Management of Children and Young People with an acute decrease in conscious level

This Guideline and evidence detailed below was created using the RCPCH guideline 'The Management of Children and Young people with an acute decrease in conscious level, a national developed evidence-based Guideline for practitioners[49].

POPULATION

Children aged **>28 days** and **up to 18 years old.**

EXCLUDING

Pre-term infant survivors in NICU, Children with previously diagnosed conditions, Children who score ≤14 on GCS on a daily basis, children with agreed management plan for acute illness[2].

Assessment

- **At First Assessment and Hourly record Respiratory rate, SpO2, Heart Rate, Blood pressure, temperature, physical state/appearance.**
- **Continuously monitor SpO2 and Cardiac monitoring.**

A to E assessment –

DON'T EVER FORGET GLUCOSE! (Important cause of decreased conscious level in children).
Capillary blood Glc should be done within 15 minutes of presentation[1].

Neurological assessment

Glasgow Coma Scale		
EYES	**MOTOR**	**VOICE**
4 **Open**	**6** Obeys commands	**5** Converses
3 **To command**	**5** Localises pain	**4** Confused
2 **To pain**	**4** Flexion Withdrawal	**3** Inappropriate words
1 **No Response**	**3** Abnormal Flexion	**2** Incomprehensible
	2 Abnormal Extension	**1** No Response
	1 No Response	
Glasgow Coma Scale Modification for children <5 years		
4 **Open**	**6** Normal spontaneous movements	**5** Alert, babbles, coos, words or sentences to usual ability
3 **To command**	**5** Localises to supraorbital pain or withdraws from touch	**4** Less than usual ability, irritable cry
2 **To pain**	**4** Withdraws from nailbed pain	**3** Cries to pain
1 **No Response**	**3** Abnormal Flexion	**2** Moans to pain
	2 Abnormal Extension	**1** No Response
	1 No Response	

AVPU			
A = **Alert**	**V** = Verbal	**P** = Responds to Pain	**U** = Unresponsive

Important Features in History

Consider whether the following are before or after presentation.

- Vomiting
- Headache
- Fever
- Convulsions
- Alternating periods of consciousness
- Trauma
- Ingestion of medication, alcohol or recreational drugs
- Presence of any medications in the child's home
- Any infant deaths in the family
- Duration of symptoms
- DON'T FORGET TO CONSIDER POSSIBILITY OF NON-ACCIDENTAL INJURY

Investigations

Point of Care	Laboratory	Saved Samples
Capillary Blood Glucose	Lab Glucose	10ml urine (inc. for toxicology)
Blood Gas (CBG or venous– pH, pCO2, Base excess, lactate)	FBC and Blood Film	Consider separating and freezing plasma sample
Urine Dipstick	U&E's	Consider saving serum sample
	LFT's	
	Plasma Lactate	
	Plasma Ammonia (must be venous or arterial)	
	Blood Cultures	

CRANIAL IMAGING

URGENT CT/MRI IF SUSPECTED RAISED INTRACRANIAL PRESSURE[2]

BE AWARE THAT NORMAL CT DOES NOT EXCLUDE RAISED ICP

Consider CT/MRI if suspected diagnosis is:

- Unknown
- Intracranial abscess

LUMBAR PUNCTURE

Perform LP if working diagnosis[3-6]:

- Viral Encephalitis, inc.Herpes Simplex Encephalitis
- TB Meningitis

Consider performing LP if working diagnosis:

- Sepsis
- Bacterial Meningitis
- Unknown

Only perform LP if no contraindications

****WARNING****

Contraindications to LP[8-11]…

- Signs of Raised ICP
- GCS of ≤8
- Deteriorating GCS
- Focal Neurological Signs
- Seizure >10 minutes with GCS ≤12
- Shock
- Clinical Evidence of Systemic Meningococcal Disease
- A CT or MRI scan suggesting blockage or impairment of the cerebrospinal fluid pathways

Beware performing LP in children with abnormal clotting

ANALYSIS[7]

- Microscopy (urgent), Culture and Sensitivity, Gram stain
- Glucose ***Compare to plasma Glc***
- Protein
- PCR for Herpes Simplex [3-6], PCR for other viruses
- Opening CSF pressure
- Consider analysing cerebrospinal fluid culture for mycobacterium tuberculosis when clinically suspected

Good practice to take sample to store for future Investigation

Be aware, the decision to perform a lumbar puncture in a child with a decreased conscious level should be made by an experienced paediatrician or consultant with paediatric experience who has examined the child.

