCALE/	30818
2	exp confusion/ or exp coma/ or exp coma, post-head injury/	37909
3	exp Glasgow Coma Scale/	6857
4	1 or 2 or 3	44100
5	exp infant, newborn/ or exp infant/ or exp infants/	957469
6	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1466907
7	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1672285
8	5 or 6 or 7	2877645
9	airway$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	149535
10	intubat$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	71583
11	obstruct$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	293903
12	or/9-11	448606
13	4 and 8 and 12	392

Results
A total of 13 abstracts were reviewed from 392 titles. No papers met the inclusion criteria. The hand search of journals and references identified no other papers for further review.

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

Clinical Questions:

(ii) What are the indications for intubation in children with a reduced conscious level?

Selection criteria
Criteria for choosing papers were drawn up before the search took place. Papers would be included if they were randomised controlled trails of intubating verses not intubating children for a specific cause, validating studies of guidelines for intubation of children, prospective cohort studies determining the prognosis of children who were intubated for any reason compared to those who were not, or case-control studies of children with poor outcome to determine if intubation was a factor. Studies were excluded if they were retrospective cohort studies. Studies involving both children and adults were only included if the results for children could be analysed separately.

Search
A review of the Cochrane library, MEDLINE (1966-present), EMBASE (1980-present), CINAHL (1982-present), British Nursing Index (1985-present) and AMED (1985-present) was performed using the search terms below. A review of the references of the selected papers for further evidence was included in the search strategy and a hand search of five key journals in the field in the previous 12 months.

Search filters

#	Search terms	No. of articles
1	RANDOMIZED CONTROLLED TRIAL.pt.	201483
2	CONTROLLED CLINICAL TRIAL.pt.	68371
3	randomized controlled trials.sh.	38427
4	random allocation.sh.	53364
5	double blind method.sh.	81867
6	single blind method.sh.	8937
7	or/1-6	344028
8	Animal.sh.	15946
9	human.sh.	4921945
10	8 not 9	12975
11	7 not 10	344028
12	clinical trial.pt.	420085
13	exp clinical trials/	551410
14	(clin$ adj25 trial$).ti,ab.	225257
15	((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.	164579
16	placebos.sh.	26883
17	placebo$.ti,ab.	182146
18	random$.ti,ab.	623271
19	research design.sh.	42203
20	or/12-19	1402157
21	20 not 10	1402018
22	21 not 11	1078561
23	comparative study.sh.	1257302
24	exp evaluation studies/	560809
25	follow up studies.sh.	300213
26	prospective studies.sh.	225920
27	(control$ or prospectiv$ or volunteer$).ti,ab.	2955681
28	or/23-27	4583898
29	28 not 10	4582466
30	29 not (11 or 22)	3813789
31	11 or 22 or 28	5237810
32	exp infant, newborn/ or exp infant/ or exp infants/	957603
33	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1467148
34	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1672638
35	newborn.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	640297

36	or/32-34 not 35	2337903
37	airway$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	149546
38	intubat$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	71592
39	37 or 38	207077
40	31 and 36 and 39	4352

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	956588
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1465344
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1670568
4	newborn.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	640297
5	1 or 2 or 3 not 4	2337903
6	airway$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	149546
7	intubat$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	71592
8	5 or 6	207077
9	guideline$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	223821
10	validat$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	168454
11	8 or 9	386657
12	4 and 7 and 11	764

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	956588
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1465344
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1670568
4	newborn.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	640297
5	1 or 2 or 3 not 3	2337903
6	airway$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	149546
7	intubat$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	71592
8	6 or 7	207077
9	prognos$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	505197
10	(first and episode).mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	16527
11	cohort.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	174683
12	or/9-11	679172
13	5 and 8 and 12	781

Results
A total of 47 abstracts were reviewed from 5897 titles. A total of 10 papers were selected for further review. The hand search of journals and references identified no other papers for further review.
6 papers were included in the final analysis.

Papers excluded from the final analysis are listed in table 5.2.i
Papers included in the final analysis are listed in table 5.2.ii(a) and 5.2.ii(b)

Reference	**Reason for exclusion**
Nieman (52)	Retrospective cohort study. Included as grey literature to focus the Delpi process in round 1.
Boswell (53)	Retrospective cohort study including both children and adults.
Ehrlich (54)	Retrospective cohort study.
Suominen (55)	Retrospective cohort study.

Table 5.2.i Papers excluded from the analysis of indications for intubation in children with a reduced conscious level

Study	Methods	Participants	Interventions	Allocation concealment	Outcomes	Results	Notes	Evidence level
Gausche (56)	RCT across California, USA comparing out-of-hospital intubation (ETI) with bag-valve-mask control (BVM) of the airway for children. Data was collected on indication for ETI, attempts at ETI (structured interview with paramedic after patient care transferred), condition at arrival in hospital (provided by emergency department physician), and outcome (hospital records).	Consecutive patients between March 1994 and Jan 1997 aged 12 or less requiring airway management for the following criteria: cardiopulmonary arrest; respiratory arrest; respiratory failure; unresponsive to pain; airway obstruction.	Children were allocated to ETI or BVM depending on the day on the week. No blinding of intervention was attempted.	No allocation concealment as randomisation was based on days of the week.	Death or neurological sequelae at discharge from hospital (based on a modified Pediatric cerebral performance category scale).	830 children enrolled with 23 protocol violations analysed as intention-to-treat and 10 lost to follow-up). Survival in the BVM group 123/404 (30%) was not statistically different from that in the ETI group 110/416 (26%). No difference was seen in the neurological outcome overall either. In some subgroups (respiratory arrest, foreign body aspiration and child abuse), children had a better outcome if not intubated.	The paramedics were being trained to intubate children at the start of the study and some of the skills at intubation would improve with time and therefore outcome of the intubated children may change with more skilled airway practitioners. Well designed study.	Therapy/Harm 1b

Table 5.2.ii(a) Papers included in the analysis of indications for intubation in children with a reduced conscious level (randomised controlled trials)

Study	Methods	Participant definition	Length of follow-up	Outcomes	Results	Notes	Evidence level
Sagarin (57)	Prospective cohort study to determine the methods of and adverse events associated with intubation of children in 11 emergency departments (ED) in US.	Children (aged less than 18 years) who required intubating in the ED. Study period from June 1996 to Sept 1997.	Immediately following intubation. No long term follow up was ascertained.	Data were collected on indication for intubation, method of intubation (with drugs or without drugs), number of attempts, experience of staff, complication rate (e.g. dental trauma, unrecognised oesophageal intubation), technical difficulties.	156 children were included in the study (159 patients out of 1288 records of adult and paediatric patients were discarded as no age was recorded, but the majority of these were likely to be adult patients). Of the 156 children 81% were intubated using neuromuscular blockade. The indications for intubation included coma (1%), epilepsy (16%), asthma (4%), pneumonia (2%), other medical(13%), head injury (24%), general management (15%). Failure to intubate occurred in 1% of cases. The majority of cases (78%) were intubated successfully on the first attempt using RSI. Complications occurred in 1% of cases.	This paper is cohort study about harm primarily, as well as an aetiological survey.	Harm 2b
Easley(58)	Prospective cohort study to determine the methods of and indications for intubation in children prior to admission to PICU in 2 US centres.	Children (aged <18 years) referred to PICU having been intubated prior to arrival at PICU. Children were excluded if the reason for intubating was for cardiovascular	Complications were assessed on admission to PICU. No long term assessment of outcome was made.	Data were collected on indication for intubation, method / drugs used for intubation and adequacy of intubation (e.g. attempts made, position of ETT,	250 children were identified who satisfied the criteria. The indication for intubation were recorded as respiratory failure (63%), depressed sensorium (23%), airway protection (13%), unspecified (1%). Large variations in drugs used to sedate/paralyse the	This study recommends improved training to reduce variation in practice and reduce inadequacies in intubation. This is primarily an aetiological study.	Aetiology 2b

		arrest. Study period over 18 months (dates not given)		securing ETT)	patients were used depending on the setting of the intubation (ED vs children's hospital vs out-of-hospital). Major inadequacies in intubation were detected in 37% of children being intubated.		
Oglesby (59)	Prospective cohort study to determine the current practice of intubation in the ED and the indications for intubation.	Children (aged < 13 years) requiring intubation in the ED of 7 Scottish hospitals (excluding children's hospitals). Study period from Jan 1999 to Jan 2001.	Immediately following intubation. No long term follow up was ascertained.	Data were collected on indication for intubation, clinical condition of patient prior to intubation, who performed the intubation and number of attempts.	44 children were eligible for study over the 2 year period (median age = 4 years). 57% were intubated because of trauma (majority head injuries); 22% were intubated because of airway compromise or respiratory failure; 2% because of shock; and 18% because of cardiac arrest. 68% were intubated with RSI. 80% were intubated on first attempt. Complications were seen in those requiring multiple attempts.	Primarily an aetiological study as well as an observational study of current practice.	Aetiology 2b
Marvez-Valls(60)	Prospective cohort study to determine the success and complication rate in intubation using a protocol for RSI in children in a level 1 trauma centre in US.	Children (aged <18 years) who required intubation in the ED. Study period Feb 1996 to Feb 2000.	Immediately following intubation attempts.	Data were collected on reason for intubation, adherence to the protocol and any protocol violations, complications of intubation including number of	83 patients were eligible for the study. Indications for intubation were: trauma 86%; smoke inhalation (5%); overdose (4%); seizure (1%); decreased level of consciousness (1%); near drowning (1%). Intubations were successful in 78% of cases on first attempt. 98% of patients were	This is primarily data from an audit of the process of intubation, but does provide aetiological data as well.	Aetiology 2b

				attempts.	intubated within 2 attempts. Minor deviations from protocol were recorded in 46% of cases with no increase in complication rates found.		
Sirbaugh (61)	Prospective cohort study in city in US of paediatric out-of-hospital cardiac arrests to determine the incidence, prognosis and any risk factors associated with outcome following paediatric cardiac arrest.	Children (aged <18 years) treated by paramedics for apnoeic and pulseless conditions. Study period Jan 1992 to June 1995.	Survivors were followed up to 6 months post hospital discharge.	Death or neurological sequelae according to the Pediatric cerebral performance category scale. Data were also collected about cause of arrest and resuscitation provided along with demographic details.	300 patients were identified of which 45 were excluded due to signs of rigor mortis and therefore no resuscitation attempts were made. Of 255 cases, 33 (13%) had a return of circulation at scene of arrest. Of these 6 (2.3%) survived, with only 1 without any neurological deficit (0.4%). 76% of non-injury related arrests occurred in the first 4 years of life. The only resuscitation treatment which was associated with on scene return of spontaneous circulation was intubation.	This study provides details of epidemiology of cardiac arrests outside hospital and the rates of successful resuscitation. The only improved chance of regaining a circulation was intubation on scene.	Prognosis 1b

Table 5.2.ii(b) Papers included in the analysis of indications for intubation in children with a reduced conscious level (prospective cohort studies)

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

Clinical Questions:

(i) In children with a reduced conscious level, what is the incidence of respiratory depression or apnoea?

Selection criteria
Criteria for choosing papers were drawn up before the search took place. Papers would be included if they were prospective cohort studies of children with reduced conscious level of any cause reporting the rates of respiratory depression or apnoea or prospective cohort studies indicating the reasons for intubation children with reduced conscious level. Studies were excluded if they were retrospective cohort studies or case-control studies (as the incidence could not be accurately calculated using these methods). Studies involving both children and adults were only included if the results for children could be analysed separately.

Search
A review of the Cochrane library, MEDLINE (1966-present), EMBASE (1980-present), CINAHL (1982-present), British Nursing Index (1985-present) and AMED (1985-present) was performed using the search terms below. A review of the references of the selected papers for further evidence was included in the search strategy and a hand search of five key journals in the field in the previous 12 months.

Search filters

#	Search terms	No. of articles
1	exp COMA/ or exp GLASGOW COMA SCALE/	30818
2	exp confusion/ or exp coma/ or exp coma, post-head injury/	37909
3	exp Glasgow Coma Scale/	6857
4	1 or 2 or 3	44100
5	exp infant, newborn/ or exp infant/ or exp infants/	957469
6	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1466907
7	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1672285
8	5 or 6 or 7	2877645
9	respirat$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	651874
10	rate$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	2080695
11	9 and 10	108069
12	apnoe$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	7544
13	apne$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	39458
14	12 or 13	41458
15	14 or 11	145745
16	4 and 8 and 15	287

Results
A total of 8 abstracts were reviewed from 287 titles. None of the abstracts met the inclusion criteria. The hand search of journals and references identified no other papers for further review.

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

Clinical Questions:

(ii) What are the indications for additional oxygen therapy in children with a reduced conscious level?

Selection criteria
Criteria for choosing papers were drawn up before the search took place. Papers would be included if they were randomised controlled trails of additional oxygen therapy verses no additional oxygen therapy for children at various levels of oxygen saturation, validating studies of guidelines for additional oxygen therapy for children, prospective cohort studies determining the prognosis of children who were provided with additional oxygen therapy for any reason compared to those who were not, or case-control studies of children with poor outcome to determine if additional oxygen therapy was a factor. Studies were excluded if they were retrospective cohort studies. Studies involving both children and adults were only included if the results for children could be analysed separately.

Search
A review of the Cochrane library, MEDLINE (1966-present), EMBASE (1980-present), CINAHL (1982-present), British Nursing Index (1985-present) and AMED (1985-present) was performed using the search terms below. A review of the references of the selected papers for further evidence was included in the search strategy and a hand search of five key journals in the field in the previous 12 months.

Search filters

#	Search terms	No. of articles
1	RANDOMIZED CONTROLLED TRIAL.pt.	201483
2	CONTROLLED CLINICAL TRIAL.pt.	68371
3	randomized controlled trials.sh.	38427
4	random allocation.sh.	53364
5	double blind method.sh.	81867
6	single blind method.sh.	8937
7	or/1-6	344028
8	Animal.sh.	15946
9	human.sh.	4921945
10	8 not 9	12975
11	7 not 10	344028
12	clinical trial.pt.	420085
13	exp clinical trials/	551410
14	(clin$ adj25 trial$).ti,ab.	225257
15	((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.	164579
16	placebos.sh.	26883
17	placebo$.ti,ab.	182146
18	random$.ti,ab.	623271
19	research design.sh.	42203
20	or/12-19	1402157
21	20 not 10	1402018
22	21 not 11	1078561
23	comparative study.sh.	1257302
24	exp evaluation studies/	560809
25	follow up studies.sh.	300213
26	prospective studies.sh.	225920
27	(control$ or prospectiv$ or volunteer$).ti,ab.	2955681
28	or/23-27	4583898
29	28 not 10	4582466
30	29 not (11 or 22)	3813789
31	11 or 22 or 28	5237810
32	exp infant, newborn/ or exp infant/ or exp infants/	957603
33	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1467148

34	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1672638
35	newborn.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	640297
36	or/32-34 not 35	2337903
37	oxygen$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	526057
38	hypoxi$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	102448
39	saturat$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	131969
40	(37 or 38) and 39	34119
41	31 and 36 and 40	1804

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	956588
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1465344
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1670568
4	newborn.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	640297
5	1 or 2 or 3 not 4	2337903
6	oxygen$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	526057
7	hypoxi$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	102448
8	saturat$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	131969
9	(6 or 7) and 8	34119
10	guideline$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	223821
11	validat$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	168454
12	8 or 9	386657
13	4 and 9 and 12	131

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	956588
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1465344
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1670568
4	newborn.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	640297
5	1 or 2 or 3 not 3	2337903
6	oxygen$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	526057
7	hypoxi$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	102448
8	saturat$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	131969
9	(6 or 7) and 8	34119
9	prognos$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	505197
10	(first and episode).mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	16527
11	cohort.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	174683
12	or/9-11	679172
13	5 and 8 and 12	246

Results

A total of 47 abstracts were reviewed from 2181 titles. A total of 20 papers were selected for further review. The hand search of journals and references identified 4 other papers for further review. 12 papers were included in the final analysis.

Papers not included in the final analysis are listed in table 6.2.i
Papers included in the final analysis are listed in table 6.2.ii(a), 6.2.ii(b) and 6.2.ii(c)

Reference	**Reason for exclusion**
Rubin(62)	Foreign language
Ortiz(63)	Foreign language
Mulholland(64)	Study aim to determine signs of hypoxaemia not the outcome
Wazeka(65)	Guideline validation study for asthma guideline including oxygen therapy. The oxygen therapy guidance within the guideline is not prescriptive and is down to the “clinical assessment”. This evidence cannot be included as evidence of improved outcome if oxygen is used as it is only one factor in a guideline and not clear what the guidance on oxygen was.
Huoicho(66)	Population data for oxygen saturation levels in children living at high altitude

Hunt(67)	Population data for oxygen saturation levels in healthy infants in first 6 months of life
Hunt(68)	Data included in previous paper
Homi(69)	Population data for oxygen saturation levels in children with sickle cell disease
Poets(70)	Population data for oxygen saturation levels in healthy children
Levene(71)	Population data for oxygen saturation levels in healthy infants in different positions (prone or supine)
Mok(72)	Population data for oxygen saturation levels in healthy infants in first 6 months of life
Rackoff(73)	Population data for oxygen saturation levels in children with sickle cell disease and determining the oxygen-haemoglobin dissociation curve in this population.

Table 6.2.i Papers excluded from the analysis of indications for additional oxygen therapy in children with a reduced conscious level

Study	Method	Inclusion criteria	Search	Evidence appraisal	Summarizing evidence	Results	Notes	Evidence level
Bass(74)	Systematic review to determine the prognosis of children exposed to hypoxia	Peer-reviewed published papers reporting cognitive outcomes of children <15 years old with clinical conditions in which exposure to either chronic or intermittent hypoxia was likely. The review excluded papers relating to extremely preterm infants.	Medline 1966-2000 using 2 reviewers.	Critical appraisal check list was standardised for reviewers. A measure of the strength of the study design was incorporated into the analysis.	Evidence was combined into groups of conditions (congenital heart disease [CHD], sleep behaviour disorders [SBD], asthma, chronic ventilatory impairment and respiratory instability in infants). It was also combined into levels of hypoxia by oxygen saturation stratification.	55 papers reviewed, of which 42 were reports into CHD and SBD (which were the only two groups of conditions which it was thought there was enough evidence to state causation / association). 19 of these studies had specific SaO2 data. For CHD and SBD there was a clear association between poor cognition and development and exposure to hypoxia. For the other conditions causation could not be confirmed.	Large heterogeneity between studies many of them of questionable design (e.g. case series, or using historical cohorts). The systematic review is unable to quantify the effect of different saturations due to the heterogeneity of studies.	Prognosis 2a(-)

Table 6.2.ii(a) Papers included in the analysis of indications for additional oxygen therapy in children with a reduced conscious level (Systematic Reviews)

Study	Methods	Participant definition	Length of follow-up	Outcomes	Results	Notes	Evidence level
Usen(75)	Prospective cohort study to determine clinical indicators of hypoxaemia and to determine the prognosis of hypoxic children with lower respiratory tract infections (LRTI)	Children (aged >2 months to two years) admitted with pneumonia (defined in the paper) to 2 hospitals in Gambia. Clinical signs were recorded and oxygen saturation measured. Children with Down's syndrome and signs of structural heart lesions were excluded. Study period from March 1993 to December 1995.	To hospital discharge.	Death before hospital discharge, and the derivation of a clinical diagnostic decision rule for hypoxaemia.	1114 children with LRTI were enrolled in the study and 42 were excluded. Of 1072 children 63 (5.9%) had hypoxaemia (oxygen saturations <90% in air). 8 (12.7%) of the hypoxaemic children died compared with 36 (3.4%) of the non-hypoxaemic children (relative risk 4.6; CI 2.2-9.6; p<0.00001).	Increased risk of death in children with hypoxaemia secondary to LRTI. Difficult to know how to relate to population with reduced conscious level and to children in the UK who have different confounding factors.	Prognosis 1b
Smith(76)	Prospective cohort study of children with lower respiratory tract infections (LRTI) to assess the prognosis of children with and without hypoxia (saturations <92% in air).	Children (aged >9 months to 5 years) admitted to a children's ward in Zambia with a severe pneumonia according to WHO guidelines. Study period Oct 1994 to June 1995.	To hospital discharge.	Death before hospital discharge.	167 children enrolled with 9 exclusions (4 had wheeze and 5 left before assessment). Of 158 children, 55 were hypoxaemic. 10 hypoxaemic children died and 13 children without hypoxaemia died (RR 1.44, CI 0.67 – 3.07)	Not a statistically significant result but could still be a clinically significant finding if a larger population had been enrolled. Difficult to know how to relate to population with reduced conscious level and to children in the UK who have different confounding factors.	Prognosis 1b
Keahey (77)	Prospective cohort study of children with asthma to assess the outcome of being hypoxaemic at	Children (aged 2-17 years) attending 48 emergency departments in north America.	To hospital admission.	Hospital admission rates.	1600 eligible for inclusion, 1184 enrolled. 1040 had documented saturations in room air. The risk of admission	Risk factor directly affects likelihood of being admitted to hospital. No blinding of oxygen saturation to clinicians making	Prognosis 4

	presentation to hospital.	Study period October 1997 to December 1997 and March 1998 to April 1998.			was 73% if oxygen saturations were <89% compared to 8% if saturations were 100%.	decisions about admission. Therefore outcome measure influenced by knowledge of prognostic indicator (i.e. a self-fulfilling prophecy)	
Belesis (78)	Case-control study to assess the risk factors associated with admission to paediatric intensive care unit (PICU) in children with severe asthma.	Cases: children (aged 1-16 years) admitted to PICU with severe asthma. Controls: children admitted to general ward with acute asthma. Study period from Feb 2000 to June 2001.	Retrospective review of risk factors.	Hypoxaemia as a risk factor for admission to PICU	70 cases and 71 controls. Mean oxygen saturations for PICU cases at admission was 90% compared with 94% for controls.	Risk factor directly affects likelihood of being admitted to PICU. No blinding of oxygen saturation to clinicians making decisions about admission. Therefore outcome measure influenced by knowledge of prognostic indicator (i.e. a self-fulfilling prophecy). Oxygen saturations will be non-parametric data which has been analysed using parametric tests.	Prognosis 4
Mehta(79)	Prospective cohort study to assess the value of oxygen saturations in predicting the need for regular bronchodilator therapy.	Children (aged >12 months) with a diagnosis of asthma, attending an emergency department in the USA. Exclusions included children with neurological disease or cardio-pulmonary disease. Study period not stated.	Main outcome followed up for just over 24 hours. Secondary outcomes were followed up at 1 week with telephone interviews.	The need for frequent bronchodilator therapy.	278 children enrolled with 273 having their oxygen saturations recorded in air. 107 were discharged within 4 hours of corticosteroids. 166 were treated for >4 hours. Mean baseline saturations were 95.5% in the <4 hours of treatment group vs. 93.3% in the >4 hours treatment group ($p<0.001$)	Knowledge of the risk factor directly affects likelihood of further treatment. No blinding of oxygen saturation to clinicians making decisions about further treatment. Therefore outcome measure influenced by knowledge of prognostic indicator (i.e. a self-fulfilling prophecy). Oxygen saturations will	Prognosis 4

						be non-parametric data which has been analysed using parametric tests.	
Geelhoed (80)	Prospective cohort study to assess the value of oxygen saturations and hypoxaemia (oxygen saturations <92%) in predicting the need for admission to hospital.	Children (aged 1-15 years) diagnosed with asthma by a physician who presented to the emergency department for children in Australia. Excluded were those children already receiving oxygen on arrival to the emergency department.	To hospital discharge.	Need for admission; the need for intravenous beta2agonists or steroids.	280 children enrolled. Mean saturations were lower in those with a worse outcome defined as admission to hospital and subsequent need for intravenous asthma therapy.	Knowledge of the risk factor directly affects likelihood of hospital admission and further treatment. No blinding of oxygen saturation to clinicians making decisions about further treatment. Therefore outcome measure influenced by knowledge of prognostic indicator (i.e. a self-fulfilling prophecy). Oxygen saturations will be non-parametric data which has been analysed using parametric tests.	Prognosis 4
Hilliard (81)	Prospective cohort study of children admitted to hospital with asthma across UK to audit asthma guidelines and assess oxygen saturation as a predictor of prolonged admission.	Children (aged 1-14 years) admitted to 16 UK hospitals with asthma. Study period Feb 1995 to Jan 1996. Six centres were excluded from the data analysis as they had not collected the data prospectively on the proformas.	To hospital discharge and re-admission within 2 weeks of discharge.	Length of stay in hospital.	1578 admissions involving 1352 children were recorded. Children with initial saturations <92% were admitted for longer (median 36 hours) compared to those with saturations >92% (26 hours) ($p<0.001$).	Knowledge of the risk factor may directly affect likelihood of longer hospital stay. No blinding of oxygen saturation to clinicians making decisions about admission. Therefore outcome measure influenced by knowledge of prognostic indicator (i.e. a self-fulfilling prophecy)	Prognosis 4
Yama-moto (82)	Prospective cohort study of children	Children (aged 5 - 20 years)	To hospital admission or	Hospital admission and	785 children eligible with 653 children	Knowledge of the risk factor may directly	Prognosis 4

	with wheeze to assess the prognosis of those with and without hypoxaemia	attending emergency department in US (Hawaii) with wheeze for any reason. Study period Nov 1990 to Sept 1991.	discharge from the ED.	need for prolonged bronchodilator therapy.	having a peak flow recorded (another prognostic factor being measured in the study). A further 19 patients were excluded because of inadequate data. There were more children admitted and given prolonged broncholdilator treatment if they had lower oxygen saturations at presentation. No definition of hypoxaemia was provided but from raw data using a cut off oxygen saturation of 90% the relative risk of admission was 2.37 (CI 1.9-2.9).	affect likelihood of longer hospital stay. No blinding of oxygen saturation to clinicians making decisions about admission. Therefore outcome measure influenced by knowledge of prognostic indicator (i.e. a self-fulfilling prophecy). Data in tables does not add up. The denominator is 789 when in the text it should be 632. The RR calculated is therefore flawed as well.	

Table 6.2.ii(b) Papers included in the analysis of indications for additional oxygen therapy in children with a reduced conscious level (Prognosis studies)

Study	Methods	Participants	Diagnostic dilemma	Blinded comparison	Gold standard tested	Results	Notes	Evidence level
Betancourt(83)	Diagnostic test study to determine if oxygen saturations are related to other measures of disease severity in children with cystic fibrosis.	100 Children (aged 5-6 years) attending outpatient clinic in UK children's hospital with cystic fibrosis. Study period not stated.	Did the children have infection or a poor FEV1 or a poor Shwachman-Kulczycki score, based on their oxygen saturation result.	No as clinicians probably had a fair idea of what the gold standard results would be and may have interpreted the oxygen saturations differently with that knowledge	Candidate test of oxygen saturations. Gold standards: a) Shwachman-Kulczycki score; b) cough swab result (infection or no infection); c) FEV1	No specificity or sensitivity discussed only correlations. There was correlation between lower oxygen saturations and the gold standards of prognosis	This study is difficult to use as the results are not presented in a way which assesses oxygen saturations as a reliable indicator of prognosis.	Diagnosis 4

				and vice versa.		performed.	Poorly defined aim of study and no blinding of interpretive tests.	
Blaisdell(84)	Diagnostic test study to determine the accuracy of pulse oximetry compared to arterial oxygen saturations in children with sickle cell disease.	21 children (aged 3-18 years) with sickle cell disease attending the outpatient department in US hospital. Study period March 1992 to April 1998.	Did the children with low pulse oximetry have low oxygen saturations? pulse oximetry of 93% relate to an arterial oxygen saturations result of 70mmHg in a population of normal individuals. 70mmHg is defined as hypoxaemia.	No, as the pulse oximetry result was known to the person interpreting the oxygen saturation result. However, there is very no subjective interpretation in the gold standard test and very little in the candidate test.	Candidate test: pulse oximetry. Gold standard: arterial oxygen saturations	Pulse oximetry of <93% was able to predict arterial oxygen saturations <70mmHg in the population of sickle cell children with a specificity of 67%. As there was only one child who had an arterial oxygen saturation <70mmHg the sensitivity is not meaningful.	Children with sickle cell disease may have more falsely low reading pulse oximetry than populations with normal haemoglobins.	Diagnosis 1b
Sole(85)	Diagnostic study to determine the ability of pulse oximetry to predict a poor asthma severity score	174 children (aged 2 months to 14 years) seen in both the emergency department and outpatient clinic of a hospital in Brazil with wheezing.	Did the children with a low pulse oximetry also have a high asthma severity score defined as 3 or more on a described clinical scale.	No, the person assessing the clinical severity score knew the oxygen saturations.	Candidate test: pulse oximetry. Gold standard test: clinical severity score	Pulse oximetry <=92% had a specificity of 92.8% but a sensitivity of only 44.5% for detecting a severity score >3.	No blinding of two tests therefore considerable bias may have entered into the subjective clinical assessment. Also, the results for the severity score are presented as >3 and <3. It is unclear about what happened	Diagnosis 4

							to children with a score = 3.	

Table 6.2.ii(a) Papers included in the analysis of indications for additional oxygen therapy in children with a reduced conscious level (Diagnosis studies)

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

Clinical Questions:

(i) What are the non-traumatic causes of reduced conscious level in children?

Selection criteria
Criteria for choosing papers were drawn up before the search took place. Papers would be included if they were prospective cohort studies or population based studies reporting the differential diagnosis of children with reduced conscious level or coma. Studies of trauma were excluded from this search as they were searched for separately (see Clinical Question 7ii). Studies from outside the developed world were only included if the patient demographics were similar to the population in the UK. Studies were excluded if they were retrospective studies as a complete data set could not be assured. Studies involving both children and adults were only included if the results for children could be analysed separately.

Search
A review of the Cochrane library, MEDLINE (1966-present), EMBASE (1980-present), CINAHL (1982-present), British Nursing Index (1985-present) and AMED (1985-present) was performed using the search terms below. A review of the references of the selected papers for further evidence was included in the search strategy and a hand search of five key journals in the field in the previous 12 months.

Search filters

#	Search terms	No. of articles
1	exp COMA/ or exp GLASGOW COMA SCALE/	28738
2	exp confusion/ or exp coma/ or exp coma, post-head injury/	35256
3	exp Glasgow Coma Scale/	5840
4	1 or 2 or 3	40532
5	exp adolescent/ or exp child/ or exp child, preschool/ or exp infant/ or exp infant, newborn/ or exp adolescent, hospitalized/ or exp child, hospitalized/	2726715
6	4 and 5	8629
7	exp diagnosis/ or exp diagnosis, differential/	4884436
8	cause.mp.	558507
9	(aetiology or etiology).mp. [mp=ab, hw, ti, sh, it, tn, ot, dm, mf, rw]	334586
10	7 or 8 or 9	5490242
11	exp epidemiologic studies/ or exp case-control studies/ or exp retrospective studies/ or exp cohort studies/ or exp longitudinal studies/ or exp follow-up studies/ or exp prospective studies/ or exp control groups/	1427086
12	10 and 11	602098
13	6 and 12	1354

Results
A total of 21 abstracts were reviewed from 1354 titles. A total of 3 papers were selected for further review. The hand search of journals and references identified 1 other paper for further review.
1 paper was included in the final analysis.

Papers excluded from the final analysis are listed in table 7.1.i
Papers included in the final analysis are listed in table 7.1.ii

Reference	**Reason for exclusion**
Ogunmekan(86)	Hospital-based study of non-traumatic coma in Nigeria. Retrospective data collection and population differences exclude paper from analysis.
Lohr(87)	Foreign language. Population data collected from admissions to a paediatric intensive care unit.
Sofiah(88)	Hospital-based prospective study of aetiology of non-traumatic coma from Malaysia. Population differences from UK excluded paper from analysis.

Table 7.1.i Papers excluded from the analysis of the causes of reduced conscious level in children

Study	Methods	Participant definition	Length of follow-up	Outcomes	Results	Notes	Evidence level
Wong(89)	Prospective population-based study to determine the incidence and aetiology of non-traumatic coma in children.	Children (aged 1 month to 15 years) admitted to any hospital within a region of the UK with a decreased conscious level (GCS<12 for 6 hours), and children who died within the same region not reaching hospital. Children with trauma were excluded. Study period from July 1994 to December 1995.	For outcome data 12 months. 93% follow up was achieved for survivors.	Aetiology was determined by a review of the medical notes and at follow up, or the post mortem data. Neurological outcome was assessed on a 6 point scale, with validated behavioural scales as well.	Incidence: non-traumatic coma (defined as GCS <12 for >6 hours) occurs in 31 per 100000 children per year. This incidence is higher in the under 1 year population (160/100000/year). The mortality rate in this population was 46% in the first year after the episode. The causes of non-traumatic coma in this population were divided into categories of: Infection (38%); intoxication (10%); epilepsy (9%); complications of congenital abnormalities (8%); accidents (6%); metabolic causes (6%); unknown (14%); and others (e.g. asthma, complications of malignant disease, non-traumatic intracranial haemorrhage) accounted for <2% each.	The definition of coma is not universally accepted and the length of time GCS <12 makes this population less inclusive than the guidelines. However, this was a very sound epidemiological study.	Differential diagnosis 1b

Table 7.1.ii Paper included in the analysis of the causes of reduced conscious level in children

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

Clinical Questions:

(ii) How frequently does trauma cause a reduced conscious level in children?

Selection criteria
Criteria for choosing papers were drawn up before the search took place. Papers would be included if they were prospective cohort studies or population based studies reporting the incidence of reduced conscious level or coma after trauma or head injury. Studies were excluded if they were retrospective studies as a complete data set could not be assured. Studies involving both children and adults were only included if the results for children could be analysed separately.

Search
A review of the Cochrane library, MEDLINE (1966-present), EMBASE (1980-present), CINAHL (1982-present), British Nursing Index (1985-present) and AMED (1985-present) was performed using the search terms below. A review of the references of the selected papers for further evidence was included in the search strategy and a hand search of five key journals in the field in the previous 12 months.

Search filters

#	Search terms	No. of articles
1	exp COMA/ or exp GLASGOW COMA SCALE/	30949
2	exp confusion/ or exp coma/ or exp coma, post-head injury/	38072
3	exp Glasgow Coma Scale/	6920
4	1 or 2 or 3	44314
5	exp adolescent/ or exp child/ or exp child, preschool/ or exp infant/ or exp infant, newborn/ or exp adolescent, hospitalized/ or exp child, hospitalized4 and 5/	2874179
6	exp diagnosis/ or exp diagnosis, differential/	9293
7	cause.mp.	5345472
8	(aetiology or etiology).mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	636200
9	7 or 8 or 9	347066
10	exp epidemiologic studies/ or exp case-control studies/ or exp retrospective studies/ or exp cohort	6007551
11	studies/ or exp longitudinal studies/ or exp follow-up studies/ or exp prospective studies/ or exp control groups/	1615326
12	10 and 11	708208
13	6 and 12	1615
14	craniocerebral trauma/ or brain injuries/ or coma, post-head injury/ or head injuries, closed/ or head injuries, penetrating/ or intracranial hemorrhage, traumatic/ or skull fractures/	125154
15	exp head injury/ or exp brain injury/	83020
16	exp head/	171329
17	exp injuries/	987715
18	16 and 17	15106
19	exp HEAD INJURIES/	162119
20	exp head injuries/ or exp brain injuries/	162119
21	or/14-20	1164972
22	13 and 21	1150

Results
A total of 39 abstracts were reviewed from 1150 titles. A total of 13 papers were selected for further review. The hand search of journals and references identified 1 other paper for further review.
1 paper was included in the final analysis.

Papers excluded from the final analysis are listed in table 7.2.i
Papers included in the final analysis are listed in table 7.2.ii

Reference	Reason for exclusion
Dunning(90)	Meta-analysis of variables predicting poor outcome in head trauma in children. No mention of incidence of low GCS.
Fay(91)	Outcome study not incidence study.
Adelson(92)	Outcome study not incidence study.
Johnstone(93)	Retrospective data collection.
Mahoney(94)	Outcome study not incidence.
Munoz-Sanchez(95)	Outcome study not incidence.
Andronikou(96)	Outcome study not incidence.
Haydel(97)	Outcome study not incidence.
Chiaretti(98)	Outcome study not incidence.
Ratan(99)	Outcome study not incidence.
Keenan(100)	Outcome study not incidence.
Thakker(101)	Outcome study not incidence.
Massagli(102)	Outcome study not incidence.

Table 7.2.i Papers excluded from the analysis of the how frequently trauma causes a reduced conscious level in children

Study	Methods	Participant definition	Length of follow-up	Outcomes	Results	Notes	Evidence level
Wang (103)	Prospective population-based study to determine the outcome of children with a mild alteration in conscious level following trauma and to determine the incidence of different GCS scores after paediatric trauma.	Children (aged <15 years) transferred to any emergency department in the Los Angeles area by paramedic services after suffering a traumatic insult. Stab injuries or gunshot wounds were excluded. Study period not stated but data collected over 12 months.	To hospital discharge. 69% followed up (due to incomplete data)	Incidence of varying GCS scores in the field after trauma. Those with a GCS of 13 or 14 were followed up to determine the incidence of intracranial abnormalities on CT scan.	8488 children were transported by paramedics to EDs during the study period. Of those, 5822 children had a recorded GCS at the scene of trauma. The distribution of GCS scores was as follows: 15=93%; 14=3%; 13=0.6%; 12=0.5%; 11=0.4%; 10=0.2%; 9=0.3%; 8=0.2%; 7=0.2%; 6=0.3%; 5=0.2%; 4=0.2%; 3=0.9%. Therefore, 7% of children suffering trauma have a reduced level of consciousness (if transferred to hospital via paramedic. Of those children with GCS 13-14 at the scene transported to trauma centre 27% had an abnormality on cranial CT.	Population did not include data from those patients who self-presented to EDs without using the paramedic services. Significant level of incomplete data.	Symptom prevalence 2b

Table 7.2.ii Paper included in the analysis of the how frequently trauma causes a reduced conscious level in children

8. Investigating the causes of reduced conscious level in children

Clinical Questions:

(i) Which investigations will screen for the causes of reduced conscious level in children?

Selection criteria
Criteria for choosing papers were drawn up before the search took place. Papers would be included if they were validation studies of guidelines for children with reduced conscious level. High quality diagnostic test studies for the individual causes of reduced conscious level (shock, sepsis, trauma, hyperglycaemia, hypoglycaemia, hyperammonaemia, non-hyperglycaemic ketoacidosis, bacterial meningitis, herpes simplex encephalitis, intracranial abscess, tuberculous meningitis, raised intracranial pressure, hypertension, prolonged convulsions and post-convulsive state) were included. Studies involving both children and adults were only included if the results for children could be analysed separately.

Search
A review of the Cochrane library, MEDLINE (1966-present), EMBASE (1980-present), CINAHL (1982-present), British Nursing Index (1985-present) and AMED (1985-present) was performed using the search terms below. A review of the references of the selected papers for further evidence was included in the search strategy and a hand search of five key journals in the field in the previous 12 months.

Search filters

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	956588
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1465344
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1670568
4	1 or 2 or 3	2874741
5	exp COMA/ or exp GLASGOW COMA SCALE/	30780
6	exp confusion/ or exp coma/ or exp coma, post-head injury/	37862
7	exp Glasgow Coma Scale/	6836
8	5 or 6 or 7	44035
9	guideline$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	223821
10	validat$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	168454
11	9 or 10	386657
12	4 and 8 and 11	354

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	956588
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1465344
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1670568
4	1 or 2 or 3	2874741
5	sensitiv$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1196235
6	(sensitivity and specificity).mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	247943
7	diagnosis.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1764281
8	diagnostic $.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	236218
9	diagnosis,differential.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	265966
10	diagnos$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	2403697
11	test$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	2807626
12	investigation$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	541353
13	gold.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	68818
14	standard$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	744427
15	8 and 9	22794
16	or/5-12	2948991
17	15 or 16	3433790
18	shock$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	184116
19	4 and 17 and 18	2232

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	956588
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1465344
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1670568
4	1 or 2 or 3	2874741
5	sensitiv$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1196235
6	(sensitivity and specificity).mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	247943
7	diagnosis.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1764281
8	diagnostic $.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	236218
9	diagnosis,differential.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	265966
10	diagnos$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	2403697
11	test$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	2807626
12	investigation$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	541353
13	gold.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	68818
14	standard$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	744427
15	8 and 9	22794
16	or/5-12	2948991
17	15 or 16	3433790
18	sepsis$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	82011
19	septi$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	90913
20	18 or 19	151461
15	4 and 17 and 20	9110

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	956588
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1465344
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1670568
4	1 or 2 or 3	2874741
5	sensitiv$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1196235
6	(sensitivity and specificity).mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	247943
7	diagnosis.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1764281
8	diagnostic $.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	236218
9	diagnosis,differential.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	265966
10	diagnos$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	2403697
11	test$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	2807626
12	investigation$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	541353
13	gold.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	68818
14	standard$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	744427
15	8 and 9	22794
16	or/5-12	2948991
17	15 or 16	3433790
18	hyperglycaem$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	8667
19	hyperglycem$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	44831
20	18 or 19	49654
21	4 and 17 and 20	901

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	956588
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1465344
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1670568
4	1 or 2 or 3	2874741
5	sensitiv$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1196235
6	(sensitivity and specificity).mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	247943
7	diagnosis.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1764281
8	diagnostic $.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	236218
9	diagnosis,differential.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	265966

10	diagnos$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	2403697
11	test$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	2807626
12	investigation$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	541353
13	gold.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	68818
14	standard$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	744427
15	8 and 9	22794
16	or/5-12	2948991
17	15 or 16	3433790
18	hypoglycaem$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	8667
19	hypoglycem$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	44831
20	capillary glucose.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	279
21	or/18-20	49654
22	4 and 17 and 21	867

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	956588
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1465344
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1670568
4	1 or 2 or 3	2874741
5	sensitiv$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1196235
6	(sensitivity and specificity).mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	247943
7	diagnosis.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1764281
8	diagnostic $.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	236218
9	diagnosis,differential.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	265966
10	diagnos$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	2403697
11	test$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	2807626
12	investigation$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	541353
13	gold.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	68818
14	standard$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	744427
15	8 and 9	22794
16	or/5-12	2948991
17	15 or 16	3433790
18	hyperammonaemi$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	681
19	hyperammonemi$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	3812
20	plasma ammonia.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	827
21	plasma ammonium.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	147
22	or/18-21	4869
23	4 and 17 and 22	343

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	956588
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1465344
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1670568
4	1 or 2 or 3	2874741
5	sensitiv$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1196235
6	(sensitivity and specificity).mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	247943
7	diagnosis.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1764281
8	diagnostic $.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	236218
9	diagnosis,differential.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	265966
10	diagnos$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	2403697
11	test$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	2807626
12	investigation$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	541353
13	gold.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	68818
14	standard$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	744427
15	8 and 9	22794
16	or/5-12	2948991
17	15 or 16	3433790
18	ketoacido$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	9563

19	diabet$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	451487
20	18 not 19	979
21	4 and 17 and 20	87

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	956588
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1465344
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1670568
4	1 or 2 or 3	2874741
5	sensitiv$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1196235
6	(sensitivity and specificity).mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	247943
7	diagnosis.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1764281
8	diagnostic $.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	236218
9	diagnosis,differential.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	265966
10	diagnos$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	2403697
11	test$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	2807626
12	investigation$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	541353
13	gold.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	68818
14	standard$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	744427
15	8 and 9	22794
16	or/5-12	2948991
17	15 or 16	3433790
18	exp meningitis/ or exp meningitis, bacterial/ or exp meningitis, escherichia coli/ or exp meningitis, haemophilus/ or exp meningitis, listeria/ or exp meningitis, meningococcal/ or exp waterhouse-friderichsen syndrome/ or exp meningitis, pneumococcal/ or exp meningitis, viral/ or exp lymphocytic choriomeningitis/ or exp meningitis, aseptic/ or exp encephalomyelitis/ or exp meningoencephalitis/ or exp encephalitis/ or exp encephalitis, viral/	99012
19	4 and 17 and 19	7862

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	956588
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1465344
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1670568
4	1 or 2 or 3	2874741
5	sensitiv$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1196235
6	(sensitivity and specificity).mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	247943
7	diagnosis.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1764281
8	diagnostic $.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	236218
9	diagnosis,differential.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	265966
10	diagnos$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	2403697
11	test$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	2807626
12	investigation$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	541353
13	gold.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	68818
14	standard$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	744427
15	8 and 9	22794
16	or/5-12	2948991
17	15 or 16	3433790
18	abscess$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	78831
19	cerebral.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	433422
20	subdural.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	15776
21	cerebell$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	119356
22	intracran$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	116210
23	or/19-22	748399
24	18 and 23	6172
25	CT.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	197525
26	mri.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	107763
27	25 and 26	26340

28	24 and 27	7281
29	4 and 17 and 24	950

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	956588
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1465344
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1670568
4	1 or 2 or 3	2874741
5	sensitiv$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1196235
6	(sensitivity and specificity).mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	247943
7	diagnosis.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1764281
8	diagnostic $.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	236218
9	diagnosis,differential.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	265966
10	diagnos$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	2403697
11	test$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	2807626
12	investigation$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	541353
13	gold.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	68818
14	standard$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	744427
15	8 and 9	22794
16	or/5-12	2948991
17	15 or 16	3433790
18	exp brain edema/	16306
19	Neurosurgical Nursing.sh.	107
20	intracranial pressure.mp.	24307
21	exp Intracranial Pressure, Increased/	349
22	exp Intracranial Pressure/	16808
23	exp Monitoring, Intracranial Pressure/	90
24	exp "cerebral edema management (iowa nic)"/ or exp "intracranial pressure monitoring (iowa nic)"/	6
25	exp intracranial pressure/	16808
26	exp Intracranial Hypertension/	20855
27	exp cerebrospinal fluid pressure/ or exp intracranial pressure/	18336
28	exp Brain Edema/	16306
29	or/18-28	54795
30	CT.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	197525
31	mri.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	107763
32	fundoscop$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	868
33	or/30-32	279729
34	4 and 17 and 29 and 33	853

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	956588
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1465344
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1670568
4	1 or 2 or 3	2874741
5	sensitiv$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1196235
6	(sensitivity and specificity).mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	247943
7	diagnosis.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1764281
8	diagnostic $.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	236218
9	diagnosis,differential.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	265966
10	diagnos$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	2403697
11	test$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	2807626
12	investigation$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	541353
13	gold.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	68818
14	standard$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	744427
15	8 and 9	22794
16	or/5-12	2948991
17	15 or 16	3433790

18	convuls$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	38558
19	seizure$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	123942
20	63 or 64	144000
21	17 and 20	1878

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	956588
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1465344
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1670568
4	1 or 2 or 3	2874741
5	sensitiv$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1196235
6	(sensitivity and specificity).mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	247943
7	diagnosis.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1764281
8	diagnostic $.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	236218
9	diagnosis,differential.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	265966
10	diagnos$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	2403697
11	test$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	2807626
12	investigation$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	541353
13	gold.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	68818
14	standard$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	744427
15	8 and 9	22794
16	or/5-12	2948991
17	15 or 16	3433790
18	systolic blood pressure.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	52206
19	hypertensive encephalopathy.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	915
20	or/18-19	53633
21	17 and 20	272

Results

A total of 103 abstracts were reviewed from 25709 titles. One validation of a guideline paper was selected for further review. Two validation studies of clinical diagnostic decision rules were selected for further review. Three diagnostic test studies were selected for further review. The hand search of journals and references identified no other papers for further review. One paper was included in the final analysis.

Papers excluded from the final analysis are listed in table 8.1.i
Papers included in the final analysis are listed in table 8.1.ii

An economic analysis search was also undertaken for the evaluation of screening tests for the causes of reduced conscious level in children. The databases of the NHS Health Technology Assessment Programme and the NHS Economic Evaluation Database were also searched.

#	Search terms	No. of articles
1	economics/	30600
2	exp "costs and cost analysis"/	224934
3	economic value of life.sh.	35
4	economics, dental/	9066
5	exp "economics, hospital"/	171433
6	economics, medical/	12795
7	economics, nursing/	11252
8	economics, pharmaceutical/	3009
9	or/1-8	351442
10	(econom$ or cost or costs or costly or costing or price or prices or pricing or pharmoeconomic$).tw.	415004
11	(expenditure$ not energy).tw.	17630
12	(value adj1 money).tw.	833
13	budget$.tw.	18727
14	or/10-13	434366
15	9 or 14	621912
16	letter.pt.	850832

17	historical article.pt.	217988
18	editorial.pt.	377663
19	or/16-18	1438190
20	15 not 19	580031
21	animal/	3766116
22	human/	13800816
23	21 not (21 and 22)	2889655
24	20 not 23	566330
25	(metabolic adj cost).ti,ab,sh.	774
26	((energy or oxygen) adj cost).ti,ab,sh.	3815
27	24 not (25 or 26)	562326
28	exp ECONOMICS/	503310
29	exp "financial management"/	127512
30	exp "financial support"/	180959
31	exp "financing, organized"/	231449
32	exp "business"/	65967
33	or/29-32	441018
34	28 not 33	158996
35	health resource allocation.sh.	2277
36	health resource utilization.sh.	3163
37	35 or 36	5364
38	34 or 37	162550
39	(cost or costs or economic$ or pharmoeconomic$ or price$ or pricing$).tw.	393180
40	38 or 39	491119
41	news.pt.	93739
42	16 or 18 or 41	1322132
43	38 not 42	144522
44	"animal studies"/	2907
45	43 not 44	144507
46	cochrane library.so.	2305
47	anonymous.au.	414032
48	45 not (46 or 47)	136031
49	27 or 48	587544
50	exp infant, newborn/ or exp infant/ or exp infants/	956588
51	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1465344
52	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1670568
53	or/50-52	2874741
54	49 and 53	65351
55	coma.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	38833
56	GCS.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	7067
57	conscious$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	84511
58	unconscious$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	15293
59	or/55-59	133362
60	54 and 59	467

Results
A total of 3 abstracts were reviewed from 467 titles. These 3 papers were selected for further review.
No other papers were identified from a review of the references.
One paper was included in the final review.

Papers excluded from the final analysis are listed in table 8.1.i
Papers included in the final analysis are listed in table 8.1.ii

Reference	**Reason for exclusion**
Oostenbrink(41)	Clinical diagnostic decision rule not including any laboratory screening tests except CRP (which was weighted minimally in the scoring system)
Kumar(104)	Clinical diagnostic decision rule for patients with meningitis to determine whether the organism is pyogenic or tuberculous. Only laboratory test included is a cerebrospinal fluid microscopy, which was determined not to be a core investigation.

Seymour(105)	Whole population screening not target population screening. Tandem mass spectrometry assessed which was determined not to be a core investigation.
Pandor(106)	Whole population screening not target population screening. Tandem mass spectrometry assessed which was determined not to be a core investigation.
Pollitt(107)	Whole population screening not target population screening. Tandem mass spectrometry assessed which was determined not to be a core investigation.

Table 8.1.i Papers excluded from the analysis of which investigations screen for the causes of reduced conscious level in children

Study	Methods	Participants	Interventions	Allocation concealment	Outcomes	Results	Notes	Evidence level
Armon (108)	Pre and post guideline implementation study to assess the change in practice and outcome in children after a seizure.	Children (aged <15 years) attending the emergency department of a UK hospital in 1997 (before the guideline was introduced) and 1999 (after the guideline was introduced). Study period 4 months for both the pre and post implementation study.	Guideline dissemination and implementation, including the use of a care pathway. Guidance included the need for no investigations after a first "simple afebrile seizure".	The study was not randomised or blinded, and different doctors and nursing staff were taking part in the different arms of the study.	The number of investigations performed, the time spent in the emergency department, and the number of hospital admissions.	411 children enrolled: 212 pre-guideline and 199 post-guideline implementation. The number of investigations performed on these children was reduced, in particular a reduction in the number of U+Es (p=0.04), calcium (p=0.01) and magnesium (p=0.07). No increase in the re-admittance rate or other harms noted. Time in the department was reduced by 25 minutes. There was no change in admittance rates.	The guideline recommendation of no need for investigations after the first simple afebrile seizure improved throughput in the emergency department without affecting patient safety. There were cost savings associated with implementing this guideline.	Therapy 2c (Outcomes research)

Table 8.1.ii Papers included in the analysis of which investigations screen for the causes of reduced conscious level in children

8. Investigating the causes of reduced conscious level in children

Clinical Questions:

(ii) For which causes of reduced conscious level in children should a lumbar puncture be performed?

Selection criteria
Criteria for choosing papers were drawn up before the search took place. Papers would be included if they were validation studies of guidelines for children with reduced conscious level including lumbar punctures. High quality diagnostic test studies reporting cerebrospinal fluid analysis against gold standard test for specific diagnosis were included.
Studies involving both children and adults were included, as the test validity should be roughly equal in adults and children.

Search
A review of the Cochrane library, MEDLINE (1966-present), EMBASE (1980-present), CINAHL (1982-present), British Nursing Index (1985-present) and AMED (1985-present) was performed using the search terms below. A review of the references of the selected papers for further evidence was included in the search strategy and a hand search of five key journals in the field in the previous 12 months.

Search filters

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	960160
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1472076
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1677924
4	1 or 2 or 3	2887032
5	exp meningitis/ or exp meningitis, bacterial/ or exp meningitis, escherichia coli/ or exp meningitis, haemophilus/ or exp meningitis, listeria/ or exp meningitis, meningococcal/ or exp waterhouse-friderichsen syndrome/ or exp meningitis, pneumococcal/ or exp meningitis, viral/ or exp lymphocytic choriomeningitis/ or exp meningitis, aseptic/ or exp encephalomyelitis/ or exp meningoencephalitis/ or exp encephalitis/ or exp encephalitis, viral/	99112
6	risk$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1423509
7	group$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	2629592
8	cohort studies.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	61382
9	cohort$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	188734
10	or/6-9	3798361
11	sensitiv$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1196235
12	(sensitivity and specificity).mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	247943
13	diagnosis.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1764281
14	diagnostic $.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	236218
15	diagnosis,differential.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	265966
16	diagnos$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	2403697
17	test$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	2807626
18	investigation$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	541353
19	gold.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	68818
20	standard$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	744427
21	8 and 9	22794
22	or/11-21	2948991
23	pcr.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	241577
24	polymerase chain reaction.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	386912
25	23 or 24	442213
26	lp.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	17181
27	lumbar puncture$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	8404
28	26 or 27	25241
29	4 and 5 and (10 or 22)	16554
30	29 and (25 or 28)	484

Results
A total of 41 abstracts were reviewed from 484 titles. From these 24 papers were selected for further review. Two other papers were identified from a review of the references.
12 papers were included in the final review.

Papers excluded from the final analysis are listed in table 8.2.i
Papers included in the final analysis are listed in table 8.2.ii

Reference	**Reason for exclusion**
Najioullah(109)	Review of outcome after diagnosis of herpes simplex encephalitis made
Ito(110)	Derivation of a clinical diagnostic decision rule for HSE
Domingues(111)	Derivation of a clinical decision rule for adults with HSE
Powell(112)	Case study
Abbass(113)	Derivation of a clinical decision rule for HSE
Pfyffer(114)	Gold standard test of CSF and candidate test of CSF, therefore no comparison of test not requiring a lumbar puncture compared with one which does.
Johansen(115)	Gold standard test of CSF and candidate test of CSF, therefore no comparison of test not requiring a lumbar puncture compared with one which does.
Koshi(116)	Gold standard test of CSF and candidate test of CSF, therefore no comparison of test not requiring a lumbar puncture compared with one which does.
Nelson(117)	Gold standard test of CSF and candidate test of CSF, therefore no comparison of test not requiring a lumbar puncture compared with one which does.
Sato(118)	Gold standard test of CSF and candidate test of CSF, therefore no comparison of test not requiring a lumbar puncture compared with one which does.
Kearns(119)	Gold standard test of CSF and candidate test of CSF, therefore no comparison of test not requiring a lumbar puncture compared with one which does.
Chowdhury(120)	Gold standard test of CSF and candidate test of CSF, therefore no comparison of test not requiring a lumbar puncture compared with one which does.
Issa(121)	Gold standard test of CSF and candidate test of CSF, therefore no comparison of test not requiring a lumbar puncture compared with one which does.
Mancao(122)	Case reports.

Table 8.2.i Papers excluded from the analysis of which causes of reduced conscious level in children require a lumbar puncture for diagnosis

Study	Methods	Participants	Diagnostic dilemma	Blinded comparison	Gold standard tested	Results	Notes	Evidence level
Uren(123)	Retro-spective review of children with a definite diagnosis of herpes simplex encephalitis (HSE) to assess the accuracy of a HSV-PCR test on the CSF collected at the time of presentation.	16 children (aged 11 days to 12 years) presenting to a children's hospital in Australia with a gold standard diagnosis of HSE, and 14 children identified as not having HSE. Study period 1983 to1991	Could the children have been diagnosed earlier using HSV-PCR compared to using the gold standard of the time?	No but PCR a relatively objective measure which limits observer bias. PCR was applied to all children who had a stored frozen CSF sample.	Gold standard was a number of different tests: viral isolation from brain biopsy (rarely done in children); or antibodies to HSV detected to rise in CSF; or antibodies to HSV found in increasing quantities in the CSF compared with serum.	For CSF samples taken within 1-4 days of the illness, PCR had sensitivity of 70% and specificity of 100%. If CSF sample taken after 4 days of illness (and possibly on treatment) sensitivity only 33%, but specificity still 100%.	Retro-spective study therefore was there really a diagnostic dilemma. Concerns were raised about the freezing and re-freezing of samples as a cause for the reducing sensitivity of the test with time.	Diagnosis 4
Anderson (124)	Prospective study of adults and children with suspected diagnosis of HSE to assess the accuracy of HSV-PCR against gold standard.	Children and adults (aged 1 week to 70 years) presenting to hospitals across New Zealand. Study period 1989-?	Did the patients with clinical symptoms suggestive of HSE have HSE?	Not stated, but a relatively objective measure which limits potential observer bias. PCR was applied to all CSF samples obtained.	Gold standard was a number of different tests: viral isolation from brain biopsy (rarely done); or antibodies to HSV detected to rise in CSF; or antibodies to HSV found in increasing quantities in the CSF compared with serum.	Of 109 patients with suspected HSE, 20 tested +ve with PCR and 14 tested +ve with the gold standard methods. None with a +ve gold standard test tested negative with PCR. Sensitivity 100%, specificity 93%.	Concern that some of those testing negative with the gold standard test probably had HSE – ie PCR may be a more specific test than suggested here. There were 41 in the disease negative group who remained undiagnosed. Very few of these had any collaborating evidence of HSE, but it is difficult to be sure.	Diagnosis 3b
Puchhammer-	Retro-spective	Children and	Did any of	No. Follow up of	Gold standard	Of 1427 patients	Retro-spective	Diagnosis 4

Stockl (125)	analysis of the HSV-PCR negative patients to determine the number of false negative results occurring with this test.	adults suspected of having HSE and having CSF sent for PCR in Vienna, Austria. Study period 1994 to 1998.	the patients with HSV-PCR negative result have HSE?	cases who had negative PCR result known.	defined cases of HSE included antibody production in CSF, clinical features and course of illness, further PCR tests to determine other diagnoses.	included, follow up was available for 811. 12 patients were positive for HSV-PCR, and only 1 patient who had a negative PCR result had definite HSE (antibodies and clinical features). None of the other 798 had HSE (either another diagnosis was confirmed or there were no features to suggest it was HSE during the follow-up period).	analysis. Large loss to follow up (only 56%).	
Fomsgaard (126)	Retro-spective analysis of patients with confirmed HSE to determine when the PCR becomes positive in the course of the disease process compared to HSV intrathecal antibody production.	Adults and children (aged 4 days to 74 years) who had CSF sent to a central reference laboratory in Denmark, because of symptoms / signs of HSE. Study period January 1993 to September 1996.	Did combining the two tests improve the capture rate of HSE positive patients?	No, follow-up of known HSE positive patients.	Gold standard not defined. A combination of PCR and intrathecal antibody production and clinical signs (including EEG / radiology tests) and no other diagnosis.	Of 4206 CSF samples collected from 4140 patients, 33 patients were diagnosed as haiving HSE on test grounds. At first CSF sampling 23 were PCR positive, 9 were intrathecal antibody positive and 1 was positive to both tests. There was an increase in the number of positive	Not a blind study of tests but useful to show that the sensitivity and specificity of these two tests is partly determined by the time the tests are taken. Perhaps PCR and intrathecal antibody tests should both be sent so as not to miss an early or late case.	Diagnosis 4

						intrathecal antibody tests as the time from onset of symptoms increased and a reciprocal decrease in +ve PCR over a similar time period.		
Lakeman (127)	Retro-spective assessment of brain-biopsied patients with suspected HSE and the accuracy of PCR for HSV in their CSF.	Children and adults (age range not stated) who had been enrolled in previous trials for the efficacy of acyclovir and the ability to locate saved CSF samples on these patients.	Were the patients who were biopsy-positive (in an era when that was the gold standard test) also PCR positive for HSV?	No, but PCR a fairly objective test. All Patients had gold standard test, and all patients had candidate test.	Gold standard: brain biopsy and virus isolation. Candidate test: HSV-PCR.	101 Patients who had brain biopsies as part of the diagnosis in the original study protocol also had CSF samples to analyse. Some had had more than one CSF sample taken. The specificity of PCR was 94% and sensitivity 98%. Looking at the brain-biopsy +ve samples, 98% of patients (n=54) were PCR +ve 7 days after starting therapy, but this decreased to only 20% by day 15.	Although no blinding the test was applied to all patients and the PCR is an objective test in general. The failure to find all the CSF samples is a criticism (although very under-standable). The authors suggest that PCR is more specific than these figures suggest as the brain biopsy negative patients with +ve PCR probably had HSE.	Diagnosis 3b
Troendle-Atkins (128)	Prospective assessment of HSV-PCR in the diagnosis of HSE in children	Children (aged 7 days to 14 years) with suspected HSE or neonatal	How accurate is PCR in diagnosing HSE against gold standard	Not mentioned therefore unlikely. However, PCR a relatively objective	Gold standard: criteria of National Institute of Allergy and Infectious Diseases	19 children (8 neonates with HSV infection and 11 children with suspected	Small study but absolute SpIn.	Diagnosis 1c

	against the gold standard of intrathecal HSV antibody production and / or HSV isolated from brain biopsy samples and / or other evidence of HSE according to a strict research criteria.	HSV infection (including skin, eye and mouth infection as well as CNS involvement) attending a children's hospital in Texas, USA. Study period 1991 to 1992.	in patients with HSV infection and suspected HSE?	measure-ment reducing the likelihood of introducing bias.	collaborative neonatal antiviral study group for HSE proved, presumed or not proved (this included virus isolation or intrathecal production of PCR); Candidate test: PCR for HSE from CSF.	HSE) were enrolled. 9 were classed as disease +ve. The sensitivity was 67% and specificity 100% (ignoring the control group they used which did not have diagnostic uncertainty).		
Aurelius (129)	Study of to determine accuracy of "nested" PCR against gold standard of intrathecal HSV antibody production / virus isolation from brain biopsy tissue.	Consecutive patients (age range not stated) with suspected HSE. Study location Sweden (but not stated how many hospitals / regions involved). Study dates not stated.	How accurate is PCR ("nested") against gold standard in the detection of HSE?	Yes, samples were coded so that the technicians and researchers were unaware of the clinical details of each patient).	Gold standard: intrathecal HSV antibody production / virus isolation from brain biopsy tissue. Candidate test: HSV-PCR from CSF.	103 patients were involved. 43 were classed as disease +ve. The sensitivity of PCR was 95% and the specificity was 100%.	Recruitment of patients not clear but possibly retrospective from studies of antiviral therapy. Diagnostic uncertainty existed in all the patients, as those classed as disease "negative" had been treated with antiviral treatments initially.	Diagnosis 1b
Rowley (130)	Retro-spective study to determine the accuracy of HSV PCR in determining HSE.	Patients (age not stated) with brain biopsy positive HSE and patients with other diagnoses. Study dates not given.	Is PCR accurate to distinguish between HSE and other CNS diseases?	No, as retro-spective study with known cases and controls. Gold standard not applied to all patients.	Gold standard: virus isolation from brain biopsy tissue or other confirmed diagnosis. Candidate test: HSV-PCR of CSF	4 patients with disease and 6 patients with other diseases as controls. PCR was found to be 100% sensitive and 100% specific.	Poor study design. Controls not tested for HSV other than PCR. No diagnostic uncertainty which improves the results of the test	Diagnosis 4

							artificially.	
Kox(131)	Prospective study to determine the accuracy of PCR to diagnose tuberculous meningitis (TBM) in adults and children.	Patients (aged 2 to 74 years – 20% aged <16 years) with clinical features and microscopy suggestive of TBM in Holland (central reference laboratory). Study dates not given.	Is PCR for TBM accurate to distinguish between TBM and other organisms?	Yes, samples received by reference laboratory for PCR without knowing the results of microscopy / culture or patient response to treatment.	Gold standard: response to treatment plus supporting evidence of TBM (either CSF culture, PCR or microscopy). Candidate test: PCR for TBM of CSF	42 patients with clinical features of TBM included in study. 35 were started on anti-TB treatments. 23 patients responded to treatment i.e. disease positive. PCR was positive in 11 of these patients. PCR was negative in all patients without the disease. Sensitivity 48%, specificity 100%.	PCR probably superior to culture and microscopy, therefore gold standard taken as clinical response to treatment. This is acceptable as blinded test results and gold standard. This gold standard is also independent of the PCR test.	Diagnosis 1b
Shankar (132)	Study to assess the accuracy of PCR for TBM against the gold standard test of clinical signs, laboratory features and positive response to treatment. children.	Patients (age not stated) attending a centre in India with clinical features of meningitis, who had a CSF sample taken. A control group of patients with non-TB meningitis and other neurological conditions was included also.	Is PCR for TBM accurate to distinguish between TBM and other organisms?	Not stated.	Gold standard: clinical features, laboratory tests (e.g. CSF microscopy and positive culture) and a positive response to anti-TB treatments. Candidate test: PCR for TB in CSF	34 patients with suspected TBM and 51 controls were included. The sensitivity of PCR was 75% in the “highly probable TBM” patients (with an overall sensitivity of 65% for all possible TBM). This compared to 12% for TB culture. The specificity was 100% if the initial false positive results were accurately re-tested – however	Study not known to be blinded. Significant cross contamination of specimens. Controls not necessarily a cause for diagnostic uncertainty, which improves the test performance. Gold standard independent of the test.	Diagnosis 4

						there were 6 false positive results probably due to cross-contamination in the laboratory (specificity 88%).		
Kaneko (133)	To assess the accuracy of TB PCR in CSF samples against the gold standard of clinical signs and other CSF findings.	Patients (age 24 – 41 years) attending a hospital in Japan, who had clinical features of TB meningitis or other meningitis. Study period not stated.	Is PCR for TBM accurate to distinguish between TBM and other organisms?	Not stated.	Gold standard: clinical features of meningitis and CSF TB culture positive and / or adenosine deaminase activity. Candidate test: TB PCR of CSF	6 patients with TBM and 10 patients with bacterial or viral meningitis enrolled. Sensitivity was 83% and specificity was 100%.	Gold standard not met in each of the "positive" cases i.e. cases 2 and 3. Was a different gold standard applied but not described? Adults only study.	Diagnosis 4
Folgueira (134)	To assess the accuracy of TB PCR in CSF samples against the gold standard of clinical signs, other CSF findings and response to treatment.	Patients (aged 21-36 years) with HIV and clinical suspicion of TBM attending a hospital in Spain. A control group of patients with meningitis other than TB was included. Study period not stated.	Is PCR for TBM accurate to distinguish between TBM and other organisms?	Not stated.	Gold standard: clinical features of meningitis, CSF TB culture positive and response to treatment. Candidate test: TB PCR of CSF	10 patients with high clinical suspicion of TBM, 8 were PCR +ve and 2 PCR –ve. Unclear as to whether one of the –ve PCR results is false –ve.	Gold standard not applied in each case. Difficult to assess which patients were "truly" positive or "truly" negative.	Diagnosis 4

Table 8.2.ii Papers included in the analysis of which causes of reduced conscious level in children require a lumbar puncture for diagnosis

8. Investigating the causes of reduced conscious level in children

Clinical Questions:

(iii) What tests should be performed on a sample of cerebrospinal from a child with a reduced conscious level?

Selection criteria
Criteria for choosing papers were drawn up before the search took place. Papers would be included if they were validation studies of clinical prediction rules for children with reduced conscious level including lumbar punctures. High quality prospective diagnostic test studies reporting cerebrospinal fluid analysis against gold standard test for specific diagnosis were included.
Studies involving both children and adults were only included if the test was compared against a gold standard laboratory test rather than clinical signs or symptoms, which may differ between adults and children.

Search
A review of the Cochrane library, MEDLINE (1966-present), EMBASE (1980-present), CINAHL (1982-present), British Nursing Index (1985-present) and AMED (1985-present) was performed using the search terms below. A review of the references of the selected papers for further evidence was included in the search strategy and a hand search of five key journals in the field in the previous 12 months.

Search filters

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	960160
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1472076
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1677924
4	1 or 2 or 3	2887032
5	exp meningitis/ or exp meningitis, bacterial/ or exp meningitis, escherichia coli/ or exp meningitis, haemophilus/ or exp meningitis, listeria/ or exp meningitis, meningococcal/ or exp waterhouse-friderichsen syndrome/ or exp meningitis, pneumococcal/ or exp meningitis, viral/ or exp lymphocytic choriomeningitis/ or exp meningitis, aseptic/ or exp encephalomyelitis/ or exp meningoencephalitis/ or exp encephalitis/ or exp encephalitis, viral/	99112
6	risk$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1423509
7	group$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	2629592
8	cohort studies.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	61382
9	cohort$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	188734
10	or/6-9	3798361
11	sensitiv$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1196235
12	(sensitivity and specificity).mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	247943
13	diagnosis.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1764281
14	diagnostic $.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	236218
15	diagnosis,differential.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	265966
16	diagnos$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	2403697
17	test$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	2807626
18	investigation$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	541353
19	gold.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	68818
20	standard$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	744427
21	8 and 9	22794
22	or/11-21	2948991
23	csf.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	23057
24	cerebrospinal fluid.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	245912
25	23 or 24	258213
26	lp.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	17181
27	lumbar puncture$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	8404
28	26 or 27	25241
29	4 and 5 and (10 or 22)	15322

30	29 and (25 or 28)	359

Results
A total of 12 abstracts were reviewed from 359 titles. From these 4 papers were selected for further review. Three other papers were identified from a review of the references.
5 papers were included in the final review.

Papers excluded from the final analysis are listed in table 8.3.i
Papers included in the final analysis are listed in table 8.3.ii

Reference	**Reason for exclusion**
Freeman(135)	Retrospective study of CSF pleocytosis and bacterial meningitis
Negrini(136)	Retrospective study of CSF pleocytosis and meningitis

Table 8.3.i. Papers excluded from the analysis of which tests should be performed on a sample of cerebrospinal from a child with a reduced conscious level

Study	Methods	Participants	Diagnostic dilemma	Blinded comparison	Gold standard tested	Results	Notes	Evidence level
Deivana-yagam(137)	Prospective derivation study to determine the accuracy of CSF variables in predicting the presence of bacterial meningitis in children.	Children (aged 2 months to 11 years) admitted to a hospital in India with suspected meningitis. Study period January 1989 to April 1990.	Did the children have pyogenic meningitis, viral meningitis or TB meningitis.	Yes, the technician reviewing the CSF variables was unaware of the clinical signs or symptoms of the patients or the culture / LAT test results.	Gold standard: CSF culture and / or latex agglutination test (LAT). Candidiate test: CSF microscopy, Gram stain, glucose and protein.	A total of 114 children were recruited, with 55 being positive for bacterial meningitis (BM) by culture and / or LAT. If the polymorph count was fixed at >60% of total leukocytes in the CSF, the a total leukocyte count of >300/mm^3 was 80% sensitive and 55% specific for the diagnosis of BM. Protein was not seen to be useful at diagnosing BM.	No true validation set analysed against gold standard to determine if this test holds true for another population.	Diagnosis 2b
Oostenbrink (138)	Retro-spective cohort study to derive a decision rule of starting antibiotics in a patient with suspected meningitis and CSF microscopy results.	Children (aged 1 month to 15 years) attending an emergency department in Holland with neck stiffness who had a lumbar puncture. Study period 1988 to 1998.	Did the CSF microscopy result and the clinical symptoms accurately predict the presence of bacterial meningitis?	Partly. the clinical data was not known by the microbiology technician however both the microscopy and culture test would have been performed by the same person.	Gold standard: CSF culture positive for pyogenic bacteria. Candidate test: combination of CSF microscopy and clinical scoring system (previously derived from the same population).	360 children presented with neck stiffness of which 227 had a lumbar puncture (those who didn't have a lumbar puncture were considered not to have meningitis if after 2 weeks they had not returned to hospital or been treated for meningitis or had deteriorated	Retro-spective derivation study of clinical decision rule.	Diagnosis 2b

						significantly). The derived rule included the absolute CSF polymorpho-nuclear leukocyte count and the CSF-blood glucose ratio. Combining this score with the clinical scoring system accurately diagnosed the absence of 30% of the patients who would normally have been started on antibiotics. (Area under the receiver-operator curve was 0.93)		
Oostenbrink (41)	Prospective validation study of a previously derived clinical diagnostic decision rule to accurately diagnose bacterial meningitis in children with neck stiffness.	Children (aged 1 month to 15 years) presenting to one of 4 hospitals in Holland with neck stiffness. Study period Nov 1999 to May 2001.	Did the combination of the clinical score and CSF microscopy accurately diagnose those children with bacterial meningitis in a validation set.	Yes, as the clinicians performing the clinical score did not know the result of the CSF culture and the laboratory technician did not know the clinical findings. However, the laboratory worker would know the result of the microscopy before reporting	Gold standard: positive CSF culture or no clinical deterioration in patients who did not have an LP performed. Candidate test: clinical scoring system and scoring system for microscopy and CSF glucose.	226 patients were enrolled with 146 having a lumbar puncture. All those discharged made full recovery without treatment. The area under the ROC curve was 0.97 in this validation study, but slightly different cut-off values were used in the validation set. The test had	Good validation study. Quite a complicated CSF rule but demon-strates value of CSF microscopy and CSF glucose. Also absolute SpIn result.	Diagnosis 1b

				the culture result. These tests are reasonably objective though.		a specificity of 79% and sensitivity of 100%.		
Aurelius (129)	Study of to determine accuracy of "nested" PCR against gold standard of intrathecal HSV antibody production / virus isolation from brain biopsy tissue.	Consecutive patients (age range not stated) with suspected HSE. Study location Sweden (but not stated how many hospitals / regions involved). Study dates not stated.	How accurate is PCR ("nested") against gold standard in the detection of HSE?	Yes, samples were coded so that the technicians and researchers were unaware of the clinical details of each patient).	Gold standard: intrathecal HSV antibody production / virus isolation from brain biopsy tissue. Candidate test: HSV-PCR from CSF.	103 patients were involved. 43 were classed as disease +ve. The sensitivity of PCR was 95% and the specificity was 100%.	Recruitment of patients not clear but possibly retrospective from studies of antiviral therapy. Diagnostic uncertainty existed in all the patients, as those classed as disease "negative" had been treated with antiviral treatments initially.	Diagnosis 1b
Troendle-Atkins (128)	Prospective assessment of HSV-PCR in the diagnosis of HSE in children against the gold standard of intrathecal HSV antibody production and / or HSV isolated from brain biopsy samples and / or other evidence of HSE according to a strict	Children (aged 7 days to 14 years) with suspected HSE or neonatal HSV infection (including skin, eye and mouth infection as well as CNS involvement) attending a children's hospital in Texas, USA. Study period 1991 to 1992.	How accurate is PCR in diagnosing HSE against gold standard in patients with HSV infection and suspected HSE?	Not mentioned therefore unlikely. However, PCR a relatively objective measure-ment reducing the likelihood of introducing bias.	Gold standard: criteria of National Institute of Allergy and Infectious Diseases collaborative neonatal antiviral study group for HSE proved, presumed or not proved (this included virus isolation or intrathecal production of PCR); Candidate test: PCR for HSE from CSF.	19 children (8 neonates with HSV infection and 11 children with suspected HSE) were enrolled. 9 were classed as disease +ve. The sensitivity was 67% and specificity 100% (ignoring the control group they used which did not have diagnostic uncertainty).	Small study but absolute SpIn.	Diagnosis 1c

	research criteria.							

Table 8.3.ii Papers included in the analysis of which tests should be performed on a sample of cerebrospinal from a child with a reduced conscious level

8. Investigating the causes of reduced conscious level in children

Clinical Questions:

(iv) What clinical features in a child with a reduced conscious level should be considered as contraindications to performing a lumbar puncture?

Selection criteria
Criteria for choosing papers were drawn up before the search took place. Papers would be included if they were randomised controlled trials of lumbar puncture versus no lumbar puncture in a population of children with conditions requiring a CSF sample. Also included were prospective cohort studies of children having a lumbar puncture performed. High quality case-control studies of children with complications of lumbar puncture compared to those without complications of lumbar puncture were also be included if the severity of illness was matched equally in the cases and controls. Studies involving both children and adults were only included if the data for children could be extracted separately.

Search
A review of the Cochrane library, MEDLINE (1966-present), EMBASE (1980-present), CINAHL (1982-present), British Nursing Index (1985-present) and AMED (1985-present) was performed using the search terms below. A review of the references of the selected papers for further evidence was included in the search strategy and a hand search of five key journals in the field in the previous 12 months.

Search filters

#	Search terms	No. of articles
1	RANDOMIZED CONTROLLED TRIAL.pt.	203483
2	CONTROLLED CLINICAL TRIAL.pt.	68767
3	randomized controlled trials.sh.	39337
4	random allocation.sh.	53631
5	double blind method.sh.	82532
6	single blind method.sh.	9079
7	or/1-6	347668
8	Animal.sh.	15950
9	human.sh.	4958995
10	8 not 9	12976
11	7 not 10	347668
12	clinical trial.pt.	424297
13	exp clinical trials/	559113
14	(clin$ adj25 trial$).ti,ab.	228804
15	((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.	165914
16	placebos.sh.	27051
17	placebo$.ti,ab.	183729
18	random$.ti,ab.	630996
19	research design.sh.	42692
20	or/12-19	1419124
21	20 not 10	1418985
22	21 not 11	1092074
23	comparative study.sh.	1270592
24	exp evaluation studies/	568817
25	follow up studies.sh.	302736
26	prospective studies.sh.	228549
27	(control$ or prospectiv$ or volunteer$).ti,ab.	2983755
28	or/23-27	4629518
29	28 not 10	4628086
30	29 not (11 or 22)	3849451
31	11 or 22 or 28	5290625
32	exp infant, newborn/ or exp infant/ or exp infants/	962573
33	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1476454
34	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child,	1682730

	hospitalized/	
35	32 or 33 or 34	2895178
36	35 and 31	768319
37	lumbar puncture$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	8431
38	36 and 37	838

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	962573
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1476454
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1682730
4	1 or 2 or 3	2895178
5	lumbar puncture$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	8431
6	prognos$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	510067
7	(first and episode).mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	16742
8	cohort.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	177676
9	6 or 7 or 8	686921
10	4 and 5 and 9	235
11	remove duplicates from 10	178
12	from 11 keep 144	1
13	exp brain edema/	16360
14	Neurosurgical Nursing.sh.	107
15	intracranial pressure.mp.	24363
16	exp Intracranial Pressure, Increased/	354
17	exp Intracranial Pressure/	16838
18	exp Monitoring, Intracranial Pressure/	91
19	exp "cerebral edema management (iowa nic)"/ or exp "intracranial pressure monitoring (iowa nic)"/	6
20	exp intracranial pressure/	16838
21	exp Intracranial Hypertension/	20907
22	exp cerebrospinal fluid pressure/ or exp intracranial pressure/	18371
23	exp Brain Edema/	16360
24	13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23	54939
25	4 and (5 or 24) and 9	1936
26	remove duplicates from 25	1702

Results
A total of 20 abstracts were reviewed from 2540 titles. From these 3 papers were selected for further review. One other paper was identified from a review of the references.
3 papers were included in the final review.

Papers excluded from the final analysis are listed in table 8.4.i
Papers included in the final analysis are listed in table 8.4.ii

Reference	**Reason for exclusion**
Minns(139)	Cohort study to determine the CSF pressure in children with bacterial meningitis not to assess harm of lumbar puncture.

Table 8.4.i Papers excluded from the analysis of which clinical features in a child with a reduced conscious level should be considered as contraindications to performing a lumbar puncture

Study	Methods	Participant definition	Length of follow-up	Outcomes	Results	Notes	Evidence level
Rennick (140)	Retrospective cohort study of children with meningitis to determine if there was a relationship between the timing of death or onset of symptoms of cerebral herniation and a lumbar puncture being carried out.	Children (aged over 30 days) who died or were treated on the intensive care unit for meningitis.	To hospital discharge.	Death and time to herniation from lumbar puncture.	445 children were admitted with bacterial meningitis, of which 31 died and 127 were admitted to ICU. 1 set of notes was unavailable. There were 21 separate episodes of herniation among 19 patients. Of 21 episodes 15 led to death (14 patients). Relative risk of death for performing a lumbar puncture in children with herniation is 0.79; CI 0.48 – 1.32.	Wide confidence interval of RR. Retrospective study demonstrates a potentially protective role of LP. Elsewhere the authors claim that herniation follows LP in a short period of time.	Prognosis 2b
Newton (141)	Prospective cohort study of children with cerebral malaria to determine the outcome of children with raised intracranial pressure and signs of cerebral herniation with those without raised intracranial pressure or herniation syndromes.	Children (mean age 39 months; median age and range not stated) with signs of cerebral malaria (as per WHO classification) admitted to a hospital in Kenya. Study period May 1989 to August 1990.	Till hospital discharge or death (not stated if any formal follow up period in all surviving patients but one patient followed up to 3 months)	Death as primary outcome. Significant neurological disability reported.	586 children admitted with malaria, of which 61 had cerebral malaria characteristics. 47 of 61 patients had lumbar punctures and 26 of 47 had opening CSF pressures measured. There were 12 deaths in the 61 children and 10 of which were in those who had a lumbar puncture (relative risk of death if LP=1.49; CI 0.3-6.0). Those with signs of cerebral herniation syndrome 12 died and 17 survived (relative risk of death if signs present = 2.88; CI 1.96 – 4.23). Data not	Unable to determine if lumbar puncture contributed to death as data not analysed or presented in that form.	Prognosis 1b

					provided to analyse deaths amongst those who had cerebral herniating signs and were lumbar punctured compared to those who weren't.		
Akpede (142)	Part retrospective part prospective study to determine the risk of death in children with bacterial meningitis and signs of herniation or severe disease.	Children (aged >1 month to 15 years) with a diagnosis of bacterial meningitis admitted to a hospital in Nigeria. Retrospective data from 1993 to 1995 and prospective data from May 1995 to June 1996.	To hospital discharge and 3 months post discharge if noted.	Death and neurological sequelae.	123 patients were enrolled (71 prospective data collection). Patients with signs of herniation had a relative risk of death of 2.97 (95% CI = 1.18 to 7.47). Patients with signs of severe disease had a relative risk of death of 2.53 (95% CI = 1.05 to 6.08). All these patients had a lumbar puncture and data comparing those with and without LP is not presented.	High risk patients are more likely to die. However, on sensitivity analysis if the missing data were added to the figures the relative risks could be insignificant.	Prognosis 2b

Table 8.4.ii Papers included in the analysis of which clinical features in a child with a reduced conscious level should be considered as contraindications to performing a lumbar puncture

8. Investigating the causes of reduced conscious level in children

Clinical Questions:

(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?

Selection criteria
Criteria for choosing papers were drawn up before the search took place. Papers would be included if they were diagnostic studies of CT to assess raised intracranial pressure.
Studies involving both children and adults were only included if the data for children could be extracted separately.

Search
A review of the Cochrane library, MEDLINE (1966-present), EMBASE (1980-present), CINAHL (1982-present), British Nursing Index (1985-present) and AMED (1985-present) was performed using the search terms below. A review of the references of the selected papers for further evidence was included in the search strategy and a hand search of five key journals in the field in the previous 12 months.

Search filters

#	Search terms	No. of articles
1	exp brain edema/	16366
2	Neurosurgical Nursing.sh.	107
3	intracranial pressure.mp.	24380
4	exp Intracranial Pressure, Increased/	355
5	exp Intracranial Pressure/	16854
6	exp Monitoring, Intracranial Pressure/	91
7	exp "cerebral edema management (iowa nic)"/ or exp "intracranial pressure monitoring (iowa nic)"/	6
8	exp intracranial pressure/	16854
9	exp Intracranial Hypertension/	20917
10	exp cerebrospinal fluid pressure/ or exp intracranial pressure/	18387
11	exp Brain Edema/	16366
12	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11	54967
13	exp infant, newborn/ or exp infant/ or exp infants/	962840
14	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1477002
15	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1683340
16	13 or 14 or 15	2896147
17	DIAGNOSIS/ or diagnosis.mp.	1770961
18	computed tomography.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	125414
19	ct.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	198699
20	scan.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	108948
21	imaging.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	563861
22	brain.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1169197
23	intracranial.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	115420
24	18 or 19	274398
25	20 or 21	644023
26	22 or 23	1226280
27	26 and (24 or 25)	171040
28	12 and 16 and 17 and 27	1164

Results
A total of 20 abstracts were reviewed from 1164 titles. From these 12 papers were selected for further review. Two other papers were identified from a review of the references.
3 papers were included in the final review.

Papers excluded from the final analysis are listed in table 8.5.i
Papers included in the final analysis are listed in table 8.5.ii

Reference	Reason for exclusion
Demo(143)	Foreign language.
Honda(144)	Foreign language.
Yuh(145)	Adults only study.
Condon(146)	Adults only study.
Weisberg(147)	Adults only study.
Muir(148)	Study to assess clinical signs for raised intracranial pressure using CT as the gold standard.
Kishore(149)	Adults and children not analysed separately.
Nadvi(150)	Comparison of normal controls with hydrocephalic children without blinding of test results or measurement of intracranial pressure in controls.
O'Sullivan(151)	Adult only study.
Heyderman(152)	Study to assess clinical signs for raised intracranial pressure using CT as the gold standard.
Hanigan(153)	Subjective comparison of cranial CT scan with MRI scan against no objective gold standard.
Dahlerup (154)	Case series of 4 children with raised intracranial pressure but normal CT scans.

Table 8.5.i Papers excluded from the analysis of whether an intracranial scan can rule out raised intracranial pressure

Study	Methods	Participants	Diagnostic dilemma	Blinded comparison	Gold standard tested	Results	Notes	Evidence level
Hirsch(155)	Retro-spective review of cranial CT scans in children who had intracranial pressure monitoring in site to assess the accuracy of CT interpretation to diagnose raised intracranial pressure (ICP).	Children (aged 4 months to 12 years) post head injury who had ICP monitoring and a CT scan. Study period 1992 to 1997.	Did the CT scan predict the ICP in this population who may have had raised intracranial pressure?	Yes, the two radiologists did not know the ICP when the CT scan was taken.	Gold standard: ICP monitoring device in situ. Candidate test: cranial CT scan	65 children having 124 scans were assessed. Overall the sensitivity of CT was 84% and specificity of 44% for raised ICP. The sensitivity of the test improved if the ICP patients were categorised as raised and very raised ICP.	The results suggest that CT is not very good at picking up borderline high and normal ICP measurements but is good at detecting very high ICP. As the study was in patients with ICP measuring systems in situ, perhaps the radiologists were predicting higher than average ICP because of the fact that these children were being monitored.	Diagnosis 1b
Rennick (140)	Retro-spective study to assess the temporal relationship between lumbar puncture and cerebral herniation and for the ability of cranial CT to pick up cerebral herniation in	Children (aged 4 months to 15 years) presenting with bacterial meningitis and signs of cerebral herniation either clinically or on post mortem examination. Study period	Did the CT scan detect abnorm-alities in the children who had cerebral herniation on post mortem or clinically?	Yes, the radiologist did not know which children had clinical herniation or post mortem findings.	Gold standard: post mortem findings (clinical findings can be analysed separately). Candidate test: cranial CT scan	445 children had bacterial meningitis and 19 patients had cerebral herniation. 14 of these 19 patients died. Using necropsy result as gold standard (n=4) there were 2 children who had normal CT scans	Numbers are very small and the study was not designed to assess the specificity of CT. Tests were not applied to all patients.	Diagnosis 4

	the acute situation.	1984 to 1989.				despite clinical herniation occurring less than 3 hours before the scan and having positive post mortem findings (sensitivity 33%; specificity 100% [n=1]). If the gold standard was clinical signs of herniation (n=14) then CT has a sensitivity of 70% and specificity of 100% [n=1].		

Table 8.5.ii Papers included in the analysis of whether an intracranial scan can rule out raised intracranial pressure

8. Investigating the causes of reduced conscious level in children

Clinical Questions:

(vi) Can a computed tomography [CT] scan demonstrate raised intracranial pressure?

Selection criteria
Criteria for choosing papers were drawn up before the search took place. Papers would be included if they were diagnostic studies of CT to assess raised intracranial pressure.
Studies involving both children and adults were only included if the data for children could be extracted separately.

Search
A review of the Cochrane library, MEDLINE (1966-present), EMBASE (1980-present), CINAHL (1982-present), British Nursing Index (1985-present) and AMED (1985-present) was performed using the search terms below. A review of the references of the selected papers for further evidence was included in the search strategy and a hand search of five key journals in the field in the previous 12 months.

Search filters

#	Search terms	No. of articles
1	exp brain edema/	16366
2	Neurosurgical Nursing.sh.	107
3	intracranial pressure.mp.	24380
4	exp Intracranial Pressure, Increased/	355
5	exp Intracranial Pressure/	16854
6	exp Monitoring, Intracranial Pressure/	91
7	exp "cerebral edema management (iowa nic)"/ or exp "intracranial pressure monitoring (iowa nic)"/	6
8	exp intracranial pressure/	16854
9	exp Intracranial Hypertension/	20917
10	exp cerebrospinal fluid pressure/ or exp intracranial pressure/	18387
11	exp Brain Edema/	16366
12	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11	54967
13	exp infant, newborn/ or exp infant/ or exp infants/	962840
14	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1477002
15	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1683340
16	13 or 14 or 15	2896147
17	DIAGNOSIS/ or diagnosis.mp.	1770961
18	computed tomography.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	125414
19	ct.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	198699
20	scan.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	108948
21	imaging.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	563861
22	brain.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1169197
23	intracranial.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	115420
24	18 or 19	274398
25	20 or 21	644023
26	22 or 23	1226280
27	26 and (24 or 25)	171040
28	12 and 16 and 17 and 27	1164

Results
A total of 20 abstracts were reviewed from 1164 titles. From these 12 papers were selected for further review. Two other papers were identified from a review of the references.
3 papers were included in the final review.

Papers excluded from the final analysis are listed in table 8.6.i
Papers included in the final analysis are listed in table 8.6.ii

Reference	Reason for exclusion
Demo(143)	Foreign language.
Honda(144)	Foreign language.
Yuh(145)	Adults only study.
Condon(146)	Adults only study.
Weisberg(147)	Adults only study.
Muir(148)	Study to assess clinical signs for raised intracranial pressure using CT as the gold standard.
Kishore(149)	Adults and children not analysed separately.
Nadvi(150)	Comparison of normal controls with hydrocephalic children without blinding of test results or measurement of intracranial pressure in controls.
O'Sullivan(151)	Adult only study.
Heyderman(152)	Study to assess clinical signs for raised intracranial pressure using CT as the gold standard.
Hanigan(153)	Subjective comparison of cranial CT scan with MRI scan against no objective gold standard.
Dahlerup (154)	Case series demonstrating raised intracranial pressure in 4 children with normal CT scans.

Table 8.6.i Papers excluded from the analysis of whether a CT scan can demostrate raised intracranial pressure

Study	Methods	Participants	Diagnostic dilemma	Blinded comparison	Gold standard tested	Results	Notes	Evidence level
Hirsch(155)	Retro-spective review of cranial CT scans in children who had intracranial pressure monitoring in site to assess the accuracy of CT interpretation to diagnose raised intracranial pressure (ICP).	Children (aged 4 months to 12 years) post head injury who had ICP monitoring and a CT scan. Study period 1992 to 1997.	Did the CT scan predict the ICP in this population who may have had raised intracranial pressure?	Yes, the two radiologists did not know the ICP when the CT scan was taken.	Gold standard: ICP monitoring device in situ. Candidate test: cranial CT scan	65 children having 124 scans were assessed. Overall the sensitivity of CT was 84% and specificity of 44% for raised ICP. The sensitivity of the test improved as the ICP of patients increased. Therefore A CT scan has a 97.7% sensitivity of finding raised ICP in patients with ICP > 25mmHg, with a specificity of 60.6%.	The results suggest that CT is not very good at picking up borderline high and normal ICP measure-ments but is good at detecting very high ICP. As the study was in patients with ICP measuring systems in situ, perhaps the radiologists were predicting higher than average ICP because of the fact that these children were being monitored.	Diagnosis 1b
Rennick (140)	Retro-spective study to assess the temporal relationship between lumbar puncture and cerebral herniation and for the ability of cranial CT to pick up cerebral herniation in	Children (aged 4 months to 15 years) presenting with bacterial meningitis and signs of cerebral herniation either clinically or on post mortem examination. Study period	Did the CT scan detect abnorm-alities in the children who had cerebral herniation on post mortem or clinically?	Yes, the radiologist did not know which children had clinical herniation or post mortem findings.	Gold standard: post mortem findings (clinical findings can be analysed separately). Candidate test: cranial CT scan	445 children had bacterial meningitis and 19 patients had cerebral herniation. 14 of these 19 patients died. Using necropsy result as gold standard (n=4) there were 2 children who had normal CT scans	Numbers are very small and the study was not designed to assess the specificity of CT. Tests were not applied to all patients.	Diagnosis 4

	the acute situation.	1984 to 1989.				despite clinical herniation occurring less than 3 hours before the scan and having positive post mortem findings (sensitivity 33%; specificity 100% [n=1]). If the gold standard was clinical signs of herniation (n=14) then CT has a sensitivity of 70% and specificity of 100% [n=1].		
Eide(156)	Prospective study to determine the accuracy of CT in predicting intracranial pressure using ventricular size measurements in children.	Children and a few adults (aged 0 to 30 years) with ICP monitoring for hydrocephalus, cranio-synostosis or ventriculo-peritoneal shunts. Study period February 1997 to January 2001.	Can a CT scan detect raised intracranial pressure based on the size of the ventricles.	Not stated.	Gold standard: ICP monitoring. Candidate test: ventricular measurements on CT scanning.	184 patients were enrolled. There was poor correlation between the mean ICP and the CT ventricular size (linear relationship $r^2<0.02$; $p>0.15$).	Using CT measurements of ventricles, the intracranial pressure cannot be accurately predicted. The fact the study does not report blinding may be a cause for concern.	Diagnosis 1b

Table 8.6.ii Papers included in the analysis of whether a CT scan can demonstrate raised intracranial pressure

8. Investigating the causes of reduced conscious level in children

Clinical Questions:

(vii) Can a computed tomography [CT] scan demonstrate an intracranial abscess?

Selection criteria
Criteria for choosing papers were drawn up before the search took place. Papers would be included if they were diagnostic studies of CT to assess the presence of an intracranial abscess.
Studies involving both children and adults were only included if the data for children could be extracted separately.

Search
A review of the Cochrane library, MEDLINE (1966-present), EMBASE (1980-present), CINAHL (1982-present), British Nursing Index (1985-present) and AMED (1985-present) was performed using the search terms below. A review of the references of the selected papers for further evidence was included in the search strategy and a hand search of five key journals in the field in the previous 12 months.

Search filters

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	962840
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1477002
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1683340
4	1 or 2 or 3	2896147
5	DIAGNOSIS/ or diagnosis.mp.	1770961
6	computed tomography.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	125414
7	ct.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	198699
8	scan.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	108948
9	imaging.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	563861
10	brain.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1169197
11	intracranial.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	115420
12	6 or 7	274398
13	8 or 9	644023
14	10 or 11	1226280
15	14 and (12 or 13)	171040
16	exp Brain Abscess/	8580
17	intracranial abscess$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	299
18	cerebral abscess$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1171
19	cerebellar abscess$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	242
20	or/16-19	8940
21	4 and 5 and 15 and 20	398

Results
A total of 62 abstracts were reviewed from 398 titles. From these 13 papers were selected for further review. No other papers were identified from a review of the references.
No papers were included in the final review.

Papers excluded from the final analysis are listed in table 8.7.i

Reference	**Reason for exclusion**
Benjelloun-Dakhama (157)	Foreign language
Ubaidullaeva(158)	Foreign language
Bodino(159)	No gold standard comparison.
Zimmermann(160)	No gold standard comparison.
Tekkok(161)	Case reports.
Miller(162)	Adults only study.
Wu(163)	Adults only study.

Shaw(164)	Adults and children analysed together
New(165)	Adults only study.
Holtas(166)	Adults only study.
Weisberg(167)	Adults only study.
Power(168)	Adults only study.
Ferriero(169)	Description of outcomes in children with brain ascesses; no gold standard comparison of tests.

Table 8.7.i Papers excluded from the analysis of whether a CT scan can diagnose an intracranial abscess

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

Clinical Question:

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

Selection criteria
Criteria for choosing papers were drawn up before the search took place. Papers would be included if they were validation studies of guidelines for children with reduced conscious level. Studies involving both children and adults were only included if the results for children could be analysed separately.

Search
A review of the Cochrane library, MEDLINE (1966-present), EMBASE (1980-present), CINAHL (1982-present), British Nursing Index (1985-present) and AMED (1985-present) was performed using the search terms below. A review of the references of the selected papers for further evidence was included in the search strategy and a hand search of five key journals in the field in the previous 12 months.

Search filters

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	956588
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1465344
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1670568
4	1 or 2 or 3	2874741
5	exp COMA/ or exp GLASGOW COMA SCALE/	30780
6	exp confusion/ or exp coma/ or exp coma, post-head injury/	37862
7	exp Glasgow Coma Scale/	6836
8	5 or 6 or 7	44035
9	guideline$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	223821
10	validat$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	168454
11	9 or 10	386657
12	4 and 8 and 11	354

Results
A total of 3 abstracts were reviewed from 354 titles. No papers were selected for further review. The hand search of journals and references identified no other papers for further review.

10. Circulatory shock

Clinical Questions:

(i) What clinical features determine the presence of circulatory shock in a child with a reduced conscious level?

Selection criteria
Criteria for choosing papers were drawn up before the search took place. Papers would be included if they were validation studies of guidelines for children with shock, if they were validation studies of clinical diagnostic decision rules for shock in children, or if they were randomised control trials of therapy for shock in children with clear entry criteria for the trial. Studies involving both children and adults were only included if the results for children could be analysed separately.

Search
A review of the Cochrane library, MEDLINE (1966-present), EMBASE (1980-present), CINAHL (1982-present), British Nursing Index (1985-present) and AMED (1985-present) was performed using the search terms below. A review of the references of the selected papers for further evidence was included in the search strategy and a hand search of five key journals in the field in the previous 12 months.

Search filters

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	956588
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1465344
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1670568
4	1 or 2 or 3	2874741
5	exp shock/ or exp shock, cardiogenic/ or exp shock, hemorrhagic/ or exp shock, septic/ or exp toxic shock syndrome/ or exp shock, surgical/ or exp shock, traumatic/	66854
6	exp shock/ or exp capillary leak syndrome/ or exp cardiogenic shock/ or exp hemorrhagic shock/ or exp hypovolemic shock/ or exp septic shock/ or exp toxic shock syndrome/ or exp hemorrhagic hypotension/	66878
7	exp shock/ or exp sepsis syndrome/ or exp shock, cardiogenic/ or exp shock, hemorrhagic/ or exp shock, septic/ or exp shock, surgical/ or exp shock, traumatic/	92937
8	5 or 6 or 7	93342
9	guideline$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	223821
10	validat$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	168454
11	9 or 10	386657
12	4 and 8 and 11	240

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	956588
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1465344
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1670568
4	1 or 2 or 3	2874741
5	exp shock/ or exp shock, cardiogenic/ or exp shock, hemorrhagic/ or exp shock, septic/ or exp toxic shock syndrome/ or exp shock, surgical/ or exp shock, traumatic/	66854
6	exp shock/ or exp capillary leak syndrome/ or exp cardiogenic shock/ or exp hemorrhagic shock/ or exp hypovolemic shock/ or exp septic shock/ or exp toxic shock syndrome/ or exp hemorrhagic hypotension/	66878
7	exp shock/ or exp sepsis syndrome/ or exp shock, cardiogenic/ or exp shock, hemorrhagic/ or exp shock, septic/ or exp shock, surgical/ or exp shock, traumatic/	92937
8	5 or 6 or 7	93342
9	decision rule.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	772
10	diagnosis.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1771627
11	9 or 10	1772247
12	4 and 8 and 11	1972

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	956588
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1465344
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1670568
4	1 or 2 or 3	2874741
5	exp shock/ or exp shock, cardiogenic/ or exp shock, hemorrhagic/ or exp shock, septic/ or exp toxic shock syndrome/ or exp shock, surgical/ or exp shock, traumatic/	66854
6	exp shock/ or exp capillary leak syndrome/ or exp cardiogenic shock/ or exp hemorrhagic shock/ or exp hypovolemic shock/ or exp septic shock/ or exp toxic shock syndrome/ or exp hemorrhagic hypotension/	66878
7	exp shock/ or exp sepsis syndrome/ or exp shock, cardiogenic/ or exp shock, hemorrhagic/ or exp shock, septic/ or exp shock, surgical/ or exp shock, traumatic/	92937
8	5 or 6 or 7	93342
9	RANDOMIZED CONTROLLED TRIAL.pt.	203760
10	CONTROLLED CLINICAL TRIAL.pt.	68822
11	randomized controlled trials.sh.	39409
12	random allocation.sh.	53667
13	double blind method.sh.	82602
14	single blind method.sh.	9092
15	or/9-14	348114
16	Animal.sh.	15951
17	human.sh.	4964488
18	16 not 17	12976
19	15 not 18	348114
20	clinical trial.pt.	424866
21	exp clinical trials/	560031
22	(clin$ adj25 trial$).ti,ab.	229209
23	((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.	166094
24	placebos.sh.	27066
25	placebo$.ti,ab.	183949
26	random$.ti,ab.	631995
27	research design.sh.	42731
28	or/20-27	1421286
29	28 not 18	1421147
30	comparative study.sh.	1272338
31	exp evaluation studies/	569635
32	follow up studies.sh.	302944
33	prospective studies.sh.	229002
34	(control$ or prospectiv$ or volunteer$).ti,ab.	2987641
35	or/30-34	4635476
36	35 not 18	4634044
37	19 or 29 or 36	5297606
38	4 and 8 and 37	2854

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	956588
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1465344
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1670568
4	1 or 2 or 3	2874741
5	exp shock/ or exp shock, cardiogenic/ or exp shock, hemorrhagic/ or exp shock, septic/ or exp toxic shock syndrome/ or exp shock, surgical/ or exp shock, traumatic/	66854
6	exp shock/ or exp capillary leak syndrome/ or exp cardiogenic shock/ or exp hemorrhagic shock/ or exp hypovolemic shock/ or exp septic shock/ or exp toxic shock syndrome/ or exp hemorrhagic hypotension/	66878
7	exp shock/ or exp sepsis syndrome/ or exp shock, cardiogenic/ or exp shock, hemorrhagic/ or exp shock, septic/ or exp shock, surgical/ or exp shock, traumatic/	92937
8	5 or 6 or 7	93342
9	exp neurologic examination/ or exp pain measurement/ or exp reflex/ or exp reflex, abdominal/ or exp reflex, abnormal/ or exp reflex, babinski/ or exp reflex, acoustic/ or	999113

	exp reflex, pupillary/ or exp reflex, stretch/ or exp startle reaction/ or exp medical history taking/ or exp cornell medical index/ or exp reproductive history/ or exp physical examination/ or exp auscultation/ or exp heart auscultation/ or exp blood pressure determination/ or exp body constitution/ or exp body height/ or exp body surface area/ or exp body weight/ or exp fetal weight/ or exp body temperature/ or exp cephalometry/ or exp craniometry/ or exp facial expression/ or exp facies/ or exp gait/ or exp hand strength/ or exp palpation/ or exp pelvimetry/ or exp percussion/ or exp pigmentation/ or exp skin pigmentation/ or exp pulse/ or exp range of motion, articular/ or exp self-examination/ or exp breast self-examination/ or exp skinfold thickness/	
10	exp medical history taking/ or exp patient assessment/ or physical examination/ or exp palpation/ or exp pulse/	167137
11	exp patient history taking/ or exp physical examination/ or exp auscultation/ or exp heart auscultation/ or exp blood pressure determination/ or exp body temperature determination/ or exp cephalometry/ or exp "inspection (clinical)"/ or exp neurologic examination/ or exp reflex/ or exp reflex, abnormal/ or exp reflex, acoustic/ or exp reflex, pupillary/ or exp reflex, stretch/ or exp palpation/ or exp percussion/ or exp physical examination, preparticipation/ or exp pigmentation/ or exp skin pigmentation/ or exp pulse/	698046
12	exp blood pressure/ or exp body temperature/ or exp fatigue/ or exp jaundice/ or exp nausea/ or exp "pain and pain management"/ or exp paralysis/ or exp seizures/ or exp senses/ or exp shock/ or exp sleep/ or exp unconsciousness/ or exp patient assessment/	906660
13	exp medical examination/ or exp clinical examination/ or exp functional assessment/ or exp pulse oximetry/ or exp blood pressure monitoring/ or exp temperature measurement/ or exp thermometry/ or exp blood glucose monitoring/ or exp electrocardiography monitoring/ or exp neurologic examination/ or history/	290386
14	clinical feature.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	237656
15	presenting feature.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	2183
16	presenting sign.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1614
17	presenting symptom.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	4447
18	sign.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	65022
19	symptom.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	184991
20	or/9-19	2180316
21	4 and 8 and 20	5696

Results
A total of 65 abstracts were reviewed from 10762 titles. 10 papers were selected for further review.
The hand search of journals and references identified three other papers for further review.
Four papers were included in the final analysis.