Management of Decreased Conscious Level

Consider starting concurrent management strategies in a child with a decreased conscious level to treat the potential different causes, whilst waiting for test results to confirm the most likely diagnosis.

Diagnoses covered in this Guideline:

- **Circulatory Shock**
- **Sepsis**
- **Trauma**
- **Metabolic diseases** – hypoglycaemia, hyperammonaemia
- **Intracranial infection** – Bacterial meningitis, encephalitis, intracranial abscess, TB meningitis
- **Raised Intracranial pressure**
- **Prolonged Convulsion and Post convulsion state**
- **Alcohol Intoxication**

Diabetic Ketoacidosis and Peri-arrest management are NOT covered within this guideline.

CIRCULATORY SHOCK

**Shock not a diagnosis in itself – consider requesting core Ix to determine cause*

Assessment[13]

Mottled, Cool extremities, diminished peripheral pulses, ↓ Systolic BP, ↓Urine output

Differential diagnosis

Sepsis, Trauma, Anaphylaxis, Heart Failure

Initial Management[12, 14-20]

Fluid Bolus 20ml/kg Isotonic fluid *(10ml/kg if shock present in child with DKA or raised ICP)*

Re-assess[21-24]

↓ Tachycardia, ↓ Prolonged CRT, ↑ GCS, ↑ BP to normal, ↓Lactate &/or improvement in Base Excess, ↑Urine output

If more than 40ml/kg of fluid bolus has been given, consider

- *Intubation and Ventilation (to prevent uncontrolled pulmonary oedema)*
- *Starting drug treatment to support circulation*
- *Referral to PICU/HDU*

SEPSIS *Feverish Illness in Children (<5 years) Guideline*

Assessment[24-33] *(2 or more of the following OR Non-blanching/purpuric rash alone)*

Temp ≥38°c or ≤35.5, ↑HR, ↑RR, WCC >12x10^9/L or <4x10^9/L, Non-blanching rash/Purpuric Rash.

Investigation

Core Investigations + Consider the following…

- **CXR**
- **Urine Culture (If dip +ve/RHC Guideline)**
- **PCR (meningococcus and pneumococcus)**
- **Coagulation studies**
- **Skin swab if inflammation**
- **Joint aspiration if signs of septic arthritis**
- Consider Thick and thin film for malarial parasites if foreign travel to endemic area

Initial Management

- **Intravenous Broad Spectrum Antibiotics as per local guidelines.** *If possible, after appropriate cultures.*
- **Consider review by experienced paediatrician within 1st hour of presentation**

TRAUMA

Head Injury and Trauma guidelines

Assessment

Record History for evidence of trauma and Examine for evidence of trauma.
If head injury and impaired consciousness (GCS <15), child should be assessed immediately[35]

Investigation

Request Core investigations to detect underlying medical cause of trauma
Trauma may be secondary to medical condition!! (e.g. child became unconscious and therefore accidental trauma!)

Initial Management

Manage a child with a decreased conscious level and evidence of trauma according to Local protocol, Advanced Paediatric Life Support[34] and the NICE Head injury Guidelines[35]

HYPOGLYCAEMIA - See *Hypoglycaemia management Guideline*

Assessment

Capillary Blood Glucose – *Aim to do within 15 minutes of presentation with decreased conscious level[1].*

Investigation

Paediatric Hypoglycaemia grab bag. *Investigations Ideally taken before treatment given.*
Urine Ketones and Urinary Organic Acids

Initial Management

MANAGE AS PER LOCAL PROTOCOL
If not able to tolerate oral fluids

- **IV 2mg/kg 10% Dextrose Bolus followed by continuous infusion 2-5ml/kg/hr 10% dextrose.**
- **IM Glucagon**

Recheck BM in 30 mins then hourly. AIM BM 4-8mmol/L.

HYPERAMMONAEMIA

Assessment

Consider using plasma ammonia threshold of >100micromol/L to define abnormal levels[38-40]

Investigation

Plasma ammonia sample from free-flowing venous sample should be taken immediately to the Laboratory.
Inform in advance of arrival. If delay over 10 minutes expected, transport sample on ice. Even if delayed sample should be analysed and result fed back urgently. If result >100micromol/L repeat sample should be sent ASAP without delay.