Papers excluded from the final analysis are listed in table 10.1.i
Papers included in the final analysis are listed in table 10.1.ii

Reference	Reason for exclusion
Roberts(170)	Systematic review of randomised controlled trials including mainly adult data and only one study from children with shock(171)
Alderson(172)	Systematic review of randomised controlled trials including mainly adult data and no studies from children with shock. There were six studies included involving preterm infants, but these were not analysed separately and are outside the scope of this guideline
Mullner(173)	Systematic review of randomised controlled trials including only adult data,
Bunn(174)	Systematic review of randomised controlled trials of different fluid regimes including mainly adult data and no studies from children with shock. There were four studies(175-178) of children undergoing surgery but not in shock included in the analysis.
Carcillo(179)	A consensus conference paper regarding paediatric septic shock. Only one RCT was included(171).
Delinger(180)	A consensus conference paper regarding adult and paediatric septic shock. Only one paediatric RCT was included(171)
Birkhahn(181)	Adult study
Saladino(182)	Guideline without validation
Han(183)	Retrospective study of outcomes, using consensus definition of shock(179)

Table 10.1.i Papers excluded from the analysis of which clinical features determine the presence of circulatory shock in a child with a reduced conscious level

Study	Methods	Participants	Interventions	Allocation concealment	Outcomes	Results	Notes	Evidence level
Nhan(171)	Prospective RCT double-blinded to assess the benefit of using different resuscitation fluid in circulatory shock in children. Study period September 1996 to September 1997. Parameters of shock described in the study included weak rapid pulse, pulse pressure <20mmHg, no detectable BP.	Children (aged 1 – 15 years) presenting to a hospital in Vietnam with a clinical diagnosis of dengue haemorrhagic fever (DHF) grade 3 or 4 (as classified by WHO), who had not received any intravenous fluid during the course of their illness prior to presentation. Exclusions included those who were likely to need a blood transfusion due to the haemorrhagic illness and those with a chronic disorder.	The child was randomised to one of four different fluid regimes: dextran 70 (colloid); 3% gelatin (colloid); lactated Ringer's (crystalloid); and normal saline (crystalloid). Children with grade 3 DHF received the study fluid at a rate of 20ml/kg over the first hour. Children with grade 4 DHF received the study fluid at a rate of 20ml/kg over 15 minutes followed by a second 20ml/kg bolus of the study fluid over the next hour. After the initial therapy all children received	Opaque sealed envelopes containing only the treatment pack number were randomised in blocks of 10. The treatment packs contained three 500ml bags of the trial fluid all wrapped in black insulating tape so as to not reveal the identity of the trial fluid. The identity of the study fluid was attached to the child's notes in an opaque sealed envelope.	Primary outcomes: 1) Recovery from shock - the time for the pulse pressure to recover to normal defined as >30mmHg (as an indication of the successful treatment of shock). 2) Relapse -the time for the pulse pressure to relapse to <20mmHg having recovered to >30mmHg. Secondary outcomes: drop in pulse rate after first hour; complications of fluid therapy; total fluid therapy required	230 children recruited (8 having grade 4 DHF). Due to the small number of those with grade 4 DHF the analysis was limited to the 222 children with grade 3 DHF. There was a significant difference in the recovery from shock between dextran and normal saline with more rapid recovery found with the dextran solution. There was also a significant difference in the amount of extra dextran required following the study fluid regime, with those receiving dextran initially requiring the	There were differences between the 4 study arms in the severity of disease in the 222 children with grade 3 DHF as measured by pulse volume at presentation. Only a few children were randomised into the dextran group with pulse pressures <10mmHg. This may have biased the results towards favouring the Dextran group. Subgroup analysis of those children with initial pulse pressure <10mmHg still showed a significant difference between gelatin and lactated Ringer's	Therapy 1b

			lactated Ringer's solution according to the WHO guidelines and further boluses of dextran 70 as determined by the attending physician.			least and those receiving lactated Ringer's requiring the most. There were no deaths in this study.	(favouring gelatin – OR 5.76; CI 1.36-23.59). No difference was seen between lactated Ringer's and normal saline.	
Dung(184)	Prospective RCT double-blinded to assess the benefit of using different resuscitation fluid in circulatory shock in children. Study period July 1995 to November 1995. Parameters of shock described in the study were pulse pressure, pulse rate, blood pressure, cold extremities.	Children (aged 5 – 15 years) presenting to a hospital in Vietnam with a clinical diagnosis of dengue haemorrhagic fever (DHF) grade 3 (as classified by WHO), who had not received any intravenous fluid during the course of their illness prior to presentation.	The child was randomised to one of four different fluid regimes: dextran 70 (colloid); gelafundin (colloid); lactated Ringer's (crystalloid); and normal saline (crystalloid). Children with grade 3 DHF received the study fluid at a rate of 20ml/kg over the first hour, followed by 10ml/kg over the next hour. After the initial therapy all children received open label therapy	Opaque sealed envelopes containing only the treatment pack number were randomised in blocks of 10. The treatment packs contained three 500ml bags of the trial fluid all wrapped in black insulating tape so as to not reveal the identity of the trial fluid.	Primary outcomes: 1) Recovery from shock - the time for the pulse pressure to recover to normal defined as >20mmHg. 2) Number of episodes of shock.	50 children were enrolled. No differences were seen between the study arms for the recovery time from shock.	Secondary outcome measures such as recovery of haematological variables and cardiac parameters improved more rapidly in the groups receiving colloids, but the study was not designed to combine the treatment arms in this way. The study was not powered to determine equivalence.	Therapy 1b

			according to the WHO guidelines.					
Upadhyay (185)	Prospective randomized open label trial to assess the benefits of one type of fluid therapy over another in pediatric resuscitation of septic shock. Parameters for shock described in the study were hypotension, or three of the following: decreased pulse volume, capillary refill time >3 seconds, tachycardia, urine output <1ml/kg/hour.	Children (aged 1 month to 12 years) with septic shock (clear criteria described) presenting to paediatric emergency or intensive care unit of a hospital in India. Exclusion criteria included presence of disseminated intravascular coagulopathy, jaundice, coma and immunodeficiency. Study period March 1999 to April 2000.	The child was randomised to 0.9% saline or "Haemaccel" for initial fluid resuscitation. The treatment protocol was 20ml/kg boluses of the study fluid every 10-20 minutes until blood pressure returned to normal, perfusion improved or central venous pressure was >10cmH_2O.	Random numbers kept in sealed envelopes with one of the investigators. Further details of allocation concealment not described.	Outcome measures included: restoration of plasma volume; improvement of hemodynamic status at the end of 6 hours and 12 hours of initial fluid resuscitation; the need for vasoactive drug therapy; and survival.	60 patients were enrolled. Both groups were similar with regard to haemodynamic stability at 6 and 12 hours, the need for vasoactive drugs, and survival. There was a significant difference in the amount of fluid required to produce the same haemodynamic parameters (50ml/kg in the saline group compared to 30ml/kg in the gelatin group – p=0.018 Mann Whitney U).	The fact that the study was open label and the lack of details regarding allocation concealment are weaknesses of the study. The study was not powered to demonstrate equivalence.	Therapy 1b
Barton(186)	Prospective RCT double-blinded to assess the benefit of using milrinone in circulatory shock in children. Study period	Children (aged 9 months to 15 years) with a diagnosis of septic shock and a pulmonary wedge catheter in situ. Exclusions included congenital heart	Each child was randomised to receive either placebo or an infusion of milrinone to support the circulation. Fluid therapy	Not stated.	Primary outcome was the cardiac index and systemic vascular resistance index at various times	12 patients were enrolled, 4 died. Cardiac index was significantly increased in the milrinone group, as was the SVRI when	Poor reporting of allocation of concealment may weaken the study, but the placebo and treatment were blinded to the physicians	Therapy 1b

	June 1994 to March 1995. Parameters for shock described in the study were - 4 or more of the following clinical signs: peripheral cyanosis; cold, clammy skin; capillary refill time >3 s; thready pulse; shallow breathing; tachycardia – and 4 or more of the following physiological signs: oliguria (<1ml/kg/hour); decreased CI; increased SVRI; mixed oxygen saturations<65% or >85%; metabolic acidosis; high CVP; high PCWP	abnormalities, a history of cardiac arrhythmias, serum creatinine >2.0mg/dl and thyroid abnormalities.	during the 4 hour study period was strictly controlled.		during the study.	compared with the placebo group. Deaths are not reported for the groups individually.	so they should not have been able to tell the treatment being given next.	

Table 10.1.ii Papers included in the analysis of which clinical features determine the presence of circulatory shock in a child with a reduced conscious level

10. Circulatory shock

Clinical Questions:

(ii) What are the causes of circulatory shock in children with a reduced conscious level?

Selection criteria
Criteria for choosing papers were drawn up before the search took place. Papers would be included if they were prospective cohort studies or population based studies reporting the differential diagnosis of children with circulatory shock. Studies from outside the developed world were only included if the patient demographics were similar to the population in the UK. Studies were excluded if they were retrospective studies as a complete data set could not be assured. Studies involving both children and adults were only included if the results for children could be analysed separately.

Search
A review of the Cochrane library, MEDLINE (1966-present), EMBASE (1980-present), CINAHL (1982-present), British Nursing Index (1985-present) and AMED (1985-present) was performed using the search terms below. A review of the references of the selected papers for further evidence was included in the search strategy and a hand search of five key journals in the field in the previous 12 months.

Search filters

#	Search terms	No. of articles
1	exp shock/ or exp shock, cardiogenic/ or exp shock, hemorrhagic/ or exp shock, septic/ or exp toxic shock syndrome/ or exp shock, surgical/ or exp shock, traumatic/	66854
2	exp shock/ or exp capillary leak syndrome/ or exp cardiogenic shock/ or exp hemorrhagic shock/ or exp hypovolemic shock/ or exp septic shock/ or exp toxic shock syndrome/ or exp hemorrhagic hypotension/	66878
3	exp shock/ or exp sepsis syndrome/ or exp shock, cardiogenic/ or exp shock, hemorrhagic/ or exp shock, septic/ or exp shock, surgical/ or exp shock, traumatic/	92937
4	1 or 2 or 3	93342
5	exp infant, newborn/ or exp infant/ or exp infants/	956588
6	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1465344
7	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1670568
8	5 or 6 or 7	2874741
9	exp diagnosis/ or exp diagnosis, differential/	5374285
10	cause.mp.	640714
11	(aetiology or etiology).mp. [mp=ab, hw, ti, sh, it, tn, ot, dm, mf, rw]	348067
12	9 or 10 or 11	6040083
13	exp epidemiologic studies/ or exp case-control studies/ or exp retrospective studies/ or exp cohort studies/ or exp longitudinal studies/ or exp follow-up studies/ or exp prospective studies/ or exp control groups/	1629494
14	12 and 13	714773
15	4 and 8 and 14	1313

Results
A total of 21 abstracts were reviewed from 1313 titles. No papers were selected for further review.
The hand search of journals identified no other papers for further review.
No papers were included in the final analysis.

10. Circulatory shock

Clinical Questions:

(iii) What tests should be performed in the presence of circulatory shock in children with a reduced conscious level to determine the underlying diagnosis?

Selection criteria
Criteria for choosing papers were drawn up before the search took place. Papers would be included if they were validation studies of guidelines for the management of children with circulatory shock.

Studies involving both children and adults were only included if the results for children could be analysed separately.

Search
A review of the Cochrane library, MEDLINE (1966-present), EMBASE (1980-present), CINAHL (1982-present), British Nursing Index (1985-present) and AMED (1985-present) was performed using the search terms below. A review of the references of the selected papers for further evidence was included in the search strategy and a hand search of five key journals in the field in the previous 12 months.

Search filters

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	956588
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1465344
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1670568
4	1 or 2 or 3	2874741
5	exp shock/ or exp shock, cardiogenic/ or exp shock, hemorrhagic/ or exp shock, septic/ or exp toxic shock syndrome/ or exp shock, surgical/ or exp shock, traumatic/	66854
6	exp shock/ or exp capillary leak syndrome/ or exp cardiogenic shock/ or exp hemorrhagic shock/ or exp hypovolemic shock/ or exp septic shock/ or exp toxic shock syndrome/ or exp hemorrhagic hypotension/	66878
7	exp shock/ or exp sepsis syndrome/ or exp shock, cardiogenic/ or exp shock, hemorrhagic/ or exp shock, septic/ or exp shock, surgical/ or exp shock, traumatic/	92937
8	5 or 6 or 7	93342
9	guideline$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	223821
10	validat$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	168454
11	9 or 10	386657
12	4 and 8 and 11	240

Results
A total of 4 abstracts were reviewed from 240 titles. 3 papers were selected for further review. The hand search of journals and references identified no other papers for further review.
No papers were included in the final analysis.

Papers excluded from the final analysis are listed in table 10.3.i

Reference	**Reason for exclusion**
Carcillo(179)	A consensus conference paper regarding paediatric septic shock. No validation.
Delinger(180)	A consensus conference paper regarding adult and paediatric septic shock. No validation.
English(187)	Retrospective validation of guideline for diagnostic decision rules in developing countries. No validation on investigations or treatments.

Table 10.3.i Papers excluded from the analysis of which tests to perform in the presence of circulatory shock in children with a reduced conscious level.

10. Circulatory shock

Clinical Questions:

(iv) What fluid therapy should be initiated in the presence of circulatory shock in children with a reduced conscious level?

Selection criteria
Criteria for choosing papers were drawn up before the search took place. Papers would be included if they were randomised controlled trials of children in circulatory shock to determine which fluid regime improves outcome or markers of outcome. Validation studies of guidelines for the management of children with circulatory shock would also be included if they demonstrated benefit

of following the guideline and gave advice on the fluid regime to use. Studies involving both children and adults were only included if the results for children could be analysed separately.

Search
A review of the Cochrane library, MEDLINE (1966-present), EMBASE (1980-present), CINAHL (1982-present), British Nursing Index (1985-present) and AMED (1985-present) was performed using the search terms below. A review of the references of the selected papers for further evidence was included in the search strategy and a hand search of five key journals in the field in the previous 12 months.

Search filters

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	956588
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1465344
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1670568
4	1 or 2 or 3	2874741
5	exp shock/ or exp shock, cardiogenic/ or exp shock, hemorrhagic/ or exp shock, septic/ or exp toxic shock syndrome/ or exp shock, surgical/ or exp shock, traumatic/	66854
6	exp shock/ or exp capillary leak syndrome/ or exp cardiogenic shock/ or exp hemorrhagic shock/ or exp hypovolemic shock/ or exp septic shock/ or exp toxic shock syndrome/ or exp hemorrhagic hypotension/	66878
7	exp shock/ or exp sepsis syndrome/ or exp shock, cardiogenic/ or exp shock, hemorrhagic/ or exp shock, septic/ or exp shock, surgical/ or exp shock, traumatic/	92937
8	5 or 6 or 7	93342
9	RANDOMIZED CONTROLLED TRIAL.pt.	203760
10	CONTROLLED CLINICAL TRIAL.pt.	68822
11	randomized controlled trials.sh.	39409
12	random allocation.sh.	53667
13	double blind method.sh.	82602
14	single blind method.sh.	9092
15	or/9-14	348114
16	Animal.sh.	15951
17	human.sh.	4964488
18	16 not 17	12976
19	15 not 18	348114
20	clinical trial.pt.	424866
21	exp clinical trials/	560031
22	(clin$ adj25 trial$).ti,ab.	229209
23	((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.	166094
24	placebos.sh.	27066
25	placebo$.ti,ab.	183949
26	random$.ti,ab.	631995
27	research design.sh.	42731
28	or/20-27	1421286
29	28 not 18	1421147
30	comparative study.sh.	1272338
31	exp evaluation studies/	569635
32	follow up studies.sh.	302944
33	prospective studies.sh.	229002
34	(control$ or prospectiv$ or volunteer$).ti,ab.	2987641
35	or/30-34	4635476
36	35 not 18	4634044
37	19 or 29 or 36	5297606
38	exp Colloids/ or exp Fluid Therapy/	101724
39	colloid$.mp.	40937
40	crystalloid$.mp.	7036
41	fluid$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	483931
42	saline.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	156841
43	albumin.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	167715

44	dextran.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	39479
45	ringer$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	19047
46	Intravenous Therapy.sh.	2299
47	exp Intravenous Therapy/ or exp Plasma Substitutes/ or exp Solutions/ or exp CRYSTALLOID SOLUTIONS/ or exp Albumins/	295706
48	exp "Fluids and Secretions"/	927516
49	exp Colloids/ad, ae, pd, tu [Administration and Dosage, Adverse Effects, Pharmacodynamics, Therapeutic use]	5259
50	exp ALBUMIN TC 99M COLLOID/ or exp COLLOID/	7752
51	exp CRYSTALLOID/	1652
52	exp Liquid/	8122
53	or/38-52	1813223
54	4 and 8 and 37 and 53	539

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	956588
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1465344
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1670568
4	1 or 2 or 3	2874741
5	exp shock/ or exp shock, cardiogenic/ or exp shock, hemorrhagic/ or exp shock, septic/ or exp toxic shock syndrome/ or exp shock, surgical/ or exp shock, traumatic/	66854
6	exp shock/ or exp capillary leak syndrome/ or exp cardiogenic shock/ or exp hemorrhagic shock/ or exp hypovolemic shock/ or exp septic shock/ or exp toxic shock syndrome/ or exp hemorrhagic hypotension/	66878
7	exp shock/ or exp sepsis syndrome/ or exp shock, cardiogenic/ or exp shock, hemorrhagic/ or exp shock, septic/ or exp shock, surgical/ or exp shock, traumatic/	92937
8	5 or 6 or 7	93342
9	guideline$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	223821
10	validat$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	168454
11	9 or 10	386657
12	4 and 8 and 11	240

Results

A total of 33 abstracts were reviewed from 779 titles. 9 papers were selected for further review. The hand search of journals and references identified one other paper for further review.

Three papers were included in the final analysis.

Papers excluded from the final analysis are listed in table 10.4.i

Papers included in the final analysis are listed in table 10.4.ii

Reference	**Reason for exclusion**
Roberts(170)	Systematic review of randomised controlled trials including mainly adult data and only one study from children with shock(171)
Alderson(172)	Systematic review of randomised controlled trials including mainly adult data and no studies from children with shock. There were six studies included involving preterm infants, but these were not analysed separately and are outside the scope of this guideline
Bunn(174)	Systematic review of randomised controlled trials of different fluid regimes including mainly adult data and no studies from children with shock. There were four studies(175-178) of children included in the analysis undergoing surgery but not in shock.
Carcillo(179)	A consensus conference paper regarding paediatric septic shock. Only one RCT was included(171). No validation that following this guideline improves outcome.
Delinger(180)	A consensus conference paper regarding adult and paediatric septic shock. Only one paediatric RCT was included(171). No validation in children that following this guideline improves outcome.
Saladino(182)	Guideline without validation
Han(183)	Retrospective study of outcomes, using consensus definition of shock(179)

Table 10.4.i Papers excluded from the analysis of which fluid therapy should be initiated in the presence of circulatory shock in children

Study	Methods	Participants	Interventions	Allocation concealment	Outcomes	Results	Notes	Evidence level
Nhan(171)	Prospective RCT double-blinded to assess the benefit of using different resuscitation fluid in circulatory shock in children. Parameters of shock described in the study included weak rapid pulse, pulse pressure <20mmHg, no detectable BP.	Children (aged 1 – 15 years) presenting to a hospital in Vietnam with a clinical diagnosis of dengue haemorrhagic fever (DHF) grade 3 or 4 (as classified by WHO), who had not received any intravenous fluid during the course of their illness prior to presentation. Exclusions included those who were likely to need a blood transfusion due to the haemorrhagic illness and those with a chronic disorder. Study period September 1996 to September 1997.	The child was randomised to one of four different fluid regimes: dextran 70 (colloid); 3% gelatin (colloid); lactated Ringer's (crystalloid); and normal saline (crystalloid). Children with grade 3 DHF received the study fluid at a rate of 20ml/kg over the first hour. Children with grade 4 DHF received the study fluid at a rate of 20ml/kg over 15 minutes followed by a second 20ml/kg bolus of the study fluid over the next hour. After the initial therapy all children received lactated	Opaque sealed envelopes containing only the treatment pack number were randomised in blocks of 10. The treatment packs contained three 500ml bags of the trial fluid all wrapped in black insulating tape so as to not reveal the identity of the trial fluid. The identity of the study fluid was attached to the child's notes in an opaque sealed envelope.	Primary outcomes: 1) Recovery from shock - the time for the pulse pressure to recover to normal defined as >30mmHg (as an indication of the successful treatment of shock). 2) Relapse -the time for the pulse pressure to relapse to <20mmHg having recovered to >30mmHg. Secondary outcomes: drop in pulse rate after first hour; complications of fluid therapy; total fluid therapy required	230 children recruited (8 having grade 4 DHF). Due to the small number of those with grade 4 DHF the analysis was limited to the 222 children with grade 3 DHF. There was a significant difference in the recovery from shock between dextran and normal saline with more rapid recovery found with the dextran solution. There was also a significant difference in the amount of extra dextran required following the study fluid regime, with those receiving dextran initially requiring the least and those	There were differences between the 4 study arms in the severity of disease in the 222 children with grade 3 DHF as measured by pulse volume at presentation. Only a few children were randomised into the dextran group with pulse pressures <10mmHg. This may have biased the results towards favouring the Dextran group. Subgroup analysis of those children with initial pulse pressure <10mmHg still showed a significant difference between gelatin and lactated Ringer's (favouring	Therapy 1b

			Ringer's solution according to the WHO guidelines and further boluses of dextran 70 as determined by the attending physician.			receiving lactated Ringer's requiring the most. There were no deaths in this study.	gelatin – OR 5.76; CI 1.36-23.59). No difference was seen between lactated Ringer's and normal saline.	
Dung(184)	Prospective RCT double-blinded to assess the benefit of using different resuscitation fluid in circulatory shock in children. Parameters of shock described in the study were pulse pressure, pulse rate, blood pressure, cold extremities.	Children (aged 5 – 15 years) presenting to a hospital in Vietnam with a clinical diagnosis of dengue haemorrhagic fever (DHF) grade 3 (as classified by WHO), who had not received any intravenous fluid during the course of their illness prior to presentation. Study period July 1995 to November 1995.	The child was randomised to one of four different fluid regimes: dextran 70 (colloid); gelafundin (colloid); lactated Ringer's (crystalloid); and normal saline (crystalloid). Children with grade 3 DHF received the study fluid at a rate of 20ml/kg over the first hour, followed by 10ml/kg over the next hour. After the initial therapy all children received open label therapy according to	Opaque sealed envelopes containing only the treatment pack number were randomised in blocks of 10. The treatment packs contained three 500ml bags of the trial fluid all wrapped in black insulating tape so as to not reveal the identity of the trial fluid.	Primary outcomes: 1) Recovery from shock - the time for the pulse pressure to recover to normal defined as >20mmHg. 2) Number of episodes of shock.	50 children were enrolled. No differences were seen between the study arms for the recovery time from shock.	Secondary outcome measures such as recovery of haematological variables and cardiac parameters improved more rapidly in the groups receiving colloids, but the study was not designed to combine the treatment arms in this way. The study was not powered to determine equivalence.	Therapy 1b

			the WHO guidelines.					
Upadhyay (185)	Prospective randomized open label trial to assess the benefits of one type of fluid therapy over another in pediatric resuscitation of septic shock. Parameters for shock described in the study were hypotension, or three of the following: decreased pulse volume, capillary refill time >3 seconds, tachycardia, urine output <1ml/kg/hour.	Children (aged 1 month to 12 years) with septic shock (clear criteria described) presenting to paediatric emergency or intensive care unit of a hospital in India. Exclusion criteria included presence of disseminated intravascular coagulopathy, jaundice, coma and immunodeficiency. Study period March 1999 to April 2000.	The child was randomised to 0.9% saline or "Haemaccel" for initial fluid resuscitation. The treatment protocol was 20ml/kg boluses of the study fluid every 10-20 minutes until blood pressure returned to normal, perfusion improved or central venous pressure was >10cmH_2O.	Random numbers kept in sealed envelopes with one of the investigators. Further details of allocation concealment not described.	Outcome measures included: restoration of plasma volume; improvement of hemodynamic status at the end of 6 hours and 12 hours of initial fluid resuscitation; the need for vasoactive drug therapy; and survival.	60 patients were enrolled. Both groups were similar with regard to haemodynamic stability at 6 and 12 hours, the need for vasoactive drugs, and survival. There was a significant difference in the amount of fluid required to produce the same haemodynamic parameters (50ml/kg in the saline group compared to 30ml/kg in the gelatin group – p=0.018 Mann Whitney U).	The fact that the study was open label and the lack of details regarding allocation concealment are weaknesses of the study. The study was not powered to demonstrate equivalence.	Therapy 1b

Table 10.4.ii Papers included in the analysis of which fluid therapy should be initiated in the presence of circulatory shock in children

10. Circulatory shock

Clinical Questions:

(v) What monitoring should be initiated in the presence of circulatory shock in children with a reduced conscious level?

Selection criteria
Criteria for choosing papers were drawn up before the search took place. Papers would be included if they were randomised controlled trials of children in circulatory shock to determine which monitoring improves outcome or markers of outcome. Validation studies of guidelines for the management of children with circulatory shock would also be included if they demonstrated benefit of following the guideline and gave advice on the monitoring to use. Studies involving both children and adults were only included if the results for children could be analysed separately.

Search
A review of the Cochrane library, MEDLINE (1966-present), EMBASE (1980-present), CINAHL (1982-present), British Nursing Index (1985-present) and AMED (1985-present) was performed using the search terms below. A review of the references of the selected papers for further evidence was included in the search strategy and a hand search of five key journals in the field in the previous 12 months.

Search filters

#	Search terms	No. of articles
1	RANDOMIZED CONTROLLED TRIAL.pt.	203760
2	CONTROLLED CLINICAL TRIAL.pt.	68822
3	randomized controlled trials.sh.	39409
4	random allocation.sh.	53667
5	double blind method.sh.	82602
6	single blind method.sh.	9092
7	or/1-6	348114
8	Animal.sh.	15951
9	human.sh.	4964488
10	8 not 9	12976
11	7 not 10	348114
12	clinical trial.pt.	424866
13	exp clinical trials/	560031
14	(clin$ adj25 trial$).ti,ab.	229209
15	((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.	166094
16	placebos.sh.	27066
17	placebo$.ti,ab.	183949
18	random$.ti,ab.	631995
19	research design.sh.	42731
20	or/12-19	1421286
21	20 not 10	1421147
22	follow up studies.sh.	302944
23	prospective studies.sh.	229002
24	(control$ or prospectiv$ or volunteer$).ti,ab.	2987641
25	comparative study.sh.	1272338
26	exp evaluation studies/	569635
27	22 or 23 or 24 or 25 or 26	4635476
28	27 not 10	4634044
29	11 or 21 or 28	5296174
30	exp shock/ or exp shock, cardiogenic/ or exp shock, hemorrhagic/ or exp shock, septic/ or exp toxic shock syndrome/ or exp shock, surgical/ or exp shock, traumatic/	66854
31	exp shock/ or exp capillary leak syndrome/ or exp cardiogenic shock/ or exp hemorrhagic shock/ or exp hypovolemic shock/ or exp septic shock/ or exp toxic shock syndrome/ or exp hemorrhagic hypotension/	66878
32	exp shock/ or exp sepsis syndrome/ or exp shock, cardiogenic/ or exp shock, hemorrhagic/ or exp shock, septic/ or exp shock, surgical/ or exp shock, traumatic/	92937

33	30 or 31 or 32	93342
34	exp infant, newborn/ or exp infant/ or exp infants/	963219
35	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1477820
36	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1683963
37	34 or 35 or 36	2897462
38	monitor$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	644127
39	central venous line$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1045
40	central venous pressure$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	10088
41	arterial line$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1480
42	invasive blood pressure$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	642
43	pulse pressure$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	6247
44	or/38-43	659177
45	44 and 37 and 33 and 29	214

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	956588
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1465344
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1670568
4	1 or 2 or 3	2874741
5	exp shock/ or exp shock, cardiogenic/ or exp shock, hemorrhagic/ or exp shock, septic/ or exp toxic shock syndrome/ or exp shock, surgical/ or exp shock, traumatic/	66854
6	exp shock/ or exp capillary leak syndrome/ or exp cardiogenic shock/ or exp hemorrhagic shock/ or exp hypovolemic shock/ or exp septic shock/ or exp toxic shock syndrome/ or exp hemorrhagic hypotension/	66878
7	exp shock/ or exp sepsis syndrome/ or exp shock, cardiogenic/ or exp shock, hemorrhagic/ or exp shock, septic/ or exp shock, surgical/ or exp shock, traumatic/	92937
8	5 or 6 or 7	93342
9	guideline$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	223821
10	validat$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	168454
11	9 or 10	386657
12	4 and 8 and 11	240

Results
A total of 10 abstracts were reviewed from 454 titles. 3 papers were selected for further review. The hand search of journals and references identified no other papers for further review.
No papers were included in the final analysis.

Papers excluded from the final analysis are listed in table 10.5.i

Reference	**Reason for exclusion**
Holm(188)	Adult patients only.
Abou-Khalil(189)	Adult patients only.
Mendez Tena(190)	Foreign language paper.

Table 10.5.i Papers excluded from the analysis of what monitoring should be initiated in the presence of circulatory shock in children

10. Circulatory shock

Clinical Questions:

(vi) How much fluid is required for the treatment of circulatory shock in children with a reduced conscious level?

Selection criteria
Criteria for choosing papers were drawn up before the search took place. Papers would be included if they were randomised controlled trials of children in circulatory shock to determine which fluid regime improves outcome or markers of outcome. Validation studies of guidelines for the management of children with circulatory shock would also be included if they demonstrated benefit

of following the guideline and gave advice on the volume of fluid to use. Cohort studies describing the median fluid requirements for children with circulatory shock would be included if they were prospective and had clear entry criteria and a significant follow up period. Studies involving both children and adults were only included if the results for children could be analysed separately.

Search
A review of the Cochrane library, MEDLINE (1966-present), EMBASE (1980-present), CINAHL (1982-present), British Nursing Index (1985-present) and AMED (1985-present) was performed using the search terms below. A review of the references of the selected papers for further evidence was included in the search strategy and a hand search of five key journals in the field in the previous 12 months.

Search filters

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	956588
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1465344
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1670568
4	1 or 2 or 3	2874741
5	exp shock/ or exp shock, cardiogenic/ or exp shock, hemorrhagic/ or exp shock, septic/ or exp toxic shock syndrome/ or exp shock, surgical/ or exp shock, traumatic/	66854
6	exp shock/ or exp capillary leak syndrome/ or exp cardiogenic shock/ or exp hemorrhagic shock/ or exp hypovolemic shock/ or exp septic shock/ or exp toxic shock syndrome/ or exp hemorrhagic hypotension/	66878
7	exp shock/ or exp sepsis syndrome/ or exp shock, cardiogenic/ or exp shock, hemorrhagic/ or exp shock, septic/ or exp shock, surgical/ or exp shock, traumatic/	92937
8	5 or 6 or 7	93342
9	RANDOMIZED CONTROLLED TRIAL.pt.	203760
10	CONTROLLED CLINICAL TRIAL.pt.	68822
11	randomized controlled trials.sh.	39409
12	random allocation.sh.	53667
13	double blind method.sh.	82602
14	single blind method.sh.	9092
15	or/9-14	348114
16	Animal.sh.	15951
17	human.sh.	4964488
18	16 not 17	12976
19	15 not 18	348114
20	clinical trial.pt.	424866
21	exp clinical trials/	560031
22	(clin$ adj25 trial$).ti,ab.	229209
23	((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.	166094
24	placebos.sh.	27066
25	placebo$.ti,ab.	183949
26	random$.ti,ab.	631995
27	research design.sh.	42731
28	or/20-27	1421286
29	28 not 18	1421147
30	comparative study.sh.	1272338
31	exp evaluation studies/	569635
32	follow up studies.sh.	302944
33	prospective studies.sh.	229002
34	(control$ or prospectiv$ or volunteer$).ti,ab.	2987641
35	or/30-34	4635476
36	35 not 18	4634044
37	19 or 29 or 36	5297606
38	exp Colloids/ or exp Fluid Therapy/	101724
39	colloid$.mp.	40937
40	crystalloid$.mp.	7036
41	fluid$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	483931

42	saline.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	156841
43	albumin.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	167715
44	dextran.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	39479
45	ringer$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	19047
46	Intravenous Therapy.sh.	2299
47	exp Intravenous Therapy/ or exp Plasma Substitutes/ or exp Solutions/ or exp CRYSTALLOID SOLUTIONS/ or exp Albumins/	295706
48	exp "Fluids and Secretions"/	927516
49	exp Colloids/ad, ae, pd, tu [Administration and Dosage, Adverse Effects, Pharmacodynamics, Therapeutic use]	5259
50	exp ALBUMIN TC 99M COLLOID/ or exp COLLOID/	7752
51	exp CRYSTALLOID/	1652
52	exp Liquid/	8122
53	or/38-52	1813223
54	4 and 8 and 37 and 53	539

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	956588
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1465344
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1670568
4	1 or 2 or 3	2874741
5	exp shock/ or exp shock, cardiogenic/ or exp shock, hemorrhagic/ or exp shock, septic/ or exp toxic shock syndrome/ or exp shock, surgical/ or exp shock, traumatic/	66854
6	exp shock/ or exp capillary leak syndrome/ or exp cardiogenic shock/ or exp hemorrhagic shock/ or exp hypovolemic shock/ or exp septic shock/ or exp toxic shock syndrome/ or exp hemorrhagic hypotension/	66878
7	exp shock/ or exp sepsis syndrome/ or exp shock, cardiogenic/ or exp shock, hemorrhagic/ or exp shock, septic/ or exp shock, surgical/ or exp shock, traumatic/	92937
8	5 or 6 or 7	93342
9	guideline$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	223821
10	validat$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	168454
11	9 or 10	386657
12	4 and 8 and 11	240

#	Search terms	No. of articles
1	exp shock/ or exp shock, cardiogenic/ or exp shock, hemorrhagic/ or exp shock, septic/ or exp toxic shock syndrome/ or exp shock, surgical/ or exp shock, traumatic/	66854
2	exp shock/ or exp capillary leak syndrome/ or exp cardiogenic shock/ or exp hemorrhagic shock/ or exp hypovolemic shock/ or exp septic shock/ or exp toxic shock syndrome/ or exp hemorrhagic hypotension/	66878
3	exp shock/ or exp sepsis syndrome/ or exp shock, cardiogenic/ or exp shock, hemorrhagic/ or exp shock, septic/ or exp shock, surgical/ or exp shock, traumatic/	92937
4	1 or 2 or 3	93342
5	exp infant, newborn/ or exp infant/ or exp infants/	963219
6	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1477820
7	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1683963
8	5 or 6 or 7	2897462
9	exp Colloids/ or exp Fluid Therapy/	101724
10	colloid$.mp.	40937
11	crystalloid$.mp.	7036
12	fluid$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	483931
13	saline.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	156841
14	albumin.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	167715
15	dextran.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	39479
16	ringer$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	19047
17	Intravenous Therapy.sh.	2299
18	exp Intravenous Therapy/ or exp Plasma Substitutes/ or exp Solutions/ or exp CRYSTALLOID SOLUTIONS/ or exp Albumins/	295706
19	exp "Fluids and Secretions"/	927516

20	exp Colloids/ad, ae, pd, tu [Administration and Dosage, Adverse Effects, Pharmacodynamics, Therapeutic use]	5259
21	exp ALBUMIN TC 99M COLLOID/ or exp COLLOID/	7752
22	exp CRYSTALLOID/	1652
23	exp Liquid/	8122
24	or/9-23	1813223
25	prognos$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	510706
26	(first and episode).mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	16764
27	cohort.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	178118
28	25 or 26 or 27	687973
29	4 and 8 and 24 and 28	209

Results
A total of 45 abstracts were reviewed from 988 titles. 6 papers were selected for further review. The hand search of journals and references identified one other paper for further review.
3 papers were included in the final analysis.

Papers excluded from the final analysis are listed in table 10.6.i
Papers included in the final analysis are listed in table 10.6.ii(a) and (b)

Reference	**Reason for exclusion**
Mercier(191)	Retrospective case series.
Dung(184)	RCT of different fluid regimes in children with septic shock. No reporting of median fluid requirements in these children.
Barton(186)	RCT of milrinone in children with septic shock. No reporting of median fluid requirements in these children.
Booy(192)	Retrospective cohort to determine changing patterns of survival in meningococcal disease. No reporting of median fluid requirements in these children.

Table 10.6.i Papers excluded from the analysis of the amount of fluid required for resuscitation children in circulatory shock

Study	Methods	Participants	Interventions	Allocation concealment	Outcomes	Results	Notes	Evidence level
Nhan(171)	Prospective RCT double-blinded to assess the benefit of using different resuscitation fluid in circulatory shock in children. Study period September 1996 to September 1997. Parameters of shock described in the study included weak rapid pulse, pulse pressure <20mmHg, no detectable BP.	Children (aged 1 – 15 years) presenting to a hospital in Vietnam with a clinical diagnosis of dengue haemorrhagic fever (DHF) grade 3 or 4 (as classified by WHO), who had not received any intravenous fluid during the course of their illness prior to presentation. Exclusions included those who were likely to need a blood transfusion due to the haemorrhagic illness and those with a chronic disorder.	The child was randomised to one of four different fluid regimes: dextran 70 (colloid); 3% gelatin (colloid); lactated Ringer's (crystalloid); and normal saline (crystalloid). Children with grade 3 DHF received the study fluid at a rate of 20ml/kg over the first hour. Children with grade 4 DHF received the study fluid at a rate of 20ml/kg over 15 minutes followed by a second 20ml/kg bolus of the study fluid over the next hour. After the initial therapy all children received lactated Ringer's solution	Opaque sealed envelopes containing only the treatment pack number were randomised in blocks of 10. The treatment packs contained three 500ml bags of the trial fluid all wrapped in black insulating tape so as to not reveal the identity of the trial fluid. The identity of the study fluid was attached to the child's notes in an opaque sealed envelope.	Primary outcomes: 1) Recovery from shock - the time for the pulse pressure to recover to normal defined as >30mmHg (as an indication of the successful treatment of shock). 2) Relapse -the time for the pulse pressure to relapse to <20mmHg having recovered to >30mmHg. Secondary outcomes: drop in pulse rate after first hour; complications of fluid therapy; total fluid therapy required	230 children recruited (8 having grade 4 DHF). Due to the small number of those with grade 4 DHF the analysis was limited to the 222 children with grade 3 DHF. There was a significant difference in the recovery from shock between dextran and normal saline with more rapid recovery found with the dextran solution. There was also a significant difference in the amount of extra dextran required following the study fluid regime, with those receiving dextran initially requiring the least and those receiving lactated Ringer's requiring the most. There were no deaths in this	In all the cases who initially had a pulse pressure of <10mmHg (n=55), 49% of them required further fluid boluses after their intial 40ml/kg. The median extra fluid required in these patients was 33ml/kg taking the total fluid given as boluses to 73ml/kg to reverse the shock.	Therapy 1b

			according to the WHO guidelines and further boluses of dextran 70 as determined by the attending physician.			study.		
Upadhyay (185)	Prospective randomized open label trial to assess the benefits of one type of fluid therapy over another in pediatric resuscitation of septic shock. Parameters for shock described in the study were hypotension, or three of the following: decreased pulse volume, capillary refill time >3 seconds, tachycardia, urine output <1ml/kg/hour.	Children (aged 1 month to 12 years) with septic shock (clear criteria described) presenting to paediatric emergency or intensive care unit of a hospital in India. Exclusion criteria included presence of disseminated intravascular coagulopathy, jaundice, coma and immunodeficiency. Study period March 1999 to April 2000.	The child was randomised to 0.9% saline or "Haemaccel" for initial fluid resuscitation. The treatment protocol was 20ml/kg boluses of the study fluid every 10-20 minutes until blood pressure returned to normal, perfusion improved or central venous pressure was >10cmH_2O.	Random numbers kept in sealed envelopes with one of the investigators. Further details of allocation concealment not described.	Outcome measures included: restoration of plasma volume; improvement of hemodynamic status at the end of 6 hours and 12 hours of initial fluid resuscitation; the need for vasoactive drug therapy; and survival.	60 patients were enrolled. Both groups were similar with regard to haemodynamic stability at 6 and 12 hours, the need for vasoactive drugs, and survival. There was a significant difference in the amount of fluid required to produce the same haemodynamic parameters (50ml/kg in the saline group compared to 30ml/kg in the gelatin group – p=0.018 Mann Whitney U).	Median volume of fluid for initial resuscitation was 50ml/kg (10^{th}-90^{th} percentile range = 20-108ml/kg) in the saline group and in the gelatine group 30ml/kg (range 20-70ml/kg).	Therapy 1b

Table 10.6.i (a) RCT papers included in the analysis of the amount of fluid required for resuscitation children in circulatory shock

Study	Methods	Participant definition	Length of follow-up	Outcomes	Results	Notes	Evidence level
Han(183)	Retrospective	Children (aged 1	To discharge	Survival to	91 children were	Median fluid therapy in	Prognosis

	cohort study of children with septic shock to determine if following recommend-ations in a guideline (developed subsequently) made a difference in survival.	month to 11 years) referred to the retrieval service with septic shock. Each child was resuscitated by the referring hospital before the retrieval team arrived. A review of the notes determined if the resuscitation had followed guidelines for septic shock in children of if they had not. Study period 1993 to 2001,	from receiving paediatric intensive care unit.	discharge.	included in the analysis. When practice was consistent with the guideline recommendations the mortality was 8% compared with 38% in those whose management did not follow the guideline.	survivors was 20ml/kg (25^{th}-75^{th} percentile range was 9.3 to 40ml/kg). In non-survivors it was 32.9ml/kg (range 6.4 to 64.1ml/kg).	2b

Table 10.6.i (b) Prognostic papers included in the analysis of the amount of fluid required for resuscitation children in circulatory shock

10. Circulatory shock

Clinical Questions:

(vii) When should intubation and ventilation be initiated for the treatment of circulatory shock in children with a reduced conscious level?

Selection criteria
Criteria for choosing papers were drawn up before the search took place. Papers would be included if they were randomised controlled trials of children in circulatory shock to determine which ventilation strategy improves outcome or markers of outcome. Validation studies of guidelines for the management of children with circulatory shock would also be included if they demonstrated benefit of following the guideline and gave advice on the ventilation strategies. Studies involving both children and adults were only included if the results for children could be analysed separately.

Search
A review of the Cochrane library, MEDLINE (1966-present), EMBASE (1980-present), CINAHL (1982-present), British Nursing Index (1985-present) and AMED (1985-present) was performed using the search terms below. A review of the references of the selected papers for further evidence was included in the search strategy and a hand search of five key journals in the field in the previous 12 months.

Search filters

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	956588
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1465344
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1670568
4	1 or 2 or 3	2874741
5	exp shock/ or exp shock, cardiogenic/ or exp shock, hemorrhagic/ or exp shock, septic/ or exp toxic shock syndrome/ or exp shock, surgical/ or exp shock, traumatic/	66854
6	exp shock/ or exp capillary leak syndrome/ or exp cardiogenic shock/ or exp hemorrhagic shock/ or exp hypovolemic shock/ or exp septic shock/ or exp toxic shock syndrome/ or exp hemorrhagic hypotension/	66878
7	exp shock/ or exp sepsis syndrome/ or exp shock, cardiogenic/ or exp shock, hemorrhagic/ or exp shock, septic/ or exp shock, surgical/ or exp shock, traumatic/	92937
8	5 or 6 or 7	93342
9	RANDOMIZED CONTROLLED TRIAL.pt.	203760
10	CONTROLLED CLINICAL TRIAL.pt.	68822
11	randomized controlled trials.sh.	39409
12	random allocation.sh.	53667
13	double blind method.sh.	82602
14	single blind method.sh.	9092
15	or/9-14	348114
16	Animal.sh.	15951
17	human.sh.	4964488
18	16 not 17	12976
19	15 not 18	348114
20	clinical trial.pt.	424866
21	exp clinical trials/	560031
22	(clin$ adj25 trial$).ti,ab.	229209
23	((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.	166094
24	placebos.sh.	27066
25	placebo$.ti,ab.	183949
26	random$.ti,ab.	631995
27	research design.sh.	42731
28	or/20-27	1421286
29	28 not 18	1421147
30	comparative study.sh.	1272338
31	exp evaluation studies/	569635

32	follow up studies.sh.	302944
33	prospective studies.sh.	229002
34	(control$ or prospectiv$ or volunteer$).ti,ab.	2987641
35	or/30-34	4635476
36	35 not 18	4634044
37	19 or 29 or 36	5297606
38	intubat$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	72225
39	Ventilat$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	176756
40	36 or 37	232222
41	4 and 8 and 37 and 40	269

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	956588
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1465344
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1670568
4	1 or 2 or 3	2874741
5	exp shock/ or exp shock, cardiogenic/ or exp shock, hemorrhagic/ or exp shock, septic/ or exp toxic shock syndrome/ or exp shock, surgical/ or exp shock, traumatic/	66854
6	exp shock/ or exp capillary leak syndrome/ or exp cardiogenic shock/ or exp hemorrhagic shock/ or exp hypovolemic shock/ or exp septic shock/ or exp toxic shock syndrome/ or exp hemorrhagic hypotension/	66878
7	exp shock/ or exp sepsis syndrome/ or exp shock, cardiogenic/ or exp shock, hemorrhagic/ or exp shock, septic/ or exp shock, surgical/ or exp shock, traumatic/	92937
8	5 or 6 or 7	93342
9	guideline$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	223821
10	validat$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	168454
11	9 or 10	386657
12	4 and 8 and 11	240

Results
A total of 18 abstracts were reviewed from 509 titles. 6 papers were selected for further review. The hand search of journals and references identified one other paper for further review.
No papers were included in the final analysis.

Papers excluded from the final analysis are listed in table 10.7.i

Reference	**Reason for exclusion**
Roberts(170)	Systematic review of randomised controlled trials including mainly adult data and only one study from children with shock(171). Not looking at ventilation strategies.
Alderson(172)	Systematic review of randomised controlled trials including mainly adult data and no studies from children with shock. Not looking at ventilation strategies.
Bunn(174)	Systematic review of randomised controlled trials of different fluid regimes including mainly adult data and no studies from children with shock. Not looking at ventilation strategies.
Carcillo(179)	A consensus conference paper regarding paediatric septic shock. Only one RCT was included(171). No validation that following this guideline improves outcome.
Delinger(180)	A consensus conference paper regarding adult and paediatric septic shock. Only one paediatric RCT was included(171). No validation in children that following this guideline improves outcome.
Saladino(182)	Guideline without validation
Han(183)	Retrospective study of outcomes of children with shock. Not looking at ventilation strategies.

Table 10.7.i Papers excluded from the analysis of when to initiate intubation and ventilation strategies in children in circulatory shock

10. Circulatory shock

Clinical Questions:

(viii) When should specific circulatory support (including vasopressor, inotropic and vasodilatory treatments) be initiated for the treatment of circulatory shock in children with a reduced conscious level?

Selection criteria
Criteria for choosing papers were drawn up before the search took place. Papers would be included if they were randomised controlled trials of children in circulatory shock to determine which "inotropic" strategy improves outcome or markers of outcome. Validation studies of guidelines for the management of children with circulatory shock would also be included if they demonstrated benefit of following the guideline and gave advice on inotropic support of the circulation. Studies involving both children and adults were only included if the results for children could be analysed separately.

Search
A review of the Cochrane library, MEDLINE (1966-present), EMBASE (1980-present), CINAHL (1982-present), British Nursing Index (1985-present) and AMED (1985-present) was performed using the search terms below. A review of the references of the selected papers for further evidence was included in the search strategy and a hand search of five key journals in the field in the previous 12 months.

Search filters

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	956588
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1465344
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1670568
4	1 or 2 or 3	2874741
5	exp shock/ or exp shock, cardiogenic/ or exp shock, hemorrhagic/ or exp shock, septic/ or exp toxic shock syndrome/ or exp shock, surgical/ or exp shock, traumatic/	66854
6	exp shock/ or exp capillary leak syndrome/ or exp cardiogenic shock/ or exp hemorrhagic shock/ or exp hypovolemic shock/ or exp septic shock/ or exp toxic shock syndrome/ or exp hemorrhagic hypotension/	66878
7	exp shock/ or exp sepsis syndrome/ or exp shock, cardiogenic/ or exp shock, hemorrhagic/ or exp shock, septic/ or exp shock, surgical/ or exp shock, traumatic/	92937
8	5 or 6 or 7	93342
9	RANDOMIZED CONTROLLED TRIAL.pt.	203760
10	CONTROLLED CLINICAL TRIAL.pt.	68822
11	randomized controlled trials.sh.	39409
12	random allocation.sh.	53667
13	double blind method.sh.	82602
14	single blind method.sh.	9092
15	or/9-14	348114
16	Animal.sh.	15951
17	human.sh.	4964488
18	16 not 17	12976
19	15 not 18	348114
20	clinical trial.pt.	424866
21	exp clinical trials/	560031
22	(clin$ adj25 trial$).ti,ab.	229209
23	((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.	166094
24	placebos.sh.	27066
25	placebo$.ti,ab.	183949
26	random$.ti,ab.	631995
27	research design.sh.	42731
28	or/20-27	1421286
29	28 not 18	1421147
30	comparative study.sh.	1272338

31	exp evaluation studies/	569635
32	follow up studies.sh.	302944
33	prospective studies.sh.	229002
34	(control$ or prospectiv$ or volunteer$).ti,ab.	2987641
35	or/30-34	4635476
36	35 not 18	4634044
37	19 or 29 or 36	5297606
38	inotrop$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	34642
39	Vasopress$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	63489
40	vasodilat$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	118437
41	dopamine.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	179546
42	dobutamine.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	16519
43	adrenaline.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	22143
44	epinephrine.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	68401
45	noradrenaline.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	50337
46	norepinephrine.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	116798
47	milrinone.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	3941
48	nitroprusside.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	30646
49	nitroglycerin.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	18881
50	or/38-50	561995
40	4 and 8 and 37 and 50	201

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	956588
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1465344
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1670568
4	1 or 2 or 3	2874741
5	exp shock/ or exp shock, cardiogenic/ or exp shock, hemorrhagic/ or exp shock, septic/ or exp toxic shock syndrome/ or exp shock, surgical/ or exp shock, traumatic/	66854
6	exp shock/ or exp capillary leak syndrome/ or exp cardiogenic shock/ or exp hemorrhagic shock/ or exp hypovolemic shock/ or exp septic shock/ or exp toxic shock syndrome/ or exp hemorrhagic hypotension/	66878
7	exp shock/ or exp sepsis syndrome/ or exp shock, cardiogenic/ or exp shock, hemorrhagic/ or exp shock, septic/ or exp shock, surgical/ or exp shock, traumatic/	92937
8	5 or 6 or 7	93342
9	guideline$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	223821
10	validat$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	168454
11	9 or 10	386657
12	4 and 8 and 11	240

Results

A total of 16 abstracts were reviewed from 441 titles. 12 papers were selected for further review. The hand search of journals and references identified one other paper for further review.
One paper was included in the final analysis.

Papers excluded from the final analysis are listed in table 10.8.i
Papers included in the final analysis are listed in table 10.8.ii

Reference	**Reason for exclusion**
Mullner(173)	Systematic review of vasopressors for shock only including adult studies.
Matok(193)	Case series
Hamamci(194)	Case series
Eadadah(195)	Pharmacokinetic study not looking at clinically important outcomes.
Rodriguez-Nunez (196)	Case series
Ceneviva(197)	Case series
Perkin(198)	Case series
Berg(199)	Pharmacokinetic study not looking at clinically important outcomes.
Carcillo(179)	A consensus conference paper regarding paediatric septic shock. Only one RCT was included(171). No validation that following this guideline improves outcome.

Delinger(180)	A consensus conference paper regarding adult and paediatric septic shock. Only one paediatric RCT was included(171). No validation in children that following this guideline improves outcome.
Saladino(182)	Guideline without validation
Han(183)	Retrospective study of outcomes of children with shock. Not looking at ventilation strategies.

Table 10.8.i Papers excluded from the analysis of when to initiate specific circulatory support in children in circulatory shock

Study	Methods	Participants	Interventions	Allocation concealment	Outcomes	Results	Notes	Evidence level
Barton(186)	Prospective RCT double-blinded to assess the benefit of using milrinone in circulatory shock in children. Study period June 1994 to March 1995. Parameters for shock described in the study were - 4 or more of the following clinical signs: peripheral cyanosis; cold, clammy skin; capillary refill time >3 s; thready pulse; shallow breathing; tachycardia – and 4 or more of the following physiological signs: oliguria (<1ml/kg/hour); decreased CI; increased SVRI; mixed oxygen saturations<65% or >85%; metabolic acidosis; high CVP; high PCWP	Children (aged 9 months to 15 years) with a diagnosis of septic shock and a pulmonary wedge catheter in situ. Exclusions included congenital heart abnormalities, a history of cardiac arrhythmias, serum creatinine >2.0mg/dl and thyroid abnormalities.	Each child was randomised to receive either placebo or an infusion of milrinone to support the circulation. Fluid therapy during the 4 hour study period was strictly controlled.	Not stated.	Primary outcome was the cardiac index and systemic vascular resistance index at various times during the study.	12 patients were enrolled, 4 died. Cardiac index was significantly increased in the milrinone group, as was the SVRI when compared with the placebo group. Deaths are not reported for the groups individually.	The study protocol begins when children are already receiving an adrenergic agent for support of the circulation. Milrinone could only therefore be recommended as an add on agent to other inotropic agents.	Therapy 1b

Table 10.8.ii Papers included in the analysis of when to initiate specific circulatory support in children in circulatory shock

11. Sepsis

Clinical Questions:

(i) What clinical features determine the presence of sepsis in a child with a reduced conscious level?

Selection criteria
Criteria for choosing papers were drawn up before the search took place. Papers would be included if they were validation studies of guidelines for children with sepsis, if they were validation studies of clinical diagnostic decision rules for sepsis in children, or if they were randomised control trials of therapy for sepsis in children with clear entry criteria for the trial. Studies involving children with immunodeficiency or immunosuppression were excluded. Studies involving both children and adults were only included if the results for children could be analysed separately.

Search
A review of the Cochrane library, MEDLINE (1966-present), EMBASE (1980-present), CINAHL (1982-present), British Nursing Index (1985-present) and AMED (1985-present) was performed using the search terms below. A review of the references of the selected papers for further evidence was included in the search strategy and a hand search of five key journals in the field in the previous 12 months.

Search filters

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	956588
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1465344
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1670568
4	1 or 2 or 3	2874741
5	sepsis.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	82493
6	septi$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	91288
7	exp septicemia/	59182
8	exp septicaemia/	10725
9	exp sepsis/	87553
10	or/5-9	167353
11	guideline$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	223821
12	validat$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	168454
13	11 or 12	386657
14	4 and 10 and 13	615

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	956588
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1465344
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1670568
4	1 or 2 or 3	2874741
5	sepsis.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	82493
6	septi$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	91288
7	exp septicemia/	59182
8	exp septicaemia/	10725
9	exp sepsis/	87553
10	or/5-9	167353
11	decision rule.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	772
12	diagnosis.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1771627
13	validat$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	173116
14	(11 or 12) and 13	17047
15	4 and 10 and 14	40

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	956588
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1465344

3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1670568
4	1 or 2 or 3	2874741
5	sepsis.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	82493
6	septi$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	91288
7	exp septicemia/	59182
8	exp septicaemia/	10725
9	exp sepsis/	87553
10	or/5-9	167353
11	RANDOMIZED CONTROLLED TRIAL.pt.	203760
12	CONTROLLED CLINICAL TRIAL.pt.	68822
13	randomized controlled trials.sh.	39409
14	random allocation.sh.	53667
15	double blind method.sh.	82602
16	single blind method.sh.	9092
17	or/11-16	348114
18	Animal.sh.	15951
19	human.sh.	4964488
20	18 not 19	12976
21	17 not 20	348114
22	clinical trial.pt.	424866
23	exp clinical trials/	560031
24	(clin$ adj25 trial$).ti,ab.	229209
25	((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.	166094
26	placebos.sh.	27066
27	placebo$.ti,ab.	183949
28	random$.ti,ab.	631995
29	research design.sh.	42731
30	or/22-29	1421286
31	30 not 20	1421147
32	comparative study.sh.	1272338
33	exp evaluation studies/	569635
34	follow up studies.sh.	302944
35	prospective studies.sh.	229002
36	(control$ or prospectiv$ or volunteer$).ti,ab.	2987641
37	or/32-36	4635476
38	37 not 20	4634044
39	21 or 31 or 38	5297606
40	4 and 10 and 39	10874

Results
A total of 112 abstracts were reviewed from 11529 titles. 27 papers were selected for further review. The hand search of journals and references identified three other papers for further review. Nineteen papers were included in the final analysis.

Papers excluded from the final analysis are listed in table 11.1.i
Papers included in the final analysis are listed in tables 11.1.ii(a), (b) and (c)

Reference	**Reason for exclusion**
Crocker(200)	Not a clinical decision rule but a laboratory screening test for sepsis
Kornelisse(201)	Prognostic scoring rule using laboratory tests
Proulx(202)	Outcome epidemiology study not clinical prediction rule
Sharieff(203)	Guideline validation in children with fever aged less than 3 months, not trying to distinguish between high and low risk groups (all infants with fever in this study given antibiotics).
Leteurtre(204)	Outcome measures not diagnostic measures to determine which children need treatment
Olesch(205)	Retrospective review of symptoms in children with proven meningococcal disease with no controls
Baker(206)	Clinical decision rule based purely on laboratory tests.

Riordan(207)	Study of outcome scoring tools not diagnostic rules
Goldstein(208)	Consensus paper
Jacobs(209)	Cost efeectiveness study not diagnostic study
Osman (210)	Tests to determine sepsis not applied to all identified children and no mention of follow up procedure to check no septic children missed.

Table 11.1.i Papers excluded from the analysis of which clinical features determine the presence of sepsis in a child with a reduced conscious level

Study	Method	Inclusion criteria	Search	Evidence appraisal	Summarizing evidence	Results	Notes	Evidence level
Barraff(211)	Meta-analysis of studies of febrile infants to determine prevelance of bacterial illness in this group, and in sub-groups (toxic vs non-toxic and low risk vs high risk)	Trials of febrile infants less than 3 months old, reporting prevalence of bacteremia, meningitis or serious bacterial infection (SBI).	Medline from 1972 to 1991. English language only. No hand search or reference search noted.	Not discussed in detail.	Risk of having SBI in the subgroups.	Toxic vs non-toxic group: risk of having SBI was 15.2% in the toxic group and 7.4% in the non-toxic group. Using bacteraemia and bacterial meningitis as outcome this figure is still 13.6% in the toxic group but only 1.4% in the non-toxic group. High risk versus low risk: risk of having SBI was 20.6% in the high risk group compared to 2% I the low risk group. Combining bacteraemia and meningitis together risk in high risk group was 12% and low risk group 0.7%.	Using "non-toxic" as a screening test does not have a negative predictive value high enough to not miss serious bacterial infections. Low risk is a better test for not having SBI. Neither is a good test for ruling in SBI. Heterogeneity not discussed.	Diagnosis 1a-

Table 11.1.ii (a) Systematic review papers included in the analysis of which clinical features determine the presence of sepsis in a child with a reduced conscious level

Study	Methods	Participants	Diagnostic dilemma	Blinded comparison	Gold standard tested	Results	Notes	Evidence level
Ayoola (212)	Prospective derivation of a clinical decision rule to determine which children with a fever have a bacterial infection.	Children (aged 1 to 12 months) who presented with fever (rectal temperature >38C) to a hospital in Nigeria. Exclusions included children who had received antibiotics in the seven days before presentation. Study period June-November 1998.	Did the children with fever has a viral, malarial or bacterial infection?	Not stated. A positive blood culture is a relatively objective test.	Gold standard: Blood culture. Candidate test: clinical decision rule	102 infants were eligible. Bacteraemia was confirmed in 39 of these (38%). Being aged <6 months increased the risk of bacterial infection. Being restless was also associated with bacterial infection. A white blood cell count >15000/mm^3 was also associated with bacterial infection.	This was a derivation set of a clinical prediction rule. The rule may not apply to children presenting earlier in the course of illness, as in UK, or where malaria is not endemic. No sensitivity or specificity calculations made.	Diagnosis 2b
Bang(213)	Prospective derivation and validation of a clinical diagnostic decision rule to determine the signs which will predict death in untreated sepsis in neonates.	Neonates (aged 0 – 28 days) dying of sepsis in India who had been reviewed by a village health worker. Study period derivation 1995-1996 and validation 1996-1999.	Did the babies have signs of sepsis which need treating to prevent death?	Yes, the gold standard diagnosis was made without knowledge of the clinical signs found by the village health worker.	Gold standard: sepsis as the cause of death defined by an experienced neonatologist. Candidate test: Clinical signs which mothers can detect and a village health worker can assess.	763 neonates were involved in the derivation of the decision rule, with 40 deaths. Of the 40 deaths 22 were assigned to be sepsis / pneumonia. 2804 neonates were included in the validation set. 169 were treated for suspected sepsis (this did not happen during the derivation set study) and 75 died (21 with	The 2 out of seven score (including umbilical sepsis and chest indrawing) had a sensitivity of 100% and specificity of 78%. This however was only derived and not validated in a new set of patients. The rule may not apply to children	Diagnosis 2b

						sepsis). The sensitivity of using any 2 of the following: weak cry; sucking reduced; limbs loose; baby cold; vomiting in predicting death from sepsis was 90%, with a specificity of 94%. To try to improve the sensitivity of the test further analysis was done to produce a 2 out of 7 score.	presenting earlier in the course of illness, as in UK.	
Weber(214)	Prospective derivation of a clinical decision rule to determine which children presenting with possible signs of infection have a bacterial infection.	Infants (aged 0 – 59 days) presenting to a number of centres in Ethiopia, The Gambia, Papua New Guinea and the Philipines. Study period not stated.	Did children with a list of signs and symptoms have a bacterial infection (sepsis, meningitis or pneumonia)?	Not stated. A positive blood culture is a relatively objective test. The chest radiographs were all blindly assessed.	Gold standard: positive blood culture, positive CSF culture or chest X-ray positive for pneumonia (assessed by three independent radiologists). Candidate test: clinical signs and symptoms. (List of 9 symptoms or signs: feeding ability reduced; no spontaneous movement; temperature >38C; increased	3344 infants met inclusion criteria (41 had missing data). 1809 underwent blood culture testing. 401 had an LP. 78% had “no major disease”; 10% had “pneumonia or mild hypoxaemia”; 11% had bacteraemia, meningitis or severe hypoxaemia. 6% died. The clinical rule derived included a list of 9 signs / symptoms, the	The derivation set did not all have blood cultures taken so the number of children with sepsis is not truly known. The rule may not apply to children presenting earlier in the course of illness, as in UK.	Diagnosis 4

					capillary refill time; lower chest wall indrawing; respiratory rate >60; grunting; cyanosis; history of convulsion.	presence of any one of these signs had a sensitivity of 83% and a specificity of 62%.		
Dagan(215)	Prospective study to determine which infants with fever are at low risk of serious bacterial infections.	Children (aged 0 – 2 months) with fever (rectal temperature >38C) presenting to a hospital in Israel. Study period February 1985 to July 1986.	Did the infants have bacteraemia or meningitis or pneumonia requiring hospitalisation and treatment or could they be sent home?	Not stated	Gold standard: positive culture of blood, CSF or positive chest X-ray. Candidate test: clinical signs and laboratory tests. Low risk group = no findings of soft tissue infection / joint infection or otitis media; normal white blood cell count; normal urine; and <25 WBC/high powered field in microscopic stool examination.	237 febrile infants were enrolled. 148 were in the low risk group. None of these infants had serious bacterial infection –100%, specificity, 24% sensitivity.	Emphasis in this study on specificity not sensitivity. The study excluded those who looked septic therefore this rule only applies to those where there is uncertainty of sepsis.	Diagnosis 1b
Brogan (216)	Retrospective and prospective study to determine the number of children with fever and petechiae who can be identified as having serious bacterial infection on the basis of simple clinical	Children (aged 2 months to 15 years) who presented to a paediatric assessment unit in the UK with fever (>37.4C) and a petechial rash (<2mm pinpoint bruising). Study period November 1997 to April 1998 (retrospective) and	Did the children with fever and petechiae have bacterial infection needing treating?	Not stated.	Gold standard: Blood culture. Candidate test: combination of clinical signs and simple laboratory tests. Clinial signs = shock; irritability; lethargy. Laboratory signs = WBC outside 5-	55 children eligible of which 33 had blood cultures performed. 5 patients had positive blood culture. The sensitivity of the screening for tests for a positive blood culture was 100%	This study did not perform the gold standard in all the population and made no attempt to ensure that a true positive case had not been missed.	Diagnosis 4

	evaluation.	July 1998 to January 1999 (prospective).			15 x 10^9/l range; CRP > 5mg/l. "Unwell" was defined as one or more of the factors above.	with specificity 57%.		
Wells(217)	Prospective study to determine the rate of meningococcal disease in children with a non-blanching rash and various clinical and laboratory signs.	Children (aged <15 years) presenting to a hospital in UK, with a non-blanching rash. Study period November 1998 to October 1999.	Which children with a non-blanching rash had meningococcal disease?	Not stated, but all children regardless of their clinical condition were investigated with the gold standard test of blood culture and PCR for meningococcal infection.	Gold standard: Blood culture and PCR for meningo-coccaemia. Candidate test: clinical signs and simple laboratory tests.	233 children (2.5% of children presenting over the year with a medical condition) had a non-blanching rash. 15 children were excluded because of an obvious other cause for the rash (e.g. HSP, ITP). 24 of the 218 had proven meningococcal disease. 5 children with culture and PCR negative results were suspected of having meningococcal disease clinically but were counted in the non-meningococcal group. The ability of individual findings to predict meningococcal disease were: "being ill" (toxic,	This study is a derivation of a clinical decision rule but there is no prospective evaluation performed.	Diagnosis 2b

						irritable, inconsolable, or lethargic) sensitivity 79%, specificity 81%; capillary refill time <2s sensitivity 83%, specificity 85%; CRP <6mg/l sensitivity 100%, specificity 54%.		
Mandl(218)	Prospective study to determine the prediction of bacteraemia in children with fever and petechiae using screening tests of clinical signs and simple laboratory tests.	Children (aged <18 years) preneting to an emergency department in USA, with fever (temperature >38C) and petechiae. Exclusions included all those with history of malignancy, AIDS, or chronic haematological condition. Study period December 1993 to June 1995.	Did the presence of various signs predict bacteraemia in children with fever and petechial rash?	Not stated. However, blood culture results are fairly objectively interpreted.	Gold standard: positive blood culture or a negative blood culture but clinical sepsis (as defined by Bone(219)). Candidate test: various clinical signs and simple laboratory tests.	418 children were enrolled, 393 (95%) had blood cultures taken. Only 8 (1.9%) had bacteraemia or clinical sepsis. 357 of the patients were described as well. If described as “ill” (toxic, lethargic or inconsolable) the sensitivity was 100% with a specificity of 88%. WBC >15000/mm^3 or <5000/mm^3 had a sensitivity of 100% specificity 64%.	Dervation of a clinical decision rule. No validation process. Very low incidence of bacteraemia in this study 1.9%.	Diagnosis 2b
Bachur(220)	Retrospective review of children presenting with fever to determine if any signs or simple laboratory tests	Infants (aged <90 days) presenting to an emergency department in USA with fever (>38C). Study period 1993 to 1999.	Did infants with fever have serious bacterial infection?	No retrospective analysis.	Gold standard: positive blood, CSF or urine culture or a pneumonia reported on X-ray.	5279 infants with fever were reviewed. 373 (7%) had serious bacterial illness. The sensitivity with which high	Derivation of a decision rule. Not all patients had all the tests, but over 85% did.	Diagnosis 2b

	were predictive of serious bacterial infection.				Candidate test: Being ill, and simple laboratory tests.	risk infants (with one or more of the following: age <13 days; WBC <4100/mm^3; WBC >20000mm^3; temp >39.6C; positive urinalysis) predicted serious bacterial infection was 82% with a specificity of 76%.		
Isaacman (221)	Retrospective review of children with fever to determine any clinical predictors of serious bacterial infection. A second case-control study was performed to analyse the validity of the decision rule.	Children (aged 3 to 36 months) presenting to the emergency department in USA with fever (not defined) and who had had both a blood culture and full blood count sent. Study period December 1995 to December 1996 (retrospective derivation study) and December 1996 to August 1997 (case-control validation study).	Which children with fever have bacteraemia?	No as retrospective analysis.	Gold standard: positive blood culture. Candidate tests: being unwell, age, gender, laboratory tests of WBC and others.	633 patients in the derivation set. 12% had bacteraemia. The model derived used a multiple of temperature, neutrophil count and gender. From this cut off points for testing and treating could be used. Sensitivity and specificity analysis not stated as the decision rule is complicated. The validation set had similar results to the derviation set.	No definition of fever. Very complicated decision rule requiring the calculation of natural log multiples. The derviation set only included those children for whom the gold standard was sent. The validation set was retrospective and not fully described in terms of numbers.	Diagnosis 4
Nademi (222)	Prospective study to determine the signs which predict serious bacterial infection in children with fever and the	Children (aged 8 days to 16 years) presenting to 2 hospitals in England with fever (>38C). Study period 1st August to 31 October	Which children had serious bacterial infection?	No.	Gold standard: positive blood, urine or CSF culture; radiological evidence of pneumonia;	141 children enrolled with 41 (29%) having a serious bacterial infection. Sensitivity (Sn) and specificity	Gold standard not applied to all children.	Diagnosis 4

	causative organisms.	1999.			clinical sepsis but with negative culture. Candidate tests: clinical signs and simple laboratory tests.	(Sp) of various tests are reported below: temperature >39.5C = 7% Sn and 93% Sp; WBC >15000/mm^3 = 10% Sn and 95% Sp; poor feeding = 78% Sn and 43% Sp.		
Byington (223)	Prospective validation of Rochester criteria for young children with fever and to determine if those with positive viral tests affected the risk of serious bacterial infections.	Children (aged 1 to 90 days) presenting with fever to a medical centre in the USA. Exclusions were children who had started antibiotics in the 48 hours prior to presenting. Study period December 1996 to June 2002.	Which children had serious bacterial infection with a fever?	Yes.	Gold standard: positive culture of blood, urine or CSF; soft tissue infection; or pneumonia. Candidate test: Rochester criteria low risk = appear well; previously healthy; no focal infection; WBC 5-15000/mm3; <10 WBC in urine; <5 WBC per high-powered field microscopy of stool if diarrhoea.	1779 infants enrolled (364 excluded for not having viral tests sent). Of 1385 infants the sensitivity of being in the high risk group and having serious bacterial infection was 90.7% with a specificity of 35.6%	A large number of laboratory tests performed in the Rochester criteria. Study focussing on low risk infants. Guideline focuses on high risk infants.	Diagnosis 1b
Jaskiewicz (224)	Prospective validation study to determine if the Rochester criteria could identify well febrile infants without serious bacterial infection so as to avoid unnecessary treatment.	Infants (aged <60 days) presenting with fever (rectal temp >38C) to various centres in USA. Exclusions included infants who looked clinically unwell and would have been treated as having a serious bacterial	Did infants with a low risk score on the Rochester criteria not have serious bacterial infection?	No, urine and stool examination interpreted by the examining physicians.	Gold standard: not stated directly but taken to be a positive blood, urine or CSF culture; radiological evidence of pneumonia. Candidate test: Rochester criteria	1057 infants were enrolled with 54 excluded due to insufficient data and 72 due to looking ill. Of 931 well looking infants analysed, 511 met all criteria for low risk. The	A large number of laboratory tests performed in the Rochester criteria. Study focussing on low risk infants. Guideline focuses on high risk	Diagnosis 1b

		illness. Study periods July 1987 to June 1990, July 1984 to November 1984, and 1985 to 1988 – populations taken from different studies all using the Rochester criteria.			for low risk infants = appear well; previously healthy; no focal infection; WBC 5-15000/mm3; <10 WBC in urine; <5 WBC per high-powered field microscopy of stool if diarrhoea.	sensitivity of the Rochester criteria was 49.9% and specificity of 92%. The negative predictive value of the low risk group was 98.8%.	infants.	
Chiu(225)	Prospective validation study of febrile infants classed as low risk infants using the Rochester criteria and a normal CRP / ESR to determine if the rule excluded serious bacterial infection.	Children (aged <31 days) with fever (rectal temp >38C) presenting to a paediatric department in Taiwan. Study period January 1992 to June 1993.	Did those in the low risk group not have serious bacterial infection?	Not stated. However, blood culture results are fairly objectively interpreted.	Gold standard: positive culture of blood, CSF or urine (or pus, joint fluid, stool). Candidate test: Rochester criteria for low risk infants = appear well; previously healthy; no focal infection; WBC 5-15000/mm3; <10 WBC in urine; <5 WBC per high-powered field microscopy of stool if diarrhoea. In addition, a CRP <20mg/l or ESR <30mm/hr was included.	254 neonates were enrolled, 45 of whom (17.7%) had bacterial infection. 5.1% had either bacteraemia or meningitis. 6% in the low risk group had a bacterial infection. The specificity was 82% and sensitivity 60% for low risk infants. (If UTIs were excluded then the specificity was 92%; sensitivity 55%).	A large number of laboratory tests performed in the Rochester criteria. Study focussing on low risk infants. Guideline focuses on high risk infants.	Diagnosis 1b
Chiu(226)	Prospective validation of a clinical decision rule to rule out bacterial infection in neaonates with a fever.	Neonates (aged <28 days) with fever (rectal temp >38C) presenting to a paediatric department in Taiwan. Study period July	Which neonates with a fever had a serious bacterial infection?	Not stated. However, blood culture results are fairly objectively interpreted.	Gold standard: positive culture of blood, CSF or urine (or pus, joint fluid, stool). Candidate test: Rochester criteria for low risk	250 infants were enrolled, with 41 (16%) having a bacterial infection (bacteraemia or meningitis in 4.4%). 131 infants were in	A large number of laboratory tests performed in the Rochester criteria. Study focussing on low risk infants.	Diagnosis 1b

		1994 to June 1995.			infants = appear well; previously healthy; no focal infection; WBC 5-15000/mm3; <10 WBC in urine; <5 WBC per high-powered field microscopy of stool if diarrhoea. In addition, a CRP <20mg/l was included.	low risk group and 1 of these had a UTI. The specificity of the screening criteria was 62% with a sensitivity of 97.6%. The negative predictive value of the test for bacteraemia or meningitis was 100% but the positive predictive value was 33%.	Guideline focuses on high risk infants.	
Baskin(227)	Prospective study to determine if infants with fever can be safely managed in the community if they meet certain clinical criteria.	Infants (aged 28 to 89 days) with fever (rectal temp >38C) presenting to a hospital in USA. Exclusions included those receiving antibiotics in the previous 48 hrs and allergy to beta-lactams. Study period February 1987 to April 1990.	Did infants have a bacterial infection if they were screened as low risk?	Not stated. However, blood culture results are fairly objectively interpreted.	Gold standard: positive culture of blood, CSF or urine (or pus, joint fluid, stool). Candidate test: low risk infants = appear well; previously healthy; no focal infection; WBC 5-20000/mm3; <10 WBC in urine; <10 x10^6 leukocytes/l in CSF.	503 infants enrolled. 27 (5.4%) had serious bacterial infection. The sensitivity if the Rochester criteria are reported as 52% when applied to this population (these criteria are different to the study criteria). No specificity is given.	The aim of the study was not to determine the ability to predict bacterial illness but whether it is safe to use it in the outpatient setting.	Diagnosis 4
Kupperman (228)	Prospective derivation and validation of clinical decision rule to determine if specific signs and tests can identify infants at risk of	Children (aged 3 to 36 months) with a fever >39C and no focal infection. Exclusion criteria included toxic appearance, viral infection (e.g. croup, varicella), a known	Did these children have pneumococcal bacteraemia?	Not stated. However, blood culture results are fairly objectively interpreted.	Gold standard: Blood culture positive for pneumo-coccus. Candidate test: Yale observation score, white blood cell count, temperature.	6579 patients were analysed (67% in the derivation group [4384] and 33% randomly assigned to the validation group). The derivation	As no cut off points for the test has been given it is very difficult to interpret how to make decisions based on this	Diagnosis 2b

	bacteraemia.	immunodeficiency or chronic disorder. Study period 1987 to 1991.				univariate analysis produced a clinical rule based on the age of patient, neutrophil count and temperature. The sensitivity of this test was not reported as the ROC was provided.	study.	
WHO(229)	Prospective study to determine if there are clinical indicators of serious bacterial infection in young infants.	Infants (aged <91 days) attending multiple centres in developing countries with rectal temperature >37.5C or <35.5C. Study period September 1990 to December 1992 (The Gambia); August 1991 to July 1993 (Ethiopia); March 1991 to March 1993 (The Philippines); March 1991 to March 1993 (Papua New Guinea).	Did the clinical features of the infants predict severe bacterial illness or death?	Yes, the laboratory processing was provided by distant laboratories. Criteria were included for those infants enrolled to undergo tests.	Gold standard: positive culture of blood, CSF or urine, or radiological evidence of pneumonia. Candidate test: Clinical variables (a list of 59 were analysed) to determine if patients could be categorised as: no abnormality; pneumonia or mild hypoxaemia (sats 90-95%); bacteraemia, meningitis or severe hypoxaemia (sats <90%); death	4552 infants were enrolled. 2398 met the criteria for laboratory evaluation (19 clinical variables including rectal temp >38C or <35.5C). The patients were catagorised into the four groups and the decision rule derived. The final rule uses respiratory rate, rectal temperature, weight-for-age z scores; and clinical findings (poor suck, crepitations, cyanosis, convulsions, indrawing lower chest wall, not rousable, history	Derivation of clinical decision rule. Not all infants had gold standard applied. At least 2% of patients who did not meet the criteria for investigations had positive blood cultures.	Diagnosis 4

						of change in activity). Probabilities are given for each score but no sensitivity / specificity defined for cut off points.		

Table 11.1.ii (b) Diagnostic papers included in the analysis of which clinical features determine the presence of sepsis in a child with a reduced conscious level

Study	Methods	Participants	Interventions	Allocation concealment	Outcomes	Results	Notes	Evidence level
Carroll(230)	Prospective randomised trial of empirical antibiotics versus watch and wait policy in children with fever.	Children (aged 6 to 24 months) with fever (rectal temperature >40C), no focus of infection, WBC >15000/mm^3 and/or ESR >30mm/hr presenting to a clinic or emergency room in USA. All children had laboratory tests for blood culture and some for lumbar puncture. Study period January 1980 to January 1981.	Antibiotics versus watch and wait until culture results available.	Not stated.	Infection rates and complications between the two groups.	96 patients enrolled. 5 patients in each group had a positive blood culture. Those in the no treatment arm had more complications than those in the treatment arm.	This screening tool is not a good one for distinguishing bacterial infection from no bacterial infection in this group of children.	Therapy 1b

Table 11.1.ii (c) Therapy papers included in the analysis of which clinical features determine the presence of sepsis in a child with a reduced conscious level

11. Sepsis

Clinical Questions:

(ii) What investigations should be sent in a child with sepsis and a reduced conscious level to determine the cause and any predisposing factors?

Selection criteria
Criteria for choosing papers were drawn up before the search took place. Papers would be included if they were validation studies of guidelines for children with sepsis. Studies involving both children and adults were only included if the results for children could be analysed separately.

Search
A review of the Cochrane library, MEDLINE (1966-present), EMBASE (1980-present), CINAHL (1982-present), British Nursing Index (1985-present) and AMED (1985-present) was performed using the search terms below. A review of the references of the selected papers for further evidence was included in the search strategy and a hand search of five key journals in the field in the previous 12 months.

Search filters

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	956588
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1465344
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1670568
4	1 or 2 or 3	2874741
5	sepsis.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	82493
6	septi$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	91288
7	exp septicemia/	59182
8	exp septicaemia/	10725
9	exp sepsis/	87553
10	or/5-9	167353
11	guideline$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	223821
12	validat$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	168454
13	11 or 12	386657
14	4 and 10 and 13	615

Results
20 abstracts from 615 titles were reviewed. No studies were selected for further review. A hand search revealed no other papers for review.

11. Sepsis

Clinical Questions:

(iii) Which antibiotics should be started in children with sepsis and reduced level of consciousness?

Selection criteria
Criteria for choosing papers were drawn up before the search took place. Papers would be included if they were randomised controlled trials of antibiotic therapy children with bacteraemia or systematic reviews of antibiotic therapy in children with bacteraemia. Studies of children with meningitis were excluded (as this question is answered later in the guideline). Studies involving children with immunodeficiency or immunosuppression were excluded. Studies involving both children and adults were only included if the results for children could be analysed separately.

Search
A review of the Cochrane library, MEDLINE (1966-present), EMBASE (1980-present), CINAHL (1982-present), British Nursing Index (1985-present) and AMED (1985-present) was performed using the search terms below. A review of the references of the selected papers for further evidence was included in the search strategy and a hand search of five key journals in the field in the previous 12 months.

Search filters

#	Search terms	No. of articles
1	exp antibiotics/	775841
2	exp drug therapy/	995605
3	exp antibiotics/ or exp aminoglycosides/ or exp erythromycin/ or exp clarithromycin/ or exp gentamicins/ or exp kanamycin/ or exp amikacin/ or exp tobramycin/ or exp lincomycin/ or exp clindamycin/ or exp neomycin/ or exp streptomycin/ or exp antibiotics, combined/ or exp antibiotics, lactam/ or exp aztreonam/ or exp carbapenems/ or exp thienamycins/ or exp imipenem/ or exp cephalosporins/ or exp cefamandole/ or exp cefoperazone/ or exp cefazolin/ or exp cefonicid/ or exp cefotaxime/ or exp ceftriaxone/ or exp cefuroxime/ or exp cefotetan/ or exp cefoxitin/ or exp cefprozil/ or exp ceftazidime/ or exp cephalexin/ or exp cefaclor/ or exp penicillins/ or exp methicillin/ or exp nafcillin/ or exp oxacillin/ or exp penicillin g/ or exp ampicillin/ or exp amoxicillin/ or exp carbenicillin/ or exp ticarcillin/ or exp antibiotics, macrolide/ or exp azithromycin/ or exp antibiotics, peptide/ or exp bacitracin/ or exp chloramphenicol/ or exp mupirocin/ or exp tetracyclines/ or exp doxycycline/ or exp minocycline/ or exp tetracycline/ or exp vancomycin/ or exp antiinfective agents, quinolone/ or exp antiinfective agents, fluoroquinolone/ or exp ciprofloxacin/ or exp enoxacin/ or exp ofloxacin/ or exp trovafloxacin/ or exp alatrofloxacin/ or exp cinoxacin/ or exp antiinfective agents, urinary/ or exp norfloxacin/ or exp trimethoprim/ or exp trimethoprim-sulfamethoxazole combination/ or exp sulfonamides/ or exp sulfanilamides/ or exp sulfadiazine/ or exp silver sulfadiazine/ or exp sulfadoxine/ or exp sulfamethoxazole/ or exp sulfisoxazole/	917952
4	exp antibiotic agent/ or exp aminoglycoside antibiotic agent/ or exp beta lactam antibiotic/ or exp chloramphenicol derivative/ or exp macrolide/ or exp quinoline derived antiinfective agent/ or exp ciprofloxacin/ or exp sulfonamide/ or exp cotrimoxazole/ or exp urinary tract antiinfective agent/	476692
5	exp anti-infective agents/ or exp anti-bacterial agents/ or exp antibiotics, combined/	1684016
6	exp infant, newborn/ or exp infant/ or exp infants/	964319
7	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1479955
8	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1686083
9	6 or 7 or 8	2901222
10	RANDOMIZED CONTROLLED TRIAL.pt.	204312
11	CONTROLLED CLINICAL TRIAL.pt.	68903
12	randomized controlled trials.sh.	39646
13	random allocation.sh.	53770
14	double blind method.sh.	82783
15	single blind method.sh.	9121
16	or/10-15	349091
17	Animal.sh.	15954
18	human.sh.	4969487
19	17 not 18	12978
20	16 not 19	349091
21	clinical trial.pt.	425956
22	exp clinical trials/	561264
23	(clin$ adj25 trial$).ti,ab.	229901
24	((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.	166373
25	placebos.sh.	27124
26	placebo$.ti,ab.	184304
27	random$.ti,ab.	633605
28	research design.sh.	42796
29	or/21-28	1424523
30	29 not 19	1424384
31	follow up studies.sh.	303486
32	prospective studies.sh.	229708
33	(control$ or prospectiv$ or volunteer$).ti,ab.	2993762
34	or/31-33	3308501
35	34 not 19	3307096
36	20 or 30 or 35	4186032

37	sepsis.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	82588
38	septi$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	91378
39	exp septicemia/	59280
40	exp septicaemia/	10751
41	exp sepsis/	87679
42	or/37-41	167566
43	or/1-5	2481078
44	9 and 36 and 42 and 43	3615

Results

A total of 34 abstracts were reviewed from 3615 titles. 8 papers were selected for further review. The hand search of journals and references identified two other papers for further review.
Three papers were included in the final analysis.

Papers excluded from the final analysis are listed in table 11.3.i
Papers included in the final analysis are listed in table 11.3.ii

Reference	**Reason for exclusion**
Hsin(231)	Foreign language
Begue(232)	Foreign language
Villa(233)	Foreign language
Fall(234)	Foreign language
Martinez(235)	Not an RCT
Byington(236)	Bacterial prevalence in infants with fever. Not therapy.
Peltola(237)	Comparison of length of treatment not initial treatment.

Table 11.3.i Papers excluded from the analysis of which antibiotics to started in children with sepsis and reduced level of consciousness?

Study	Methods	Participants	Interventions	Allocation concealment	Outcomes	Results	Notes	Evidence level
Snedden(238)	Randomised open label trial to compare meropenem with cefotaxime-based treatment in children with suspected serious bacterial infection.	Children (aged 2 months to 12 years) with suspected non-CNS bacterial infections. Recruited from 21 centres in USA. Exclusions were children with allergy to study drugs, resistant organisms found on culture, risk of seizures, expected survival <48 hours, other antibiotic exposure within 3 days of study entry. Study period July 1992 to September 1993.	IV meropenem for at least 48 hours compared to IV cefotaxime for at least 48 hours. After first 2 days change to oral medication was allowed at discretion of medical team. Patients in cefotaxime arm could be prescribed clindamycin or tobramycin at randomisation at the discretion of medical team (if that was there local policy).	Sealed envelopes. Randomisation worked well with equal numbers in each group suggesting that concealed allocation was maintained.	Satisfactory response ("cure" or "improved" determined by well defined end-points) compared to unsatisfactory response ("no improvement" or "relapse").	505 patients enrolled (253 to meropenem; 252 to cefotaxime). Only 76% (383 patients) were evaluable due to protocol violations or wrongly enrolled or not receiving 48 hours of parentral antibiotics. 98% satisfactory response in meropenem group compared to 96% in cefotaxime group (not significant). 4 patients in each group were withdrawn because of serious drug-related reactions.	Significant numbers not evaluable. Mostly due to short course of parentral antibiotics. Study not powered for equivalence. Allocation concealment maintained.	Therapy 1b
Kaplan(239)	Randomised open label trial to compare linezolid with vancomycin in children with	Children (aged birth to 12 years) with nosocomial pneumonia, skin infections, catheter-related	IV linezolid for 3 days then oral linezolid for up to 28 days compared with	Not reported.	"Cure" after 5 days or 15 doses of treatment.	321 patients were enrolled, 219 to linezolid and 102 to vancomycin. 75 and 70% in the	No description of randomisation or concealment allocation. No description of	Therapy 1b-

	gram-positive infections resistant to other antibiotics.	sepsis, bacteraemia of unknown source in hospitals in USA and South America. Exclusions included allergy to antibiotics, cystic fibrosis, endocarditis, treatment with antibiotics within 24 hours of study period. Study period February 2001 to December 2001.	vancomycin IV for a period of time determined by individual clinicians before switching to an appropriate oral alternative. Randomisation was 2:1 linezolid to vancomycin.			respective groups completed the treatment regimes. There were no statistical significant differences between treatment groups in "cure" rate. There were more adverse events in the vancomycin group (34% versus 18%; p=0.0026)	how patients were enrolled prior to knowing culture results (were several patients excluded after culture result not confirmed as gram positive?). The study was not powered to demonstrate equivalence.	
Principi(240)	Randomised open label trial to compare meropenem with ceftazidime in children with suspected serious bacterial infection.	Children (aged 1 month to 15 years) with signs of serious bacterial infection (well defined in the study) admitted to 16 centres in Italy. Exclusions were children already on antibiotics; allergy to antibiotics; underlying condition (e.g. cystic fibrosis). Study period not stated.	IV meropenem for 5 to 10 days compared with IV ceftazidime for 5 to 10 days.	Not reported, although difference in numbers allocated to each group may suggest allocation not fully concealed or at least randomization not performed in blocks.	"Cure" or "improved" at end of course compared to "failure" or "relapse" at end of course.	185 children enrolled (98 meropenem, 87 to ceftazidime); 10 excluded from analysis due to protocol violation. 96.7% cured or improved in meropenem group compared to 95.3% in the ceftazidime group. No statistical significance between treatments in	Study not powered for equivalence and no power calculation discussed. Randomisation process not clear.	Therapy 1b-

						terms of adverse reactions in either group.		

Table 11.3.ii Papers included in the analysis of which antibiotic should be started in the presence of sepsis in a child

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.

13. Metabolic illness

b) Hypoglycaemia

Clinical Questions:

(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?

Selection criteria
Criteria for choosing papers were drawn up before the search took place. Papers would be included if they were validating studies of guidelines for the management of hypoglycaemia in children, or if they were prospective cohort studies determining the prognosis of children who had hypoglycaemia or case-control studies of children with poor outcome to determine if level of hypoglycaemia was a factor. Studies were excluded if they were retrospective cohort studies. Studies involving both children and adults were only included if the results for children could be analysed separately.

Search
A review of the Cochrane library, MEDLINE (1966-present), EMBASE (1980-present), CINAHL (1982-present), British Nursing Index (1985-present) and AMED (1985-present) was performed using the search terms below. A review of the references of the selected papers for further evidence was included in the search strategy and a hand search of five key journals in the field in the previous 12 months.

Search filters

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	936486
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1412651
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1611164
4	1 or 2 or 3	2784039
5	prognos$.mp. [mp=ab, hw, ti, sh, it, tn, ot, dm, mf, rw]	490966
6	risk$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1410795
7	group$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	2613071
8	cohort studies.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	60608
9	cohort$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	186555
10	or/5-9	4096978
11	hypoglycaemi$.mp. [mp=ab, hw, ti, sh, it, tn, ot, dm, mf, rw]	12039
12	hypoglycemi$.mp. [mp=ab, hw, ti, sh, it, tn, ot, dm, mf, rw]	57001
13	11 or 12	62118
14	4 and 10 and 13	2645

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	936486
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1412651
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1611164
4	1 or 2 or 3	2784039
5	guideline$.mp. [mp=ab, hw, ti, sh, it, tn, ot, dm, mf, rw]	155070

6	hypoglycaemi$.mp. [mp=ab, hw, ti, sh, it, tn, ot, dm, mf, rw]	12039
7	hypoglycemi$.mp. [mp=ab, hw, ti, sh, it, tn, ot, dm, mf, rw]	57001
8	6 or 7	62118
9	4 and 5 and 8	120

Results
A total of 37 abstracts were reviewed from 2765 titles. A total of 9 papers were selected for further review. The hand search of journals and references identified two other paper for further review.
9 papers were included in the final analysis.

Papers excluded from the final analysis are listed in table 13b.1.i
Papers included in the final analysis are listed in table 13b.1.ii

Reference	**Reason for exclusion**
Nordfelt (42)	Cost analysis rather than clinical outcome based study
Pildes (43)	Prospective study of preterm infants only, who are excluded in the scope of the guideline.

Table 13b.1.i Papers excluded from the analysis of outcome associated with level of hypoglycaemia

Study	Methods	Participant definition	Length of follow-up	Outcomes	Results	Notes	Evidence level
Krishna (44)	Prospective cohort study to assess the relative risk of dying if the patient has malaria and is hypoglycaemic (<2.2mmol/l) at admission. Data taken from an RCT of treatments for malaria.	Children (aged 18 months to 12 years) with severe falciparum malaria presenting to a hospital in The Gambia. Study period between 1988 and 1989.	Duration of hospital admission. 100% of those recruited followed up.	Death during period of hospital admission.	115 children were enrolled in the study. 21 (18%) children died. Being hypoglycaemic (<2.2mmol/l) at admission was an independent indicator of outcome. The relative risk of death was 6.8 (95%CI 3.5-13.4)	Numbers in tables don't add up to what is written results. Primary analysis based on lactate levels not glucose levels. Analysis not limited to one treatment arm of RCT, therefore results may be affected by different treatments.	Prognosis 4
Bondi (45)	Prospective cohort study to assess the sequelae of cerebral malaria and determine any prognostic factors relating to poor outcome at admission.	Children (mean age 5.2 years – range not stated) with cerebral malaria presenting to a hospital in Nigeria. Study period March 1987 to October 1988.	Surviving children were followed up for a minimum of 12 months. 100% children followed up or included in the analysis.	Death or neurological sequelae (these ranged from hearing loss to cortical blindness to quadriplegia)	78 children were enrolled in the study. 16 children (20%) died and 11 (17.7%) had neurological sequelae. Being hypoglycaemic (<2.2mmol/l), having severe seizures and a longer period of unconsciousness was related to a poor outcome.	Treatments given differed in only 6 patients due to chloroquine-resistance. It is difficult to determine causation from this paper.	Prognosis 1b
Molyneux (26)	Prospective cohort study to assess the sequelae of cerebral malaria and determine any prognostic factors relating to poor outcome at admission	Children (aged 7 months to 10 years) with cerebral malaria presenting to a hospital in Malawi. Definition of suspected cerebral malaria clear and exclusions noted. Study period January 1987 to June 1988.	Surviving patients were reviewed one month after hospital discharge. 100% of children included in the analysis.	Death or neurological sequelae (including hemiparesis, ataxias and inability to walk) at one month after hospital discharge.	131 children were enrolled. 99 made a full recovery, 12 (9%) had neurological sequelae, and 20 (15%) died. Being hypoglycaemic (<2.2mmol/l) on admission was associated with a poor outcome. No p values stated.	Treatments were the same for all patients. This finding was part of a derivation set of prognostic indicators at admission for cerebral malaria. Part of the group are also included in Taylor (1988).	Prognosis 1b
Taylor(46)	Prospective cohort study to assess the prognostic value of	Children (aged 7 months to 8 years) with cerebral	Surviving patients were followed up to	Death or neurological sequelae	95 children were enrolled.19 were hypoglycaemic	Treatments were the same for both the hypoglycaemic and	Prognosis 1b

	admission hypoglycaemia on the sequelae of cerebral malaria.	malaria presenting to a hospital in Malawi. Definition of suspected cerebral malaria clear and exclusions noted. Study period December 1986 to June 1987.	hospital discharge. 100% of children followed up.	(including hemiparesis, ataxias and inability to walk) at hospital discharge.	(<2.2mmol/l). Being hypoglycaemic significantly increased the chance of death (RR = 9.3) or neurological sequelae (RR = 4). (Comparing the risk in the groups the p values were highly significant)	normoglycaemic groups.	
Haworth (47)	Prospective cohort study to assess the prognosis of infants born to diabetic mothers with relation to the infants' blood glucose level in the first 3 days of life.	Infants born to diabetic mothers in a US hospital between August 1967 and 1971.	Patients were assessed up to the age of 3 years. A standardised develop-mental examination was performed on each child without the knowledge of their blood glucose at birth.	Neurological sequelae including a) develop-mental retardation b) major CNS abnormality c) delay in one field of development alone.	37 infants were followed up. 25 infants were hypoglycaemic (<1.11 mmol/l if low birth weight infant; <1.67mmol/l if normal birthweight infant). Being hypoglycaemic was not related to a poor outcome.		Prognosis 1b
Koivisto (48)	Prospective cohort study of newborn infants treated for hypoglycaemia to assess outcome. The hypoglycaemic group was divided into "symptomatic – convulsive", "symptomatic – non-convulsive" and asymptomatic". A control group of non-hypoglycaemic patients was also followed.	Infants with hypoglycaemia (<1.67mmol/l) born between 1967 and 1969 in a hospital in Finland. Infants were excluded if they had co-existing asphyxia, respiratory distress syndrome, infectious disease, haemolytic disease, cerebral haemorrhage or congenital anomaly.	Patients were followed up to between 1 and 4 years of age. Examination included develop-mental assessment and visual acuity. % followed up not reported – but the figures suggest 100%.	Neurological development at 12-48 months (graded normal, doubtful, or pathological).	151 children were included in the hypoglycaemic groups (181 excluded) with 56 in the control group. 8 in the convulsive group, 77 in the symptomatic – non-convulsive group and 66 in the asymptomatic group. The main finding was a significant difference between the convulsive group and controls in terms of neurological outcome. If the symptomatic infants were grouped together	A number of infants included were preterm infants. These infants are excluded from the guideline in the scope.	Prognosis 1b

					then they also had a significantly worse outcome than the controls. The asymptomatic group had a wide range of hypoglycaemia but this did not affect the outcome.		
Fluge (49)	Prospective cohort study of hypoglycaemic infants categorised according to severity to assess prognosis. The categories were asymptomatic, symptomatic transient and secondary hypoglycaemia.	Infants with hypoglycaemia (level not defined). Study period 3 years 1967-1969.	Patients were followed up at about 3 years of age. 81% followed up.	Neurological sequelae including develop-mental delay, hearing, vision and behaviour. Children who died in the neonatal period or later were not included in the analysis.	20 patients died. of the 37 patients assessed a description of the abnormalities is provided but no statistical analysis of the findings.	No control group and no comparison within groups provided. 19% loss to follow up and 30% patient not included in analysis because they died.	Prognosis 4
Rovet (50)	Prospective cohort study of diabetic children and controls to assess cognitive function in relation to hypoglycaemic episodes and seizures.	Children with diabetes diagnosed in early childhood selected from previous studies of diabetic outcomes. Control group age and sex matched with subjects – they were not assessed longitudinally. Study period not reported.	Standard cognitive function measures assessed at 1, 3 and 7 years post diagnosis. % followed up not reported – but the figures suggest 100%.	Cognitive function including IQ, verbal IQ, vocabulary and digit span / sentence, achievement tests.	16 children were included in the cohort with a control matched for age, sex and socio-economic background. Those children who suffered hypoglycaemic (level not defined) seizures had a significant decline in verbal IQ compared to controls. No visuospatial skills were lost.	Very small numbers and highly selective cohort. No confirmation of hypoglycaemia definition.	Prognosis 4
Wysocki (51)	Prospective cohort study of children with type 1 diabetes being treated with 2 types of insulin therapy to	Children (aged 5-15) were enrolled in a trial of intensive vs. usual insulin therapy. Diaries of severe	Follow up was for 18 months following enrolment into the trial.	The Das-Naglieri cognitive assessment system measured in all	142 children were enrolled (72 into intensive regime). 111 episodes of severe hypoglycaemia (defined as coma or seizures with a low	No difference found in severe hypoglycaemic episodes between the two treatment groups and the treatment differed only in its	Prognosis 1b

	determine the affect of severe hypoglycaemia on cognitive outcomes. The study was undertaken in 2 centres in the US.	hypoglycaemic events were kept by all participants. Study period not reported.		participants at baseline, 9 months and 18 months after enrolment.	glucose or the need for intravenous glucagons/dextrose) were recorded. The population of patients who suffered severe hypoglycaemia did not have a statistically significant reduction in their cognitive function when compared to those who did not suffer hypoglycaemia.	intensity not in the insulin type. Therefore, the fact that the cohort was made up of two groups is unlikely to have had a major effect on outcome. No clear value of hypoglycaemia reported in the study.	

Table 13b.1.ii Papers included in the analysis of outcome associated with level of hypoglycaemia.

13. Metabolic illness

b) Hypoglycaemia

Clinical Questions:

(ii) In children with a reduced conscious level and hypoglycaemia, what further investigations will diagnose the underlying cause?

Selection criteria
Criteria for choosing papers were drawn up before the search took place. Papers would be included if they were validating studies of guidelines for the management of hypoglycaemia in children, or if they were prospective cohort studies determining the accuracy of diagnostic tests for the causes of hypoglycaemia in children. Studies were excluded if they were retrospective cohort studies. Studies involving children with known insulin dependent diabetes mellitus or another chronic condition which can precipitate hypoglycaemia were excluded. Studies involving both children and adults were only included if the results for children could be analysed separately.

Search
A review of the Cochrane library, MEDLINE (1966-present), EMBASE (1980-present), CINAHL (1982-present), British Nursing Index (1985-present) and AMED (1985-present) was performed using the search terms below. A review of the references of the selected papers for further evidence was included in the search strategy and a hand search of five key journals in the field in the previous 12 months.

Search filters

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	936486
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1412651
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1611164
4	1 or 2 or 3	2784039
5	guideline$.mp. [mp=ab, hw, ti, sh, it, tn, ot, dm, mf, rw]	155070
6	hypoglycaemi$.mp. [mp=ab, hw, ti, sh, it, tn, ot, dm, mf, rw]	12039
7	hypoglycemi$.mp. [mp=ab, hw, ti, sh, it, tn, ot, dm, mf, rw]	57001
8	6 or 7	62118
9	4 and 5 and 8	120

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	956588
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1465344
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1670568
4	1 or 2 or 3	2874741
5	sensitiv$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1196235
6	(sensitivity and specificity).mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	247943
7	diagnosis.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1764281
8	diagnostic $.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	236218
9	diagnosis,differential.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	265966
10	diagnos$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	2403697
11	test$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	2807626
12	investigation$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	541353
13	gold.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	68818
14	standard$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	744427
15	8 and 9	22794
16	or/5-12	2948991
17	15 or 16	3433790
18	hypoglycaemi$.mp. [mp=ab, hw, ti, sh, it, tn, ot, dm, mf, rw]	12039
19	hypoglycemi$.mp. [mp=ab, hw, ti, sh, it, tn, ot, dm, mf, rw]	57001
20	18 or 19	62118

21	4 and 17 and 20	4748
22	diabet$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	456254
23	21 not 22	3125

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	956588
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1465344
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1670568
4	1 or 2 or 3	2874741
5	sensitiv$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1196235
6	(sensitivity and specificity).mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	247943
7	diagnosis.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1764281
8	diagnostic $.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	236218
9	diagnosis,differential.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	265966
10	diagnos$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	2403697
11	test$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	2807626
12	investigation$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	541353
13	gold.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	68818
14	standard$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	744427
15	8 and 9	22794
16	or/5-12	2948991
17	15 or 16	3433790
18	glycogen storage.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	6630
19	4 and 17 and 18	939

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	956588
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1465344
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1670568
4	1 or 2 or 3	2874741
5	sensitiv$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1196235
6	(sensitivity and specificity).mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	247943
7	diagnosis.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1764281
8	diagnostic $.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	236218
9	diagnosis,differential.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	265966
10	diagnos$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	2403697
11	test$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	2807626
12	investigation$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	541353
13	gold.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	68818
14	standard$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	744427
15	8 and 9	22794
16	or/5-12	2948991
17	15 or 16	3433790
18	Beckwith-Wiedemann.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	730
19	hyperinsulin$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1080
20	18 or 19	1679
19	4 and 17 and 20	159

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	956588
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1465344
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1670568
4	1 or 2 or 3	2874741
5	sensitiv$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1196235
6	(sensitivity and specificity).mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	247943
7	diagnosis.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1764281
8	diagnostic $.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	236218

9	diagnosis,differential.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	265966
10	diagnos$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	2403697
11	test$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	2807626
12	investigation$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	541353
13	gold.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	68818
14	standard$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	744427
15	8 and 9	22794
16	or/5-12	2948991
17	15 or 16	3433790
18	Addison$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	12630
19	hypocortisol$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	3476
20	18 or 19	14964
21	4 and 17 and 20	833

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	956588
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1465344
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1670568
4	1 or 2 or 3	2874741
5	sensitiv$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1196235
6	(sensitivity and specificity).mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	247943
7	diagnosis.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1764281
8	diagnostic $.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	236218
9	diagnosis,differential.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	265966
10	diagnos$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	2403697
11	test$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	2807626
12	investigation$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	541353
13	gold.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	68818
14	standard$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	744427
15	8 and 9	22794
16	or/5-12	2948991
17	15 or 16	3433790
18	reye$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	18630
19	hyperammonaemi$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	3476
20	hyperammonemi$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	5687
21	or/18-20	24863
22	4 and 17 and 21	521

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	956588
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1465344
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1670568
4	1 or 2 or 3	2874741
5	sensitiv$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1196235
6	(sensitivity and specificity).mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	247943
7	diagnosis.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1764281
8	diagnostic $.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	236218
9	diagnosis,differential.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	265966
10	diagnos$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	2403697
11	test$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	2807626
12	investigation$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	541353
13	gold.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	68818
14	standard$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	744427
15	8 and 9	22794
16	or/5-12	2948991
17	15 or 16	3433790
18	fatty acid oxidation.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	8887
19	acyl coa.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	9728

20	mcad.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	600
21	or/18-20	16077
22	4 and 17 and 21	653

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	956588
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1465344
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1670568
4	1 or 2 or 3	2874741
5	sensitiv$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1196235
6	(sensitivity and specificity).mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	247943
7	diagnosis.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1764281
8	diagnostic $.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	236218
9	diagnosis,differential.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	265966
10	diagnos$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	2403697
11	test$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	2807626
12	investigation$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	541353
13	gold.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	68818
14	standard$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	744427
15	8 and 9	22794
16	or/5-12	2948991
17	15 or 16	3433790
18	urea cycle.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	3567
19	defect$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	452589
20	disorder$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1362909
21	18 and (19 or 20)	957
22	4 and 17 and 21	84

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	956588
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1465344
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1670568
4	1 or 2 or 3	2874741
5	sensitiv$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1196235
6	(sensitivity and specificity).mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	247943
7	diagnosis.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1764281
8	diagnostic $.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	236218
9	diagnosis,differential.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	265966
10	diagnos$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	2403697
11	test$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	2807626
12	investigation$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	541353
13	gold.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	68818
14	standard$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	744427
15	8 and 9	22794
16	or/5-12	2948991
17	15 or 16	3433790
18	congenital adrenal hyperplasia.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	4838
19	adrenogenit$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	712
20	18 or 19	5231
21	4 and 17 and 20	67

Results

A total of 87 abstracts were reviewed from 6501 titles. A total of 5 papers were selected for further review. The hand search of journals and references identified three other papers for further review. No papers were included in the final analysis.

Papers excluded from the final analysis are listed in table 13b.2.i

Reference	Reason for exclusion
Jardim(241)	Foreign language
Mattila(242)	Adult study.
Barness(243)	Expert opinion
Walter(244)	Expert opinion
Hellstrom(245)	Expert opinion
Verrotti(246)	Expert opinion
Clayton(247)	Expert opinion
Seymour(248)	Systematic review of newborn screening for inherited metabolic diseases, not hypoglycaemia.

Table 13b.2.i Papers excluded from the analysis of which investigations to send in children with hypoglycaemia to diagnose the underlying cause

13. Metabolic illness

b) Hypoglycaemia

Clinical Questions:

(iii) In children with a reduced conscious level and hypoglycaemia, what treatment will improve their hypoglycaemia?

Selection criteria
Criteria for choosing papers were drawn up before the search took place. Papers would be included if they were randomised controlled trials of hypoglycaemia treatments in children or if they were validating studies of guidelines for the management of hypoglycaemia in children. Studies involving both children and adults were only included if the results for children could be analysed separately.

Search
A review of the Cochrane library, MEDLINE (1966-present), EMBASE (1980-present), CINAHL (1982-present), British Nursing Index (1985-present) and AMED (1985-present) was performed using the search terms below. A review of the references of the selected papers for further evidence was included in the search strategy and a hand search of five key journals in the field in the previous 12 months.

Search filters

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	956588
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1465344
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1670568
4	1 or 2 or 3	2874741
5	hypoglycaemi$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	12039
6	hypoglycemi$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	57001
7	exp HYPOGLYCEMIA/	158291
8	exp BLOOD GLUCOSE/	110527
9	dextrose$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	127543
10	or/5-9	464361
11	RANDOMIZED CONTROLLED TRIAL.pt.	203760
12	CONTROLLED CLINICAL TRIAL.pt.	68822
13	randomized controlled trials.sh.	39409
14	random allocation.sh.	53667
15	double blind method.sh.	82602
16	single blind method.sh.	9092
17	or/11-16	348114
18	Animal.sh.	15951
19	human.sh.	4964488
20	18 not 19	12976

21	17 not 20	348114
22	clinical trial.pt.	424866
23	exp clinical trials/	560031
24	(clin$ adj25 trial$).ti,ab.	229209
25	((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.	166094
26	placebos.sh.	27066
27	placebo$.ti,ab.	183949
28	random$.ti,ab.	631995
29	research design.sh.	42731
30	or/22-29	1421286
31	30 not 20	1421147
32	comparative study.sh.	1272338
33	exp evaluation studies/	569635
34	follow up studies.sh.	302944
35	prospective studies.sh.	229002
36	(control$ or prospectiv$ or volunteer$).ti,ab.	2987641
37	or/32-36	4635476
38	37 not 20	4634044
39	21 or 31 or 38	5297606
40	4 and 10 and 39	6874

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	936486
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1412651
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1611164
4	1 or 2 or 3	2784039
5	guideline$.mp. [mp=ab, hw, ti, sh, it, tn, ot, dm, mf, rw]	155070
6	hypoglycaemi$.mp. [mp=ab, hw, ti, sh, it, tn, ot, dm, mf, rw]	12039
7	hypoglycemi$.mp. [mp=ab, hw, ti, sh, it, tn, ot, dm, mf, rw]	57001
8	6 or 7	62118
9	4 and 5 and 8	120

Results
A total of 22 abstracts were reviewed from 6994 titles. A total of 11 papers were selected for further review. The hand search of journals and references identified two other papers for further review. No papers were included in the final analysis.

Papers excluded from the final analysis are listed in table 13b.3.i
Papers included in the final analysis are listed in table 13b.3.ii

Reference	**Reason for exclusion**
Wiethop(249)	Adult study
Slama(250)	Adult study
Slama(251)	Adult study
Pontiroli(252)	Adult study
Collier(253)	Adult study
Patrick(254)	Adult study
Hvidberg(255)	Adult study
Namba(256)	Adult study
MacCuish(257)	Adults and children not analysed separately
Moore(258)	Adults only

Table 13b.3.i Papers excluded from the analysis of which treatments to start in children with hypoglycaemia and a reduced conscious level

Study	Methods	Participants	Interventions	Allocation concealment	Outcomes	Results	Notes	Evidence level
Monsod(259)	Randomized controlled crossover trial of children with hypoglycaemia and type 1 diabetes to determine which method of treating hypoglycaemia was superior.	Children (aged 8-12 years) with type 1 diabetes in a hospital in USA. Study period	Overnight fasting to allow the blood glucose to drop to 2.8mmol/l followed by either: intramuscular glucagon 1.0mg or intramuscular epinephrine 0.3mg	Not reported	1. Plasma glucose levels 2. Hypo-glycaemia score by child 3. Adverse events	10 children enrolled. The plasma glucose rose faster in the group given glucagons than in the epinephrine group (increased by 1.7mmol/l by 10mins in the gluc. compared to 0.3mmol/l in the epi group)	No mention of blinding or randomisation process in the study. 9 out of 10 complained of nausea in the glucagon group. Some patients with hypoglycaemia due to other causes may not respond to glucagon.	Therapy 1b-
Aman(260)	Randomized controlled trial of children with hypoglycaemia and type 1 diabetes to determine which method of treating hypoglycaemia was superior.	Children (aged 7-15 years) with type 1 diabetes in a hospital in Sweden. Study period not stated.	Overnight fasting and a reduction in the morning meal were used to induce hypoglycaemia (blood glucose 1.3–2.5mmol/l) then randomised to receive 20mcg/kg glucagons intramuscularly or subcut-aneously. (A second study looked at 10mcg/kg glucagon).	Not reported.	1) Signs of hypoglycaemia. 2) rise in blood glucose at 10 minutes.	30 children were enrolled (15 given the lower dose of glucagon). There was no difference in the resolution of hypoglycaemic signs or the rise in blood glucose.	No mention of blinding or randomisation process in the study. Some patients with hypoglycaemia due to other causes may not respond to glucagon.	Therapy 1b-

Stenninger(261)	Randomized controlled crossover trial of children with hypoglycaemia and type 1 diabetes to determine which method of treating hypoglycaemia was superior.	Children (aged 7-12 years) with type 1 diabetes in a hospital in Sweden. Study period not stated.	Overnight fasting and insulin were used to induce hypoglycaemia (blood glucose <2.0mmol/l) then randomised to receive 0.5mg glucagon subcutaneously or 1.0mg glucagon intranasally. The alternative treatment was given one week later.	Not reported.	1) Relief of symptoms of hypoglycaemia; 2) Blood glucose levels at 15 and 30 minutes.	12 children were enrolled, with one patient excluded due to severe hypoglycaemic symptoms. No statistical difference between resolution in symptoms and blood glucose levels at 15 and 30 minutes.	Study not powered to demonstrate equivalence. Some patients with hypoglycaemia due to other causes may not respond to glucagon.	Therapy 1b-

Table 13b.3.i Papers included in the analysis of which treatments to start in children with hypoglycaemia and a reduced conscious level

13. Metabolic illness

c) Hyperammonaemia

Clinical Questions:

(i) In children with a reduced conscious level and hyperammonaemia, what plasma ammonia level should prompt treatment?

Selection criteria
Criteria for choosing papers were drawn up before the search took place. Papers would be included if they were validated guidelines for treating hyperammonaemia, randomised controlled trials of hyperammonaemia treatments in children with a specific inclusion criteria of ammonia level or if they were prognostic studies of of children with hyperammonaemia of different levels. Studies involving both children and adults were only included if the results for children could be analysed separately.