Initial Management

If Ammonia plasma level >100micromol/L or higher, discuss immediately with metabolic expert

BACTERIAL MENINGITIS

Assessment

Clinical signs and symptoms can include[12, 36-37]:

- **Non-blanching rash**
- **Stiff neck**
- **Altered mental state/Unconsciousness**
- **Shock**
- **Back Rigidity**
- **Bulging fontanelle**
- **Photophobia**
- **Kernig's sign**
- **Brudzinski's sign**
- **Toxic/moribund state**
- **Paresis**
- **Focal neurological deficit including cranial nerve involvement and abnormal pupils sizes**

Detailed list of non-specific symptoms – NICE guidance on Bacterial Meningitis and Meningococcal Septicaemia[12]

Investigation

Consider carrying out Core Investigations

Consider carrying out Lumbar Puncture if no contraindications[12]

Initial Management

Treat according to local antibiotic guidelines

Can refer to NICE guidance[12] for further advice on management.

VIRAL ENCEPHALITIS

Assessment[41]

Consider possibility of viral encephalitis, including herpes simplex encephalitis (HSE), if a child with a decreased conscious level has one or more of the following:

- **Focal neurological signs**
- **Fluctuating conscious level, for 6 hours or more**
- **Previous contact with herpetic lesions**
- **A prolonged convulsion with no obvious precipitating cause**
- **No obvious clinical signs pointing towards the cause**

Investigation

Confirm the clinical suspicion of Herpes Simplex Encephalitis by a positive CSF PCR result for herpes simplex virus DNA[3,5]

Initial Management – *Do not delay Rx if Lumbar puncture contraindicated*

If HSE is clinically suspected, administer IV Aciclovir

- **20mg/kg every 8 hours children aged 1-3 months**
- **500mg/m^2 3 times a day if after 3 month – 12 years**
- **10mg/kg every 8 hours for children >12 years.**

ALWAYS CONSULT THE BNF FOR CHILDREN

INTRACRANIAL ABSCESS

Assessment

Consider Intracranial abscess if there are:

- **Focal neurological signs +/- signs of sepsis**
- **Signs of raised ICP**

Investigation

Consider using intracranial imaging

Initial Management

- **Consider administering broad spectrum antibiotics** *(after blood cultures have been taken if possible)*[44]**.**
- **If Intracranial abscess diagnosed, obtain advice urgently from paediatric neurosurgeon.**

TUBERCULOUS MENINGITIS

Assessment

Consider Tuberculous meningitis to be the diagnosis if:

- **There has been contact with a case of pulmonary tuberculosis**

Investigation

Consider core investigations + Lumbar Puncture. Consider tuberculous meningitis if:

- **CSF opening pressure high**
- **CSF cloudy or yellow**
- **Contains slightly increased cells (<500), which are lymphocytes**
- **Low or very low CSF/plasma glucose ratio (<0.3)**
- **High or very high protein (1-5g/L)**

Initial Management

Treat a child with suspected tuberculous meningitis according to NICE Tuberculous Guideline[45]

RAISED INTRACRANIAL PRESSURE

Assessment[12]

- **Reduced or fluctuating level of consciousness**
- **Relative bradycardia and hypertension**
- **Unequal/dilated/poorly responsive pupils**
- **Abnormal posture/posturing**
- **Focal Neurological signs**
- **Papilloedema**
- **Abnormal 'doll's eye' movements**

Investigation

Consider core investigations and urgent intracranial imaging (after discussing acute managing with intensive care). ***NORMAL CT SCAN DOES NOT RULE OUT RAISED ICP****

Initial Management

Head positions to prevent coning in a child with raised ICP

- Position the patient's head in the midline
- Angle patient's head up at 20 degrees above the horizontal

If Raised ICP confirmed

- Avoid inserting Central Venous lines in neck
- Maintenance fluids *should not be* hypotonic (maintenance fluids need to be agreed at a local level)

Consider sedation, intubation and ventilation to maintain the $PaCO_2$ between 4.5 and 5.0 kPa[35] in a child with clinical diagnosis of raised ICP *(before imaging).*

HYPERTENSIVE ENCEPHALOPATHY

Assessment *Check a four-limb blood pressure*

In a child with hypertension and decreased conscious level, consider:

- **Signs of raised ICP**
- **Papilloedema**

In a child with decreased conscious level, hypertension is defined as Systolic BP >95th centile for age on TWO separate readings

Investigation

Distinguishing between hypertensive encephalopathy and hypertension secondary to raised ICP is crucial for correct management decisions.

Initial Management

Consider seeking urgent help from a paediatric nephrologist or intensivist when presented with a child with hypertension and no other caused for decreased conscious level

PROLONGED CONVULSION – See Status Epilepticus Management guideline

Assessment

Convulsion lasting longer than 5 minutes

Investigation

Consider core investigations at first clinical assessment in a child not known to have epilepsy.
Consider checking plasma calcium and magnesium levels in prolonged convulsion

Initial Management

Consider treating child with a convulsion lasting >5 minutes[34,46] in line with Status Epilepticus Management guideline.

Consider discussing treatment with paediatric intensivist if child has:

- Plasma Sodium <125mmol/L
- Ionized Calcium level <0.75mmol/L or plasma calcium level <1.7mmol/L
- Plasma magnesium <0.65mmol/L

And convulsion ongoing despite anticonvulsant treatment

POST CONVULSIVE STATE:

- **Detailed history and examination within first hour of post-convulsive state**
- **Consider observing child with a normal capillary glucose and not performing further tests during the first hour of the post-convulsive state**
- **Reassess a child following convulsion if they have not awoken from the post-convulsive state within one hour – if the child has not recovered normal consciousness, consider core investigations.**

ALCOHOL INTOXICATION

Assessment

History of alcohol intoxication

Consider identifying all likely substances or drugs that may be contributing to decreased conscious level

Investigation

Consider carrying out a blood alcohol test in a child with a decreased conscious level with suspected alcohol intoxication[47,48]

Initial Management

Consider the need to treat the following in a child with a decreased conscious level and suspected alcohol intoxication:

- **Hypoglycaemia with Intravenous glucose and maintenance dextrose/saline**
- **Respiratory failure and/or aspiration pneumonia**
- **Hypotension**
- **Other drugs ingested at the same time e.g. Opiates, benzodiazepines, paracetamol.**

Avoid emetics (in case of aspiration)

If the cause of decreased conscious level remains unclear:

- **Consider performing additional tests in discussion with a specialist e.g. neurologist or metabolic expert** (dependent on clinical picture) **after reviewing core investigations. This may include Cranial CT or MRI, Lumbar Puncture, Urine toxicology, Urine organic and plasma aminoacids, Plasma lactate.**

- **Consider performing EEG after reviewing core investigations, CT or MRI scan results or initial CSF results**

Evidence Base

This Guideline and evidence detailed below was created using the RCPCH guideline 'The Management of Children and Young people with an acute decrease in conscious level, a national developed evidence-based Guideline for practitioners.'

- Capillary Blood Glucose should be carried out within 15 minutes of presentation. An audit completed in 2011[1] found this to be an achievable time frame for capillary blood glucose monitoring, which was in clear agreement with the Delphi survey for the RCPCH guideline.

- A study has shown that If intracranial pressure is greater than 25mmHg sensitivity of CT scan 97.7% and specificity 60.6% for diagnosing raised ICP[2]. MRI should also be considered as an alternative to CT scan. Cross-referral to the NICE Guideline on bacterial meningitis and meningococcal septicaemia[3] helped to inform this recommendation, alongside the Delphi consensus.

- RCPCH guideline suggests Lumbar Puncture should be performed if Viral Encephalitis, (inc.Herpes Simplex Encephalitis) and TB Meningitis as studies [3-6] have shown high diagnostic accuracy of PCR on Cerebrospinal fluid for herpes simplex encephalitis and tuberculous meningitis. (Delphi panel consensus was used to add other diagnoses such as sepsis, bacterial meningitis and causes unknown).

- Initial tests that should be carried out on CSF showed evidence supporting microscopy and glucose testing when used as part of a clinical decision rule[7].

- RCPCH guideline used a Delphi panel consensus for list of contraindications to LP with supporting evidence from studies that outlined risk factors associated with children who died after having LP performed[8-11]. The updated guideline cross referenced the NICE guideline on bacterial meningitis and meningococcal septicaemia[12].