Search
A review of the Cochrane library, MEDLINE (1966-present), EMBASE (1980-present), CINAHL (1982-present), British Nursing Index (1985-present) and AMED (1985-present) was performed using the search terms below. A review of the references of the selected papers for further evidence was included in the search strategy and a hand search of five key journals in the field in the previous 12 months.

Search filters

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	956588
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1465344
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1670568
4	1 or 2 or 3	2874741
5	exp HYPERAMMONEMIA/	1893
6	hyperammonemi$.mp. [mp=ab, hw, ti, sh, it, tn, ot, dm, mf, rw]	3635
7	hyperammonaemi$.mp. [mp=ab, hw, ti, sh, it, tn, ot, dm, mf, rw]	657
8	5 or 6 or 7	4015
9	guideline$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	223821
10	validat$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	168454
11	9 or 10	386657
12	4 and 8 and 11	125

#	Search terms	No. of articles
1	exp HYPERAMMONEMIA/	1893
2	hyperammonemi$.mp. [mp=ab, hw, ti, sh, it, tn, ot, dm, mf, rw]	3635
3	hyperammonaemi$.mp. [mp=ab, hw, ti, sh, it, tn, ot, dm, mf, rw]	657
4	1 or 2 or 3	4015
5	exp infant, newborn/ or exp infant/ or exp infants/	964319
6	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1479955
7	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1686083
8	5 or 6 or 7	2901222
9	RANDOMIZED CONTROLLED TRIAL.pt.	204312
10	CONTROLLED CLINICAL TRIAL.pt.	68903
11	randomized controlled trials.sh.	39646
12	random allocation.sh.	53770
13	double blind method.sh.	82783
14	single blind method.sh.	9121
15	or/9-14	349091
16	Animal.sh.	15954
17	human.sh.	4969487
18	16 not 17	12978
19	15 not 18	349091

20	clinical trial.pt.	425956
21	exp clinical trials/	561264
22	(clin$ adj25 trial$).ti,ab.	229901
23	((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.	166373
24	placebos.sh.	27124
25	placebo$.ti,ab.	184304
26	random$.ti,ab.	633605
27	research design.sh.	42796
28	or/20-27	1424523
29	28 not 18	1424384
30	follow up studies.sh.	303486
31	prospective studies.sh.	229708
32	(control$ or prospectiv$ or volunteer$).ti,ab.	2993762
33	or/30-32	3308501
34	33 not 18	3307096
35	19 or 29 or 34	4186032
36	4 and 8 and 35	82
37	dialys$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	149647
38	sodium benzo$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1254
39	sodium phenylbutyr$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	142
40	37 or 38 or 39	150989
41	(4 or 40) and 8 and 35	768

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	936096
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1412001
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1610549
4	1 or 2 or 3	2782880
5	exp HYPERAMMONEMIA/	1893
6	hyperammonemi$.mp. [mp=ab, hw, ti, sh, it, tn, ot, dm, mf, rw]	3635
7	hyperammonaemi$.mp. [mp=ab, hw, ti, sh, it, tn, ot, dm, mf, rw]	657
8	5 or 6 or 7	4015
9	prognosis.mp. [mp=ab, hw, ti, sh, it, tn, ot, dm, mf, rw]	429004
10	prognos$.mp. [mp=ab, hw, ti, sh, it, tn, ot, dm, mf, rw]	481276
11	or/9-10	831589
12	first.mp. [mp=ab, hw, ti, sh, it, tn, ot, dm, mf, rw]	1481995
13	episode.mp. [mp=ab, hw, ti, sh, it, tn, ot, dm, mf, rw]	53596
14	cohort.mp. [mp=ab, hw, ti, sh, it, tn, ot, dm, mf, rw]	128446
15	mortality.mp. [mp=ab, hw, ti, sh, it, tn, ot, dm, mf, rw]	422855
16	morbidity.mp. [mp=ab, hw, ti, sh, it, tn, ot, dm, mf, rw]	228260
17	or/12-16	2070805
18	4 and 8 and 11 and 17	22

Results

A total of 53 abstracts were reviewed from 915 titles. A total of 9 papers were selected for further review. The hand search of journals and references identified three other papers for further review. 7 papers were included in the final analysis.

Papers excluded from the final analysis are listed in table 13c.1.i
Papers included in the final analysis are listed in table 13c.1.ii

Reference	Reason for exclusion
Jenkins(262)	Assessment of intracranial pressure monitoring rather than plasma ammonia levels
Tokatli(263)	Epidemiology study of causes of hyperammonaemia rather than prognosis
Schaefer(264)	Retrospective review of outcomes compared to treatments not plasma ammonia level.
Bachmann(265)	Retrospective review of outcomes compared to age at diagnosis not plasma ammonia level.
Yoshino(266)	Retrospective questionnaire survey of transient neonatal hyperammonaemia. No analysis of outcome with plasma ammonia reported.

Table 13c.1.i Papers excluded from the final analysis of which level of plasma ammonia should treatment be started

Study	Methods	Participant definition	Length of follow-up	Outcomes	Results	Notes	Evidence level
Corey (267)	Case series of patients with Reye's syndrome in USA.	Children (ages not defined) the Centre for disease Control in USA with Reye's syndrome (meeting specific clinical criteria. The patients were then split according to different treatment groups and different illness severity. Study period December 1973 to June 1974.	To hospital discharge.	Death or neurological impairment at discharge.	369 patients identified. 69% presented with stage 0-2/5 disease severity. A worse prognosis was seen in those patients presenting with severe disease, in those patients whose coma score deteriorated after admission by more than 3 points (Lovejoy scale), and in patients whose blood ammonia level was greater than 300mcg/dl (176micromol/l) – mortality rate 27% vs 65% ($p<0.001$).	This study demonstrates a relationship between plasma ammonia and outcome. However, collection of data was not uniform.	Prognosis 4
Picca(268)	Case series of neonates with hyper-ammonaemia treated with a variety of therapies.	Neonates (aged 3 – 21 days) with raised ammonia referred to a neonatal unit in Italy for haemodialysis. Study period not reported.	To death or one year post discharge.	Death and neurological sequelae at follow up.	10 neonates were included in the analysis. Duration of coma before starting dialysis was associated with a poor outcome. There was a borderline difference between peak plasma ammonia values in the group with poor outcome (median 1534micromol/l) compared with good outcome (1099micromol/l) ($p=0.05$)	Peak ammonia level seems to have some effect on outcome. The study was small and a selective population.	Prognosis 4
Uchino (269)	Case series of children in Japan with urea cycle disorders to determine the outcome of cases.	Children (ages not defined) with a urea cycle disorder (carbomoyl-phosphate synthase deficiency, ornithine trans-	Not defined as question-naire based survey	Death and neurological abnormality at long term follow up	216 patients with urea cycle disorders were identified. 49% died during the first hyperammonaemic episode. Of those who survived and in whom cognitive outcome was	The study required detection of cases from multicentres of several years.	Prognosis 4

		carbamylase deficiency, arginino-succinic acid synthase deficiency, arginino-succinase deficiency and arginase deficiency) from 121 centres in Japan. Study period 1978 to 1985.			known (n=108), a peak level of plasma ammonia <180 micromol/l was not associated with severe neurological damage, however a peak level of >350micromol/l all patients sustained neurological damage or died. Between 180 and 350micromol/l the effect was variable.		
Maestri (270)	Case series of patients with ornithine trans-carbamylase (OTC) deficiency presenting in infancy.	Neonates referred to a metabolic centre in USA with neonatal onset OTC deficiency. Study period 1976 to 1996.	Dependent on the patient survival and follow up (up to 16 years of age in some cases)	Death and neurological sequelae.	128 males with OTC were identified. Of which data could be analysed on 74. Peak ammonium levels were significantly different between the group who survived (1547micromol/l) and those who died (2574micromol/l) [p<0.001].	Large amount of patients excluded due to data not available.	Prognosis 4
Nicholaides (271)	Case series of patients with OTC to determine outcome.	Children (aged birth to 12 years) diagnosed with OTC at a single centre in UK. Study period 1977 to 2001	Long term follow up in clinic up to age 16 years.	Death and neurological sequelae.	28 patients were identified (23 girls, who have a better prognosis to boys with OTC) of whom 20 had late onset disease and 4 were identified before birth. Plasma ammonia concentration at diagnosis was significantly different between the group who did well and the group who had neurological sequelae, but the plasma levels are not quoted.	Small numbers and significantly more girls in the study, which affects the prognosis results.	Prognosis 4
Msall(272)	Case series of children with	Neonates (age not stated) with	Follow up to 12 months.	Survival and neurological	26 patients identified. 2 died within the first year.	Case series from single unit.	Prognosis 4

	hyperammo-naemic coma to determine outcome with using an alternative nitrogen pathway treatment to reduce plasma ammonia.	hyperammonaemia treated in a metabolic unit in USA. Study period not stated.		sequelae.	Of the remaining 24 patients, 19 (79%) had one or more developmental disability. This was correlated with the length of coma. No relationship between peak ammonia level and outcome was calculated.		
Fitzgerald (273)	Case series of children with Reye syndrome to determine the association between mortality and plasma ammonia levels.	Patients (aged 4 months to 30 years) diagnosed with Reye's syndrome in a US hospital. Study period 1972 to 1981.	Follow up period not stated.	Death.	95 patients identified. They were grouped into plasma ammonia <3 times normal, 3-5 times norma, and >5 times normal. None died in the first 2 groups. In the group with plasma ammonia >5 times normal had a survival rate of between 0 and 100% depending on which year they were treated (the treatment regimes over the 10 years changed with improving survival being found in the latter years).	Case series from a single unit. No length of follow up provided therefore impossible to produce a survival curve from the data.	Prognosis 4

Table 13c.1.ii Papers included in the final analysis of which level of plasma ammonia should treatment be started

13. Metabolic illness

c) Hyperammonaemia

Clinical Questions:

(ii) In children with a reduced conscious level and hyperammonaemia, what tests should be performed to diagnose the underlying cause?

Selection criteria
Criteria for choosing papers were drawn up before the search took place. Papers would be included if they were validated guidelines for treating hyperammonaemia, diagnostic studies of hyperammonaemia in children or if they were epidemiological studies of children with hyperammonaemia reporting the underlying causes. Studies involving both children and adults were only included if the results for children could be analysed separately.

Search
A review of the Cochrane library, MEDLINE (1966-present), EMBASE (1980-present), CINAHL (1982-present), British Nursing Index (1985-present) and AMED (1985-present) was performed using the search terms below. A review of the references of the selected papers for further evidence was included in the search strategy and a hand search of five key journals in the field in the previous 12 months.

Search filters

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	956588
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1465344
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1670568
4	1 or 2 or 3	2874741
5	exp HYPERAMMONEMIA/	1893
6	hyperammonemi$.mp. [mp=ab, hw, ti, sh, it, tn, ot, dm, mf, rw]	3635
7	hyperammonaemi$.mp. [mp=ab, hw, ti, sh, it, tn, ot, dm, mf, rw]	657
8	5 or 6 or 7	4015
9	guideline$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	223821
10	validat$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	168454
11	9 or 10	386657
12	4 and 8 and 11	125

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	956588
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1465344
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1670568
4	1 or 2 or 3	2874741
5	sensitiv$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1196235
6	(sensitivity and specificity).mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	247943
7	diagnosis.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1764281
8	diagnostic $.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	236218
9	diagnosis,differential.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	265966
10	diagnos$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	2403697
11	test$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	2807626
12	investigation$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	541353
13	gold.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	68818
14	standard$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	744427
15	8 and 9	22794
16	or/5-12	2948991
17	15 or 16	3433790
18	exp HYPERAMMONEMIA/	1893
19	hyperammonemi$.mp. [mp=ab, hw, ti, sh, it, tn, ot, dm, mf, rw]	3635

20	hyperammonaemi$.mp. [mp=ab, hw, ti, sh, it, tn, ot, dm, mf, rw]	657
21	or/18-20	4015
22	17 and 21	272

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	956588
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1465344
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1670568
4	1 or 2 or 3	2874741
5	sensitiv$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1196235
6	(sensitivity and specificity).mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	247943
7	diagnosis.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1764281
8	diagnostic $.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	236218
9	diagnosis,differential.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	265966
10	diagnos$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	2403697
11	test$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	2807626
12	investigation$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	541353
13	gold.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	68818
14	standard$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	744427
15	8 and 9	22794
16	or/5-12	2948991
17	15 or 16	3433790
18	reye$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	3669
19	urea cycle$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	3573
20	fatty acid oxidation$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	8899
21	amino aciduria$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	139
22	amino acidemi$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	31
23	amino acidaemi$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	11
24	organic aciduri$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	502
25	or/18-24	16437
26	17 and 25	827

#	Search terms	No. of articles
1	exp HYPERAMMONEMIA/	1893
2	hyperammonemi$.mp. [mp=ab, hw, ti, sh, it, tn, ot, dm, mf, rw]	3635
3	hyperammonaemi$.mp. [mp=ab, hw, ti, sh, it, tn, ot, dm, mf, rw]	657
4	1 or 2 or 3	4015
5	exp adolescent/ or exp child/ or exp child, preschool/ or exp infant/ or exp infant, newborn/ or exp adolescent, hospitalized/ or exp child, hospitalized/	2726715
6	4 and 5	3523
7	exp diagnosis/ or exp diagnosis, differential/	4884436
8	cause.mp.	558507
9	(aetiology or etiology).mp. [mp=ab, hw, ti, sh, it, tn, ot, dm, mf, rw]	334586
10	7 or 8 or 9	5490242
11	exp epidemiologic studies/ or exp case-control studies/ or exp retrospective studies/ or exp cohort studies/ or exp longitudinal studies/ or exp follow-up studies/ or exp prospective studies/ or exp control groups/	1427086
12	10 and 11	602098
13	6 and 12	104

Results

A total of 12 abstracts were reviewed from 1203 titles. A total of 4 papers were selected for further review. The hand search of journals and references identified one other paper for further review. 1 paper was included in the final analysis.

Papers excluded from the final analysis are listed in table 13c.2.i
Papers included in the final analysis are listed in table 13c.2.ii

Reference	Reason for exclusion
Schaefer(264)	Retrospective case series of patients with hyperammonaemia. Not population based.
Yoshino(266)	Population based study looking at only one cause of hyperammonaemia – transient hyperammonaemia of the newborn.
Uchino(269)	Population based survey of outcomes in only one cause of hyperammonaemia – urea cycle disorders.
Bachmann(265)	Retrospcetive case series of patients with hyperammonaemia. Not population based.

Table 13c.2.i Papers excluded from the analysis of which tests to perform in children with hyperammonaemia to determine the underlying cause

Study	Methods	Participant definition	Length of follow-up	Outcomes	Results	Notes	Evidence level
Tokatli (263)	Case series of children with hyper-ammonaemia to determine the causes, clinical features and outcomes.	Children (aged <17 years) with a raised plasma ammonia level reviewed in a metabolic centre in Turkey. Study period 1975 to 1990.	Determined by hospital follow up data.	Diagnosis and aetiological data.	212 children with hyperammonaemia were identified (46% aged <1year). The final diagnoses were as follows: hepatic failure (35%); organic aciduria (12%); Reye's syndrome (10%); urea cycle defect (10%); unknown (9%); perinatal "asphyxia" (8%); sodium valproate use (7.5%); convulsion (4%); amino-acid transport defiect (2%); transient hyperammonaemia of the newborn (1%)	Hospital-based population study of differential diagnosis of hyper-ammonaemia. Case identification not fully described therefore uncertainty as to its rigour.	Differential diagnosis 4

Table 13c.2.ii Papers included in the analysis of which tests to perform in children with hyperammonaemia to determine the underlying cause

13. Metabolic illness

c) Hyperammonaemia

Clinical Questions:

(iii) In children with a reduced conscious level and hyperammonaemia, what treatments should be performed to reduce the plasma ammonia level?

Selection criteria
Criteria for choosing papers were drawn up before the search took place. Papers would be included if they were randomised controlled trial of treatments for hyperammonaemia in children or validated guidelines for treating hyperammonaemia. Prospective cohort studies would be considered if randomised controlled trials were not found. Studies involving both children and adults were only included if the results for children could be analysed separately.

Search
A review of the Cochrane library, MEDLINE (1966-present), EMBASE (1980-present), CINAHL (1982-present), British Nursing Index (1985-present) and AMED (1985-present) was performed using the search terms below. A review of the references of the selected papers for further evidence was included in the search strategy and a hand search of five key journals in the field in the previous 12 months.

Search filters

#	Search terms	No. of articles
1	exp HYPERAMMONEMIA/	1893
2	hyperammonemi$.mp. [mp=ab, hw, ti, sh, it, tn, ot, dm, mf, rw]	3635
3	hyperammonaemi$.mp. [mp=ab, hw, ti, sh, it, tn, ot, dm, mf, rw]	657
4	1 or 2 or 3	4015
5	exp infant, newborn/ or exp infant/ or exp infants/	964319
6	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1479955
7	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1686083
8	5 or 6 or 7	2901222
9	RANDOMIZED CONTROLLED TRIAL.pt.	204312
10	CONTROLLED CLINICAL TRIAL.pt.	68903
11	randomized controlled trials.sh.	39646
12	random allocation.sh.	53770
13	double blind method.sh.	82783
14	single blind method.sh.	9121
15	or/9-14	349091
16	Animal.sh.	15954
17	human.sh.	4969487
18	16 not 17	12978
19	15 not 18	349091
20	clinical trial.pt.	425956
21	exp clinical trials/	561264
22	(clin$ adj25 trial$).ti,ab.	229901
23	((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.	166373
24	placebos.sh.	27124
25	placebo$.ti,ab.	184304
26	random$.ti,ab.	633605
27	research design.sh.	42796
28	or/20-27	1424523
29	28 not 18	1424384
30	follow up studies.sh.	303486
31	prospective studies.sh.	229708
32	(control$ or prospectiv$ or volunteer$).ti,ab.	2993762
33	or/30-32	3308501
34	33 not 18	3307096

35	19 or 29 or 34	4186032
36	4 and 8 and 35	82
37	dialys$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	149647
38	sodium benzo$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1254
39	sodium phenylacet$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1642
40	37 or 38 or 39	150989
41	(4 or 40) and 8 and 35	768

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	956588
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1465344
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1670568
4	1 or 2 or 3	2874741
5	exp HYPERAMMONEMIA/	1893
6	hyperammonemi$.mp. [mp=ab, hw, ti, sh, it, tn, ot, dm, mf, rw]	3635
7	hyperammonaemi$.mp. [mp=ab, hw, ti, sh, it, tn, ot, dm, mf, rw]	657
8	5 or 6 or 7	4015
9	guideline$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	223821
10	validat$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	168454
11	9 or 10	386657
12	4 and 8 and 11	125

Results

A total of 41 abstracts were reviewed from 893 titles. A total of 12 papers were selected for further review. The hand search of journals and references identified ten other papers for further review. 8 papers were included in the final analysis.

Papers excluded from the final analysis are listed in table 13c.3.i
Papers included in the final analysis are listed in table 13c.3.ii

Reference	**Reason for exclusion**
Perez Rodriguez (274)	Foreign language study.
Ermisch(275)	Foreign language study.
Vossbeck(276)	Foreign language study.
Lettgen(277)	Foreign language study.
Donn(278)	Case report.
Summar(279)	Case report.
Sadowski(280)	Case report.
Tuchman(281)	Case report.
Wong(282)	Case report.
Msall(272)	Case series of hyperammonaemic coma. Outcome data not related to treatments given.
Ring(283)	Case report
Thompson(284)	Case report
Sperl(285)	Case report
Rutledge(286)	Case report
Brusilow(287)	Review not systematic.

Table 13c.3.i Papers excluded from the analysis of which treatments to start to reduce plasma ammonia level in children with hyperammonaemia

Study	Methods	Participants	Interventions	Allocation concealment	Outcomes	Results	Notes	Evidence level
Batshaw (288)	Case series of children with hyper-ammonaemia due to urea-cycle enzyme defects to determine which treatment modality had favourable outcome.	Children (aged birth to 22 years) with hyper-ammonaemic coma due to urea-cycle enzymo-pathies managed in consultation with a metabolic centre (in 29 local centres across the USA). Study period 1975 to 1979.	Double-volume exchange transfusion, peritoneal dialysis, sodium benzoate administ-ration, and arginine administ-ration.	Not a randomised controlled trial.	Reduction in plasma ammonia level post treatment. Survival to one week post coma.	31 patients identified. 5 neonates underwent exchange transfusion. The fall in ammonia values immediately after exchange transfusion were not statistically significant and by 12 hours post treatment had risen back to pre-exchange levels or higher in all cases. Only one patient survived. 20 patients were treated with peritoneal dialysis. There was a significant fall in plasma ammonia in 7 (all neonates) but no fall in the older patients. 6 of the 13 older patients survived. 10 patients had exchange followed by peritoneal dialysis. The fall in plasma ammonia was significant after PD but not after exchange. 5 infants survived. Sodium benzoate was used before other treatments in 7 patients. 2 out of 3 neonates responded, and all the older children responded. Arginine was given to all patients. In those with	No control of therapy and no description of why different therapies were started.	Therapy 4

						argininosuccinase deficiency (n=4) the plasma ammonia level fell significantly.		
Maestri (289)	Prospective cohort validation of a guideline for therapy of urea cycle disorders diagnosed before birth.	Fetuses at risk of urea cycle enzyme defectes were identified and parents offered the choice of preventative treatment (the protocol), crisis treatment (if hyperammon-aemic coma occurred) or no treatment. Study period 1981 to 1988.	The protocol included sodium benzoate from birth and dietary supplementatio n along with haemo-dialysis.	Not a randomised controlled trial.	Survival and develop-mental progress at 6 months.	32 infants were enrolled into the preventative protocol out of 43 fetuses identified. 17 infants were diagnosed as not having a metabolic problem within 48 hours of birth. 12 of 15 affected infants survived the neonatal period (3 deaths in the 8 with OTC deficiency), with a further 3 dying (2 with OTC and 1 with carbamoyl phosphate synthetase deficiency) after the neonatal period with hyperammonaemic episodes.	The survival rate of these patients is poor in general. The protocol improved survival when compared with other case series.	Therapy 2b
Rajpoot (290)	Case series of neonates with hyperammonae mia to determine if haemo-dialysis is effective.	Neonates weighing <4kg with raised plasma ammonia (500-700 micromol/l) with a variety of conditions (2 x transient hyperammon-aemia of newborn; 1 OTCD; and 1 methyl malonic acidaemia.	Haemo-dialysis with sodium benzoate or phenyl-butyrate also administered	Not a randomised controlled trial.	Reduction in plasma ammonia.	4 patients were identified. All tolerated haemodialysis. All patients had a significant fall in plasma ammonia during dialysis. Rebound was seen in the patients with OTCD and MMA. Only the patient with MMA had a profound mental retardation at discharge.	Small case series.	Therapy 4
Schaefer (264)	Case series of neonates with hyperammo-naemia to determine if	Children (aged <4 weeks) treated in a hospital in Germany for	Haemo-dialysis or peritoneal dialysis. Other therapy including	Not a randomised controlled trial.	Reduction in plasma ammonia level. Survival and	12 patients were identified. 7 underwent haemodialysis. Reduction in metabolite concentrations was	Case series. Complic-ations of haemo-	Therapy 4

	haemo-dialysis is more successful than peritoneal dialysis.	inborn errors of metabolism. Study period 1988 to 1997.	sodium benzoate was also provided.		neuro-logical outcome	significantly faster with haemodialysis than peritoneal dialysis. Plasma ammonia level reduction was only slightly more efficient with haemodialysis. Survival was dependent on the underlying diagnosis.	dialysis included circulatory failure in 2 cases (1 due to puncture of right atrium). Complic-ations of peritoneal dialysis included blocked catheter and need to change the catheter.	
Picca(268)	Cohort of children with hyperammo-naemia to determine which method of dialysis reduced the ammonia level.	Children (aged 2 to 21 days) referred to a neonatal unit in Italy for management of hyperammonae mia. Study period not stated.	Haemo-dialysis of three diffeent modalities (CVVHD, CAVHD and HD)	Not a randomised controlled trial.	Reduction in plasma ammonia level. Survival and neuro-logical outcome	20 patients were referred with 10 patients included in the study. All dialysis modalities reduced the plasma ammonia level significantly (median 1419 to 114 micromol/l). 5 had a good outcome. No differences in outcome between treatment groups were detected.	The marker of poor outcome was duration of coma prior to starting dialysis (>33 hours). No mention of why 10 patients were excluded from the study.	Therapy 4
Corey (267)	Retro-spective cohort study of Reyes syndrome to determine the therapeutic options used.	All identified cases of Reye's syndrome reported to the Center for Disease Control in USA. Study period	Supportive care alone or with either peritoneal dialysis or exchange transfusion.	Not a randomised controlled trial.	Survival and neuro-logical outcome	369 cases were identified with clinical data of outcome available in 279 (79%). 142 (51%) received supportive therapy alone – 35% died. 87 (31%) had exchange transfusion – 46% died. 44 (17%) received dialysis – 54%	No control made for severity of illness in the analysis. It looks like dialysis is harmful, whereas it	Therapy 4

		December 1973 and June 1974.				died.	may be that children sent for dialysis are more sick.	
Brusilow (291)	Prospective case series of patients with hyperammo-naemia to determine if a new treatment protocol reduced plasma ammonia.	Children (age not stated) treated in a metabolic unit in USA for urea cycle enzyme defects. Study period	A combin-ation of sodium benzoate, sodium phenyl-acetate and arginine.	Not a randomised controlled trial.	Reduction in plasma ammonia level.	7 cases were treated on 12 occasions with hyperammonaemia. 11 times the plasma ammonia decreased to normal limits. 3 patients had rebound hyperammonaemia.	No controls or compare-ison to previous treatments.	Therapy 4
Gortner (292)	Case series of neonates with inborn errors of metabolism to determine if peritoneal dialysis reduced the hyperammo-naemia.	Neonates (aged 4 to 8 days) presenting with a metabolic illness to a hospital in Germany. Study period not stated.	Peritoneal dialysis.	Not a randomised controlled trial.	Reduction in plasma ammonia level and other metabol-ites.	4 cases were identified. Peritoneal dialysis reduced the plasma ammonia to normal within 24 hours of treatment. The other metabolites remained elevated in some cases (2 x citrullinaemic patients). There was one death due to indicators of severe brain damage.	Small case series.	Therapy 4
Batshaw (293)	Prospective cohort to determine the benefit of using sodium benzoate and sodium phenyl-acetate in the treatment of hyperammo-naemia due to urea cycle disorders.	Neonates (ages not stated when enrolled) with hyperammo-naemic coma secondary to urea cycle disorders seen in 26 institutions in USA and Europe. Study period	Intravenous sodium benzoate +/- arginine +/- peritoneal dialysis. After treating hyperammo-naemia a tailored protein-restricted diet was prescribed.	Not a randomised controlled trial	Develop-mental outcomes (Bayley scale or Stanford-Binet scale). Resolution of hyperamm-onaemia with treatment.	26 patients were enrolled. There were 64 postnatal episodes of hyperammonaemia in 19 of the 26 patients. In 61 of the 64 episodes the ammonia resolved (from mean 251micromol/l to 86 micromol/l) with sodium benzoate and arginine alone. In the three non-responsive cases, the plasma ammonia level was mean 420 micromol/l. A	The only side effect of benzoate was vomiting if givenover 30 minutes rather than one hour.	Therapy 2b

		1978 to 1982.				fatal outcome ensued despite peritoneal or haemodialysis. Among the 23 survivors, neurological outcome was dependent on peak level of plasma ammonia and duration of coma.		

Table 13c.3.ii Papers included in the analysis of which treatments to start to reduce plasma ammonia level in children with hyperammonaemia

13. Metabolic illness

d) Non-hyperglycaemic ketoacidosis

Clinical Questions:

(i) In children with a reduced conscious level, what are the causes of non-hyperglycaemic ketoacidosis?

Selection criteria
Criteria for choosing papers were drawn up before the search took place. Papers would be included if they were population studies in children with acidosis and ketonuria without hyperglycaemia describing the incidence of the various causes. Studies involving both children and adults were only included if the results for children could be analysed separately.

Search
A review of the Cochrane library, MEDLINE (1966-present), EMBASE (1980-present), CINAHL (1982-present), British Nursing Index (1985-present) and AMED (1985-present) was performed using the search terms below. A review of the references of the selected papers for further evidence was included in the search strategy and a hand search of five key journals in the field in the previous 12 months.

Search filters

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	966274
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1484010
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1690390
4	1 or 2 or 3	2908448
5	risk$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1446071
6	group$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	2661197
7	cohort studies.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	62821
8	cohort$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	192914
9	or/5-8	3848749
10	exp diagnosis/ or exp diagnosis, differential/	5400661
11	cause.mp.	644644
12	(aetiology or etiology).mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	348946
13	exp epidemiologic studies/ or exp case-control studies/ or exp retrospective studies/ or exp cohort studies/ or exp longitudinal studies/ or exp follow-up studies/ or exp prospective studies/ or exp control groups/	1642661
14	or/10-13	6991272
15	4 and 9 and 14	389304
16	acid$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	2826083
17	ketonuria.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	952
18	ketosis.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	2738
19	ketotic.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1488
20	ketone$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	42255
21	or/17-20	45815
22	hyperglycaemi$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	8766
23	hyperglycemi$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	45550
24	or/22-23	50411
25	15 and 16 and 21	132
26	25 not 24	112

Results
A total of 16 abstracts were reviewed from 112 titles. A total of 4 papers were selected for further review. The hand search of journals and references identified 3 other papers for further review. No papers were included in the final analysis.

Papers excluded from the final analysis are listed in table 13d.1.i

Reference	Reason for exclusion
Ozand(294)	Review not systematic
Morton(295)	Not a population study determining causes of ketoacidosis
Jackson(296)	Not a population study determining causes of ketoacidosis
Wasant(297)	Population study to determine the presenting features of children with inborn errors of metabolism. No analysis performed on the types of inborn errors of metabolism diagnosed depending on the presenting feature of metabolic acidosis.
Ogier de Baulny(298)	Review not systematic
Chiaratti de Oliveira(299)	Foreign language
Seymour(248)	Systematic review of newborn screening for inherited metabolic diseases, not ketoacidosis.

Table 13d.1.i Papers excluded from the analysis of the causes of non-hyperglycaemic ketoacidosis

13. Metabolic illness

d) Non-hyperglycaemic ketoacidosis

Clinical Questions:

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

Selection criteria
Criteria for choosing papers were drawn up before the search took place. Papers would be included if they were diagnostic studies in children with maple syrup urine disease, organic acidopathies, glycogen storage disease and disorders of gluconeogenesis. Studies involving both children and adults were only included if the results for children could be analysed separately.

Search
A review of the Cochrane library, MEDLINE (1966-present), EMBASE (1980-present), CINAHL (1982-present), British Nursing Index (1985-present) and AMED (1985-present) was performed using the search terms below. A review of the references of the selected papers for further evidence was included in the search strategy and a hand search of five key journals in the field in the previous 12 months.

Search filters

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	956588
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1465344
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1670568
4	1 or 2 or 3	2874741
5	sensitiv$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1196235
6	(sensitivity and specificity).mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	247943
7	diagnosis.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1764281
8	diagnostic $.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	236218
9	diagnosis,differential.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	265966
10	diagnos$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	2403697
11	test$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	2807626
12	investigation$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	541353
13	gold.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	68818
14	standard$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	744427
15	8 and 9	22794
16	or/5-12	2948991
17	15 or 16	3433790
18	maple syrup urine.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1390

19	organic acid$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	8294
20	amino acid$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	829313
21	fatty acid$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	198709
22	electron transport.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	47155
23	or/18-22	1063127
26	17 and 23	1423

Results
A total of 52 abstracts were reviewed from 1423 titles. A total of 10 papers were selected for further review. The hand search of journals and references identified 3 other papers for further review.
6 papers were included in the final analysis.

Papers excluded from the final analysis are listed in table 13d.2.i
Papers included in the final analysis are listed in tables 13d.2.ii(a) and (b)

Reference	**Reason for exclusion**
Pronicka(300)	Foreign language
Van Naarden Braun (301)	Outcome study not diagnostic study.
Hoffman(302)	Review not systematic
Pourfarzam(303)	Retrospective diagnostic study
Pontoni(304)	Review article
Plochl(305)	Foreign language
Yoshida(306)	Only one sample tested against normal controls

Table 13d.2.i Papers excluded from the analysis of the tests to determine the cause of non-hyperglycaemic ketoacidosis

Study	Methods	Participants	Diagnostic dilemma	Blinded comparison	Gold standard tested	Results	Notes	Evidence level
Clayton(307)	Prospective study to determine the accuracy of a new test for MCAD (electrospray tandem mass spectroscopy) compared to gold standard tests.	Children (aged 4 days to 16 years) in UK region with suspected MCAD, known MCAD, with siblings with known MCAD or control population samples. Study period 1993 to 1997	Did the control patients have MCAD?	Not stated but all samples underwent all the tests.	Gold standard: plasma non-esterified fatty acid ratio, and /or gas chromatography-mass spectroscopy for organic acids, and / or genetic allele A985G. Candidate test: electrospray tandem mass spectroscopy looking in particularly at octanoylcarnitine and free carnitine.	2168 samples were obtained. The candidate test performed well against the gold standard tests. A cut off point for a positive test was derived as >0.38micromol/l octanoylcarnitine for samples taken after 10 days of life, and >1.2micromol/l if taken before day 10.	This is a derivation of a population screening test. It compares well to gold standard at the curt off point but the population was heterogenous.	Diagnosis 2b
Yoon(308)	Prospective screening study of all infants in Korea to detect inborn errors of metabolism.	Infants (aged <1 month) born in South Korea were screened for inherited metabolic disorders. Study period 2001 to 2004.	Did the infants have a fatty acid oxidation disorder, an aminoacidopathy or an organic acidopathy?	No, only children with suspected condition on screening were given the gold standard test.	Gold standard: acylcarnitine profile, urine organic acid analysis, plasma amino acid analysis, direct enzyme assay, or molecular testing. Candidate test: electrospray tandem mass spectroscopy.	From a possible population of 1.5 million, 79,179 healthy infants were screened (~5.4%). 6795 were screened as high risk infants. 48 metabolic disorders were detected (28 in the healthy infant population and 20 in the high risk group). The sensitivity of the test was 97.6% and specificity 99.2%. The diagnoses included were	No mention is made of how the study determined if all possible inherited disorders had been identified as follow up is not specified.	Diagnosis 4

						PKU, PA, LCHAD.		

Table 13d.2.ii(a) Papers included in the analysis of the tests to determine the cause of non-hyperglycaemic ketoacidosis (individual studies)

Study	Method	Inclusion criteria	Search	Evidence appraisal	Summarizing evidence	Results	Notes	Evidence level
Pollitt(107)	Systematic review of all neonatal screening tests for inherited metabolic disorders in the UK.	Papers were searched for 5 different information fields: 1) birth frequency; 2) natural history of disease; 3) performance of screening test; 4) uptake of screening; and 5) effectiveness of early treatment.	Medline, Embase and BIDS. Conference papers were also reviewed.	2 independent appraisers.	Descriptive summaries – no meta-analysis provided.	PKU warrants screening (measuring phenylalanine on blood spot = sensitivity 99.8%; specificity); Tyrosinaemia type I does not warrant screening as the tests are not adequate (measuring plasma amino acid chromatograms = sensitivity 71%; specificity 100%); Homocystinuria does not warrant screening as the treament is not adequate (measuring methionine in urine/blood = sensitivity >90%); maple syrup urine disease is too rare to warrant screening (measuring leucine on dried blood spot = sensitivity 100%); urea cycle defects (measuring urinary orotic acid and urinary citrilline = sensitivity not known) need to be detected earlier than 6-10 days to prevent decompensation; MMA, PA and IVA (measuring organic acids on tandem MS = sensitivity >90%) no effective treatment for early onset disease; MCAD (measuring octanoylcarnitine in tandem MS = sensitivity >95%) warrants screening for in UK.	The quality of the literature to produce the sensitivities ranged from 1 for PKU to 2b for MCAD. The question answered by this paper relates to newborn screening but the test accuracies apply to target populations as well.	Diagnosis 3a

Pandor(106)	Systematic review of tandem mass spectroscopy for neonatal screening tests for inherited metabolic disorders in the UK.	Papers were searched for reviews of the accuracy of tandem mass spectroscopy on detecting metabolic illnesses in neonatal patients, the epidemiology of inherited metabolic diseases, and their treatments. Papers were excluded if they were in a foreign language, or they were published before 1995.	11 electronic databases were searched: Biological abstracts, CINAHL, Cochrane Controlled trials Register, Cochrane Database of Systematic reviews, Database of Abstracts of Reviews of Effectiveness, EBM reviews, EMBASE, Health Management Information Consortium, HTA database, MEDLINE, PreMedline, Science Citation Index. Search was limited to after 1995 as this review was updating previous reviews by Pollitt (107) and Seymour (105).	Single reviewer selected the papers and extracted the data. Evidence appraised according to a checklist and graded according to NHS-CRD.	Descriptive summaries – no meta-analysis provided	15 studies were included in the review. The studies of population screening using tandem MS found the test highly sensitive (90-100%) and highly specific (99-100%) for amino acids and acylcarnitines. Economic modelling suggested that changing to tandem MS for PKU alone would not be viable. However, if MCAD were also screened for then using tandem MS for both would be economically viable.	A comprehensive systematic review, which is based on level 1 and level 2 evidence. The paper does not study target population testing, but it is of value to know that tandem MS is economical for testing for MCAD.	Diagnosis 3a

Seymour (105)	Systematic review of all neonatal screening tests for inherited metabolic disorders in the UK.	Inclusion criteria were papers studying the incidence, effectiveness of screening, health outcomes, and treatment/ screening costs for a number of conditions including: PKU, amino acidopathies, disorders of carbohydrate metabolism, organic acidopathies, fatty acid oxidation defects. Excluded papers were pure laboratory-based studies, methodologies not suitable for mass screening, not neonatal screening, not well baby screening.	5 electronic databases were searched: MEDLINE EMBASE, BIDS, Science Citation Index, and Index to Science and Technical Proceedings. A hand search of textbooks and conference proceedings was also undertaken.	2 or three experts appraised the evidence using a checklist.	The evidence was not subjected to a meta-analysis, but instead for each inborn error of metabolism a checklist of whether it was suitable for neonatal screening was produced. The checklist was as follows: Clinically and biochemically well defined disorder; Known incidence in populations relevant to UK; Disorder associated with significant morbidity and mortality; Effective treatment available; Period before onset during which intervention improves	Number of studies included not stated (407 papers reviewed). The conditions which the study identified as meeting all the screening criteria were PKU (using dried blood spots and a variety of testing modalities); MCAD (using tandem MS); glutaric aciduria type 1 (tandem MS); congenital adrenal hyperplasia (using 17-OHP from a dried blood spot); biotinase deficiency (using PABA on dried blood spots).	A comprehensive systematic review but with sparse details of the quality of evidence used. Tandem mass spectroscopy can be used to pick up MCAD and other metabolic disorders.	Diagnosis 3a-

					outcome; Ethical, safe and robust screening test.			

Table 13d.2.ii(b) Papers included in the analysis of the tests to determine the cause of non-hyperglycaemic ketoacidosis (Systematic reviews)

Study	Methods	Question being asked	Participants	What costs are included?	What outcomes are included	Results and sensitivity analysis	Notes	Evidence level
Durand-Zaleski (309)	Cost-effectiveness analysis, retrospectively based on a single unit's data set. Study was performed in 1991 in France.	Is it better value to refer a child with a suspected metabolic illness to a specialist clinic or to perform 1 of 2 tests in a non-specialist centre?	1494 children (age not stated) who had tests sent for analysis for metabolic conditions, specifically inborn errors of amino acid metabolism.	Cost of specialist clinic visit, performing ion-exchange chromatography, performing thin-layer gas chromatography, performing no tests, and complications associated with not reaching a diagnosis. The costs are estimated from the French Social security and healthcare system database. Test accuracy data was taken from the literature.	Diagnosing correctly an inborn error of metabolism (IEM) and incorrectly missing an IEM. Assumptions are made that the costs are only incurred once a paediatrician decides to suspect an IEM (i.e. no costs are incurred if a paediatrician never suspects an IEM). The cost of missing a diagnosis is giving a value of $4000 (the cost of a diagnostic test and hospitalisation at the specialist centre). No future costs are analysed after a diagnosis has been reached	Of the five options (no specialist and ion-exchange; no specialist and thin-layer; specialist and no test; specialist and ion-exchange; and specialist and thin-layer) the most effective was specialist plus ion-exchange chromatography. The cost of specialist plus ion-exchange chromatography had a total cost of $232 with a diagnostic efficiency of 24% or $1000 per diagnosis. This compares with $8400 per diagnosis for no	This study suggests that expert assessment will improve diagnostic efficiency without reducing the costs. This study uses an outpatient setting and therefore the cost analysis would be different for the inpatient group.	Economic analysis 2b

						specialist plus ion-exchange chromatography. A sensitivity analysis changing the accuracy of the tests did not change the overall result.		

Table 13d.2.ii(c) Papers included in the analysis of the tests to determine the cause of non-hyperglycaemic ketoacidosis (Economic reviews)

14. Intracranial infections

a) Bacterial meningitis

Clinical Questions:

(i) In children with a reduced conscious level, what are the clinical signs of bacterial meningitis?

Selection criteria
Criteria for choosing papers were drawn up before the search took place. Papers were selected if they were validating cohort studies of clinical decision rules or derivation studies of such rules for meningitis. Prospective cohort studies or case control studies, which reported on the rates of different signs and symptoms of meningitis would be included if no other studies were found. Studies involving both children and adults were only included if the results for children could be analysed separately.

Search
A review of the Cochrane library, MEDLINE (1966-present), EMBASE (1980-present), CINAHL (1982-present), British Nursing Index (1985-present) and AMED (1985-present) was performed using the search terms below. A review of the references of the selected papers for further evidence was included in the search strategy and a hand search of five key journals in the field in the previous 12 months.

Search filters

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	951169
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1439069
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1639690
4	1 or 2 or 3	2832537
5	exp neurologic examination/ or exp pain measurement/ or exp reflex/ or exp reflex, abdominal/ or exp reflex, abnormal/ or exp reflex, babinski/ or exp reflex, acoustic/ or exp reflex, pupillary/ or exp reflex, stretch/ or exp startle reaction/ or exp medical history taking/ or exp cornell medical index/ or exp reproductive history/ or exp physical examination/ or exp auscultation/ or exp heart auscultation/ or exp blood pressure determination/ or exp body constitution/ or exp body height/ or exp body surface area/ or exp body weight/ or exp fetal weight/ or exp body temperature/ or exp cephalometry/ or exp craniometry/ or exp facial expression/ or exp facies/ or exp gait/ or exp hand strength/ or exp palpation/ or exp pelvimetry/ or exp percussion/ or exp pigmentation/ or exp skin pigmentation/ or exp pulse/ or exp range of motion, articular/ or exp self-examination/ or exp breast self-examination/ or exp skinfold thickness/	892433
6	exp medical history taking/ or exp patient assessment/ or physical examination/ or exp palpation/ or exp pulse/	153287
7	exp patient history taking/ or exp physical examination/ or exp auscultation/ or exp heart auscultation/ or exp blood pressure determination/ or exp body temperature determination/ or exp cephalometry/ or exp "inspection (clinical)"/ or exp neurologic examination/ or exp reflex/ or exp reflex, abnormal/ or exp reflex, acoustic/ or exp reflex, pupillary/ or exp reflex, stretch/ or exp palpation/ or exp percussion/ or exp physical examination, preparticipation/ or exp pigmentation/ or exp skin pigmentation/ or exp pulse/	553576
8	exp blood pressure/ or exp body temperature/ or exp fatigue/ or exp jaundice/ or exp nausea/ or exp "pain and pain management"/ or exp paralysis/ or exp seizures/ or exp senses/ or exp shock/ or exp sleep/ or exp unconsciousness/ or exp patient assessment/	880816
9	exp medical examination/ or exp clinical examination/ or exp functional assessment/ or exp pulse oximetry/ or exp blood pressure monitoring/ or exp temperature measurement/ or exp thermometry/ or exp blood glucose monitoring/ or exp electrocardiography monitoring/ or exp neurologic examination/ or history/	274711
10	clinical feature.mp. [mp=ab, hw, ti, sh, it, tn, ot, dm, mf, rw]	217941
11	presenting feature.mp. [mp=ab, hw, ti, sh, it, tn, ot, dm, mf, rw]	2084
12	presenting sign.mp. [mp=ab, hw, ti, sh, it, tn, ot, dm, mf, rw]	1575
13	presenting symptom.mp. [mp=ab, hw, ti, sh, it, tn, ot, dm, mf, rw]	4282

14	sign.mp. [mp=ab, hw, ti, sh, it, tn, ot, dm, mf, rw]	61333
15	symptom.mp. [mp=ab, hw, ti, sh, it, tn, ot, dm, mf, rw]	145112
16	or/5-15	2013529
17	exp meningitis/ or exp meningitis, bacterial/ or exp meningitis, escherichia coli/ or exp meningitis, haemophilus/ or exp meningitis, listeria/ or exp meningitis, meningococcal/ or exp waterhouse-friderichsen syndrome/ or exp meningitis, pneumococcal/ or exp meningitis, viral/ or exp lymphocytic choriomeningitis/ or exp meningitis, aseptic/ or exp encephalomyelitis/ or exp meningoencephalitis/ or exp encephalitis/ or exp encephalitis, viral/	96573
18	4 and 16 and 17	2385

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	956588
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1465344
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1670568
4	1 or 2 or 3	2874741
5	exp meningitis/ or exp meningitis, bacterial/ or exp meningitis, escherichia coli/ or exp meningitis, haemophilus/ or exp meningitis, listeria/ or exp meningitis, meningococcal/ or exp waterhouse-friderichsen syndrome/ or exp meningitis, pneumococcal/ or exp meningitis, viral/ or exp lymphocytic choriomeningitis/ or exp meningitis, aseptic/ or exp encephalomyelitis/ or exp meningoencephalitis/ or exp encephalitis/ or exp encephalitis, viral/	96573
6	decision rule.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	772
7	diagnosis.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1771627
8	6 or 7	1772247
9	4 and 5 and 8	461

Results

A total of 205 abstracts were reviewed from 2846 titles. A total of 8 papers were selected for further review. The hand search of journals and references identified 2 other papers for further review.
2 papers were included in the final analysis.

Papers excluded from the final analysis are listed in table 14a.1.i
Papers included in the final analysis are listed in table 14a.1.ii

Reference	**Reason for exclusion**
Oostenbrink(310)	Retrospective hospital population study to determine the frequency of neck stiffness in cases of bacterial meningitis
Riordan (311)	Retrospective hospital case review of signs of bacterial meningitis in infants
Andersen(312)	Retrospective case series to determine the signs of bacterial meningitis
Kirkpatrick(313)	Retrospective case series to determine the signs of pneumococcal meningitis
Andersen(314)	Retrospective case series to determine the signs of meningococcal meningitis
Schildkamp(315)	Adults and children analysed together
Tucci (316)	Retrospective case review
Almuneef (317)	Retrospective case review

Table 14a.1.i Papers excluded from the analysis of the clinical signs which predict bacterial meningitis

Study	Methods	Participants	Diagnostic dilemma	Blinded comparison	Gold standard tested	Results	Notes	Evidence level
Oostenbrink (41)	Prospective validation study of a clinical diagnostic decision rule to determine the accuracy of a clinical test to detect bacterial meningitis in children.	Children (aged 1 month to 15 years) presenting to 4 centres in Holland with neck stiffness. Study period Nov 1999 to May 2001.	Did the children with neck stiffness have bacterial meningitis?	The clinical decision rule was applied to them along with the gold standard of lumbar puncture (or follow-up to one week if no LP or antibiotics – i.e. no clinical deterioration in one week without treatment ruled out the diagnosis bacterial meningitis).	Gold standard: CSF culture or no clinical deterioration without treatment within one week of presenting (if no lumbar puncture performed). Comparison test:Clinical decision rule previously derived. (The rule included the following clinical features: duration of main complaint; vomiting; meningeal irritation; cyanosis; petechiae or ecchymoses; disturbed consciousness; serum CRP).	Children with score of less than 8.5 never had bacterial meningitis, while children with a score of more than 20 always had bacterial meningitis. Sensitivity of the test set at 100% with a specificity of 60%.	The clinical signs and symptoms can be used for the diagnosis of bacterial meningitis. Bacterial meningitis is only one of several diagnoses which children who present with reduced conscious level have. During the study they reduced the cut-off value from 9.5 to 8.5 and did not re-validate prospectively. Therefore this is really a derivation study.	Diagnosis 2b

Table 14a.1.ii (a) Papers included in the analysis of the clinical signs which predict bacterial meningitis (diagnostic test studies)

Study	Methods	Participant definition	Length of follow-up	Outcomes	Results	Notes	Evidence level
Walsh-Kelly (318)	Prospective cohort study of children who underwent a lumbar puncture in a US hospital, to	Children (aged 0 to 17 years) who underwent a lumbar puncture at the discretion	Resolution of illness or until a positive diagnosis was reached (from culture or	Presence of the following signs were recorded: Bulging fontanelle,	There were 547 children recruited (having a lumbar puncture) of which 172 (31.5%) had meningitis, 53 (10.5%) had bacterial	Useful hospital population data. Reduced conscious level is the most common finding.	Symptom prevalence 1b

	determine the proportion of children with various clinical signs who had bacterial meningitis.	of the admitting doctor to determine if they had bacterial meningitis or aseptic meningitis. The children were subdivided into age ranges 0-6 months, 6-12 months, 12-18 months and >18 months. Study period August 1985 to February 1988.	latex agglutination).	Nuchal rigidity, positive Kernig's, positive Brudzinski's, looks toxic, looks moribund, lethargy, comatosed. The frequency of these signs were analysed for children with bacterial meningitis and compared to the frequency of these signs for aseptic meningitis.	meningitis, 119 (21%) had aseptic meningitis. Of those children 0-6 months with bacterial meningitis 55% had bulging fontanelle, 27% had nuchal rigidity, 18% had Kernig's sign, and 73% were lethargic / comatose. For those over 18 months, 95% had nuchal rigidity, 75% had Kernig's sign, and 100% were lethargic / moribund.	The predictive values of these signs is not given.	

Table 14a.1.ii (b) Papers included in the analysis of the clinical signs which predict bacterial meningitis (symptom prevalence)

14. Intracranial infections

a) Bacterial meningitis

Clinical Questions

(ii) In children with a reduced conscious level, which rapid investigations help screen for or diagnose bacterial meningitis?

Selection criteria
Criteria for choosing papers were drawn up before the search took place. Papers were selected if they were diagnostic studies of bacterial meningitis, which objectively or blindly compared a diagnostic test with the gold standard. Studies examining CSF microscopy or ELISA or rapid PCR were specifically included. Studies involving both children and adults were included as the performance of the tests would be unlikely to differ between age groups.

Search
A review of the Cochrane library, MEDLINE (1966-present), EMBASE (1980-present), CINAHL (1982-present), British Nursing Index (1985-present) and AMED (1985-present) was performed using the search terms below. A review of the references of the selected papers for further evidence was included in the search strategy and a hand search of five key journals in the field in the previous 12 months.

Search filters

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	956588
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1465344
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1670568
4	1 or 2 or 3	2874741
5	exp meningitis/ or exp meningitis, bacterial/ or exp meningitis, escherichia coli/ or exp meningitis, haemophilus/ or exp meningitis, listeria/ or exp meningitis, meningococcal/ or exp waterhouse-friderichsen syndrome/ or exp meningitis, pneumococcal/ or exp meningitis, viral/ or exp lymphocytic choriomeningitis/ or exp meningitis, aseptic/ or exp encephalomyelitis/ or exp meningoencephalitis/ or exp encephalitis/ or exp encephalitis, viral/	100833
6	diagnos$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	2447207
7	gold.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	70563
8	standard$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	765982
9	test$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	2870847
10	investigation$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	553876
11	7 and 8	23804
12	6 or 9 or 10 or 11	5228589
13	sensitiv$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1225333
14	(sensitivity and specificity).mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	257964
15	diagnosis.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1791155
16	diagnostic $.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	243816
17	diagnosis,differential.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	269904
18	or/13-17	3005354
19	12 and 18	2283239
20	cerebrospinal fluid.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	99667
21	csf.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	94644
22	20 or 21	157151
23	4 and 5 and 19 and 22	2891

Results
A total of 54 abstracts were reviewed from 2891 titles. A total of 7 papers were selected for further review. The hand search of journals and references identified 2 other papers for further review.
2 papers were included in the final analysis.

Papers excluded from the final analysis are listed in table 14a.2.i
Papers included in the final analysis are listed in table 14a.2.ii

Reference	Reason for exclusion
Freeman(135)	Retrospective study of CSF pleocytosis and bacterial meningitis
Negrini(136)	Retrospective study of CSF pleocytosis and meningitis
Nelson (117)	Retrospective study of CSF lactate without blinding
Kearns (119)	Retrospective study of PCR
Chowdhury (120)	Study applied only to positive cases
Issa(121)	Retrospective study of PCR
Negrini (136)	Retrospective study

Table 14a.2.i Papers excluded from the analysis of which rapid tests diagnose bacterial meningitis

Study	Methods	Participants	Diagnostic dilemma	Blinded comparison	Gold standard tested	Results	Notes	Evidence level
Deivana-yagam(137)	Prospective derivation study to determine the accuracy of CSF variables in predicting the presence of bacterial meningitis in children.	Children (aged 2 months to 11 years) admitted to a hospital in India with suspected meningitis. Study period January 1989 to April 1990.	Did the children have pyogenic meningitis, viral meningitis or TB meningitis.	Yes, the technician reviewing the CSF variables was unaware of the clinical signs or symptoms of the patients or the culture / LAT test results.	Gold standard: CSF culture and / or latex agglutination test (LAT). Candidiate test: CSF microscopy, Gram stain, glucose and protein.	A total of 114 children were recruited, with 55 being positive for bacterial meningitis (BM) by culture and / or LAT. If the polymorph count was fixed at >60% of total leukocytes in the CSF, the a total leukocyte count of >300/mm^3 was 80% sensitive and 55% specific for the diagnosis of BM. Protein was not seen to be useful at diagnosing BM.	No true validation set analysed against gold standard to determine if this test holds true for another population.	Diagnosis 2b
Oostenbrink (138)	Retro-spective cohort study to derive a decision rule of starting antibiotics in a patient with suspected meningitis and CSF microscopy results.	Children (aged 1 month to 15 years) attending an emergency department in Holland with neck stiffness who had a lumbar puncture. Study period 1988 to 1998.	Did the CSF microscopy result and the clinical symptoms accurately predict the presence of bacterial meningitis?	Partly. the clinical data was not known by the microbiology technician however both the microscopy and culture test would have been performed by the same person.	Gold standard: CSF culture positive for pyogenic bacteria. Candidate test: combination of CSF microscopy and clinical scoring system (previously derived from the same population).	360 children presented with neck stiffness of which 227 had a lumbar puncture (those who didn't have a lumbar puncture were considered not to have meningitis if after 2 weeks they had not returned to hospital or been treated for meningitis or had deteriorated	Retro-spective derivation study of clinical decision rule.	Diagnosis 2b

						significantly). The derived rule included the absolute CSF polymorpho-nuclear leukocyte count and the CSF-blood glucose ratio. Combining this score with the clinical scoring system accurately diagnosed the absence of 30% of the patients who would normally have been started on antibiotics. (Area under the receiver-operator curve was 0.93)		

Table 14a.2.i Papers included in the analysis of which rapid tests diagnose bacterial meningitis

14. Intracranial infections

a) Bacterial meningitis

Clinical Questions

(iii) In children with a reduced conscious level and suspected bacterial meningitis, which antibiotics should be started?