- RCPCH guideline used information from a cohort study validating septic shock[13] guidance in the USA alongside the original 2005 guideline regarding reduced conscious level to identify features to be aware of in circulatory shock.

- The previous RCPCH 2005 guideline recommendation did not suggest that either crystalloid or colloid fluid should be used preferentially in the treatment of shock, based on 3 systematic reviews[14-16]. The evidence search update for the 2015 RCPCH guideline found further evidence in agreement with this[17-20]. This is in line with NICE bacterial meningitis and meningococcal septicaemia guideline[12].

- Evidence from 2 studies[21,22] showed higher shock index was related to increased mortality. One retrospective chart analysis concluded that lactate can be used as a predictor of outcome in children with septic shock[23]. This evidence is in line with 'Surviving Sepsis Campaign Guideline.'[24]

- The recommendation from the RCPCH guideline to consider intubation, use of drugs to support circulation and referral to HDU/ITU if >40ml/kg fluid has been given is in line with NICE 'Bacterial meningitis and meningococcal septicaemia in children' Guideline[12.]

- The initial recommendation of the 2005 RCPCH guideline identifying signs of sepsis was based on multiple studies[25-32] that investigated whether fever in children will have a 'serious bacterial infection grown on culture.' To ensure the recommendation was up to date in the 2015 guideline, the Surviving sepsis campaign[24] and the NICE Feverish illness in children Guideline[33] was used, alongside Delphi consensus survey to identify features suggesting sepsis.

- RCPCH guideline states 'Traumatic causes of decreased conscious level in children were determined to be outside the scope of the Guideline'. Therefore, they have referenced Acute Paediatric Life support[34] and NICE Head Injury guidelines[35] as guidelines for management of decreased conscious level relating to trauma.

- With meningitis, the RCPCH guideline states specific signs and symptoms of bacterial meningitis that were validated by 2 systemic reviews[36, 37] and then adjusted alongside NICE guidance[12]. The Guideline development group pointed out that there is not enough evidence to suggest a single clinical feature is distinctive to bacterial meningitis and therefore included the NICE guideline[12] for additional non-specific signs.

- The British Inherited Metabolic Diseases group guideline[38,39], states plasma ammonia concentrations are usually >100micromol/L during an episode of decompensation and any patient with values above 200micromol/L require urgent treatment[40]. The RCPCH guideline recommends the threshold of 100micromol/L in a child with decreased conscious level should be discussed with a metabolic expert to to ensure safest practice.

- The signs and symptoms that could identify a diagnosis of Viral encephalitis (especially Herpes simplex encephalitis) which are included in the RCPCH guideline were developed using information from the Association of British Neurologists, British Paediatric Allergy Immunology and Infection Group's Guideline[41]. Although during the Delphi panel survey, neurologists on the panel commented that HSE is a diagnosis of exclusion.

- The 2005 RCPCH decreased conscious level guideline considered 2 studies comparing the use of a PCR of CSF to a brain biopsy to base the recommendation on[3,5]. The gold standard investigation was previously a brain biopsy, however these comparative studies showed PCR of CSF to be less invasive, but also highly sensitive and specific to diagnose early HSE.

- The RCPCH decreased conscious level guideline based the original recommendation on 2 studies[42, 43] that demonstrated that aciclovir is an effective treatment for HSE. Doseages are based on the British National Formulary for Children guidance.

- Broad spectrum antibiotics should be considered in a diagnosis of intracranial abscess as the majority are caused by bacterial infections[44].

- In a child with decreased conscious level and raised ICP, the RCPCH guideline recommends sedation, intubation and ventilation to maintain PaCO2 between 4.5 and 5.0 kPa, a range which is in line with NICE guidelines[35].

- The RCPCH guideline recommends considering treating a child with a convulsion lasting longer than 5 minutes, which reflects NICE epilepsy guidance[46] and APLS guidance[34].

- Two studies[47,48] were referenced in the RCPCH guideline to determine whether testing blood alcohol concentration was useful in diagnosing alcohol intoxication. The first study[47] found serum alcohol concentration alongside physician's clinical judgement led to an average 67.7% accuracy to determine alcohol intoxication severity. The second study[48] found patients who had an alcohol related diagnosis in medical records tended to have a higher blood alcohol concentration. The recommendation in the RCPCH guideline suggests considering the use of blood alcohol tests as they may be beneficial but are not always necessary. Its use should be based on individual clinical judgement.