Selection criteria
Criteria for choosing papers were drawn up before the search took place. Papers would be included if they were randomised controlled trials of children with bacterial meningitis to determine which antibiotic regime improves outcome or markers of outcome. Validation studies of guidelines for the management of children with bacterial meningitis would also be included if they demonstrated benefit of following the guideline and gave advice on the antibiotic regime to use. Studies involving both children and adults were only included if the results for children could be analysed separately.

Search
A review of the Cochrane library, MEDLINE (1966-present), EMBASE (1980-present), CINAHL (1982-present), British Nursing Index (1985-present) and AMED (1985-present) was performed using the search terms below. A review of the references of the selected papers for further evidence was included in the search strategy and a hand search of five key journals in the field in the previous 12 months.

Search filters

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	973072
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1496225
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1702543
4	1 or 2 or 3	2930261
5	exp meningitis/ or exp meningitis, bacterial/ or exp meningitis, escherichia coli/ or exp meningitis, haemophilus/ or exp meningitis, listeria/ or exp meningitis, meningococcal/ or exp waterhouse-friderichsen syndrome/ or exp meningitis, pneumococcal/ or exp meningitis, viral/ or exp lymphocytic choriomeningitis/ or exp meningitis, aseptic/ or exp encephalomyelitis/ or exp meningoencephalitis/ or exp encephalitis/ or exp encephalitis, viral/	100833
6	exp antibiotics/	784000
7	exp drug therapy/	1008784
8	exp antibiotics/ or exp aminoglycosides/ or exp erythromycin/ or exp clarithromycin/ or exp gentamicins/ or exp kanamycin/ or exp amikacin/ or exp tobramycin/ or exp lincomycin/ or exp clindamycin/ or exp neomycin/ or exp streptomycin/ or exp antibiotics, combined/ or exp antibiotics, lactam/ or exp aztreonam/ or exp carbapenems/ or exp thienamycins/ or exp imipenem/ or exp cephalosporins/ or exp cefamandole/ or exp cefoperazone/ or exp cefazolin/ or exp cefonicid/ or exp cefotaxime/ or exp ceftriaxone/ or exp cefuroxime/ or exp cefotetan/ or exp cefoxitin/ or exp cefprozil/ or exp ceftazidime/ or exp cephalexin/ or exp cefaclor/ or exp penicillins/ or exp methicillin/ or exp nafcillin/ or exp oxacillin/ or exp penicillin g/ or exp ampicillin/ or exp amoxicillin/ or exp carbenicillin/ or exp ticarcillin/ or exp antibiotics, macrolide/ or exp azithromycin/ or exp antibiotics, peptide/ or exp bacitracin/ or exp chloramphenicol/ or exp mupirocin/ or exp tetracyclines/ or exp doxycycline/ or exp minocycline/ or exp tetracycline/ or exp vancomycin/ or exp antiinfective agents, quinolone/ or exp antiinfective agents, fluoroquinolone/ or exp ciprofloxacin/ or exp enoxacin/ or exp ofloxacin/ or exp trovafloxacin/ or exp alatrofloxacin/ or exp cinoxacin/ or exp antiinfective agents, urinary/ or exp norfloxacin/ or exp trimethoprim/ or exp trimethoprim-sulfamethoxazole combination/ or exp sulfonamides/ or exp sulfanilamides/ or exp sulfadiazine/ or exp silver sulfadiazine/ or exp sulfadoxine/ or exp sulfamethoxazole/ or exp sulfisoxazole/	927580
9	exp antibiotic agent/ or exp aminoglycoside antibiotic agent/ or exp beta lactam antibiotic/ or exp chloramphenicol derivative/ or exp macrolide/ or exp quinoline derived antiinfective agent/ or exp ciprofloxacin/ or exp sulfonamide/ or exp cotrimoxazole/ or	482397

	exp urinary tract antiinfective agent/	
10	exp anti-infective agents/ or exp anti-bacterial agents/ or exp antibiotics, combined/	1704553
11	RANDOMIZED CONTROLLED TRIAL.pt.	207390
12	CONTROLLED CLINICAL TRIAL.pt.	69509
13	randomized controlled trials.sh.	40568
14	random allocation.sh.	54174
15	double blind method.sh.	83749
16	single blind method.sh.	9322
17	or/11-16	354172
18	Animal.sh.	15964
19	human.sh.	5029060
20	18 not 19	12982
21	17 not 20	354172
22	clinical trial.pt.	432187
23	exp clinical trials/	571720
24	(clin$ adj25 trial$).ti,ab.	234670
25	((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.	168351
26	placebos.sh.	27378
27	placebo$.ti,ab.	186850
28	random$.ti,ab.	645128
29	research design.sh.	43436
30	or/22-29	1448836
31	30 not 20	1448697
32	31 not 21	1115655
33	comparative study.sh.	1294711
34	exp evaluation studies/	579470
35	follow up studies.sh.	307099
36	prospective studies.sh.	234394
37	(control$ or prospectiv$ or volunteer$).ti,ab.	3037750
38	or/33-37	4712196
39	38 not 20	4710763
40	39 not (21 or 32)	3915447
41	21 or 32 or 38	5386707
42	6 or 7 or 8 or 9 or 10	2511553
43	4 and 5 and 41 and 42	2135

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	956588
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1465344
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1670568
4	1 or 2 or 3	2874741
5	exp meningitis/ or exp meningitis, bacterial/ or exp meningitis, escherichia coli/ or exp meningitis, haemophilus/ or exp meningitis, listeria/ or exp meningitis, meningococcal/ or exp waterhouse-friderichsen syndrome/ or exp meningitis, pneumococcal/ or exp meningitis, viral/ or exp lymphocytic choriomeningitis/ or exp meningitis, aseptic/ or exp encephalomyelitis/ or exp meningoencephalitis/ or exp encephalitis/ or exp encephalitis, viral/	100833
6	guideline$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	223821
7	validat$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	168454
8	6 or 7	386657
9	4 and 5 and 8	453

Results

A total of 63 abstracts were reviewed from 2688 titles. 3 systematic reviews were found and selected for further review. The hand search of journals and references identified no other systematic reviews for further assessment. One other paper was identified which was not already included in the systematic reviews

One paper was included in the final analysis.

Papers excluded from the final analysis are listed in table 14a.3.i

Papers included in the final analysis are listed in table 14a.3.ii

Reference	Reason for exclusion
Shah (319)	Neonatal studies only using intraventricular route
Krysan (320)	Systematic review of studies of antibiotics and meningitis in children to determine how many studies demonstrate equivalence statistically rather than merely conclude it imprecisely.
Jacobs(209)	Cost comparison study not a cost-effectiveness analysis

Table 14a.3.i Papers excluded from the analysis of which antibiotic should be initiated in the presence of suspected meningitis in children

Study	Method	Inclusion criteria	Search	Evidence appraisal	Summarizing evidence	Results	Notes	Evidence level
Prasad (321)	Systematic review of trials of intravenous antibiotics used for bacterial meningitis, comparing third generation cephalosporins to other antibiotics.	Eligible studies were published or non-published randomized controlled trials in which a third generation cephalosporin was compared to the conventional treatment in patients with acute bacterial meningitis	Cochrane Central Register of Controlled Clinical Trials (CENTRAL), Medline, and Embase were reviewed. Unpublished material also searched for.	2 independent appraisers. They considered concealment of randomisation, blinding, completeness of follow up and intention-to-treat analysis	Meta-analysis provided including tests for homogeneity. Important outcomes included death and neurological sequelae.	18 studies included (the majority of which were paediatric studies). No heterogeneity was found. There was no significant different between using a third generation cephalosporin and conventional antibiotics which covered a broad spectrum of bacterial pathogens.	Absence of evidence of an effect does not equal evidence of absence of an effect.	Therapy 1a

Table 14a.3.ii Papers included in the analysis of which antibiotic should be initiated in the presence of suspected meningitis in children

14. Intracranial infections

a) Bacterial meningitis

Clinical Questions

(iv) In children with a reduced conscious level and suspected bacterial meningitis, does adjuvant treatment with steroids improve survival or neurological morbidity?

Selection criteria
Criteria for choosing papers were drawn up before the search took place. Papers would be included if they were randomised controlled trials of children with bacterial meningitis to determine whether adjuvant steroid treatment improves outcome or markers of outcome. Validation studies of guidelines for the management of children with bacterial meningitis would also be included if they demonstrated benefit of following the guideline and gave advice on the steroid therapy. Studies involving both children and adults were only included if the results for children could be analysed separately.

Search
A review of the Cochrane library, MEDLINE (1966-present), EMBASE (1980-present), CINAHL (1982-present), British Nursing Index (1985-present) and AMED (1985-present) was performed using the search terms below. A review of the references of the selected papers for further evidence was included in the search strategy and a hand search of five key journals in the field in the previous 12 months.

Search filters

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	973072
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1496225
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1702543
4	1 or 2 or 3	2930261
5	exp meningitis/ or exp meningitis, bacterial/ or exp meningitis, escherichia coli/ or exp meningitis, haemophilus/ or exp meningitis, listeria/ or exp meningitis, meningococcal/ or exp waterhouse-friderichsen syndrome/ or exp meningitis, pneumococcal/ or exp meningitis, viral/ or exp lymphocytic choriomeningitis/ or exp meningitis, aseptic/ or exp encephalomyelitis/ or exp meningoencephalitis/ or exp encephalitis/ or exp encephalitis, viral/	100833
6	steroid$.mp. [mp=ab, hw, ti, sh, it, tn, ot, dm, mf, rw]	276647
7	dexamethasone.mp. [mp=ab, hw, ti, sh, it, tn, ot, dm, mf, rw]	89241
8	exp drug therapy/	1008784
9	6 or 7 or 8	450509
10	RANDOMIZED CONTROLLED TRIAL.pt.	
11	CONTROLLED CLINICAL TRIAL.pt.	207390
12	randomized controlled trials.sh.	69509
13	random allocation.sh.	40568
14	double blind method.sh.	54174
15	single blind method.sh.	83749
16	or/11-16	9322
17	Animal.sh.	354172
18	human.sh.	15964
19	18 not 19	5029060
20	17 not 20	12982
21	clinical trial.pt.	354172
22	exp clinical trials/	432187
23	(clin$ adj25 trial$).ti,ab.	571720
24	((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.	234670
25	placebos.sh.	168351
26	placebo$.ti,ab.	27378
27	random$.ti,ab.	186850
28	research design.sh.	645128

29	or/22-29	43436
30	30 not 20	1448836
31	31 not 21	1448697
32	comparative study.sh.	1115655
33	exp evaluation studies/	1294711
34	follow up studies.sh.	579470
35	prospective studies.sh.	307099
36	(control$ or prospectiv$ or volunteer$).ti,ab.	234394
37	or/33-37	3037750
38	38 not 20	4712196
39	39 not (21 or 32)	4710763
40	21 or 32 or 38	3915447
41	4 and 5 and 9 and 40	385

Results

A total of 42 abstracts were reviewed from 385 titles. 6 systematic reviews were found and selected for further review. The hand search of journals and references identified no other systematic reviews for further assessment. No other papers were identified which were not already included in the systematic reviews
Four papers were included in the final analysis.

Papers excluded from the final analysis are listed in table 14a.4.i
Papers included in the final analysis are listed in table 14a.4.ii

Reference	Reason for exclusion
Contreras (322)	Foreign language systematic review
Prasad (323)	Systematic review of steroid treatment of tuberculous meningitis

Table 14a.4.i Papers excluded from the final analysis of adjuvant steroid treatment for bacterial meningitis

Study	Method	Inclusion criteria	Search	Evidence appraisal	Summarizing evidence	Results	Notes	Evidence level
Geiman (324)	Systematic review of dexamethasone as an adjuvant treatment for bacterial meningitis.	Randomized, controlled trials using dexamethasone as adjunctive treatment for bacterial meningitis in children	Medline 1989-1991 and studies found in a previous meta-analysis	Outcome data for case fatality rate, neurological sequelae, hearing loss and CSF sterilisation at 24hours. No mention of appraisal methodology.	Meta-analysis provided. No discussion or statistical analsis of heterogeneity.	5 studies found – 1 study included adults and children and was only included in the analysis where children could be analysed separately. Relative risk of pooled data. Dexamethasone had no effect on fatality. There was a reduction in neurological sequelae > 6 months (poorly defined "sequelae") in 3 trials (RR=3.9 95%CI 1.72-8.85) and a reduction in bilateral hearing loss in the dexamethasone group (RR=4.12 95%CI 1.74-9.79)	Limited search using only Medline and no notes on evidence appraisal. Review undertaken in pre-HIB vaccine era and doesn't comment on species specific effects.	Therapy 1a -
McIntyre (325)	Systematic review of dexamethasone as an adjuvant treatment for bacterial meningitis.	Randomised controlled trials of dexamethasone in childhood meningitis	Medline, Healthline, Aidsline (MeSH headings "dexamethasone", "meningitis") any language between 1986-1996 and a hand-search for other references	Predetermined protocol used for appraisal and data extraction. Outcome data for mortality, severe hearing loss and non-hearing neurological deficits	Meta-analysis of results available. No tests for heterogeneity. Side effects given.	11 papers eligible and analysed for species-specific effects. Reduction in severe hearing loss for HIB meningitis (OR 0.31 [95% CI = 0.14-0.69]) but	Heterogeneity of antibiotics may have effected the results but good review	Therapy 1a

						only for Streptococcal meningitis if given early (OR 0.09 [95% CI = 0.0-0.71]) but numbers too small for analysis of Meningococcal meningitis. Risk of harm calculated as NNT = 250 for one extra death although this result was not significant.		
van de Beek (326)	Systematic review of dexamethasone as an adjuvant treatment for bacterial meningitis.	Randomised controlled trials on corticosteroids (any type) as adjuvant therapy in acute bacterial meningitis, At least rates of case fatality rate or hearing loss had to be recorded for inclusion of studies	Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library issue 1, 2003); MEDLINE (1966 to January 2003); EMBASE (1974 to April 2002); and HEALTHLINE (1988 to April 2002) and Current Contents for trials published before April 1st 2002 without language limitations, a search of references listed in published studies, hand-searching abstracts of congresses, personal communication with researchers and	2 independent blinded assessors selected 28 papers for inclusion. Outcomes looked at mortality, severe hearing loss, neurological sequelae.	Meta-analysis provided. Analysis of heterogeneity discussed. Harm of corticosteroids also provided.	18 papers included stratified by organism. Relative risk of severe hearing loss reduced for all organisms causing bacterial meningitis (RR 0.42 [95% CI = 0.2-0.89]) not just Hib (RR 0.31 [95% CI = 0.15-0.62]). Mortality was also reduced in the steroid treated groups although this result was not statistically significant.	Robust systematic review.	Therapy 1a

			experts in the field, and from literature lists of pharmaceutical companies					
Yurkowski (327)	Systematic review of dexamethasone as an adjuvant treatment for bacterial meningitis.	Prospective, randomised controlled studies comparing IV antibiotics and / or corticosteroids vs placebo. Studies limited to children aged 1 month to 16 years.	Medline and Current contents between 1977-1991. Limited to English language papers	2 independent judges of methodology, with standard forms. Outcome data extracted for degree of hearing loss and bilateral/unilateral hearing loss	Meta-analysis provided. No description of heterogeneity.	3 studies identified for corticosteroids vs placebo. 10 studies identified for antibiotic type. Differences in antibiotic type did not influence hearing loss. Placebo vs corticosteroid (all dexamethasone) resulted in dexamethasone protecting against hearing loss. This result was consistent when analysed in sub-groups of antibiotics used.	74% had HIB meningitis. Only 3 studies included. No analysis of heterogeneity but discussed in the text.	Therapy 1a

Table 14a.4.ii Papers included in the final analysis of adjuvant steroid treatment for bacterial meningitis

14. Intracranial infections

b) Herpes simplex encephalitis

Clinical Questions:

(i) In children with a reduced conscious level, what are the clinical signs of herpes simplex encephalitis?

Selection criteria
Criteria for choosing papers were drawn up before the search took place. Papers were selected if they were validating cohort studies of clinical decision rules or derivation studies of such rules for herpes simplex encephalitis. Prospective cohort studies or case control studies, which reported on the rates of different signs and symptoms of herpes simplex encephalitis would be included if no other studies were found. Studies involving both children and adults were only included if the results for children could be analysed separately.

Search
A review of the Cochrane library, MEDLINE (1966-present), EMBASE (1980-present), CINAHL (1982-present), British Nursing Index (1985-present) and AMED (1985-present) was performed using the search terms below. A review of the references of the selected papers for further evidence was included in the search strategy and a hand search of five key journals in the field in the previous 12 months.

Search filters

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	951169
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1439069
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1639690
4	1 or 2 or 3	2832537
5	exp neurologic examination/ or exp pain measurement/ or exp reflex/ or exp reflex, abdominal/ or exp reflex, abnormal/ or exp reflex, babinski/ or exp reflex, acoustic/ or exp reflex, pupillary/ or exp reflex, stretch/ or exp startle reaction/ or exp medical history taking/ or exp cornell medical index/ or exp reproductive history/ or exp physical examination/ or exp auscultation/ or exp heart auscultation/ or exp blood pressure determination/ or exp body constitution/ or exp body height/ or exp body surface area/ or exp body weight/ or exp fetal weight/ or exp body temperature/ or exp cephalometry/ or exp craniometry/ or exp facial expression/ or exp facies/ or exp gait/ or exp hand strength/ or exp palpation/ or exp pelvimetry/ or exp percussion/ or exp pigmentation/ or exp skin pigmentation/ or exp pulse/ or exp range of motion, articular/ or exp self-examination/ or exp breast self-examination/ or exp skinfold thickness/	892433
6	exp medical history taking/ or exp patient assessment/ or physical examination/ or exp palpation/ or exp pulse/	153287
7	exp patient history taking/ or exp physical examination/ or exp auscultation/ or exp heart auscultation/ or exp blood pressure determination/ or exp body temperature determination/ or exp cephalometry/ or exp "inspection (clinical)"/ or exp neurologic examination/ or exp reflex/ or exp reflex, abnormal/ or exp reflex, acoustic/ or exp reflex, pupillary/ or exp reflex, stretch/ or exp palpation/ or exp percussion/ or exp physical examination, preparticipation/ or exp pigmentation/ or exp skin pigmentation/ or exp pulse/	553576
8	exp blood pressure/ or exp body temperature/ or exp fatigue/ or exp jaundice/ or exp nausea/ or exp "pain and pain management"/ or exp paralysis/ or exp seizures/ or exp senses/ or exp shock/ or exp sleep/ or exp unconsciousness/ or exp patient assessment/	880816
9	exp medical examination/ or exp clinical examination/ or exp functional assessment/ or exp pulse oximetry/ or exp blood pressure monitoring/ or exp temperature measurement/ or exp thermometry/ or exp blood glucose monitoring/ or exp electrocardiography monitoring/ or exp neurologic examination/ or history/	274711
10	clinical feature.mp. [mp=ab, hw, ti, sh, it, tn, ot, dm, mf, rw]	217941
11	presenting feature.mp. [mp=ab, hw, ti, sh, it, tn, ot, dm, mf, rw]	2084
12	presenting sign.mp. [mp=ab, hw, ti, sh, it, tn, ot, dm, mf, rw]	1575

13	presenting symptom.mp. [mp=ab, hw, ti, sh, it, tn, ot, dm, mf, rw]	4282
14	sign.mp. [mp=ab, hw, ti, sh, it, tn, ot, dm, mf, rw]	61333
15	symptom.mp. [mp=ab, hw, ti, sh, it, tn, ot, dm, mf, rw]	145112
16	or/5-15	2013529
17	encephalitis.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	39617
18	exp encephalitis/	48772
19	18 or 19	60236
20	4 and 16 and 19	152

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	956588
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1465344
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1670568
4	1 or 2 or 3	2874741
5	encephalitis.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	39617
6	exp encephalitis/	48772
7	5 or 6	60236
8	decision rule.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	772
9	diagnosis.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1771627
10	8 or 9	1772247
11	4 and 7 and 10	61

Results

A total of 16 abstracts were reviewed from 213 titles. A total of 3 papers were selected for further review. The hand search of journals and references identified 1 other paper for further review. No papers were included in the final analysis.

Papers excluded from the final analysis are listed in table 14b.1.i
Papers included in the final analysis are listed in table 14b.1.ii

Reference	**Reason for exclusion**
Behzad-Behbahani (328)	Retrospective case series ncluding adults and children.
Marton (329)	Retrospective case series
Wang (330)	Case report
Aurelius (331)	Review of tests not clinical symptoms or signs

Table 14b.1.i Papers excluded from the analysis of which clinical features indicate herpes simplex encephalitis

14. Intracranial infections

b) Herpes simplex encephalitis

Clinical Questions:

(ii) In children with a reduced conscious level, which investigations help screen for or diagnose herpes simplex encephalitis?

Selection criteria
Criteria for choosing papers were drawn up before the search took place. Papers were selected if they were diagnostic studies of herpes simplex encephalitis, which objectively or blindly compared a diagnostic test with the gold standard. Studies examining CSF antibody production or PCR were specifically included. Studies involving both children and adults were included as the performance of the tests would be unlikely to differ between age groups.

Search
A review of the Cochrane library, MEDLINE (1966-present), EMBASE (1980-present), CINAHL (1982-present), British Nursing Index (1985-present) and AMED (1985-present) was performed using the search terms below. A review of the references of the selected papers for further evidence

was included in the search strategy and a hand search of five key journals in the field in the previous 12 months.

Search filters

#	Search terms	No. of articles
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4	1 or 2 or 3	2874741
5	encephalitis.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	39617
6	exp encephalitis/	48772
7	5 or 6	60236
8	diagnos$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	2447207
9	gold.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	70563
10	standard$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	765982
11	test$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	2870847
12	investigation$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	553876
13	9 and 10	23804
14	8 or 11 or 12 or 13	5228589
15	sensitiv$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1225333
16	(sensitivity and specificity).mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	257964
17	diagnosis.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1791155
18	diagnostic $.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	243816
19	diagnosis,differential.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	269904
20	or/15-19	3005354
21	14 and 20	2283239
22	cerebrospinal fluid.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	99667
23	csf.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	94644
24	22 or 23	157151
25	pcr.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	241577
26	polymerase chain reaction.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	386912
27	25 or 26	442213
28	24 and 27	7046
29	4 and 7 and 21 and 28	258

Results
A total of 54 abstracts were reviewed from 28 titles. A total of 10 papers were selected for further review. The hand search of journals and references identified 2 other paper for further review.
9 papers were included in the final analysis.

Papers excluded from the final analysis are listed in table 14b.2.i
Papers included in the final analysis are listed in table 14b.2.ii(a) and (b)

Reference	**Reason for exclusion**
Munoz-Almagro (332)	Foreign language
Revello (333)	No blinding or clinical dilemma involved in study.
Boivin (334)	Guideline not validated

Table 14b.2.i Papers excluded from the analysis of which tests screen for or diagnose herpes simplex encephalitis

Study	Methods	Participants	Diagnostic dilemma	Blinded comparison	Gold standard tested	Results	Notes	Evidence level
Uren(123)	Retro-spective review of children with a definite diagnosis of herpes simplex encephalitis (HSE) to assess the accuracy of a HSV-PCR test on the CSF collected at the time of presentation.	16 children (aged 11 days to 12 years) presenting to a children's hospital in Australia with a gold standard diagnosis of HSE, and 14 children identified as not having HSE. Study period 1983 to1991	Could the children have been diagnosed earlier using HSV-PCR compared to using the gold standard of the time?	No but PCR a relatively objective measure which limits observer bias. PCR was applied to all children who had a stored frozen CSF sample.	Gold standard was a number of different tests: viral isolation from brain biopsy (rarely done in children); or antibodies to HSV detected to rise in CSF; or antibodies to HSV found in increasing quantities in the CSF compared with serum.	For CSF samples taken within 1-4 days of the illness, PCR had sensitivity of 70% and specificity of 100%. If CSF sample taken after 4 days of illness (and possibly on treatment) sensitivity only 33%, but specificity still 100%.	Retro-spective study therefore was there really a diagnostic dilemma. Concerns were raised about the freezing and re-freezing of samples as a cause for the reducing sensitivity of the test with time.	Diagnosis 4
Anderson (124)	Prospective study of adults and children with suspected diagnosis of HSE to assess the accuracy of HSV-PCR against gold standard.	Children and adults (aged 1 week to 70 years) presenting to hospitals across New Zealand. Study period 1989-?	Did the patients with clinical symptoms suggestive of HSE have HSE?	Not stated, but a relatively objective measure which limits potential observer bias. PCR was applied to all CSF samples obtained.	Gold standard was a number of different tests: viral isolation from brain biopsy (rarely done); or antibodies to HSV detected to rise in CSF; or antibodies to HSV found in increasing quantities in the CSF compared with serum.	Of 109 patients with suspected HSE, 20 tested +ve with PCR and 14 tested +ve with the gold standard methods. None with a +ve gold standard test tested negative with PCR. Sensitivity 100%, specificity 93%.	Concern that some of those testing negative with the gold standard test probably had HSE – ie PCR may be a more specific test than suggested here. There were 41 in the disease negative group who remained undiagnosed. Very few of these had any collaborating evidence of HSE, but it is difficult to be sure.	Diagnosis 3b

Puchhammer-Stockl (125)	Retro-spective analysis of the HSV-PCR negative patients to determine the number of false negative results occurring with this test.	Children and adults suspected of having HSE and having CSF sent for PCR in Vienna, Austria. Study period 1994 to 1998.	Did any of the patients with HSV-PCR negative result have HSE?	No. Follow up of cases who had negative PCR result known.	Gold standard defined cases of HSE included antibody production in CSF, clinical features and course of illness, further PCR tests to determine other diagnoses.	Of 1427 patients included, follow up was available for 811. 12 patients were positive for HSV-PCR, and only 1 patient who had a negative PCR result had definite HSE (antibodies and clinical features). None of the other 798 had HSE (either another diagnosis was confirmed or there were no features to suggest it was HSE during the follow-up period).	Retro-spective analysis. Large loss to follow up (only 56%).	Diagnosis 4
Fomsgaard (126)	Retro-spective analysis of patients with confirmed HSE to determine when the PCR becomes positive in the course of the disease process compared to HSV intrathecal antibody production.	Adults and children (aged 4 days to 74 years) who had CSF sent to a central reference laboratory in Denmark, because of symptoms / signs of HSE. Study period January 1993 to September 1996.	Did combining the two tests improve the capture rate of HSE positive patients?	No, follow-up of known HSE positive patients.	Gold standard not defined. A combination of PCR and intrathecal antibody production and clinical signs (including EEG / radiology tests) and no other diagnosis.	Of 4206 CSF samples collected from 4140 patients, 33 patients were diagnosed as haiving HSE on test grounds. At first CSF sampling 23 were PCR positive, 9 were intrathecal antibody positive and 1 was positive to both tests. There was an increase in the number of	Not a blind study of tests but useful to show that the sensitivity and specificity of these two tests is partly determined by the time the tests are taken. Perhaps PCR and intrathecal antibody tests should both be sent so as not to miss an early or late case.	Diagnosis 4

						positive intrathecal antibody tests as the time from onset of symptoms increased and a reciprocal decrease in +ve PCR over a similar time period.		
Lakeman (127)	Retro-spective assessment of brain-biopsied patients with suspected HSE and the accuracy of PCR for HSV in their CSF.	Children and adults (age range not stated) who had been enrolled in previous trials for the efficacy of acyclovir and the ability to locate saved CSF samples on these patients.	Were the patients who were biopsy-positive (in an era when that was the gold standard test) also PCR positive for HSV?	No, but PCR a fairly objective test. All Patients had gold standard test, and all patients had candidate test.	Gold standard: brain biopsy and virus isolation. Candidate test: HSV-PCR.	101 Patients who had brain biopsies as part of the diagnosis in the original study protocol also had CSF samples to analyse. Some had had more than one CSF sample taken. The specificity of PCR was 94% and sensitivity 98%. Looking at the brain-biopsy +ve samples, 98% of patients (n=54) were PCR +ve 7 days after starting therapy, but this decreased to only 20% by day 15.	Although no blinding the test was applied to all patients and the PCR is an objective test in general. The failure to find all the CSF samples is a criticism (although very under-standable). The authors suggest that PCR is more specific than these figures suggest as the brain biopsy negative patients with +ve PCR probably had HSE.	Diagnosis 3b
Troendle-Atkins (128)	Prospective assessment of HSV-PCR in	Children (aged 7 days to 14 years) with	How accurate is PCR in diagnosing	Not mentioned therefore unlikely. However, PCR a	Gold standard: criteria of National Institute of Allergy	19 children (8 neonates with HSV infection	Small study but absolute SpIn.	Diagnosis 1c

	the diagnosis of HSE in children against the gold standard of intrathecal HSV antibody production and / or HSV isolated from brain biopsy samples and / or other evidence of HSE according to a strict research criteria.	suspected HSE or neonatal HSV infection (including skin, eye and mouth infection as well as CNS involvement) attending a children's hospital in Texas, USA. Study period 1991 to 1992.	HSE against gold standard in patients with HSV infection and suspected HSE?	relatively objective measure-ment reducing the likelihood of introducing bias.	and Infectious Diseases collaborative neonatal antiviral study group for HSE proved, presumed or not proved (this included virus isolation or intrathecal production of PCR); Candidate test: PCR for HSE from CSF.	and 11 children with suspected HSE) were enrolled. 9 were classed as disease +ve. The sensitivity was 67% and specificity 100% (ignoring the control group they used which did not have diagnostic uncertainty).		
Aurelius (129)	Study of to determine accuracy of "nested" PCR against gold standard of intrathecal HSV antibody production / virus isolation from brain biopsy tissue.	Consecutive patients (age range not stated) with suspected HSE. Study location Sweden (but not stated how many hospitals / regions involved). Study dates not stated.	How accurate is PCR ("nested") against gold standard in the detection of HSE?	Yes, samples were coded so that the technicians and researchers were unaware of the clinical details of each patient).	Gold standard: intrathecal HSV antibody production / virus isolation from brain biopsy tissue. Candidate test: HSV-PCR from CSF.	103 patients were involved. 43 were classed as disease +ve. The sensitivity of PCR was 95% and the specificity was 100%.	Recruitment of patients not clear but possibly retrospective from studies of antiviral therapy. Diagnostic uncertainty existed in all the patients, as those classed as disease "negative" had been treated with antiviral treatments initially.	Diagnosis 1b
Rowley (130)	Retro-spective study to determine the accuracy of HSV PCR in	Patients (age not stated) with brain biopsy positive HSE and patients	Is PCR accurate to distinguish between HSE and other	No, as retro-spective study with known cases and controls. Gold standard	Gold standard: virus isolation from brain biopsy tissue or other confirmed diagnosis.	4 patients with disease and 6 patients with other diseases as controls. PCR	Poor study design. Controls not tested for HSV other than	Diagnosis 4

	determining HSE.	with other diagnoses. Study dates not given.	CNS diseases?	not applied to all patients.	Candidate test: HSV-PCR of CSF	was found to be 100% sensitive and 100% specific.	PCR. No diagnostic uncertainty which improves the results of the test artificially.	

Table 14b.2.ii(a) Papers included in the analysis of which tests screen for or diagnose herpes simplex encephalitis (Diagnostic studies)

Study	Methods	Question being asked	Participants	What costs are included?	What outcomes are included	Results and sensitivity analysis	Notes	Evidence level
Tebas (335)	Cost-utility analysis using retrospective data from a single centre in the USA and published resources. Study period 1993 to 1995.	Is a strategy of testing for herpes simplex PCR in patients with suspected HSV encephalitis more economical than treating with empirical aciclovir until another diagnosis is made?	Data taken from the literature and the experience of 606 patients (age not stated) at a hospital in USA treated with aciclovir.	Cost of PCR test, treatment with 14 days aciclovir, treatment with average length of empirical aciclovir, and "bad outcomes" relating to misdiagnosis. Costs were based on pharmacy information using patient weight as 70kg.	Death, severe neurological morbidity, moderate neurological morbidity and normal. The frequencies of these outcomes were based on published evidence of the natural history of herpes simplex encephalitis (HSE) with and without aciclovir treatment.	PCR based approach reduced the number of doses of aciclovir prescribed per patient suspected of having HSE from 17 to 8. A sensitivity analysis did not reduce the finding and all the estimated values of sensitivity and specificity were conservative. The cost of this strategy will be determine by the cost of the aciclovir.	The study uses adults and therefore the cost of aciclovir will be different to that for child doses.	Economic analysis 2b

Table 14b.2.ii(b) Papers included in the analysis of which tests screen for or diagnose herpes simplex encephalitis (Economic studies)

14. Intracranial infections

b) Herpes simplex encephalitis

Clinical Questions:

(iii) In children with a reduced conscious level and suspected herpes simplex encephalitis, is aciclovir an effective treatment?

Selection criteria
Criteria for choosing papers were drawn up before the search took place. Papers would be included if they were randomised controlled trials of children with herpes simplex encephalitis to determine if aciclovir improves outcome or markers of outcome compared with placebo or another treatment. Validation studies of guidelines for the management of children with herpes simplex encephalitis would also be included if they demonstrated benefit of following the guideline and gave advice on the aciclovir use. Studies involving both children and adults were included if the results for children could be analysed separately.

Search
A review of the Cochrane library, MEDLINE (1966-present), EMBASE (1980-present), CINAHL (1982-present), British Nursing Index (1985-present) and AMED (1985-present) was performed using the search terms below. A review of the references of the selected papers for further evidence was included in the search strategy and a hand search of five key journals in the field in the previous 12 months.

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#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	973072
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3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1702543
4	1 or 2 or 3	2930261
5	encephalitis.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	39617
6	exp encephalitis/	48772
7	5 or 6	60236
8	aciclovir.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	17204
9	acyclovir.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	12167
10	8 or 9	24486
11	RANDOMIZED CONTROLLED TRIAL.pt.	207390
12	CONTROLLED CLINICAL TRIAL.pt.	69509
13	randomized controlled trials.sh.	40568
14	random allocation.sh.	54174
15	double blind method.sh.	83749
16	single blind method.sh.	9322
17	or/11-16	354172
18	Animal.sh.	15964
19	human.sh.	5029060
20	18 not 19	12982
21	17 not 20	354172
22	clinical trial.pt.	432187
23	exp clinical trials/	571720
24	(clin$ adj25 trial$).ti,ab.	234670
25	((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.	168351
26	placebos.sh.	27378
27	placebo$.ti,ab.	186850
28	random$.ti,ab.	645128
29	research design.sh.	43436
30	or/22-29	1448836
31	30 not 20	1448697
32	31 not 21	1115655

33	comparative study.sh.	1294711
34	exp evaluation studies/	579470
35	follow up studies.sh.	307099
36	prospective studies.sh.	234394
37	(control$ or prospectiv$ or volunteer$).ti,ab.	3037750
38	or/33-37	4712196
39	38 not 20	4710763
40	39 not (21 or 32)	3915447
41	21 or 32 or 38	5386707
42	4 and 7 and 9 and 42	151

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	956588
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1465344
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1670568
4	1 or 2 or 3	2874741
5	encephalitis.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	39617
6	exp encephalitis/	48772
7	5 or 6	60236
8	guideline$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	223821
9	validat$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	168454
10	8 or 9	386657
11	4 and 7 and 10	61

Results
A total of 10 abstracts were reviewed from 211 titles. 4 papers were selected for further review. The hand search of journals and references identified 2 other papers for further assessment.
Three papers were included in the final analysis.

Papers excluded from the final analysis are listed in table 14b.3.i
Papers included in the final analysis are listed in table 14b.3.ii

Reference	**Reason for exclusion**
Enright (336)	Review of evidence not systematic
Whitley (337)	Uncontrolled trial to determine mortality in treated and untreated patients with suspected HSE
Mendiratta (338)	Economic analysis on small group of adult patients with suspected HSE

Table 14b.3.i Papers excluded from the final analysis of aciclovir therapy for herpes simplex encephalitis

Study	Methods	Participants	Interventions	Allocation concealment	Outcomes	Results	Notes	Evidence level
Skoldenberg (339)	Randomised controlled multicentre trail in Sweden comparing vidaribine against aciclovir for the treatment of herpes simplex encephalitis.	Patients (aged over 4 weeks) with suspected HSE and confirmed with brain biopsy for HSV immunofluoresence / ELISA / culture, and / or CSF antibody levels against HSV. Study period March 1981 to July 1982.	Aciclovir 10mg/kg IV TDS or Vidaribine 15mg/kg over 12 hours. Not blinded as difference in mode of delivery. All other treatments (inc. steroids) at discretion of participating centre.	Randomisation in blocks of 12 using sealed opaque envelopes.	Mortality and neurological sequelae at 6 months (no statement regarding primary / secondary outcomes or initial power calculation)	127 patients with suspected HSE were enrolled and 53 of these had confirmed HSE. Of 53 patients, 27 were randomised to aciclovir. Of 27 acyclovir treated patients 5 (19%) died compared to 12 of 24 (50%) vidaribine treated patients – significant difference (p=0.04). Two excluded from vidaribine treated group as they relapsed and were started on acyclovir. 15/27 (56%) acyclovir treated patients had no or minor sequelae at 6 months compared to 3/24 (25%) – significant difference (p=0.002). No difference in moderate to severe sequelae between treatment groups.	During study period 5 cases of HSE were not enrolled – no reason given. Non-HSE group completed course of treatment with 2 deaths in 42 acyclovir treated patients compared to 4 / 32 vidaribine treated patients. No power calculation stated before study and no analysis in intention-to-treat groups for 2 dropouts in vidaribine group. The mortality rate in the vidaribine and acyclovir groups are similar to other studies. Drug toxicity was assessed during treatment with an erythematous rash noted in 1 acyclovir treated patient and 12 moderate but transient elevated alanine aminotransferase	Therapy 1b

						The lower the conscious level at presentation the worse the outcome. 17% of patients with HSE aged <16, but results not analysed separately.	levels noted in the acyclovir group. (3 rashes and 21 raised ALT levels in vidaribine group)	
Whitley (340)	Randomised controlled multicentre trail in America comparing vidaribine against aciclovir for the treatment of herpes simplex encephalitis	Patients (aged over 6 months) with suspected HSE and confirmed with brain biopsy for HSV. Study period September 1981 to December 1984.	Acyclovir 10mg/kg IV TDS or Vidaribine 15mg/kg over 12 hours. Not blinded as difference in mode of delivery.	Not stated therefore potential for bias in study.	Mortality and neurological sequelae at 1, 6, 12 and 24 months (no statement regarding primary / secondary outcomes or initial power calculation)	208 patients over 6 months old with suspected HSE were enrolled and 69 were confirmed to have HSE. Of 32 acyclovir treated patients 6 (19%) died within 6 months compared to 20 of 37 (54%) vidaribine treated patients – significant difference (p=0.008). In the under 30 year old patients mortality rate was 6% (1 of 18) in the acyclovir group compared to 45% (5 of 11) in the vidaribine group (p=0.01). 12/32 (28%) acyclovir treated patients had no or minor sequelae at	All study participants followed-up. Analysis allows for results to apply to those <30 but cannot separate children from within this group. However 80% of patients aged under 30 were aged <20 years.	Therapy 1b

						6 months compared to 5/37 (13%) – significant difference (p=0.02). The lower the conscious level at presentation the worse the outcome. Multivariate-regression model for variables affecting outcome – age and GCS at presentation – still demonstrated a significant difference between the two groups.		
Whitley (341)	Randomised controlled multicentre trail in America comparing vidaribine against placebo for the treatment of herpes simplex encephalitis	Patients (age not stated) with suspected HSE and confirmed with brain biopsy for HSV. Study period not stated.	Vidaribine 15mg/kg IV over 12 hours for 10 days or placebo with double-blinding	Not stated how randomisation took place. Double-blind therapy should prevent randomisation being unconcealed.	Mortality and neurological sequelae at 2, 3, 6, 12 and 24 months (no statement regarding primary / secondary outcomes or initial power calculation)	52 patients with suspected HSE were enrolled, of which 28 had HSV confirmed with brain biopsy culture. Of 18 vidaribine treated patients 5 (28%) died compared with 7 / 10 (70%) in the placebo group (p=0.03). Due to this finding the study was stopped early and the numbers were therefore too small to analyse	Analysis of children in study not separated from others in group. No mention of age of group.	Therapy 1b

						neurological outcome data. The lower the conscious level at presentation the worse the outcome.		

Table 14b.3.ii Papers included in the final analysis of aciclovir therapy for herpes simplex encephalitis

14. Intracranial infections

b) Herpes simplex encephalitis

Clinical Questions:

(iv) In children with a reduced conscious level and suspected herpes simplex encephalitis, how long should aciclovir be continued for?

Selection criteria
Criteria for choosing papers were drawn up before the search took place. Papers would be included if they were randomised controlled trials of children with herpes simplex encephalitis comparing different lengths of aciclovir treatment. Validation studies of guidelines for the management of children with herpes simplex encephalitis would also be included if they demonstrated benefit of following the guideline and gave advice on the aciclovir course. Studies involving both children and adults were only included if the results for children could be analysed separately.

Search
A review of the Cochrane library, MEDLINE (1966-present), EMBASE (1980-present), CINAHL (1982-present), British Nursing Index (1985-present) and AMED (1985-present) was performed using the search terms below. A review of the references of the selected papers for further evidence was included in the search strategy and a hand search of five key journals in the field in the previous 12 months.

Search filters

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	973072
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1496225
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1702543
4	1 or 2 or 3	2930261
5	encephalitis.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	39617
6	exp encephalitis/	48772
7	5 or 6	60236
8	aciclovir.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	17204
9	acyclovir.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	12167
10	8 or 9	24486
11	RANDOMIZED CONTROLLED TRIAL.pt.	207390
12	CONTROLLED CLINICAL TRIAL.pt.	69509
13	randomized controlled trials.sh.	40568
14	random allocation.sh.	54174
15	double blind method.sh.	83749
16	single blind method.sh.	9322
17	or/11-16	354172
18	Animal.sh.	15964
19	human.sh.	5029060
20	18 not 19	12982
21	17 not 20	354172
22	clinical trial.pt.	432187
23	exp clinical trials/	571720
24	(clin$ adj25 trial$).ti,ab.	234670
25	((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.	168351
26	placebos.sh.	27378
27	placebo$.ti,ab.	186850
28	random$.ti,ab.	645128
29	research design.sh.	43436
30	or/22-29	1448836
31	30 not 20	1448697
32	31 not 21	1115655
33	comparative study.sh.	1294711

34	exp evaluation studies/	579470
35	follow up studies.sh.	307099
36	prospective studies.sh.	234394
37	(control$ or prospectiv$ or volunteer$).ti,ab.	3037750
38	or/33-37	4712196
39	38 not 20	4710763
40	39 not (21 or 32)	3915447
41	21 or 32 or 38	5386707
42	day$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1566877
43	dose$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1516664
44	course$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	616938
45	duration.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	445557
46	length.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	445858
47	or/42-46	3832670
48	4 and 7 and 9 and 42 and 47	2

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	956588
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1465344
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1670568
4	1 or 2 or 3	2874741
5	encephalitis.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	39617
6	exp encephalitis/	48772
7	5 or 6	60236
8	guideline$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	223821
9	validat$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	168454
10	8 or 9	386657
11	4 and 7 and 10	61

Results
A total of 2 abstracts were reviewed from 63 titles. No other papers were identified for inclusion.

14. Intracranial infections

c) Intracranial abscess

Clinical Questions:

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

Selection criteria
Criteria for choosing papers were drawn up before the search took place. Papers were selected if they were validating cohort studies of clinical decision rules or derivation studies of such rules for intracranial abscesses. Prospective cohort studies or case control studies, which reported on the rates of different signs and symptoms of abscesses would be included if no other studies were found. Studies involving both children and adults were only included if the results for children could be analysed separately.

Search
A review of the Cochrane library, MEDLINE (1966-present), EMBASE (1980-present), CINAHL (1982-present), British Nursing Index (1985-present) and AMED (1985-present) was performed using the search terms below. A review of the references of the selected papers for further evidence was included in the search strategy and a hand search of five key journals in the field in the previous 12 months.

Search filters

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	951169
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1439069
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1639690
4	1 or 2 or 3	2832537
5	exp neurologic examination/ or exp pain measurement/ or exp reflex/ or exp reflex, abdominal/ or exp reflex, abnormal/ or exp reflex, babinski/ or exp reflex, acoustic/ or exp reflex, pupillary/ or exp reflex, stretch/ or exp startle reaction/ or exp medical history taking/ or exp cornell medical index/ or exp reproductive history/ or exp physical examination/ or exp auscultation/ or exp heart auscultation/ or exp blood pressure determination/ or exp body constitution/ or exp body height/ or exp body surface area/ or exp body weight/ or exp fetal weight/ or exp body temperature/ or exp cephalometry/ or exp craniometry/ or exp facial expression/ or exp facies/ or exp gait/ or exp hand strength/ or exp palpation/ or exp pelvimetry/ or exp percussion/ or exp pigmentation/ or exp skin pigmentation/ or exp pulse/ or exp range of motion, articular/ or exp self-examination/ or exp breast self-examination/ or exp skinfold thickness/	892433
6	exp medical history taking/ or exp patient assessment/ or physical examination/ or exp palpation/ or exp pulse/	153287
7	exp patient history taking/ or exp physical examination/ or exp auscultation/ or exp heart auscultation/ or exp blood pressure determination/ or exp body temperature determination/ or exp cephalometry/ or exp "inspection (clinical)"/ or exp neurologic examination/ or exp reflex/ or exp reflex, abnormal/ or exp reflex, acoustic/ or exp reflex, pupillary/ or exp reflex, stretch/ or exp palpation/ or exp percussion/ or exp physical examination, preparticipation/ or exp pigmentation/ or exp skin pigmentation/ or exp pulse/	553576
8	exp blood pressure/ or exp body temperature/ or exp fatigue/ or exp jaundice/ or exp nausea/ or exp "pain and pain management"/ or exp paralysis/ or exp seizures/ or exp senses/ or exp shock/ or exp sleep/ or exp unconsciousness/ or exp patient assessment/	880816
9	exp medical examination/ or exp clinical examination/ or exp functional assessment/ or exp pulse oximetry/ or exp blood pressure monitoring/ or exp temperature measurement/ or exp thermometry/ or exp blood glucose monitoring/ or exp electrocardiography monitoring/ or exp neurologic examination/ or history/	274711
10	clinical feature.mp. [mp=ab, hw, ti, sh, it, tn, ot, dm, mf, rw]	217941
11	presenting feature.mp. [mp=ab, hw, ti, sh, it, tn, ot, dm, mf, rw]	2084
12	presenting sign.mp. [mp=ab, hw, ti, sh, it, tn, ot, dm, mf, rw]	1575
13	presenting symptom.mp. [mp=ab, hw, ti, sh, it, tn, ot, dm, mf, rw]	4282
14	sign.mp. [mp=ab, hw, ti, sh, it, tn, ot, dm, mf, rw]	61333
15	symptom.mp. [mp=ab, hw, ti, sh, it, tn, ot, dm, mf, rw]	145112
16	or/5-15	2013529
17	exp Brain Abscess/	8665
18	4 and 16 and 17	448

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	956588
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1465344
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1670568
4	1 or 2 or 3	2874741
5	exp Brain Abscess/	8665
6	decision rule.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	772
7	diagnosis.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1771627
8	6 or 7	1772247
9	4 and 5 and 8	16

Results

A total of 12 abstracts were reviewed from 464 titles. A total of 3 papers were selected for further review. The hand search of journals and references identified 2 other papers for further review. One paper was included in the final analysis.

Papers excluded from the final analysis are listed in table 14c.1.i
Papers included in the final analysis are listed in table 14c.1.ii

Reference	Reason for exclusion
Abdullah (342)	Retrospective case review analysing children and adults together
Benjelloun-Dakhama(157)	Foreign language, case series.
Domingo (343)	Retrospective case review
Goodkin (344)	Retrospective case review

Table 14c.1.i Papers excluded from the analysis of the clinical signs which predict intracranial abscesses

Study	Methods	Participant definition	Length of follow-up	Outcomes	Results	Notes	Evidence level
Veerappan (345)	Prospective cohort study to determine the clinical features and outcomes of children with brain abscesses presenting to a tertiary care centre in India.	Children (aged 1 to 12 years) presenting consecutively to a tertiary centre with a brain abscess. The diagnosis of an intracranial abscess was made by contrast enhanced CT scan, evidence of pus on needle aspiration or at time of surgery. Subdural empyemas and subdural abscesses were excluded. Study period September 1990 to May 1992.	To diagnosis and hospital discharge or death.	The relationship between signs and symptoms at presentation and the final diagnosis of a brain abscess.	24 patients were enrolled. The most common presenting features were as follows: fever (91%); vomiting (83%); headache (75%); neck stiffness (41%); papilloedema (41%); hemiparesis (33%); altered sensorium (25%); cranial nerve palsy (25%); cerebellar signs (12%); aniscoria (8%); and dysphasia (4%).	This patient group include some very late presenting signs which may not equate to the UK population. No mention is made of the symptom prevalence in population suspected of but not having a brain abscess for comparison. Follow-up was not standardised.	Symptom prevalence 2b

Table 14c.1.ii Papers included in the analysis of the clinical signs which predict intracranial abscesses

14. Intracranial infections

c) Intracranial abscess

Clinical Questions:

(ii) In children with a reduced conscious level, which investigations help screen for or diagnose intracranial abscess?

Selection criteria
Criteria for choosing papers were drawn up before the search took place. Papers would be included if they were diagnostic studies in children with intracranial abscesses. Studies involving both children and adults were only included if the results for children could be analysed separately.

Search
A review of the Cochrane library, MEDLINE (1966-present), EMBASE (1980-present), CINAHL (1982-present), British Nursing Index (1985-present) and AMED (1985-present) was performed using the search terms below. A review of the references of the selected papers for further evidence was included in the search strategy and a hand search of five key journals in the field in the previous 12 months.

Search filters

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	956588
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1465344
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1670568
4	1 or 2 or 3	2874741
5	sensitiv$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1196235
6	(sensitivity and specificity).mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	247943
7	diagnosis.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1764281
8	diagnostic $.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	236218
9	diagnosis,differential.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	265966
10	diagnos$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	2403697
11	test$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	2807626
12	investigation$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	541353
13	gold.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	68818
14	standard$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	744427
15	8 and 9	22794
16	or/5-12	2948991
17	15 or 16	3433790
18	exp Brain Abscess/	8665
19	intracranial abscess$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	302
20	cerebral abscess$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1182
21	cerebellar abscess$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	243
22	or/18-21	9029
23	17 and 22	265

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	956588
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1465344
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1670568
4	1 or 2 or 3	2874741
5	computed tomography.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	127917
6	ct.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	201844
7	scan.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	110797
8	imaging.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	576404
9	or/5-8	803671
10	exp Brain Abscess/	8665

11	intracranial abscess$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	302
12	cerebral abscess$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1182
13	cerebellar abscess$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	243
14	or/10-13	9029
15	4 and 9 and 14	403

Results
A total of 12 abstracts were reviewed from 668 titles. A total of 3 papers were selected for further review. The hand search of journals and references identified no other papers for further review. No papers were included in the final analysis.

Papers excluded from the final analysis are listed in table 14c.2.i

Reference	**Reason for exclusion**
Stevens (346)	Retrospective case series
Shaw (164)	Retrospective case series
Dev (347)	No blinded comparison of MRI with aspiration

Table 14c.2.i Papers excluded from the analysis of which tests diagnose intracranial abscesses

14. Intracranial infections

c) Intracranial abscess

Clinical Questions:

(iii) In children with a reduced conscious level and suspected intracranial abscess, which treatments should be started?

Selection criteria
Criteria for choosing papers were drawn up before the search took place. Papers would be included if they were diagnostic studies in children with intracranial abscesses. Studies involving both children and adults were only included if the results for children could be analysed separately.

Search
A review of the Cochrane library, MEDLINE (1966-present), EMBASE (1980-present), CINAHL (1982-present), British Nursing Index (1985-present) and AMED (1985-present) was performed using the search terms below. A review of the references of the selected papers for further evidence was included in the search strategy and a hand search of five key journals in the field in the previous 12 months.

Search filters

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	956588
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1465344
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1670568
4	1 or 2 or 3	2874741
5	exp Brain Abscess/	8665
6	intracranial abscess$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	302
7	cerebral abscess$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1182
8	cerebellar abscess$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	243
9	or/5-8	9029
10	RANDOMIZED CONTROLLED TRIAL.pt.	207390
11	CONTROLLED CLINICAL TRIAL.pt.	69509
12	randomized controlled trials.sh.	40568
13	random allocation.sh.	54174
14	double blind method.sh.	83749
15	single blind method.sh.	9322
16	or/10-15	354172

17	Animal.sh.	15964
18	human.sh.	5029060
19	17 not 18	12982
20	16 not 19	354172
21	clinical trial.pt.	432187
22	exp clinical trials/	571720
23	(clin$ adj25 trial$).ti,ab.	234670
24	((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.	168351
25	placebos.sh.	27378
26	placebo$.ti,ab.	186850
27	random$.ti,ab.	645128
28	research design.sh.	43436
29	or/21-28	1448836
30	29 not 19	1448697
31	30 not 20	1115655
32	comparative study.sh.	1294711
33	exp evaluation studies/	579470
34	follow up studies.sh.	307099
35	prospective studies.sh.	234394
36	(control$ or prospectiv$ or volunteer$).ti,ab.	3037750
37	or/32-36	4712196
38	37 not 19	4710763
39	38 not (20 or 31)	3915447
40	20 or 31 or 37	5386707
41	4 and 9 and 40	413

Results

A total of 42 abstracts were reviewed from 413 titles. A total of 10 papers were selected for further review. The hand search of journals and references identified one other paper for further review. No papers were included in the final analysis.

Papers excluded from the final analysis are listed in table 14c.2.i

Reference	**Reason for exclusion**
Qureshi (348)	Small historical comparative study without true randomisation
Liao (349)	Foreign language article
Asensi (350)	Not a comparative study
Sjolin (351)	Not a comparative study
Yamamoto (352)	Not a comparative study
Gomez (353)	Foreign language article
Strowitzki (354)	Case series
Kariev (355)	Foreign language article
Akova (356)	Case series
Stapleton (357)	Case series
Tekkok (161)	Retrospective case series

Table 14c.3.i Papers excluded from the analysis of which treatments to use for intracranial abscesses

14. Intracranial infections

d) Tuberculous (TB) meningitis

Clinical Questions:

(i) In children with a reduced conscious level, what are the clinical signs of tuberculous (TB) meningitis?

Selection criteria
Criteria for choosing papers were drawn up before the search took place. Papers were selected if they were validating cohort studies of clinical decision rules or derivation studies of such rules for TB meningitis. Prospective cohort studies or case control studies, which reported on the rates of different signs and symptoms of abscesses would be included if no other studies were found. Studies involving both children and adults were only included if the results for children could be analysed separately.

Search
A review of the Cochrane library, MEDLINE (1966-present), EMBASE (1980-present), CINAHL (1982-present), British Nursing Index (1985-present) and AMED (1985-present) was performed using the search terms below. A review of the references of the selected papers for further evidence was included in the search strategy and a hand search of five key journals in the field in the previous 12 months.

Search filters

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	951169
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1439069
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1639690
4	1 or 2 or 3	2832537
5	exp neurologic examination/ or exp pain measurement/ or exp reflex/ or exp reflex, abdominal/ or exp reflex, abnormal/ or exp reflex, babinski/ or exp reflex, acoustic/ or exp reflex, pupillary/ or exp reflex, stretch/ or exp startle reaction/ or exp medical history taking/ or exp cornell medical index/ or exp reproductive history/ or exp physical examination/ or exp auscultation/ or exp heart auscultation/ or exp blood pressure determination/ or exp body constitution/ or exp body height/ or exp body surface area/ or exp body weight/ or exp fetal weight/ or exp body temperature/ or exp cephalometry/ or exp craniometry/ or exp facial expression/ or exp facies/ or exp gait/ or exp hand strength/ or exp palpation/ or exp pelvimetry/ or exp percussion/ or exp pigmentation/ or exp skin pigmentation/ or exp pulse/ or exp range of motion, articular/ or exp self-examination/ or exp breast self-examination/ or exp skinfold thickness/	892433
6	exp medical history taking/ or exp patient assessment/ or physical examination/ or exp palpation/ or exp pulse/	153287
7	exp patient history taking/ or exp physical examination/ or exp auscultation/ or exp heart auscultation/ or exp blood pressure determination/ or exp body temperature determination/ or exp cephalometry/ or exp "inspection (clinical)"/ or exp neurologic examination/ or exp reflex/ or exp reflex, abnormal/ or exp reflex, acoustic/ or exp reflex, pupillary/ or exp reflex, stretch/ or exp palpation/ or exp percussion/ or exp physical examination, preparticipation/ or exp pigmentation/ or exp skin pigmentation/ or exp pulse/	553576
8	exp blood pressure/ or exp body temperature/ or exp fatigue/ or exp jaundice/ or exp nausea/ or exp "pain and pain management"/ or exp paralysis/ or exp seizures/ or exp senses/ or exp shock/ or exp sleep/ or exp unconsciousness/ or exp patient assessment/	880816
9	exp medical examination/ or exp clinical examination/ or exp functional assessment/ or exp pulse oximetry/ or exp blood pressure monitoring/ or exp temperature measurement/ or exp thermometry/ or exp blood glucose monitoring/ or exp electrocardiography monitoring/ or exp neurologic examination/ or history/	274711
10	clinical feature.mp. [mp=ab, hw, ti, sh, it, tn, ot, dm, mf, rw]	217941
11	presenting feature.mp. [mp=ab, hw, ti, sh, it, tn, ot, dm, mf, rw]	2084
12	presenting sign.mp. [mp=ab, hw, ti, sh, it, tn, ot, dm, mf, rw]	1575
13	presenting symptom.mp. [mp=ab, hw, ti, sh, it, tn, ot, dm, mf, rw]	4282

14	sign.mp. [mp=ab, hw, ti, sh, it, tn, ot, dm, mf, rw]	61333
15	symptom.mp. [mp=ab, hw, ti, sh, it, tn, ot, dm, mf, rw]	145112
16	or/5-15	2013529
17	tubercul$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	175259
18	tb$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	70374
19	exp meningitis/ or exp meningitis, bacterial/ or exp meningitis, escherichia coli/ or exp meningitis, haemophilus/ or exp meningitis, listeria/ or exp meningitis, meningococcal/ or exp waterhouse-friderichsen syndrome/ or exp meningitis, pneumococcal/ or exp meningitis, viral/ or exp lymphocytic choriomeningitis/ or exp meningitis, aseptic/ or exp encephalomyelitis/ or exp meningoencephalitis/ or exp encephalitis/ or exp encephalitis, viral/	100833
20	(17 or 18) and 19	6825
21	4 and 15 and 20	385

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	956588
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1465344
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1670568
4	1 or 2 or 3	2874741
5	decision rule.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	772
6	diagnosis.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1771627
7	7 or 8	1772247
8	tubercul$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	175259
9	tb$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	70374
10	exp meningitis/ or exp meningitis, bacterial/ or exp meningitis, escherichia coli/ or exp meningitis, haemophilus/ or exp meningitis, listeria/ or exp meningitis, meningococcal/ or exp waterhouse-friderichsen syndrome/ or exp meningitis, pneumococcal/ or exp meningitis, viral/ or exp lymphocytic choriomeningitis/ or exp meningitis, aseptic/ or exp encephalomyelitis/ or exp meningoencephalitis/ or exp encephalitis/ or exp encephalitis, viral/	100833
11	(8 or 9) and 10	6825
12	4 and 7 and 11	612

Results

A total of 72 abstracts were reviewed from 997 titles. A total of 10 papers were selected for further review. The hand search of journals and references identified 2 other papers for further review. One paper was included in the final analysis.

Papers excluded from the final analysis are listed in table 14d.1.i
Papers included in the final analysis are listed in table 14d.1.ii

Reference	**Reason for exclusion**
Ertekin (358)	Retrospective case series
Al-Abbasi (359)	Retrospective case series
De Pontual (360)	Retrospective case series, foreign language
Amdekar (361)	Expert opinion
Kumar (362)	Retrospective case series
Pagliano (363)	Foreign language
Farinha (364)	Retrospective case series
Kovac (365)	Foreign language
Paganini (366)	Case series
Janner (367)	Retrospective case series
Udani (368)	Case series

Table 14d.1.i Papers excluded from the analysis of the clinical signs which predict TB meningitis

Study	Methods	Participants	Diagnostic dilemma	Blinded comparison	Gold standard tested	Results	Notes	Evidence level
Kumar(104)	Validation study of a previously derived clinical decision rule to help predict TB meningitis in India.	Children (aged 1 month to 12 years) admitted to hospital with "meningo-encephalitis" on the basis of clinical features and pleocytosis on CSF examination.	Did these children have TB meningitis or another form of meningitis?	Not described. The definition of TB meningitis included a clinical response to anti-TB drugs which could be subjective, therefore blinding would be important.	Gold standard: TB diagnosed if positive culture or stain, or positive response to anti TB drugs. TB excluded if another positive CSF culture result demonstrated or no clinical response to anti-TB drugs. Candidate test: Decision rule using the following symptoms/signs: prodromal stage >7days, fundal optic atrophy, focal deficit, extrapyramidal movements, CSF leucocytes <50% polymorphs.	232 children enrolled out of 248 who satisfied the entry criteria. 110 had TB meningitis and 94 had non-TB meningitis. 28 patients excluded as they died without a definitive diagnosis being made. Number of children used to derive decision rule not stated. Number of children in validation set was 128. If three of the symptoms were present then the specificity was 98% (sensitivity = 54%). If only one of the symptoms was present the sensitivity was 98% (specificity = 43%).	Not clear whether the validation set was also part of the derivation set, which would improve the performance of the rule. The rule does not perform very well at recognising cases, but at the extremes it can recognise who does not have TB meningitis.	Diagnosis 2b

Table 14d.1.ii Papers included in the analysis of the clinical signs which predict TB meningitis

14. Intracranial infections

d) Tuberculous (TB) meningitis

Clinical Questions:

(ii) In children with a reduced conscious level, which investigations help screen for or diagnose TB meningitis?

Selection criteria
Criteria for choosing papers were drawn up before the search took place. Papers were selected if they were diagnostic studies of TB meningitis, which objectively or blindly compared a diagnostic test with the gold standard. Studies involving both children and adults were included as the performance of the tests would be unlikely to differ between age groups.

Search
A review of the Cochrane library, MEDLINE (1966-present), EMBASE (1980-present), CINAHL (1982-present), British Nursing Index (1985-present) and AMED (1985-present) was performed using the search terms below. A review of the references of the selected papers for further evidence was included in the search strategy and a hand search of five key journals in the field in the previous 12 months.

Search filters

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	956588
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1465344
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1670568
4	1 or 2 or 3	2874741
5	sensitiv$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1196235
6	(sensitivity and specificity).mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	247943
7	diagnosis.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1764281
8	diagnostic $.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	236218
9	diagnosis,differential.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	265966
10	diagnos$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	2403697
11	test$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	2807626
12	investigation$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	541353
13	gold.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	68818
14	standard$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	744427
15	8 and 9	22794
16	or/5-12	2948991
17	15 or 16	3433790
18	tubercul$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	175259
19	tb$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	70374
20	exp meningitis/ or exp meningitis, bacterial/ or exp meningitis, escherichia coli/ or exp meningitis, haemophilus/ or exp meningitis, listeria/ or exp meningitis, meningococcal/ or exp waterhouse-friderichsen syndrome/ or exp meningitis, pneumococcal/ or exp meningitis, viral/ or exp lymphocytic choriomeningitis/ or exp meningitis, aseptic/ or exp encephalomyelitis/ or exp meningoencephalitis/ or exp encephalitis/ or exp encephalitis, viral/	100833
21	(18 or 19) and 20	6825
22	17 and 21	332

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	956588
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1465344
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1670568
4	1 or 2 or 3	2874741

5	computed tomography.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	127917
6	ct.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	201844
7	scan.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	110797
8	imaging.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	576404
9	or/5-8	803671
10	tubercul$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	175259
11	tb$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	70374
12	exp meningitis/ or exp meningitis, bacterial/ or exp meningitis, escherichia coli/ or exp meningitis, haemophilus/ or exp meningitis, listeria/ or exp meningitis, meningococcal/ or exp waterhouse-friderichsen syndrome/ or exp meningitis, pneumococcal/ or exp meningitis, viral/ or exp lymphocytic choriomeningitis/ or exp meningitis, aseptic/ or exp encephalomyelitis/ or exp meningoencephalitis/ or exp encephalitis/ or exp encephalitis, viral/	100833
13	(10 or 11) and 12	6825
14	4 and 9 and 13	56

Results
A total of 19 abstracts were reviewed from 388 titles. A total of 5 papers were selected for further review. The hand search of journals and references identified 1 other paper for further review.
4 papers were included in the final analysis.

Papers excluded from the final analysis are listed in table 14d.2.i

Reference	**Reason for exclusion**
Kashyap (369)	Retrospective analysis without blinding
Seth (370)	Adults only study

Table 14d.2.i Papers excluded from the analysis of which tests diagnose TB meningitis

Study	Methods	Participants	Diagnostic dilemma	Blinded comparison	Gold standard tested	Results	Notes	Evidence level
Kox(131)	Prospective study to determine the accuracy of PCR to diagnose tuberculous meningitis (TBM) in adults and children.	Patients (aged 2 to 74 years – 20% aged <16 years) with clinical features and microscopy suggestive of TBM in Holland (central reference laboratory). Study dates not given.	Is PCR for TBM accurate to distinguish between TBM and other organisms?	Yes, samples received by reference laboratory for PCR without knowing the results of microscopy / culture or patient response to treatment.	Gold standard: response to treatment plus supporting evidence of TBM (either CSF culture, PCR or microscopy). Candidate test: PCR for TBM of CSF	42 patients with clinical features of TBM included in study. 35 were started on anti-TB treatments. 23 patients responded to treatment i.e. disease positive. PCR was positive in 11 of these patients. PCR was negative in all patients without the disease. Sensitivity 48%, specificity 100%.	PCR probably superior to culture and microscopy, therefore gold standard taken as clinical response to treatment. This is acceptable as blinded test results and gold standard. This gold standard is also independent of the PCR test.	Diagnosis 1b
Shankar (132)	Study to assess the accuracy of PCR for TBM against the gold standard test of clinical signs, laboratory features and positive response to treatment. children.	Patients (age not stated) attending a centre in India with clinical features of meningitis, who had a CSF sample taken. A control group of patients with non-TB meningitis and other neurological conditions was included also.	Is PCR for TBM accurate to distinguish between TBM and other organisms?	Not stated.	Gold standard: clinical features, laboratory tests (e.g. CSF microscopy and positive culture) and a positive response to anti-TB treatments. Candidate test: PCR for TB in CSF	34 patients with suspected TBM and 51 controls were included. The sensitivity of PCR was 75% in the “highly probable TBM” patients (with an overall sensitivity of 65% for all possible TBM). This compared to 12% for TB culture. The specificity was 100% if the initial false positive results were accurately re-	Study not known to be blinded. Significant cross contamination of specimens. Controls not necessarily a cause for diagnostic uncertainty, which improves the test performance. Gold standard independent of the test.	Diagnosis 4

						tested – however there were 6 false positive results probably due to cross-contamination in the laboratory (specificity 88%).		
Kaneko (133)	To assess the accuracy of TB PCR in CSF samples against the gold standard of clinical signs and other CSF findings.	Patients (age 24 – 41 years) attending a hospital in Japan, who had clinical features of TB meningitis or other meningitis. Study period not stated.	Is PCR for TBM accurate to distinguish between TBM and other organisms?	Not stated.	Gold standard: clinical features of meningitis and CSF TB culture positive and / or adenosine deaminase activity. Candidate test: TB PCR of CSF	6 patients with TBM and 10 patients with bacterial or viral meningitis enrolled. Sensitivity was 83% and specificity was 100%.	Gold standard not met in each of the "positive" cases i.e. cases 2 and 3. Was a different gold standard applied but not described? Adults only study.	Diagnosis 4
Folgueira (134)	To assess the accuracy of TB PCR in CSF samples against the gold standard of clinical signs, other CSF findings and response to treatment.	Patients (aged 21-36 years) with HIV and clinical suspicion of TBM attending a hospital in Spain. A control group of patients with meningitis other than TB was included. Study period not stated.	Is PCR for TBM accurate to distinguish between TBM and other organisms?	Not stated.	Gold standard: clinical features of meningitis, CSF TB culture positive and response to treatment. Candidate test: TB PCR of CSF	10 patients with high clinical suspicion of TBM, 8 were PCR +ve and 2 PCR –ve. Unclear as to whether one of the –ve PCR results is false –ve.	Gold standard not applied in each case. Difficult to assess which patients were "truly" positive or "truly" negative.	Diagnosis 4

Table 14d.2.ii Papers included in the analysis of which tests diagnose TB meningitis

14. Intracranial infections

d) Tuberculous (TB) meningitis

Clinical Questions:

(iii) In children with a reduced conscious level and suspected TB meningitis, which treatments should be started?

This clinical question fell outside the scope of the guideline.

15. Raised intracranial pressure

Clinical Questions:

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

Selection criteria
Criteria for choosing papers were drawn up before the search took place. Papers would be included if they were validating studies of diagnostic decision rules for raised intracranial pressure, validated guidelines for treating raised intracranial pressure or randomised controlled trial of treatments for raised intracranial pressure in children with clinical entry criteria. Studies involving both children and adults were only included if the results for children could be analysed separately.

Search
A review of the Cochrane library, MEDLINE (1966-present), EMBASE (1980-present), CINAHL (1982-present), British Nursing Index (1985-present) and AMED (1985-present) was performed using the search terms below. A review of the references of the selected papers for further evidence was included in the search strategy and a hand search of five key journals in the field in the previous 12 months.

Search filters

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	956588
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1465344
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1670568
4	1 or 2 or 3	2874741
5	exp Intracranial Pressure, Increased/	358
6	exp Intracranial Pressure/	16898
7	exp Brain Edema/	16437
8	or/5-7	28764
9	guideline$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	223821
10	validat$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	168454
11	9 or 10	386657
12	4 and 8 and 11	129

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	956588
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1465344
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1670568
4	1 or 2 or 3	2874741
5	sensitiv$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1196235
6	(sensitivity and specificity).mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	247943
7	diagnosis.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1764281
8	diagnostic $.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	236218
9	diagnosis,differential.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	265966
10	diagnos$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	2403697
11	test$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	2807626

12	investigation$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	541353
13	gold.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	68818
14	standard$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	744427
15	8 and 9	22794
16	or/5-12	2948991
17	15 or 16	3433790
18	exp Intracranial Pressure, Increased/	358
19	exp Intracranial Pressure/	16898
20	exp Brain Edema/	16437
21	or/18-20	28764
22	17 and 21	263

#	Search terms	No. of articles
1	RANDOMIZED CONTROLLED TRIAL.pt.	203483
2	CONTROLLED CLINICAL TRIAL.pt.	68767
3	randomized controlled trials.sh.	39337
4	random allocation.sh.	53631
5	double blind method.sh.	82532
6	single blind method.sh.	9079
7	or/1-6	347668
8	Animal.sh.	15950
9	human.sh.	4958995
10	8 not 9	12976
11	7 not 10	347668
12	clinical trial.pt.	424297
13	exp clinical trials/	559113
14	(clin$ adj25 trial$).ti,ab.	228804
15	((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.	165914
16	placebos.sh.	27051
17	placebo$.ti,ab.	183729
18	random$.ti,ab.	630996
19	research design.sh.	42692
20	or/12-19	1419124
21	20 not 10	1418985
22	21 not 11	1092074
23	comparative study.sh.	1270592
24	exp evaluation studies/	568817
25	follow up studies.sh.	302736
26	prospective studies.sh.	228549
27	(control$ or prospectiv$ or volunteer$).ti,ab.	2983755
28	or/23-27	4629518
29	28 not 10	4628086
30	29 not (11 or 22)	3849451
31	11 or 22 or 28	5290625
32	exp infant, newborn/ or exp infant/ or exp infants/	962573
33	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1476454
34	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1682730
35	32 or 33 or 34	2895178
36	35 and 31	768319
37	exp Intracranial Pressure, Increased/	358
38	exp Intracranial Pressure/	16898
39	exp Intracranial Hypertension/	21012
40	exp cerebrospinal fluid pressure/	18454
41	intracranial pressure.mp	24482
42	exp Brain Edema/	16437
43	or/37-42	55227
44	36 and 43	634

Results

A total of 41 abstracts were reviewed from 1026 titles. A total of 12 papers were selected for further review. The hand search of journals and references identified 4 other papers for further review. One paper was included in the final analysis.

Papers excluded from the final analysis are listed in table 15.1.i
Papers included in the final analysis are listed in table 15.1.ii

Reference	**Reason for exclusion**
Vats(371)	No clinical features described
Burkhard(372)	No clinical features described
Plum(373)	Case reports
Biestro(374)	Adult study
Le Roux(375)	No clinical features described
Chandler(376)	Adult study
Rennick(140)	No validation of signs of raised intracranial pressure
Newton(141)	No validation of signs of raised intracranial pressure
Akpede(142)	No validation of signs of raised intracranial pressure
Khanna(377)	No clinical features described
Skippen(378)	No clinical features described
Peterson(379)	No clinical features described
Shaywitz(380)	No validation of signs of raised intracranial pressure
MacDonald(381)	No clinical features described
Kindt(382)	Case reports

Table 15.1.i Papers excluded from the analysis of the clinical signs of raised intracranial pressure in children

Study	Methods	Participants	Diagnostic dilemma	Blinded comparison	Gold standard tested	Results	Notes	Evidence level
Yu(383)	Retrospective review of children with cerebral oedema to determine what clinical signs they had and which fluid therapy regime improved outcome.	Children (aged 1 day to 13 years) who had cerebral oedema at post mortem in a hospital in China. Study period 1958 to 1985.	How accurate are the clinical signs in detecting cerebral oedema?	No.	Post mortem.	52 children died with cerebral oedema found at post mortem. The frequencies of various signs are reported: 100% had irregular respirations; 97% had “mental disturbance”; 70% had change in pupil size; 60% had convulsions; 60% had high blood pressure; 56% had vomiting; 39% had bulging fontanelle; 24% had papilloedema.	A prospective part of this study could have validated the decision rule they created from the data, but this was not reported.	Diagnosis 4

Table 15.1.ii Papers included in the analysis of the clinical signs of raised intracranial pressure in children

15. Raised intracranial pressure

Clinical Questions:

(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?

Selection criteria
Criteria for choosing papers were drawn up before the search took place. Papers would be included if they were studies comparing candidate tests against the gold standard test of raised intracranial pressure or studies validating guidelines for managing raised intracranial pressure in children. Studies involving both children and adults were only included if the results for children could be analysed separately.

Search
A review of the Cochrane library, MEDLINE (1966-present), EMBASE (1980-present), CINAHL (1982-present), British Nursing Index (1985-present) and AMED (1985-present) was performed using the search terms below. A review of the references of the selected papers for further evidence was included in the search strategy and a hand search of five key journals in the field in the previous 12 months.

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1	exp infant, newborn/ or exp infant/ or exp infants/	956588
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3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1670568
4	1 or 2 or 3	2874741
5	sensitiv$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1196235
6	(sensitivity and specificity).mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	247943
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8	diagnostic $.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	236218
9	diagnosis,differential.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	265966
10	diagnos$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	2403697
11	test$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	2807626
12	investigation$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	541353
13	gold.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	68818
14	standard$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	744427
15	8 and 9	22794
16	or/5-12	2948991
17	15 or 16	3433790
18	exp Intracranial Pressure, Increased/	358
19	exp Intracranial Pressure/	16898
20	exp Brain Edema/	16437
21	or/18-20	28764
22	17 and 21	263

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	956588
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1465344
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1670568
4	1 or 2 or 3	2874741
5	exp Intracranial Pressure, Increased/	358
6	exp Intracranial Pressure/	16898
7	exp Brain Edema/	16437
8	or/5-7	28764
9	guideline$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	223821
10	validat$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	168454
11	9 or 10	386657

12	4 and 8 and 11	129

Results
A total of 20 abstracts were reviewed from 392 titles. From these 13 papers were selected for further review. Two other papers were identified from a review of the references.
3 papers were included in the final review.

Papers excluded from the final analysis are listed in table 15.2.i
Papers included in the final analysis are listed in table 15.2.ii

Reference	**Reason for exclusion**
Demo(143)	Foreign language.
Honda(144)	Foreign language.
Yuh(145)	Adults only study.
Condon(146)	Adults only study.
Weisberg(147)	Adults only study.
Muir(148)	Study to assess clinical signs for raised intracranial pressure using CT as the gold standard.
Kishore(149)	Adults and children not analysed separately.
Nadvi(150)	Comparison of normal controls with hydrocephalic children without blinding of test results or measurement of intracranial pressure in controls.
O'Sullivan(151)	Adult only study.
Heyderman(152)	Study to assess clinical signs for raised intracranial pressure using CT as the gold standard.
Hanigan(153)	Subjective comparison of cranial CT scan with MRI scan against no objective gold standard.
Dahlerup (154)	Case series demonstrating raised intracranial pressure in 4 children with normal CT scans.

Table 15.2.i Papers excluded from the analysis of whether a CT scan can demostrate raised intracranial pressure

Study	Methods	Participants	Diagnostic dilemma	Blinded comparison	Gold standard tested	Results	Notes	Evidence level
Hirsch(155)	Retro-spective review of cranial CT scans in children who had intracranial pressure monitoring in site to assess the accuracy of CT interpretation to diagnose raised intracranial pressure (ICP).	Children (aged 4 months to 12 years) post head injury who had ICP monitoring and a CT scan. Study period 1992 to 1997.	Did the CT scan predict the ICP in this population who may have had raised intracranial pressure?	Yes, the two radiologists did not know the ICP when the CT scan was taken.	Gold standard: ICP monitoring device in situ. Candidate test: cranial CT scan	65 children having 124 scans were assessed. Overall the sensitivity of CT was 84% and specificity of 44% for raised ICP. The sensitivity of the test improved as the ICP of patients increased. Therefore A CT scan has a 97.7% sensitivity of finding raised ICP in patients with ICP > 25mmHg, with a specificity of 60.6%.	The results suggest that CT is not very good at picking up borderline high and normal ICP measure-ments but is good at detecting very high ICP. As the study was in patients with ICP measuring systems in situ, perhaps the radiologists were predicting higher than average ICP because of the fact that these children were being monitored.	Diagnosis 1b
Rennick (140)	Retro-spective study to assess the temporal relationship between lumbar puncture and cerebral herniation and for the ability of cranial CT to pick up cerebral herniation in	Children (aged 4 months to 15 years) presenting with bacterial meningitis and signs of cerebral herniation either clinically or on post mortem examination. Study period	Did the CT scan detect abnorm-alities in the children who had cerebral herniation on post mortem or clinically?	Yes, the radiologist did not know which children had clinical herniation or post mortem findings.	Gold standard: post mortem findings (clinical findings can be analysed separately). Candidate test: cranial CT scan	445 children had bacterial meningitis and 19 patients had cerebral herniation. 14 of these 19 patients died. Using necropsy result as gold standard (n=4) there were 2 children who had normal CT scans	Numbers are very small and the study was not designed to assess the specificity of CT. Tests were not applied to all patients.	Diagnosis 4

	the acute situation.	1984 to 1989.				despite clinical herniation occurring less than 3 hours before the scan and having positive post mortem findings (sensitivity 33%; specificity 100% [n=1]). If the gold standard was clinical signs of herniation (n=14) then CT has a sensitivity of 70% and specificity of 100% [n=1].		
Eide(156)	Prospective study to determine the accuracy of CT in predicting intracranial pressure using ventricular size measurements in children.	Children and a few adults (aged 0 to 30 years) with ICP monitoring for hydrocephalus, cranio-synostosis or ventriculo-peritoneal shunts. Study period February 1997 to January 2001.	Can a CT scan detect raised intracranial pressure based on the size of the ventricles.	Not stated.	Gold standard: ICP monitoring. Candidate test: ventricular measurements on CT scanning.	184 patients were enrolled. There was poor correlation between the mean ICP and the CT ventricular size (linear relationship $r^2<0.02$; $p>0.15$).	Using CT measurements of ventricles, the intracranial pressure cannot be accurately predicted. The fact the study does not report blinding may be a cause for concern.	Diagnosis 1b

Table 15.2.ii Papers included in the analysis of whether a CT scan can demonstrate raised intracranial pressure

15. Raised intracranial pressure

Clinical Questions:

(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?

Selection criteria
Criteria for choosing papers were drawn up before the search took place. Papers would be included if they were studies comparing candidate tests against the gold standard tests for a list of causes of raised intracranial pressure or studies validating guidelines for managing raised intracranial pressure in children. Studies involving both children and adults were only included if the results for children could be analysed separately.

Search
A review of the Cochrane library, MEDLINE (1966-present), EMBASE (1980-present), CINAHL (1982-present), British Nursing Index (1985-present) and AMED (1985-present) was performed using the search terms below. A review of the references of the selected papers for further evidence was included in the search strategy and a hand search of five key journals in the field in the previous 12 months.

Search filters

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	956588
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1465344
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1670568
4	1 or 2 or 3	2874741
5	sensitiv$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1196235
6	(sensitivity and specificity).mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	247943
7	diagnosis.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1764281
8	diagnostic $.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	236218
9	diagnosis,differential.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	265966
10	diagnos$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	2403697
11	test$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	2807626
12	investigation$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	541353
13	gold.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	68818
14	standard$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	744427
15	8 and 9	22794
16	or/5-12	2948991
17	15 or 16	3433790
18	exp Intracranial Pressure, Increased/	358
19	exp Intracranial Pressure/	16898
20	exp Brain Edema/	16437
21	or/18-20	28764
22	17 and 21	263

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	956588
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1465344
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1670568
4	1 or 2 or 3	2874741
5	exp Intracranial Pressure, Increased/	358
6	exp Intracranial Pressure/	16898
7	exp Brain Edema/	16437
8	or/5-7	28764
9	guideline$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	223821
10	validat$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	168454
11	9 or 10	386657
12	4 and 8 and 11	129

Results
A total of 20 abstracts were reviewed from 392 titles. From these no papers were selected for further review. No other papers were identified from a review of the references.
No papers were included in the final review.

15. Raised intracranial pressure

Clinical Questions:

(iv) In children with a reduced conscious level and raised intracranial pressure, what head position should be maintained to reduce the raised intracranial pressure?

Selection criteria
Criteria for choosing papers were drawn up before the search took place. Papers would be included if they were randomised controlled trials of patient positions for raised intracranial pressure. Studies validating guidelines for managing raised intracranial pressure in children would also be included. Studies involving both children and adults were only included if the results for children could be analysed separately.

Search
A review of the Cochrane library, MEDLINE (1966-present), EMBASE (1980-present), CINAHL (1982-present), British Nursing Index (1985-present) and AMED (1985-present) was performed using the search terms below. A review of the references of the selected papers for further evidence was included in the search strategy and a hand search of five key journals in the field in the previous 12 months.

Search filters

#	Search terms	No. of articles
1	RANDOMIZED CONTROLLED TRIAL.pt.	203483
2	CONTROLLED CLINICAL TRIAL.pt.	68767
3	randomized controlled trials.sh.	39337
4	random allocation.sh.	53631
5	double blind method.sh.	82532
6	single blind method.sh.	9079
7	or/1-6	347668
8	Animal.sh.	15950
9	human.sh.	4958995
10	8 not 9	12976
11	7 not 10	347668
12	clinical trial.pt.	424297
13	exp clinical trials/	559113
14	(clin$ adj25 trial$).ti,ab.	228804
15	((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.	165914
16	placebos.sh.	27051
17	placebo$.ti,ab.	183729
18	random$.ti,ab.	630996
19	research design.sh.	42692
20	or/12-19	1419124
21	20 not 10	1418985
22	21 not 11	1092074
23	comparative study.sh.	1270592
24	exp evaluation studies/	568817
25	follow up studies.sh.	302736
26	prospective studies.sh.	228549
27	(control$ or prospectiv$ or volunteer$).ti,ab.	2983755
28	or/23-27	4629518
29	28 not 10	4628086
30	29 not (11 or 22)	3849451
31	11 or 22 or 28	5290625

32	exp infant, newborn/ or exp infant/ or exp infants/	962573
33	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1476454
34	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1682730
35	32 or 33 or 34	2895178
36	35 and 31	768319
37	exp Intracranial Pressure, Increased/	358
38	exp Intracranial Pressure/	16898
39	exp Intracranial Hypertension/	21012
40	exp cerebrospinal fluid pressure/	18454
41	intracranial pressure.mp	24482
42	exp Brain Edema/	16437
43	or/37-42	55227
44	head position$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	4229
45	tilt$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	24054
46	elevat$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	553862
47	head$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	408076
48	or/44-47	964403
49	36 and 43 and 48	227

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	956588
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1465344
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1670568
4	1 or 2 or 3	2874741
5	exp Intracranial Pressure, Increased/	358
6	exp Intracranial Pressure/	16898
7	exp Brain Edema/	16437
8	or/5-7	28764
9	guideline$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	223821
10	validat$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	168454
11	9 or 10	386657
12	4 and 8 and 11	129

Results
A total of 14 abstracts were reviewed from 356 titles. From these no papers were selected for further review. No other papers were identified from a review of the references.
No papers were included in the final review.

15. Raised intracranial pressure

Clinical Questions:

(v) In children with a reduced conscious level and raised intracranial pressure, what maintenance fluid strategy should be used?

Selection criteria
Criteria for choosing papers were drawn up before the search took place. Papers would be included if they were randomised controlled trials of fluid strategies for raised intracranial pressure. Studies validating guidelines for managing raised intracranial pressure in children would also be included. Studies involving both children and adults were only included if the results for children could be analysed separately.

Search
A review of the Cochrane library, MEDLINE (1966-present), EMBASE (1980-present), CINAHL (1982-present), British Nursing Index (1985-present) and AMED (1985-present) was performed using the search terms below. A review of the references of the selected papers for further evidence was included in the search strategy and a hand search of five key journals in the field in the previous 12 months.

Search filters

#	Search terms	No. of articles
1	RANDOMIZED CONTROLLED TRIAL.pt.	203483
2	CONTROLLED CLINICAL TRIAL.pt.	68767
3	randomized controlled trials.sh.	39337
4	random allocation.sh.	53631
5	double blind method.sh.	82532
6	single blind method.sh.	9079
7	or/1-6	347668
8	Animal.sh.	15950
9	human.sh.	4958995
10	8 not 9	12976
11	7 not 10	347668
12	clinical trial.pt.	424297
13	exp clinical trials/	559113
14	(clin$ adj25 trial$).ti,ab.	228804
15	((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.	165914
16	placebos.sh.	27051
17	placebo$.ti,ab.	183729
18	random$.ti,ab.	630996
19	research design.sh.	42692
20	or/12-19	1419124
21	20 not 10	1418985
22	21 not 11	1092074
23	comparative study.sh.	1270592
24	exp evaluation studies/	568817
25	follow up studies.sh.	302736
26	prospective studies.sh.	228549
27	(control$ or prospectiv$ or volunteer$).ti,ab.	2983755
28	or/23-27	4629518
29	28 not 10	4628086
30	29 not (11 or 22)	3849451
31	11 or 22 or 28	5290625
32	exp infant, newborn/ or exp infant/ or exp infants/	962573
33	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1476454
34	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1682730
35	32 or 33 or 34	2895178
36	35 and 31	768319
37	exp Intracranial Pressure, Increased/	358
38	exp Intracranial Pressure/	16898
39	exp Intracranial Hypertension/	21012
40	exp cerebrospinal fluid pressure/	18454
41	intracranial pressure.mp	24482
42	exp Brain Edema/	16437
43	or/37-42	55227
44	exp Fluid Therapy/	37128
45	fluid resuscitation.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	3169
46	fluid restriction.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1060
47	fluid maintenance.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	66
48	fluid management.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1018
49	intravenous fluid$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	3903
50	IV fluid$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1037
51	or/44-50	43678
52	36 and 43 and 51	512

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	956588
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1465344
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1670568
4	1 or 2 or 3	2874741
5	exp Intracranial Pressure, Increased/	358
6	exp Intracranial Pressure/	16898
7	exp Brain Edema/	16437
8	or/5-7	28764
9	guideline$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	223821
10	validat$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	168454
11	9 or 10	386657
12	4 and 8 and 11	129

Results
A total of 19 abstracts were reviewed from 641 titles. From these 4 papers were selected for further review. No other papers were identified from a review of the references.
2 papers were included in the final review.

Papers excluded from the final analysis are listed in table 15.5.i
Papers included in the final analysis are listed in table 15.5.ii

Reference	**Reason for exclusion**
Oates-Whitehead (384)	Systematic review of fluid therapy for bacterial meningitis not specifically raised intracranial pressure.
Peterson (379)	Retrospective case note review of children treated with hypertonic saline.

Table 15.5.i Papers excluded from the analysis of what maintenance fluid strategy should be used in children with raised intracranial pressure

Study	Methods	Participants	Interventions	Allocation concealment	Outcomes	Results	Notes	Evidence level
Simma(385)	An open randomized controlled trial to determine if hypertonic saline (1.8%) compared to isotonic saline (Ringer's lactate) resulted in better outcome after head injury.	Children (aged 1 to 14 years) admitted to a PICU in Switzerland after severe head injury. All patients had ICP monitoring in place. Study period August 1992 to November 1995.	Maintenance fluid was randomised to either Ringer's lactate or 1.8% saline at a rate of no more than 1.2 litres/m^2 body surface area. Standardised therapy for ICP spikes included sedation, ventilation, head position, normothermia, mannitol and thiopental sodium (in severe cases)	Randomisation was concealed by an independent investigator. No further details of randomisation are provided.	Primary outcome measures were the correlations between ICP and CPP with serum sodium concentration. Secondary outcome measures were the number of days of ICU stay and number of interventions to reduce ICP required.	35 children were enrolled with 3 exclusions due to not having an initial GCS<8. Both groups showed an inverse correlation between serum sodium and ICP / CPP. No difference was found for primary outcomes. Children in the Ringer's lactate group had more interventions than those in the 1.8% saline group.This group also stayed longer on ICU. 2 patients in the Ringer's lactate group died with none in the 1.8% saline group – although the study was not powered for this outcome.	Good study. Not blinded and not comparing mannitol with hypertonic saline.	Therapy 1b
Khanna (377)	Prospective observational study of the use of 3% saline as maintenance fluid to determine its ability to reduce intracranial hypertension after traumatic brain injury.	Children (aged 4 months to 13 years) admitted to a PICU in USA with head trauma requiring ICP monitoring and whose ICP had failed to respond to conventional therapy (including	No comparison therapies. Correlation between ICP and serum sodium using 3% saline as the maintenance fluid.	Not a randomised controlled trial	Correlation between serum sodium and ICP.	10 patients were eligible for the study out of 48 patients who had ICP monitoring. There was a significant correlation between serum sodium and CPP, and an inverse relationship between serum sodium and ICP.	Useful basic science data but no comparison data.	Therapy 4

		mannitol, hyper-ventilation, head elevation and thiopental sodium). Study period August 1996 to March 1998.						

Table 15.5.ii Papers included in the analysis of what maintenance fluid strategy should be used in children with raised intracranial pressure

15. Raised intracranial pressure

Clinical Questions:

(vi) In children with a reduced conscious level and raised intracranial pressure, what are the indications for mannitol or hypertonic saline?

Selection criteria
Criteria for choosing papers were drawn up before the search took place. Papers would be included if they were randomised controlled trials of mannitol and/or hypertonic saline for raised intracranial pressure. Studies validating guidelines for managing raised intracranial pressure in children would also be included. Studies involving both children and adults were only included if the results for children could be analysed separately.

Search
A review of the Cochrane library, MEDLINE (1966-present), EMBASE (1980-present), CINAHL (1982-present), British Nursing Index (1985-present) and AMED (1985-present) was performed using the search terms below. A review of the references of the selected papers for further evidence was included in the search strategy and a hand search of five key journals in the field in the previous 12 months.

Search filters

#	Search terms	No. of articles
1	RANDOMIZED CONTROLLED TRIAL.pt.	203483
2	CONTROLLED CLINICAL TRIAL.pt.	68767
3	randomized controlled trials.sh.	39337
4	random allocation.sh.	53631
5	double blind method.sh.	82532
6	single blind method.sh.	9079
7	or/1-6	347668
8	Animal.sh.	15950
9	human.sh.	4958995
10	8 not 9	12976
11	7 not 10	347668
12	clinical trial.pt.	424297
13	exp clinical trials/	559113
14	(clin$ adj25 trial$).ti,ab.	228804
15	((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.	165914
16	placebos.sh.	27051
17	placebo$.ti,ab.	183729
18	random$.ti,ab.	630996
19	research design.sh.	42692
20	or/12-19	1419124
21	20 not 10	1418985
22	21 not 11	1092074
23	comparative study.sh.	1270592
24	exp evaluation studies/	568817
25	follow up studies.sh.	302736
26	prospective studies.sh.	228549
27	(control$ or prospectiv$ or volunteer$).ti,ab.	2983755
28	or/23-27	4629518
29	28 not 10	4628086
30	29 not (11 or 22)	3849451
31	11 or 22 or 28	5290625
32	exp infant, newborn/ or exp infant/ or exp infants/	962573
33	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1476454
34	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1682730
35	32 or 33 or 34	2895178
36	35 and 31	768319

37	exp Intracranial Pressure, Increased/	358
38	exp Intracranial Pressure/	16898
39	exp Intracranial Hypertension/	21012
40	exp cerebrospinal fluid pressure/	18454
41	intracranial pressure.mp	24482
42	exp Brain Edema/	16437
43	or/37-42	55227
44	exp Mannitol/	20324
45	mannitol.mp.	28774
46	hypertonic saline.mp.	5791
47	exp hypertonic solutions/ or exp saline solution, hypertonic/	48744
48	exp Hypertonic Solution/	1720
49	exp hypertonic solutions/ or exp glucose solution, hypertonic/ or exp saline solution, hypertonic/	128851
50	or/44-49	156554
51	36 and 43 and 50	109

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	956588
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1465344
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1670568
4	1 or 2 or 3	2874741
5	exp Intracranial Pressure, Increased/	358
6	exp Intracranial Pressure/	16898
7	exp Brain Edema/	16437
8	or/5-7	28764
9	guideline$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	223821
10	validat$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	168454
11	9 or 10	386657
12	4 and 8 and 11	129

Results
A total of 14 abstracts were reviewed from 238 titles. From these 9 papers were selected for further review. Two other papers were identified from a review of the references.
3 papers were included in the final review.

Papers excluded from the final analysis are listed in table 15.6.i
Papers included in the final analysis are listed in table 15.6.ii

Reference	**Reason for exclusion**
James(386)	Adults and children not analysed separately
Barbosa(387)	Foreign language
Miller(388)	Mannitol compared to barbiturates not to other fluid regimes. 6 children included.
Okoromah(389)	Systematic review of mannitol therapy for cerebral malaria not specifically raised intracranial pressure
Roberts(390)	Systematic review of mannitol therapy only including adult studies
Lovejoy(391)	Cohort of patients mannitol as part of the management strategy. Not a formal guideline validation study or randomised controlled trial.
Peterson (379)	Retrospective case note review of children treated with hypertonic saline.
Anonymous(392)	Review of literature, not systematically performed.

Table 15.6.i Papers excluded from the analysis of the indication of mannitol or hypertonic saline for raised intracranial pressure in children

Study	Methods	Participants	Interventions	Allocation concealment	Outcomes	Results	Notes	Evidence level
MacDonald (381)	Crossover study to determine the safety and efficacy of mannitol and glycerol in the treatment of raised intracranial pressure in children.	Children (aged 2 to 15 years) with monitored intracranial hypertension of any cause (mainly encephalitis and Reye's syndrome) in a hospital in USA. Study period not stated.	Mannitol 20% as 0.5-1.0g/kg dose IV. Glyerol 20% as 0.5-1g/kg dose IV. Other interventions occurring in the population included hyper-ventilation, paralysis, maintenance of stable blood glucose, and fluid restriction.	No randomisation stated.	Intracranial pressure fall within the first hour after administ-ration. Side effects in terms of haemato-logical derange-ments.	14 children were included in the study. There was no significant difference between the two treatments in the ability to reduce ICP over the first hour. Very few side effects were seen with either study.	No clinical outcomes assessed. No randomis-ation described.	Therapy 4
Simma(385)	An open randomized controlled trial to determine if hypertonic saline (1.8%) compared to isotonic saline (Ringer's lactate) resulted in better outcome after head injury.	Children (aged 1 to 14 years) admitted to a PICU in Switzerland after severe head injury. All patients had ICP monitoring in place. Study period August 1992 to November 1995.	Maintenance fluid was randomised to either Ringer's lactate or 1.8% saline at a rate of no more than 1.2 litres/m^2 body surface area. Standardised therapy for ICP spikes included sedation, ventilation, head position, normothermia, mannitol and thiopental sodium (in	Randomisation was concealed by an independent investigator. No further details of randomisation are provided.	Primary outcome measures were the correlations between ICP and CPP with serum sodium concentration. Secondary outcome measures were the number of days of ICU stay and number of interventions to reduce ICP required.	35 children were enrolled with 3 exclusions due to not having an initial GCS<8. Both groups showed an inverse correlation between serum sodium and ICP / CPP. No difference was found for primary outcomes. Children in the Ringer's lactate group had more interventions than those in the 1.8% saline group.This group also stayed longer on ICU. 2 patients in the Ringer's lactate group died with	Good study. Not blinded and not comparing mannitol with hypertonic saline.	Therapy 1b

			severe cases)			none in the 1.8% saline group – although the study was not powered for this outcome.		
Khanna (377)	Prospective observational study of the use of 3% saline as maintenance fluid to determine its ability to reduce intracranial hypertension after traumatic brain injury.	Children (aged 4 months to 13 years) admitted to a PICU in USA with head trauma requiring ICP monitoring and whose ICP had failed to respond to conventional therapy (including mannitol, hyper-ventilation, head elevation and thiopental sodium). Study period August 1996 to March 1998.	No comparison therapies. Correlation between ICP and serum sodium using 3% saline as the maintenance fluid.	Not a randomised controlled trial	Correlation between serum sodium and ICP.	10 patients were eligible for the study out of 48 patients who had ICP monitoring. There was a significant correlation between serum sodium and CPP, and an inverse relationship between serum sodium and ICP.	Useful basic science data but no comparison data.	Therapy 4

Table 15.6.ii Papers included in the analysis of the indication of mannitol or hypertonic saline for raised intracranial pressure in children

15. Raised intracranial pressure

Clinical Questions:

(vii) In children with a reduced conscious level and raised intracranial pressure, what are the indications for sedation and ventilation?

Selection criteria
Criteria for choosing papers were drawn up before the search took place. Papers would be included if they were randomised controlled trials of ventilation strategies for raised intracranial pressure. Studies validating guidelines for managing raised intracranial pressure in children would also be included. Studies involving both children and adults were only included if the results for children could be analysed separately.

Search
A review of the Cochrane library, MEDLINE (1966-present), EMBASE (1980-present), CINAHL (1982-present), British Nursing Index (1985-present) and AMED (1985-present) was performed using the search terms below. A review of the references of the selected papers for further evidence was included in the search strategy and a hand search of five key journals in the field in the previous 12 months.

Search filters

#	Search terms	No. of articles
1	RANDOMIZED CONTROLLED TRIAL.pt.	203483
2	CONTROLLED CLINICAL TRIAL.pt.	68767
3	randomized controlled trials.sh.	39337
4	random allocation.sh.	53631
5	double blind method.sh.	82532
6	single blind method.sh.	9079
7	or/1-6	347668
8	Animal.sh.	15950
9	human.sh.	4958995
10	8 not 9	12976
11	7 not 10	347668
12	clinical trial.pt.	424297
13	exp clinical trials/	559113
14	(clin$ adj25 trial$).ti,ab.	228804
15	((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.	165914
16	placebos.sh.	27051
17	placebo$.ti,ab.	183729
18	random$.ti,ab.	630996
19	research design.sh.	42692
20	or/12-19	1419124
21	20 not 10	1418985
22	21 not 11	1092074
23	comparative study.sh.	1270592
24	exp evaluation studies/	568817
25	follow up studies.sh.	302736
26	prospective studies.sh.	228549
27	(control$ or prospectiv$ or volunteer$).ti,ab.	2983755
28	or/23-27	4629518
29	28 not 10	4628086
30	29 not (11 or 22)	3849451
31	11 or 22 or 28	5290625
32	exp infant, newborn/ or exp infant/ or exp infants/	962573
33	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1476454
34	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1682730
35	32 or 33 or 34	2895178
36	35 and 31	768319

37	exp Intracranial Pressure, Increased/	358
38	exp Intracranial Pressure/	16898
39	exp Intracranial Hypertension/	21012
40	exp cerebrospinal fluid pressure/	18454
41	intracranial pressure.mp	24482
42	exp Brain Edema/	16437
43	or/37-42	55227
44	ventilat$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	177478
45	hyperventilat$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	13444
46	sedat$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	70061
47	relaxant$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	22146
48	or/44-47	271771
49	36 and 43 and 48	398

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	956588
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1465344
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1670568
4	1 or 2 or 3	2874741
5	exp Intracranial Pressure, Increased/	358
6	exp Intracranial Pressure/	16898
7	exp Brain Edema/	16437
8	or/5-7	28764
9	guideline$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	223821
10	validat$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	168454
11	9 or 10	386657
12	4 and 8 and 11	129

Results
A total of 32 abstracts were reviewed from 527 titles. From these two papers were selected for further review. No other papers were identified from a review of the references.
One paper was included in the final review.

Papers excluded from the final analysis are listed in table 15.7.i
Papers included in the final analysis are listed in table 15.7.ii

Reference	**Reason for exclusion**
Anonymous(393)	Review of literature, not performed systematically.

Table 15.7.i Papers excluded from the analysis of the indications for sedation and ventilation of children with raised intracranial pressure

Study	Methods	Participants	Interventions	Allocation concealment	Outcomes	Results	Notes	Evidence level
Skippen (378)	Prospective observational crossover study to determine the effects of hyperventilation on cerebral blood flow.	Children (aged 3 months to 16 years) with traumatic brain injury requiring ICP monitoring on PICU in Canada. Study period not stated.	Each patient was ventilated to achieve $PaCO_2$ 4.7-5.3kPa, 3.3-4.7 kPa, and <3.3kPa. During each period of ventilation measurements of cerebral perfusion, cerebral oxygen consumption, CPP and ICP were made. Other therapy was standardised for the trial.	Not a randomised controlled trial.	Cerebral perfusion at different $PaCO_2$ levels. A 6 month follow up was arranged, but as all children received the same ventilation strategies no valuable comparison could be made.	23 patients had 38 measurements performed. When the patients were hyperventilated, the ICP fell however there was also a fall in local cerebral blood flow.	This study adds to our basic understand-ing of the mechanism of cerebral blood flow. Clinically relevant outcome data has not been described.	Therapy 4

Table 15.7.ii Papers included in the analysis of the indications for sedation and ventilation of children with raised intracranial pressure

15. Raised intracranial pressure

Clinical Questions:

(viii) In children with a reduced conscious level and raised intracranial pressure, what are the indications for paralysing agents?

Selection criteria
Criteria for choosing papers were drawn up before the search took place. Papers would be included if they were randomised controlled trials of paralysing agents for raised intracranial pressure. Studies validating guidelines for managing raised intracranial pressure in children would also be included. Studies involving both children and adults were only included if the results for children could be analysed separately.

Search
A review of the Cochrane library, MEDLINE (1966-present), EMBASE (1980-present), CINAHL (1982-present), British Nursing Index (1985-present) and AMED (1985-present) was performed using the search terms below. A review of the references of the selected papers for further evidence was included in the search strategy and a hand search of five key journals in the field in the previous 12 months.

Search filters

#	Search terms	No. of articles
1	RANDOMIZED CONTROLLED TRIAL.pt.	203483
2	CONTROLLED CLINICAL TRIAL.pt.	68767
3	randomized controlled trials.sh.	39337
4	random allocation.sh.	53631
5	double blind method.sh.	82532
6	single blind method.sh.	9079
7	or/1-6	347668
8	Animal.sh.	15950
9	human.sh.	4958995
10	8 not 9	12976
11	7 not 10	347668
12	clinical trial.pt.	424297
13	exp clinical trials/	559113
14	(clin$ adj25 trial$).ti,ab.	228804
15	((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.	165914
16	placebos.sh.	27051
17	placebo$.ti,ab.	183729
18	random$.ti,ab.	630996
19	research design.sh.	42692
20	or/12-19	1419124
21	20 not 10	1418985
22	21 not 11	1092074
23	comparative study.sh.	1270592
24	exp evaluation studies/	568817
25	follow up studies.sh.	302736
26	prospective studies.sh.	228549
27	(control$ or prospectiv$ or volunteer$).ti,ab.	2983755
28	or/23-27	4629518
29	28 not 10	4628086
30	29 not (11 or 22)	3849451
31	11 or 22 or 28	5290625
32	exp infant, newborn/ or exp infant/ or exp infants/	962573
33	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1476454
34	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1682730
35	32 or 33 or 34	2895178
36	35 and 31	768319

37	exp Intracranial Pressure, Increased/	358
38	exp Intracranial Pressure/	16898
39	exp Intracranial Hypertension/	21012
40	exp cerebrospinal fluid pressure/	18454
41	intracranial pressure.mp	24482
42	exp Brain Edema/	16437
43	or/37-42	55227
44	relaxant$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	22146
45	paralysi$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	64785
46	neuromuscular block$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	16034
47	or/44-46	98753
48	36 and 43 and 47	331

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	956588
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1465344
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1670568
4	1 or 2 or 3	2874741
5	exp Intracranial Pressure, Increased/	358
6	exp Intracranial Pressure/	16898
7	exp Brain Edema/	16437
8	or/5-7	28764
9	guideline$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	223821
10	validat$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	168454
11	9 or 10	386657
12	4 and 8 and 11	129

Results
A total of 25 abstracts were reviewed from 460 titles. From these 2 papers were selected for further review. No other papers were identified from a review of the references.
No papers were included in the final review.

Papers excluded from the final analysis are listed in table 15.8.i

Reference	**Reason for exclusion**
Anonymous(394)	Review of literature not performed systematically.
Vernon(395)	Observational study of paralysis in children with traumatic brain injury assessing oxygen consumption as the outcome measure.

Table 15.8.i Papers excluded from the analysis of the indication for invasive monitoring of raised intracranial pressure in children

15. Raised intracranial pressure

Clinical Questions:

(ix) In children with non-traumatic reduced conscious level and raised intracranial pressure, what are the indications for invasive intracranial pressure monitoring?

Selection criteria
Criteria for choosing papers were drawn up before the search took place. Papers would be included if they were randomised controlled trials of monitoring for raised intracranial pressure versus no monitoring. Studies validating guidelines for managing raised intracranial pressure in children would also be included. Studies involving children with severe head injuries were excluded, as there are guidelines for the monitoring of ICP in head trauma available. Studies involving both children and adults were only included if the results for children could be analysed separately.

Search
A review of the Cochrane library, MEDLINE (1966-present), EMBASE (1980-present), CINAHL (1982-present), British Nursing Index (1985-present) and AMED (1985-present) was performed using the search terms below. A review of the references of the selected papers for further evidence

was included in the search strategy and a hand search of five key journals in the field in the previous 12 months.

Search filters

#	Search terms	No. of articles
1	RANDOMIZED CONTROLLED TRIAL.pt.	203483
2	CONTROLLED CLINICAL TRIAL.pt.	68767
3	randomized controlled trials.sh.	39337
4	random allocation.sh.	53631
5	double blind method.sh.	82532
6	single blind method.sh.	9079
7	or/1-6	347668
8	Animal.sh.	15950
9	human.sh.	4958995
10	8 not 9	12976
11	7 not 10	347668
12	clinical trial.pt.	424297
13	exp clinical trials/	559113
14	(clin$ adj25 trial$).ti,ab.	228804
15	((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.	165914
16	placebos.sh.	27051
17	placebo$.ti,ab.	183729
18	random$.ti,ab.	630996
19	research design.sh.	42692
20	or/12-19	1419124
21	20 not 10	1418985
22	21 not 11	1092074
23	comparative study.sh.	1270592
24	exp evaluation studies/	568817
25	follow up studies.sh.	302736
26	prospective studies.sh.	228549
27	(control$ or prospectiv$ or volunteer$).ti,ab.	2983755
28	or/23-27	4629518
29	28 not 10	4628086
30	29 not (11 or 22)	3849451
31	11 or 22 or 28	5290625
32	exp infant, newborn/ or exp infant/ or exp infants/	962573
33	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1476454
34	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1682730
35	32 or 33 or 34	2895178
36	35 and 31	768319
37	exp Intracranial Pressure, Increased/	358
38	exp Intracranial Pressure/	16898
39	exp Intracranial Hypertension/	21012
40	exp cerebrospinal fluid pressure/	18454
41	intracranial pressure.mp	24482
42	exp Brain Edema/	16437
43	or/37-42	55227
44	monitor$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	648104
45	intraventric$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	34017
46	intraparenchym$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	3576
47	bolt.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	711
48	or/10-13	684097
49	36 and 43 and 48	194

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	956588
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1465344

3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1670568
4	1 or 2 or 3	2874741
5	exp Intracranial Pressure, Increased/	358
6	exp Intracranial Pressure/	16898
7	exp Brain Edema/	16437
8	or/5-7	28764
9	guideline$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	223821
10	validat$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	168454
11	9 or 10	386657
12	4 and 8 and 11	129

Results
A total of 8 abstracts were reviewed from 323 titles. From these 6 papers were selected for further review. No other papers were identified from a review of the references.
No papers were included in the final review.

Papers excluded from the final analysis are listed in table 15.9.i

Reference	**Reason for exclusion**
Anonymous(396)	Trauma as exclusive cause for raised ICP
Segal(397)	Survey of intracranial pressure monitoring use. Not a trial.
Shaywitz(380)	Case series of the use of ICP monitoring in Reye's syndrome. Not a comparison trial.
Shaywitz(398)	Case reports
Kindt(382)	Case reports
Pfenninger(399)	Foreign language

Table 15.9.i Papers excluded from the analysis of the indication for invasive monitoring of raised intracranial pressure in children

16. Hypertensive encephalopathy

Clinical Questions:

(i) In children with a reduced conscious level, what are the clinical signs of hypertensive encephalopathy?

Selection criteria

Criteria for choosing papers were drawn up before the search took place. Papers were selected if they were validating cohort studies of clinical decision rules or derivation studies of such rules for hypertensive encephalopathy. Prospective cohort studies or case control studies, which reported on the rates of different signs and symptoms of hypertensive encephalopathy would be included if no other studies were found. Studies involving both children and adults were only included if the results for children could be analysed separately.

Search

A review of the Cochrane library, MEDLINE (1966-present), EMBASE (1980-present), CINAHL (1982-present), British Nursing Index (1985-present) and AMED (1985-present) was performed using the search terms below. A review of the references of the selected papers for further evidence was included in the search strategy and a hand search of five key journals in the field in the previous 12 months.

Search filters

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	951169
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1439069
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1639690
4	1 or 2 or 3	2832537
5	exp neurologic examination/ or exp pain measurement/ or exp reflex/ or exp reflex, abdominal/ or exp reflex, abnormal/ or exp reflex, babinski/ or exp reflex, acoustic/ or exp reflex, pupillary/ or exp reflex, stretch/ or exp startle reaction/ or exp medical history taking/ or exp cornell medical index/ or exp reproductive history/ or exp physical examination/ or exp auscultation/ or exp heart auscultation/ or exp blood pressure determination/ or exp body constitution/ or exp body height/ or exp body surface area/ or exp body weight/ or exp fetal weight/ or exp body temperature/ or exp cephalometry/ or exp craniometry/ or exp facial expression/ or exp facies/ or exp gait/ or exp hand strength/ or exp palpation/ or exp pelvimetry/ or exp percussion/ or exp pigmentation/ or exp skin pigmentation/ or exp pulse/ or exp range of motion, articular/ or exp self-examination/ or exp breast self-examination/ or exp skinfold thickness/	892433
6	exp medical history taking/ or exp patient assessment/ or physical examination/ or exp palpation/ or exp pulse/	153287
7	exp patient history taking/ or exp physical examination/ or exp auscultation/ or exp heart auscultation/ or exp blood pressure determination/ or exp body temperature determination/ or exp cephalometry/ or exp "inspection (clinical)"/ or exp neurologic examination/ or exp reflex/ or exp reflex, abnormal/ or exp reflex, acoustic/ or exp reflex, pupillary/ or exp reflex, stretch/ or exp palpation/ or exp percussion/ or exp physical examination, preparticipation/ or exp pigmentation/ or exp skin pigmentation/ or exp pulse/	553576
8	exp blood pressure/ or exp body temperature/ or exp fatigue/ or exp jaundice/ or exp nausea/ or exp "pain and pain management"/ or exp paralysis/ or exp seizures/ or exp senses/ or exp shock/ or exp sleep/ or exp unconsciousness/ or exp patient assessment/	880816
9	exp medical examination/ or exp clinical examination/ or exp functional assessment/ or exp pulse oximetry/ or exp blood pressure monitoring/ or exp temperature measurement/ or exp thermometry/ or exp blood glucose monitoring/ or exp electrocardiography monitoring/ or exp neurologic examination/ or history/	274711
10	clinical feature.mp. [mp=ab, hw, ti, sh, it, tn, ot, dm, mf, rw]	217941
11	presenting feature.mp. [mp=ab, hw, ti, sh, it, tn, ot, dm, mf, rw]	2084
12	presenting sign.mp. [mp=ab, hw, ti, sh, it, tn, ot, dm, mf, rw]	1575
13	presenting symptom.mp. [mp=ab, hw, ti, sh, it, tn, ot, dm, mf, rw]	4282
14	sign.mp. [mp=ab, hw, ti, sh, it, tn, ot, dm, mf, rw]	61333

15	symptom.mp. [mp=ab, hw, ti, sh, it, tn, ot, dm, mf, rw]	145112
16	or/5-15	2013529
17	hypertension.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	441855
18	hypertensi$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	463202
19	18 or 19	463202
20	encephalopath$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	44361
21	GCS.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	7354
22	coma.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	39717
23	coma$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	44198
24	or/20-23	89255
25	19 and 24	6107
26	4 and 16 and 25	15

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	956588
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1465344
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1670568
4	1 or 2 or 3	2874741
5	hypertension.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	441855
6	hypertensi$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	463202
7	5 or 6	463202
8	encephalopath$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	44361
9	GCS.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	7354
10	coma.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	39717
11	coma$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	44198
12	or/8-11	89255
13	7 and 12	6107
14	decision rule.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	772
15	diagnosis.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1771627
16	14 or 15	1772247
17	4 and 13 and 16	2

Results

A total of 5 abstracts were reviewed from 17 titles. One paper was selected for further review. The hand search of references identified no other papers for further review.
No papers were included in the final analysis.

Papers excluded from the final analysis are listed in table 16.1.i

Reference	**Reason for exclusion**
N.H.B.P.E.P.W.G. (400)	Unvalidated guideline

Table 16.1.i Papers excluded from the analysis of which clinical features indicate hypertensive encephalopathy

16. Hypertensive encephalopathy

Clinical Questions:

(ii) In children with a reduced conscious level and hypertension, what investigation screen for or diagnose the causes of hypertensive encephalopathy?

Selection criteria
Criteria for choosing papers were drawn up before the search took place. Papers were selected if they were diagnostic studies of the causes of hypertensive encephalopathy, which objectively or blindly compared a diagnostic test with the gold standard. Studies involving both children and adults were included if the data for children could be analysed separately.

Search
A review of the Cochrane library, MEDLINE (1966-present), EMBASE (1980-present), CINAHL (1982-present), British Nursing Index (1985-present) and AMED (1985-present) was performed using the search terms below. A review of the references of the selected papers for further evidence was included in the search strategy and a hand search of five key journals in the field in the previous 12 months.

Search filters

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	956588
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1465344
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1670568
4	1 or 2 or 3	2874741
5	hypertension.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	441855
6	hypertensi$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	463202
7	5 or 6	463202
8	encephalopath$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	44361
9	GCS.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	7354
10	coma.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	39717
11	coma$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	44198
12	or/8-11	89255
13	7 and 12	6107
14	diagnos$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	2447207
15	gold.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	70563
16	standard$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	765982
17	test$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	2870847
18	investigation$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	553876
19	15 and 16	23804
20	14 or 17 or 18 or 19	5228589
21	sensitiv$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1225333
22	(sensitivity and specificity).mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	257964
23	diagnosis.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1791155
24	diagnostic $.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	243816
25	diagnosis,differential.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	269904
26	or/21-25	3005354
27	4 and 13 and 20 and 26	69

Results
A total of 24 abstracts were reviewed from 69 titles. One paper was selected for further review. The hand search of journals and references identified no other papers for further review.
No papers were included in the final analysis.

Papers excluded from the final analysis are listed in table 16.2.i

Reference	Reason for exclusion
N.H.B.P.E.P.W.G. (400)	Unvalidated guideline

Table 16.2.i Papers excluded from the analysis of which tests screen for or diagnose the causes of hypertensive encephalopathy

16. Hypertensive encephalopathy

Clinical Questions:

(iii) In children with a reduced conscious level and hypertension, what treatments should be started to reduce morbidity associated with hypertensive encephalopathy?

Selection criteria
Criteria for choosing papers were drawn up before the search took place. Papers would be included if they were randomised controlled trials of children with hypertensive encephalopathy to determine which treatments reduce hypertension, reduce mortality or neurological outcome. Validation studies of guidelines for the management of children with hypertensive encephalopathy would also be included if they demonstrated benefit of following the guideline and gave advice on the treatment to use. Studies involving both children and adults were included if the results for children could be analysed separately.

Search
A review of the Cochrane library, MEDLINE (1966-present), EMBASE (1980-present), CINAHL (1982-present), British Nursing Index (1985-present) and AMED (1985-present) was performed using the search terms below. A review of the references of the selected papers for further evidence was included in the search strategy and a hand search of five key journals in the field in the previous 12 months.

Search filters

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	973072
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1496225
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1702543
4	1 or 2 or 3	2930261
5	hypertension.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	441855
6	hypertensi$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	463202
7	5 or 6	463202
8	encephalopath$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	44361
9	GCS.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	7354
10	coma.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	39717
11	coma$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	44198
12	or/8-11	89255
13	7 and 12	6107
14	RANDOMIZED CONTROLLED TRIAL.pt.	207390
15	CONTROLLED CLINICAL TRIAL.pt.	69509
16	randomized controlled trials.sh.	40568
17	random allocation.sh.	54174
18	double blind method.sh.	83749
19	single blind method.sh.	9322
20	or/14-19	354172
21	Animal.sh.	15964
22	human.sh.	5029060
23	21 not 22	12982
24	20 not 23	354172
25	clinical trial.pt.	432187
26	exp clinical trials/	571720
27	(clin$ adj25 trial$).ti,ab.	234670
28	((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.	168351

29	placebos.sh.	27378
30	placebo$.ti,ab.	186850
31	random$.ti,ab.	645128
32	research design.sh.	43436
33	or/25-32	1448836
34	33 not 23	1448697
35	34 not 24	1115655
36	comparative study.sh.	1294711
37	exp evaluation studies/	579470
38	follow up studies.sh.	307099
39	prospective studies.sh.	234394
40	(control$ or prospectiv$ or volunteer$).ti,ab.	3037750
41	or/37-40	4712196
42	41 not 23	4710763
43	42 not (24 or 35)	3915447
44	24 or 35 or 43	5386707
45	4 and 13 and 44	92

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	956588
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1465344
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1670568
4	1 or 2 or 3	2874741
5	hypertension.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	441855
6	hypertensi$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	463202
7	5 or 6	463202
8	encephalopath$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	44361
9	GCS.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	7354
10	coma.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	39717
11	coma$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	44198
12	or/8-11	89255
13	7 and 12	6107
14	decision rule.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	772
15	diagnosis.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1771627
16	14 or 15	1772247
17	4 and 13 and 16	2

Results

A total of 10 abstracts were reviewed from 94 titles. 1 paper was selected for further review. The hand search of journals and references identified no other papers for further assessment.
No papers were included in the final analysis.

Papers excluded from the final analysis are listed in table 16.3.i

Reference	**Reason for exclusion**
N.H.B.P.E.P.W.G. (400)	Unvalidated guideline

Table 16.3.i Papers excluded from the final analysis of treatments for hypertensive encephalopathy in children

17. Prolonged convulsion

Clinical Questions:

(i) In children with a reduced conscious level, what is the neurological outcome after a prolonged convulsion?

Selection criteria
Criteria for choosing papers were drawn up before the search took place. Papers would be included if they were validating studies of guidelines for the management of prolonged convulsions in children, or if they were prospective cohort studies determining the prognosis of children who had prolonged convulsions or case-control studies of children with poor outcome to determine if length of time of a convulsion was a factor. Studies involving both children and adults were only included if the results for children could be analysed separately.

Search
A review of the Cochrane library, MEDLINE (1966-present), EMBASE (1980-present), CINAHL (1982-present), British Nursing Index (1985-present) and AMED (1985-present) was performed using the search terms below. A review of the references of the selected papers for further evidence was included in the search strategy and a hand search of five key journals in the field in the previous 12 months.

Search filters

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	936486
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1412651
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1611164
4	1 or 2 or 3	2784039
5	prognos$.mp. [mp=ab, hw, ti, sh, it, tn, ot, dm, mf, rw]	490966
6	risk$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1410795
7	group$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	2613071
8	cohort studies.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	60608
9	cohort$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	186555
10	or/5-9	4096978
11	convulsion$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	28116
12	epileps$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	116480
13	SEIZURES/ or seizure.mp.	96764
14	exp CONVULSION/	11166
15	exp SEIZURES/	63183
16	exp EPILEPSY/	146026
17	or/11-16	200901
18	mortality.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	500289
19	morbidity.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	255390
20	18 or 19	620628
21	4 and 10 and 17 and 20	264

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	936486
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1412651
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1611164
4	1 or 2 or 3	2784039
5	guideline$.mp. [mp=ab, hw, ti, sh, it, tn, ot, dm, mf, rw]	155070
6	convulsion$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	28116
7	epileps$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	116480
8	SEIZURES/ or seizure.mp.	96764
9	exp CONVULSION/	11166
10	exp SEIZURES/	63183
11	exp EPILEPSY/	146026

12	or/6-11	200901
13	4 and 5 and 12	30

Results
A total of 37 abstracts were reviewed from 294 titles. A total of 7 papers were selected for further review. The hand search of journals and references identified two other papers for further review. 2 papers were included in the final analysis.

Papers excluded from the final analysis are listed in table 17.1.i
Papers included in the final analysis are listed in table 17.1.ii

Reference	**Reason for exclusion**
Brorson (401)	No description of length of seizure duration as part of analysis
Weber (402)	Study to determine the incidence of SUDEP in children
Callenbach(403)	Study to determine the incidence of mortality in children with epilepsy. No description of length of seizure duration as part of analysis.
Holtkamp (404)	Adult study of refractory status epilepticus
Donner (405)	Study to determine the incidence of mortality in children with epilepsy. No description of length of seizure duration as part of analysis.
Camfield (406)	Study to determine the incidence of mortality in children with epilepsy. No description of length of seizure duration as part of analysis.
Pellock (407)	Study to determine the time to treatment but with no analysis on outcome if treatment delayed.

Table 17.1.i Papers excluded from the analysis of outcome associated with length of convulsion

Study	Method	Inclusion criteria	Search	Evidence appraisal	Summarizing evidence	Results	Notes	Evidence level
Tellez-Zenteno (408)	Systematic review to determine the incidence and risk factors in sudden unexplained death in epilepsy (SUDEP).	Cohort (prospective and retrospective) and case-control studies focusing on SUDEP in children and adults.	Cochrane, Medline, Embase and a review of references and experts.	Two independent appraisors assessed eligibility and data extraction. A scoring system (Kotsopoulos) was used to help appraise the papers.	No statistical meta-analysis could be performed on due to heterogeneity of study types.	29 papers were included looking at the incidence of SUDEP. In those conducted on children the incidence was significantly less than 1 per 1000 population per year. 5 papers were included looking at the risk factors associated with SUDEP. None of them looked specifically at seizure duration, but 60% of the papers found a correlation between SUDEP and high seizure frequency.	Significant heterogeneity hence no attempt at meta-analysis. Not directly looking at the prognosis of prolonged seizures.	Prognosis 1a-

Table 17.1.ii Papers included in the analysis of outcome associated with length of convulsion (Systematic reviews)

Study	Methods	Participant definition	Length of follow-up	Outcomes	Results	Notes	Evidence level
Metsaranta (409)	Retrospective cohort study to determine if length of seizure is an indicator of poor prognosis in children.	Children (aged <16 years) presenting to a hospital in Finland with a seizure lasting more than 5 minutes.	Variable depending on patient. Mean follow-up time was 2 years and 1 month (range 0 to 7	Death and neurological dysfunction based on a neurological examination.	279 seizure episodes in 186 children lasted more than 5 minutes. 31% of the patients had a previous neurological abnormality diagnosed. 9.7% of seizures stopped	Retrospective study with poorly defined follow up. Unable to draw a conclusion about the safety of prolonged seizure and the	Prognosis 2b

		Study period 1993 to 1999.	years).		spontaneously after more than 5 minutes of seizing. 4 patients died in the follow-up period, none directly due to seizures or their sequelae. 4 patients had severe neurological sequelae. The duration of seizures in this group was 10–30 minutes compared to the average duration of 42 minutes. In 3 of the 4 children the neurological outcome was related to the underlying cause of the epilepsy rather than the seizure itself.	decision to stop a seizure at 5 minutes or 10 minutes.	

Table 17.1.ii Papers included in the analysis of outcome associated with length of convulsion (Prognosis studies)

17. Prolonged convulsion

Clinical Questions:

(ii) In children with a reduced conscious level and a prolonged convulsion, what tests screen for or diagnose the underlying treatable causes?

Selection criteria
Criteria for choosing papers were drawn up before the search took place. Papers were selected if they were diagnostic studies of the causes of a prolonged convulsion, or population studies of prolonged convulsions to determine the frequency of underlying causes. Particular searches were undertaken to determine the frequency of hyponatraemia, hypocalcaemia and hypomagnesaemia. Studies involving both children and adults were included if the data for children could be analysed separately.

Search
A review of the Cochrane library, MEDLINE (1966-present), EMBASE (1980-present), CINAHL (1982-present), British Nursing Index (1985-present) and AMED (1985-present) was performed using the search terms below. A review of the references of the selected papers for further evidence was included in the search strategy and a hand search of five key journals in the field in the previous 12 months.

Search filters

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	956588
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1465344
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1670568
4	1 or 2 or 3	2874741
5	convulsion$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	28116
6	epileps$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	116480
7	SEIZURES/ or seizure.mp.	96764
8	exp CONVULSION/	11166
9	exp SEIZURES/	63183
10	exp EPILEPSY/	146026
11	or/5-10	200901
12	diagnos$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	2447207
13	gold.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	70563
14	standard$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	765982
15	test$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	2870847
16	investigation$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	553876
17	13 and 14	23804
18	12 or 15 or 16 or 17	5228589
19	sensitiv$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1225333
20	(sensitivity and specificity).mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	257964
21	diagnosis.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1791155
22	diagnostic $.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	243816
23	diagnosis,differential.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	269904
24	or/19-23	3005354
25	4 and 11 and 18 and 24	116

#	Search terms	No. of articles
1	exp adolescent/ or exp child/ or exp child, preschool/ or exp infant/ or exp infant, newborn/ or exp adolescent, hospitalized/ or exp child, hospitalized4 and 5/	2874179
2	exp diagnosis/ or exp diagnosis, differential/	9293
3	cause.mp.	5345472
4	(aetiology or etiology).mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	636200
5	2 or 3 or 4	347066
6	exp epidemiologic studies/ or exp case-control studies/ or exp retrospective studies/ or exp cohort	6007551

7	studies/ or exp longitudinal studies/ or exp follow-up studies/ or exp prospective studies/ or exp control groups/	1615326
8	6 and 7	708208
9	5 and 8	1615
10	convulsion$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	28116
11	Epilepsy$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	116480
12	SEIZURES/ or seizure.mp.	96764
13	exp CONVULSION/	11166
14	exp SEIZURES/	63183
15	exp EPILEPSY/	146026
16	or/10-15	200901
17	1 and 9 and 16	1652
18	hyponatremi$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	12748
19	hyponatraemi$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	2102
20	low sodium.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	3802
21	or/18-20	17048
22	magnesium.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	121517
23	hypocalcem$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	13720
24	hypocalcaemi$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	2225
25	23 or 24	14722
26	17 and 21	403
27	17 and 22	166
28	17 and 25	263

Results
A total of 37 abstracts were reviewed from 379 titles. Five papers were selected for further review. The hand search of journals and references identified no other papers for further review. Two papers were included in the final analysis.

Papers excluded from the final analysis are listed in table 17.2.i
Papers included in the final analysis are listed in table 17.2.ii

Reference	**Reason for exclusion**
Armon (108)	Validated guideline on management after a convulsion has finished
Appleton (410)	Unvalidated guideline, not giving advice on tests to send.
Murtaza (411)	Symptom prevalence amongst children with severe dehydration rather than convulsing children

Table 17.2.i Papers excluded from the analysis of which tests screen for or diagnose the causes of a prolonged convulsion

Study	Methods	Participant definition	Length of follow-up	Outcomes	Results	Notes	Evidence level
Eriksson (412)	Retrospective cohort of neonatal convulsions to determine the causes of the convulsions and short term prognosis.	Full term infants (aged less than 4 weeks) presenting to a referral hospital in Sweden with convulsions. Preterm infants were excluded. Study period 1970 to 1976.	One year by clinic assessment.	Causes of seizures were grouped into: hypoxia; infection; hypoglycaemia (blood glucose <1.7mmol/l); hypocalcaemia (serum calcium <1.9mmol/l); other metabolic cause; and unknown.	77 infants were enrolled. The mortality rate was 13% in the first year. 6% of infants had convulsions due to hypoglycaemia. A further 22% of the infants were hypoglycaemic but were convulsing due to another primary cause (i.e. correcting hypoglycaemia did not stop the convulsion). 3% of infants had convulsions due to hypocalcaemia. A further 9% of the infants were hypocalcaemic but were convulsing due to another primary cause (i.e. correcting hypocalcaemia did not stop the convulsion).	In this series 12% of convulsing infants were hypocalcaemic. Retrospective cohort study prone to miss cases. Referral hospital population, therefore may indicate more severe end of spectrum.	Symptom prevalence 4
Brown (413)	Prospective cohort study to determine the incidence of underlying causes of neonatal convulsions and the outcomes at one year of age.	Infants born at two hospitals in Scotland who had convulsions in the first two weeks of life. Exclusions not stated. Study period over two years (dates not stated).	One year with assessments after the convulsion, at four months and at one year.	Causes of the seizures especially metabolic derangements of calcium, sodium and glucose. Neurological outcomes at one year as assessed by the Pretchl scheme.	142 infants were enrolled. 39% at one year had died or were severely handicapped. Convulsions occurring during the first four days of life were associated with a significantly worse outcome. 47% had a low calcium (2 standard deviations below the comparison value for controls). 24% were found to have a low magnesium.	Prospective cohort study with good follow-up and little data loss. Data from hospitals where infants born so not seeing the severe end of spectrum.	Symptom prevalence 1b

					24% had a low blood glucose.		

Table 17.2.ii Papers included in the analysis of which tests screen for or diagnose the causes of a prolonged convulsion

17. Prolonged convulsion

Clinical Questions:

(iii) In children with a reduced conscious level and a prolonged convulsion, what treatment is required to stop the convulsion?

Selection criteria
Criteria for choosing papers were drawn up before the search took place. Papers would be included if they were randomised controlled trials of children with a prolonged convulsion to determine which treatments reduce mortality or improve neurological outcome. Validation studies of guidelines for the management of children with a prolonged convulsion would also be included if they demonstrated benefit of following the guideline and gave advice on the treatment to use. Studies involving both children and adults were included if the results for children could be analysed separately.

Search
A review of the Cochrane library, MEDLINE (1966-present), EMBASE (1980-present), CINAHL (1982-present), British Nursing Index (1985-present) and AMED (1985-present) was performed using the search terms below. A review of the references of the selected papers for further evidence was included in the search strategy and a hand search of five key journals in the field in the previous 12 months.

Search filters

#	Search terms	No. of articles
1	RANDOMIZED CONTROLLED TRIAL.pt.	207645
2	CONTROLLED CLINICAL TRIAL.pt.	69541
3	randomized controlled trials.sh.	40656
4	random allocation.sh.	54187
5	double blind method.sh.	83813
6	single blind method.sh.	9333
7	or/1-6	354565
8	Animal.sh.	15966
9	human.sh.	5043029
10	8 not 9	12983
11	7 not 10	354565
12	clinical trial.pt.	432720
13	exp clinical trials/	573648
14	(clin$ adj25 trial$).ti,ab.	235335
15	((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.	168647
16	placebos.sh.	27397
17	placebo$.ti,ab.	187228
18	random$.ti,ab.	646809
19	research design.sh.	43470
20	or/12-19	1452441
21	20 not 10	1452302
22	21 not 11	1118878
23	comparative study.sh.	1296264
24	exp evaluation studies/	580326
25	follow up studies.sh.	307370
26	prospective studies.sh.	234810
27	(control$ or prospectiv$ or volunteer$).ti,ab.	3043825
28	or/23-27	4720246
29	28 not 10	4718813
30	29 not (11 or 22)	3921781
31	11 or 22 or 28	5396657
32	exp infant, newborn/ or exp infant/ or exp infants/	974282
33	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1498335
34	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1704979
35	32 or 33 or 34	2934196

36	convulsion$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	28116
37	epileps$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	116480
38	SEIZURES/ or seizure.mp.	96764
39	exp CONVULSION/	11166
40	exp SEIZURES/	63183
41	exp EPILEPSY/	146026
42	or/36-41	200901
43	anticonvulsant.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	22593
44	31 and 35 and 42 and 43	1458

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	936486
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1412651
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1611164
4	1 or 2 or 3	2784039
5	guideline$.mp. [mp=ab, hw, ti, sh, it, tn, ot, dm, mf, rw]	155070
6	convulsion$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	28116
7	epileps$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	116480
8	SEIZURES/ or seizure.mp.	96764
9	exp CONVULSION/	11166
10	exp SEIZURES/	63183
11	exp EPILEPSY/	146026
12	or/6-11	200901
13	4 and 5 and 12	30

Results

A total of 43 abstracts were reviewed from 1488 titles. One paper was selected for further review. The hand search of journals and references identified no other papers for further review. No papers were included in the final analysis.

Papers excluded from the final analysis are listed in table 17.3.i

Reference	**Reason for exclusion**
Appleton (410)	Unvalidated guideline.

Table 17.3.i Papers excluded from the final analysis of how to treat a prolonged convulsion

17. Prolonged convulsion

Clinical Questions:

(iv) In children with a reduced conscious level and a prolonged convulsion secondary to hyponatraemia, what treatment is required to stop the convulsion?

Selection criteria

Criteria for choosing papers were drawn up before the search took place. Papers would be included if they were randomised controlled trials of children with a prolonged convulsion secondary to hyponatraemia to determine which treatments reduce mortality or improve neurological outcome. Validation studies of guidelines for the management of children with a prolonged convulsion would also be included if they demonstrated benefit of following the guideline and gave advice on the treatment to use. Studies involving both children and adults were included if the results for children could be analysed separately.

Search

A review of the Cochrane library, MEDLINE (1966-present), EMBASE (1980-present), CINAHL (1982-present), British Nursing Index (1985-present) and AMED (1985-present) was performed using the search terms below. A review of the references of the selected papers for further evidence was included in the search strategy and a hand search of five key journals in the field in the previous 12 months.

Search filters

#	Search terms	No. of articles
1	RANDOMIZED CONTROLLED TRIAL.pt.	207645
2	CONTROLLED CLINICAL TRIAL.pt.	69541
3	randomized controlled trials.sh.	40656
4	random allocation.sh.	54187
5	double blind method.sh.	83813
6	single blind method.sh.	9333
7	or/1-6	354565
8	Animal.sh.	15966
9	human.sh.	5043029
10	8 not 9	12983
11	7 not 10	354565
12	clinical trial.pt.	432720
13	exp clinical trials/	573648
14	(clin$ adj25 trial$).ti,ab.	235335
15	((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.	168647
16	placebos.sh.	27397
17	placebo$.ti,ab.	187228
18	random$.ti,ab.	646809
19	research design.sh.	43470
20	or/12-19	1452441
21	20 not 10	1452302
22	21 not 11	1118878
23	comparative study.sh.	1296264
24	exp evaluation studies/	580326
25	follow up studies.sh.	307370
26	prospective studies.sh.	234810
27	(control$ or prospectiv$ or volunteer$).ti,ab.	3043825
28	or/23-27	4720246
29	28 not 10	4718813
30	29 not (11 or 22)	3921781
31	11 or 22 or 28	5396657
32	exp infant, newborn/ or exp infant/ or exp infants/	974282
33	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1498335
34	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1704979
35	32 or 33 or 34	2934196
36	convulsion$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	28116
37	epileps$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	116480
38	SEIZURES/ or seizure.mp.	96764
39	exp CONVULSION/	11166
40	exp SEIZURES/	63183
41	exp EPILEPSY/	146026
42	or/36-41	200901
43	hyponatremi$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	12748
44	hyponatraemi$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	2102
45	low sodium.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	3802
46	or/43-45	17048
47	31 and 35 and 42 and 46	124

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	936486
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1412651
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1611164
4	1 or 2 or 3	2784039
5	guideline$.mp. [mp=ab, hw, ti, sh, it, tn, ot, dm, mf, rw]	155070
6	convulsion$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	28116

7	epileps$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	116480
8	SEIZURES/ or seizure.mp.	96764
9	exp CONVULSION/	11166
10	exp SEIZURES/	63183
11	exp EPILEPSY/	146026
12	or/6-11	200901
13	4 and 5 and 12	30

Results

A total of 3 abstracts were reviewed from 154 titles. One paper was selected for further review. The hand search of journals and references identified no other papers for further review.
No papers were included in the final analysis.

Papers excluded from the final analysis are listed in table 17.4.i

Reference	Reason for exclusion
Sarnaik (414)	Case reports

Table 17.4.i Papers excluded from the analysis of how to treat a prolonged convulsion secondary to hyponatraemia

17. Prolonged convulsion

Clinical Questions:

(v) In children with a reduced conscious level and a prolonged convulsion secondary to hypocalcaemia, what treatment is required to stop the convulsion?

Selection criteria
Criteria for choosing papers were drawn up before the search took place. Papers would be included if they were randomised controlled trials of children with a prolonged convulsion secondary to hypocalcaemia to determine which treatments reduce mortality or improve neurological outcome. Validation studies of guidelines for the management of children with a prolonged convulsion would also be included if they demonstrated benefit of following the guideline and gave advice on the treatment to use. Studies involving both children and adults were included if the results for children could be analysed separately.

Search
A review of the Cochrane library, MEDLINE (1966-present), EMBASE (1980-present), CINAHL (1982-present), British Nursing Index (1985-present) and AMED (1985-present) was performed using the search terms below. A review of the references of the selected papers for further evidence was included in the search strategy and a hand search of five key journals in the field in the previous 12 months.

Search filters

#	Search terms	No. of articles
1	RANDOMIZED CONTROLLED TRIAL.pt.	207645
2	CONTROLLED CLINICAL TRIAL.pt.	69541
3	randomized controlled trials.sh.	40656
4	random allocation.sh.	54187
5	double blind method.sh.	83813
6	single blind method.sh.	9333
7	or/1-6	354565
8	Animal.sh.	15966
9	human.sh.	5043029
10	8 not 9	12983
11	7 not 10	354565
12	clinical trial.pt.	432720
13	exp clinical trials/	573648
14	(clin$ adj25 trial$).ti,ab.	235335
15	((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.	168647

16	placebos.sh.	27397
17	placebo$.ti,ab.	187228
18	random$.ti,ab.	646809
19	research design.sh.	43470
20	or/12-19	1452441
21	20 not 10	1452302
22	21 not 11	1118878
23	comparative study.sh.	1296264
24	exp evaluation studies/	580326
25	follow up studies.sh.	307370
26	prospective studies.sh.	234810
27	(control$ or prospectiv$ or volunteer$).ti,ab.	3043825
28	or/23-27	4720246
29	28 not 10	4718813
30	29 not (11 or 22)	3921781
31	11 or 22 or 28	5396657
32	exp infant, newborn/ or exp infant/ or exp infants/	974282
33	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1498335
34	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1704979
35	32 or 33 or 34	2934196
36	convulsion$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	28116
37	epileps$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	116480
38	SEIZURES/ or seizure.mp.	96764
39	exp CONVULSION/	11166
40	exp SEIZURES/	63183
41	exp EPILEPSY/	146026
42	or/36-41	200901
43	hypocalcem$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	13720
44	hypocalcaemi$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	2225
45	43 or 33	14722
46	31 and 35 and 42 and 45	43

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	936486
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1412651
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1611164
4	1 or 2 or 3	2784039
5	guideline$.mp. [mp=ab, hw, ti, sh, it, tn, ot, dm, mf, rw]	155070
6	convulsion$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	28116
7	epileps$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	116480
8	SEIZURES/ or seizure.mp.	96764
9	exp CONVULSION/	11166
10	exp SEIZURES/	63183
11	exp EPILEPSY/	146026
12	or/6-11	200901
13	4 and 5 and 12	30

Results

A total of 5 abstracts were reviewed from 73 titles. Three papers were selected for further review. The hand search of journals and references identified no other papers for further review. One paper was included in the final analysis.

Papers excluded from the final analysis are listed in table 17.5.i
Papers included in the final analysis are listed in table 17.5.ii

Reference	Reason for exclusion
Kulaylat (415)	Case reports
Sheth (416)	Case reports

Table 17.5.i Papers excluded from the analysis of how to treat prolonged convulsions due to hypocalcaemia

Study	Methods	Participants	Interventions	Allocation concealment	Outcomes	Results	Notes	Evidence level
Turner (417)	Randomised controlled trial comparing oral calcium, oral phenobarbitone and intramuscular magnesium to determine which of these treatments reduces the number of seizures secondary to hypocalcaemia in the newborn period.	Newborn term infants (aged 4 to 8 days old) fed on full cream evaporated milk from birth in a Scottish hospital, who had a seizure and were hypocalcaemic (plasma calcium <7.4mg/dl or <1.5mmol/l). Study period not stated.	Oral calcium gluconate (10 ml of 10% with every feed for 48 hours) or oral phenobarbitone (7.5mg QDS) or intramuscular magnesium sulphate (0.2ml/kg or 10mg/kg BD).	Not stated how randomisation achieved.	Not stated in the method. Plasma concentrations of calcium and magnesium were measured before and after treatment. Number of infants still convulsing after 48 hours was recorded.	104 infants were enrolled: 34 into the Calcium group, 33 into the phenobarbitone group and 37 into the magnesium group. Number of convulsions vefore treatment was started was similar in each group. The pre-treatment plasma calcium was lower in the calcium group. The post-treatment plasma calcium concentration and plasma magnesium concentration was significantly higher in the magnesium group when compared to the other groups. One infant in the magnesium group was convulsing after 48 hours, which was significantly less than 13 convulsing infants in the calcium group and the 10 convulsing infants in the phenobarbitone group.	Random-isation method not explicit (not uncommon for a paper published in 1977). The treatments differ in mode of administra-tion which is likely to affect the results towards favouring the perentral route.	Therapy 2b

Table 17.5.ii Papers included in the analysis of how to treat prolonged convulsions due to hypocalcaemia

17. Prolonged convulsion

Clinical Questions:

(vi) In children with a reduced conscious level and a prolonged convulsion secondary to hypomagnesaemia, what treatment is required to stop the convulsion?

Selection criteria
Criteria for choosing papers were drawn up before the search took place. Papers would be included if they were randomised controlled trials of children with a prolonged convulsion secondary to hypomagnesaemia to determine which treatments reduce mortality or improve neurological outcome. Validation studies of guidelines for the management of children with a prolonged convulsion would also be included if they demonstrated benefit of following the guideline and gave advice on the treatment to use. Studies involving both children and adults were included if the results for children could be analysed separately.

Search
A review of the Cochrane library, MEDLINE (1966-present), EMBASE (1980-present), CINAHL (1982-present), British Nursing Index (1985-present) and AMED (1985-present) was performed using the search terms below. A review of the references of the selected papers for further evidence was included in the search strategy and a hand search of five key journals in the field in the previous 12 months.

Search filters

#	Search terms	No. of articles
1	RANDOMIZED CONTROLLED TRIAL.pt.	207645
2	CONTROLLED CLINICAL TRIAL.pt.	69541
3	randomized controlled trials.sh.	40656
4	random allocation.sh.	54187
5	double blind method.sh.	83813
6	single blind method.sh.	9333
7	or/1-6	354565
8	Animal.sh.	15966
9	human.sh.	5043029
10	8 not 9	12983
11	7 not 10	354565
12	clinical trial.pt.	432720
13	exp clinical trials/	573648
14	(clin$ adj25 trial$).ti,ab.	235335
15	((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.	168647
16	placebos.sh.	27397
17	placebo$.ti,ab.	187228
18	random$.ti,ab.	646809
19	research design.sh.	43470
20	or/12-19	1452441
21	20 not 10	1452302
22	21 not 11	1118878
23	comparative study.sh.	1296264
24	exp evaluation studies/	580326
25	follow up studies.sh.	307370
26	prospective studies.sh.	234810
27	(control$ or prospectiv$ or volunteer$).ti,ab.	3043825
28	or/23-27	4720246
29	28 not 10	4718813
30	29 not (11 or 22)	3921781
31	11 or 22 or 28	5396657
32	exp infant, newborn/ or exp infant/ or exp infants/	974282
33	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1498335
34	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child,	1704979

	hospitalized/	
35	32 or 33 or 34	2934196
36	convulsion$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	28116
37	epileps$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	116480
38	SEIZURES/ or seizure.mp.	96764
39	exp CONVULSION/	11166
40	exp SEIZURES/	63183
41	exp EPILEPSY/	146026
42	or/36-41	200901
43	magnesium.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	121517
44	31 and 35 and 42 and 43	27

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	936486
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1412651
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1611164
4	1 or 2 or 3	2784039
5	guideline$.mp. [mp=ab, hw, ti, sh, it, tn, ot, dm, mf, rw]	155070
6	convulsion$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	28116
7	epileps$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	116480
8	SEIZURES/ or seizure.mp.	96764
9	exp CONVULSION/	11166
10	exp SEIZURES/	63183
11	exp EPILEPSY/	146026
12	or/6-11	200901
13	4 and 5 and 12	30

Results

A total of 3 abstracts were reviewed from 57 titles. Two papers were selected for further review. The hand search of journals and references identified no other papers for further review.
One paper was included in the final analysis.

Papers excluded from the final analysis are listed in table 17.6.i
Papers included in the final analysis are listed in table 17.6.ii

Reference	**Reason for exclusion**
Tsau (418)	Foreign language journal

Table 17.6.i Papers excluded from the analysis of how to treat prolonged convulsions due to hypomagnesaemia

Study	Methods	Participants	Interventions	Allocation concealment	Outcomes	Results	Notes	Evidence level
Turner (417)	Randomised controlled trial comparing oral calcium, oral phenobarbitone and intramuscular magnesium to determine which of these treatments reduces the number of seizures secondary to hypocalcaemia in the newborn period.	Newborn term infants (aged 4 to 8 days old) fed on full cream evaporated milk from birth in a Scottish hospital, who had a seizure and were hypocalcaemic (plasma calcium <7.4mg/dl or <1.5mmol/l). Study period not stated.	Oral calcium gluconate (10 ml of 10% with every feed for 48 hours) or oral phenobarbitone (7.5mg QDS) or intramuscular magnesium sulphate (0.2ml/kg or 10mg/kg BD).	Not stated how randomisation achieved.	Not stated in the method. Plasma concentrations of calcium and magnesium were measured before and after treatment. Number of infants still convulsing after 48 hours was recorded.	104 infants were enrolled: 34 into the Calcium group, 33 into the phenobarbitone group and 37 into the magnesium group. Number of convulsions vefore treatment was started was similar in each group. The pre-treatment plasma calcium was lower in the calcium group. The post-treatment plasma calcium concentration and plasma magnesium concentration was significantly higher in the magnesium group when compared to the other groups. One infant in the magnesium group was convulsing after 48 hours, which was significantly less than 13 convulsing infants in the calcium group and the 10 convulsing infants in the phenobarbitone group.	Random-isation method not explicit (not uncommon for a paper published in 1977). The treatments differ in mode of administra-tion which is likely to affect the results towards favouring the perentral route.	

Table 17.6.ii Papers included in the analysis of how to treat prolonged convulsions due to hypomagnesaemia

18. Post convulsion state

Clinical Questions:

(i) In children after a convulsion, what is the incidence of a reduced conscious level (post convulsion state)?

Selection criteria
Criteria for choosing papers were drawn up before the search took place. Papers would be included if they were epidemiological studies of children who have had a convulsion to determine the incidence of decreased conscious level after the convulsion. Studies involving both children and adults were included if the results for children could be analysed separately.

Search
A review of the Cochrane library, MEDLINE (1966-present), EMBASE (1980-present), CINAHL (1982-present), British Nursing Index (1985-present) and AMED (1985-present) was performed using the search terms below. A review of the references of the selected papers for further evidence was included in the search strategy and a hand search of five key journals in the field in the previous 12 months.

Search filters

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	974282
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1498335
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1704979
4	1 or 2 or 3	2934196
5	risk$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1471379
6	group$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	2693860
7	exp epidemiologic studies/ or exp case-control studies/ or exp retrospective studies/ or exp cohort	6007551
8	studies/ or exp longitudinal studies/ or exp follow-up studies/ or exp prospective studies/ or exp control groups/	1615326
9	or/5-8	3902543
10	convuls$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	39101
11	seizure$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	126379
12	fit$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	197023
13	epilep$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	133343
14	or/10-13	411555
15	post-ictal.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	443
16	time.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	2561614
17	post$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	2070527
18	or/15-17	4246362
19	4 and 9 and 14 and 18	7752
20	coma$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	44198
21	19 and 20	232

Results

A total of 12 abstracts were reviewed from 232 titles. No papers were selected for further review.
The hand search of journals identified no other papers for further review.
No papers were included in the final analysis.

18. Post convulsion state

Clinical Questions:

(ii) In children after a convulsion, what is the duration of a reduced conscious level (post convulsion state)?

Selection criteria
Criteria for choosing papers were drawn up before the search took place. Papers would be included if they were epidemiological studies of children who have had a convulsion to determine the time period of decreased conscious level after the convulsion. Studies involving both children and adults were included if the results for children could be analysed separately.

Search
A review of the Cochrane library, MEDLINE (1966-present), EMBASE (1980-present), CINAHL (1982-present), British Nursing Index (1985-present) and AMED (1985-present) was performed using the search terms below. A review of the references of the selected papers for further evidence was included in the search strategy and a hand search of five key journals in the field in the previous 12 months.

Search filters

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	974282
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1498335
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1704979
4	1 or 2 or 3	2934196
5	risk$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1471379
6	group$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	2693860
7	exp epidemiologic studies/ or exp case-control studies/ or exp retrospective studies/ or exp cohort	6007551
8	studies/ or exp longitudinal studies/ or exp follow-up studies/ or exp prospective studies/ or exp control groups/	1615326
9	or/5-8	3902543
10	convuls$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	39101
11	seizure$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	126379
12	fit$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	197023
13	epilep$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	133343
14	or/10-13	411555
15	post-ictal.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	443
16	time.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	2561614
17	post$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	2070527
18	or/15-17	4246362
19	4 and 9 and 14 and 18	7752
20	coma$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	44198
21	19 and 20	232

Results

A total of 12 abstracts were reviewed from 232 titles. No papers were selected for further review.
The hand search of journals identified no other papers for further review.
No papers were included in the final analysis.

18. Post convulsion state

Clinical Questions:

(iii) In children after a convulsion, what tests should be performed to determine the underlying cause of the convulsion?

Selection criteria
Criteria for choosing papers were drawn up before the search took place. Papers were selected if they were diagnostic studies of the causes of a convulsion, or population studies of convulsions to determine the frequency of underlying causes. Studies involving both children and adults were included if the data for children could be analysed separately.

Search
A review of the Cochrane library, MEDLINE (1966-present), EMBASE (1980-present), CINAHL (1982-present), British Nursing Index (1985-present) and AMED (1985-present) was performed using the search terms below. A review of the references of the selected papers for further evidence was included in the search strategy and a hand search of five key journals in the field in the previous 12 months.

Search filters

#	Search terms	No. of articles
1	exp adolescent/ or exp child/ or exp child, preschool/ or exp infant/ or exp infant, newborn/ or exp adolescent, hospitalized/ or exp child, hospitalized4 and 5/	2874179
2	exp diagnosis/ or exp diagnosis, differential/	9293
3	cause.mp.	5345472
4	(aetiology or etiology).mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	636200
5	2 or 3 or 4	347066
6	exp epidemiologic studies/ or exp case-control studies/ or exp retrospective studies/ or exp cohort	6007551
7	studies/ or exp longitudinal studies/ or exp follow-up studies/ or exp prospective studies/ or exp control groups/	1615326
8	6 and 7	708208
9	5 and 8	1615
10	convulsion$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	28116
11	Epilepsy$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	116480
12	SEIZURES/ or seizure.mp.	96764
13	exp CONVULSION/	11166
14	exp SEIZURES/	63183
15	exp EPILEPSY/	146026
16	or/10-15	200901
17	post-ictal.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	443
18	1 and 9 and 16 and 17	24

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	956588
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1465344
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1670568
4	1 or 2 or 3	2874741
5	convulsion$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	28116
6	epileps$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	116480
7	SEIZURES/ or seizure.mp.	96764
8	exp CONVULSION/	11166
9	exp SEIZURES/	63183
10	exp EPILEPSY/	146026
11	or/5-10	200901
12	diagnos$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	2447207
13	gold.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	70563
14	standard$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	765982

15	test$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	2870847
16	investigation$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	553876
17	13 and 14	23804
18	12 or 15 or 16 or 17	5228589
19	sensitiv$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1225333
20	(sensitivity and specificity).mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	257964
21	diagnosis.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1791155
22	diagnostic $.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	243816
23	diagnosis,differential.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	269904
24	or/19-23	3005354
25	4 and 11 and 18 and 24	116

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	936486
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1412651
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1611164
4	1 or 2 or 3	2784039
5	guideline$.mp. [mp=ab, hw, ti, sh, it, tn, ot, dm, mf, rw]	155070
6	convulsion$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	28116
7	epileps$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	116480
8	SEIZURES/ or seizure.mp.	96764
9	exp CONVULSION/	11166
10	exp SEIZURES/	63183
11	exp EPILEPSY/	146026
12	or/6-11	200901
13	4 and 5 and 12	30

Results

A total of 31 abstracts were reviewed from 170 titles. One paper was selected for further review. The hand search of journals and references identified no other papers for further review.
One paper was included in the final analysis.

Papers included in the final analysis are listed in table 18.3.ii

Study	Methods	Participants	Interventions	Allocation concealment	Outcomes	Results	Notes	Evidence level
Armon (108)	Pre and post guideline implementation study to assess the change in practice and outcome in children after a seizure.	Children (aged <15 years) attending the emergency department of a UK hospital in 1997 (before the guideline was introduced) and 1999 (after the guideline was introduced). Study period 4 months for both the pre and post implementation study.	Guideline dissemination and implementation, including the use of a care pathway. Guidance included the need for no investigations after a first "simple afebrile seizure".	The study was not randomised or blinded, and different doctors and nursing staff were taking part in the different arms of the study.	The number of investigations performed, the time spent in the emergency department, and the number of hospital admissions.	411 children enrolled: 212 pre-guideline and 199 post-guideline implementation. The number of investigations performed on these children was reduced, in particular a reduction in the number of U+Es (p=0.04), calcium (p=0.01) and magnesium (p=0.07). No increase in the re-admittance rate or other harms noted. Time in the department was reduced by 25 minutes. There was no change in admittance rates.	The guideline recommendation of no need for investigations after the first simple afebrile seizure improved throughput in the emergency department without affecting patient safety. There were cost savings associated with implementing this guideline.	Therapy 2c (Outcomes research)

Table 18.3.ii Papers included in the final analysis of which tests to perform on a child in a post convulsion state

18. Post convulsion state

Clinical Questions:

(iv) In children after a convulsion, what treatment is required?

Selection criteria
Criteria for choosing papers were drawn up before the search took place. Papers would be included if they were randomised controlled trials of therapies for children after a convulsion. Validation studies of guidelines for the management of children after a convulsion would also be included if they demonstrated benefit of following the guideline and gave advice on the treatment to use. Studies involving both children and adults were included if the results for children could be analysed separately.

Search
A review of the Cochrane library, MEDLINE (1966-present), EMBASE (1980-present), CINAHL (1982-present), British Nursing Index (1985-present) and AMED (1985-present) was performed using the search terms below. A review of the references of the selected papers for further evidence was included in the search strategy and a hand search of five key journals in the field in the previous 12 months.

Search filters

#	Search terms	No. of articles
1	RANDOMIZED CONTROLLED TRIAL.pt.	207645
2	CONTROLLED CLINICAL TRIAL.pt.	69541
3	randomized controlled trials.sh.	40656
4	random allocation.sh.	54187
5	double blind method.sh.	83813
6	single blind method.sh.	9333
7	or/1-6	354565
8	Animal.sh.	15966
9	human.sh.	5043029
10	8 not 9	12983
11	7 not 10	354565
12	clinical trial.pt.	432720
13	exp clinical trials/	573648
14	(clin$ adj25 trial$).ti,ab.	235335
15	((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.	168647
16	placebos.sh.	27397
17	placebo$.ti,ab.	187228
18	random$.ti,ab.	646809
19	research design.sh.	43470
20	or/12-19	1452441
21	20 not 10	1452302
22	21 not 11	1118878
23	comparative study.sh.	1296264
24	exp evaluation studies/	580326
25	follow up studies.sh.	307370
26	prospective studies.sh.	234810
27	(control$ or prospectiv$ or volunteer$).ti,ab.	3043825
28	or/23-27	4720246
29	28 not 10	4718813
30	29 not (11 or 22)	3921781
31	11 or 22 or 28	5396657
32	exp infant, newborn/ or exp infant/ or exp infants/	974282
33	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1498335
34	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1704979
35	32 or 33 or 34	2934196
36	convulsion$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	28116

37	epileps$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	116480
38	SEIZURES/ or seizure.mp.	96764
39	exp CONVULSION/	11166
40	exp SEIZURES/	63183
41	exp EPILEPSY/	146026
42	or/36-41	200901
43	post-ictal.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	443
44	31 and 35 and 42 and 43	6

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	936486
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1412651
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1611164
4	1 or 2 or 3	2784039
5	guideline$.mp. [mp=ab, hw, ti, sh, it, tn, ot, dm, mf, rw]	155070
6	convulsion$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	28116
7	epileps$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	116480
8	SEIZURES/ or seizure.mp.	96764
9	exp CONVULSION/	11166
10	exp SEIZURES/	63183
11	exp EPILEPSY/	146026
12	or/6-11	200901
13	4 and 5 and 12	30

Results

A total of 2 abstracts were reviewed from 36 titles. No papers were selected for further review. The hand search of journals identified no other papers for further review.
No papers were included in the final analysis.

19. No clinical clues to the cause

Clinical Questions:

(i) In children with a reduced conscious level and no clinical clues to the cause, what tests should be performed to determine the diagnosis?

Selection criteria
Criteria for choosing papers were drawn up before the search took place. Papers would be included if they were validation studies of guidelines for children with reduced conscious level other than the causes already identified (i.e. shock, sepsis, trauma, metabolic illness, intracranial infection, raised intracranial pressure, hypertensive encephalopathy, prolonged convulsion, post convulsion state). Diagnostic test studies for unknown causes of reduced conscious level were included.Studies involving both children and adults were only included if the results for children could be analysed separately.

Search
A review of the Cochrane library, MEDLINE (1966-present), EMBASE (1980-present), CINAHL (1982-present), British Nursing Index (1985-present) and AMED (1985-present) was performed using the search terms below. A review of the references of the selected papers for further evidence was included in the search strategy and a hand search of five key journals in the field in the previous 12 months.

Search filters

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	956588
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1465344
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1670568
4	1 or 2 or 3	2874741
5	exp COMA/ or exp GLASGOW COMA SCALE/	30780
6	exp confusion/ or exp coma/ or exp coma, post-head injury/	37862
7	exp Glasgow Coma Scale/	6836
8	5 or 6 or 7	44035
9	guideline$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	223821
10	validat$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	168454
11	9 or 10	386657
12	4 and 8 and 11	354

#	Search terms	No. of articles
1	exp infant, newborn/ or exp infant/ or exp infants/	956588
2	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1465344
3	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1670568
4	1 or 2 or 3	2874741
5	sensitiv$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1196235
6	(sensitivity and specificity).mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	247943
7	diagnosis.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	1764281
8	diagnostic $.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	236218
9	diagnosis,differential.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	265966
10	diagnos$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	2403697
11	test$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	2807626
12	investigation$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	541353
13	gold.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	68818
14	standard$.mp. [mp=ab, hw, ti, it, sh, tn, ot, dm, mf, nm]	744427
15	8 and 9	22794
16	or/5-12	2948991
17	15 or 16	3433790
18	exp COMA/ or exp GLASGOW COMA SCALE/	30780
19	exp confusion/ or exp coma/ or exp coma, post-head injury/	37862
20	exp Glasgow Coma Scale/	6836
21	or/18-20	44035
22	4 and 17 and 21	437

Results
A total of 23 abstracts were reviewed from 791 titles. No papers were selected for further review.
The hand search of journals identified no other papers for further review.
No papers were included in the final analysis.

19. No clinical clues to the cause

Clinical Questions:

(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?

Selection criteria
Criteria for choosing papers were drawn up before the search took place. Papers would be included if they were randomised controlled trials of therapies for children with a decreased conscious level other than the causes already identified (i.e. shock, sepsis, trauma, metabolic illness, intracranial infection, raised intracranial pressure, hypertensive encephalopathy, prolonged convulsion, post convulsion state). Validation studies of guidelines for the management of children with a decreased

conscious level would also be included if they demonstrated benefit of following the guideline and gave advice on the treatment to use. Studies involving both children and adults were included if the results for children could be analysed separately.

Search
A review of the Cochrane library, MEDLINE (1966-present), EMBASE (1980-present), CINAHL (1982-present), British Nursing Index (1985-present) and AMED (1985-present) was performed using the search terms below. A review of the references of the selected papers for further evidence was included in the search strategy and a hand search of five key journals in the field in the previous 12 months.

Search filters

#	Search terms	No. of articles
1	RANDOMIZED CONTROLLED TRIAL.pt.	207645
2	CONTROLLED CLINICAL TRIAL.pt.	69541
3	randomized controlled trials.sh.	40656
4	random allocation.sh.	54187
5	double blind method.sh.	83813
6	single blind method.sh.	9333
7	or/1-6	354565
8	Animal.sh.	15966
9	human.sh.	5043029
10	8 not 9	12983
11	7 not 10	354565
12	clinical trial.pt.	432720
13	exp clinical trials/	573648
14	(clin$ adj25 trial$).ti,ab.	235335
15	((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.	168647
16	placebos.sh.	27397
17	placebo$.ti,ab.	187228
18	random$.ti,ab.	646809
19	research design.sh.	43470
20	or/12-19	1452441
21	20 not 10	1452302
22	21 not 11	1118878
23	comparative study.sh.	1296264
24	exp evaluation studies/	580326
25	follow up studies.sh.	307370
26	prospective studies.sh.	234810
27	(control$ or prospectiv$ or volunteer$).ti,ab.	3043825
28	or/23-27	4720246
29	28 not 10	4718813
30	29 not (11 or 22)	3921781
31	11 or 22 or 28	5396657
32	exp infant, newborn/ or exp infant/ or exp infants/	974282
33	exp adolescent/ or exp adolescence/ or exp adolescent, hospitalized/	1498335
34	exp child/ or exp children/ or exp child, preschool/ or exp childhood/ or exp child, hospitalized/	1704979
35	32 or 33 or 34	2934196
36	exp COMA/ or exp GLASGOW COMA SCALE/	30780
37	exp confusion/ or exp coma/ or exp coma, post-head injury/	37862
38	exp Glasgow Coma Scale/	6836
39	or/36-38	44035
40	31 and 35 and 39	176

Results
A total of 17abstracts were reviewed from 176 titles. No papers were selected for further review. The hand search of journals identified no other papers for further review.
No papers were included in the final analysis.

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.

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