References

1. Smith, S. A., Long, C. N., Denney, G., et al. Care of children and young people with a decreased conscious level (multi-site audit 2010-2011). Archives of Disease in Childhood 2012;97:A143-A144.
2. Hirsch W, B. R., Behrmann C, Schobess A, Spielmann R. Reliability of cranial CT versus intracranial pressure measurement for the evaluation of generalised cerebral oedema. Pediatric Radiology 2000;30:439-443.
3. Aurelius E, J. B., Skoldenberg B, Staland A, Forsgren M. Rapid diagnosis of herpes simplex encephalitis by nested polymerase chain reaction assay of cerebrospinal fluid. Lancet 1991;337:189- 192.
4. Anderson N, P. K., Croxon M. A polymerase chain reaction assay of cerebrospinal fluid in patients with suspected herpes simplex encephalitis. Journal of Neurology, Neurosurgery, and Psychiatry 1993;56:520-525.
5. Troendle-Atkins J, D. G., Buffone G. Rapid diagnosis of herpes simplex virus encephalitis by using the polymerase chain reaction. Journal of Pediatrics 1993;123:376-380.
6. Lakeman F, W. R. Diagnosis of herpes simplex encephalitis: application of polymerase chain reaction to cerebrospinal fluid from brain-biopsied patients and correlation with disease. Journal of Infectious Diseases 1995;171:857-863.
7. Oostenbrink R, M. K., Derksen-Lubsen G, Grobbee D, Moll H. A diagnostic decision rule for management of children with meningeal signs. European Journal of Epidemiology 2004;19(2):109- 116.
8. Newton C, K. F., Winstanley P, et al. Intracranial pressure in African children with cerebral malaria. Lancet 1991;337:573-576.
9. Rennick G, S. F., de Campo J. Cerebral herniation during bacterial meningitis in children. British Medical Journal 1993;306:953-955.
10. Akpede G, A. J. Cerebral herniation in pyogenic meningitis: prevalence and related dilemmas in emergency room populations in developing countries. Developmental medicine and child neurology 2000;42:462-469.
11. A.L.S.G. Advanced Paediatric Life Support -The Practical Approach. BMJ. 2004.
12. National Institute for Health and Care Excellence (2010). Bacterial meningitis and meningococcal septicaemia: Management of bacterial meningitis and meningococcal septicaemia in children and young people younger than 16 years in primary and secondary care [CG102].
13. Larsen, G. Y., Mecham, N., Greenberg, R. An emergency department septic shock protocol and care guideline for children initiated at triage. Pediatrics 2011;127:e1585-e1592.
14. Roberts I, A. P., Bunn F, Chinnock P, Ker K, Schierhout G. Colloids versus crystalloids for fluid resuscitation in critically ill patients. The Cochrane Database of Sytematic Reviews 2004;(4).
15. Alderson P, B. F., Li Wan Po A, Li L, Roberts I, Schierhout G. Human albumin solution for resuscitation and volume expansion in critically ill patients. The Cochrane Database of Sytematic Reviews 2004;(4).
16. Bunn F, A. P., Hawkins V. . Colloid solutions for fluid resuscitation. The Cochrane Database of Sytematic Reviews 2003;(1).
17. Chopra, A., Kumar, V., Dutta, A. Hypertonic versus normal saline as initial fluid bolus in pediatric septic shock. Indian Journal of Pediatrics 2011;78:833-837.
18. Upadhyay, M., Singhi, S., Murlidharan, J., et al. Randomized evaluation of fluid resuscitation with crystalloid (saline) and colloid (polymer from degraded gelatin in saline) in pediatric septic shock. Indian Pediatrics 2005;42:223-231.
19. Ford, N., Hargreaves, S., Shanks, L. Mortality after fluid bolus in children with shock due to sepsis or severe infection: a systematic review and meta-analysis. PLoS ONE [Electronic Resource] 2012;7:e43953.
20. Abulebda, K., Cvijanovich, N. Z., Thomas, N. J., et al. Post-ICU admission fluid balance and pediatric septic shock outcomes: A risk-stratified analysis. Critical Care Medicine 2014;42:397-403.
21. Rousseaux, J., Grandbastien, B., Dorkenoo, A., et al. Prognostic value of shock index in children with septic shock. Pediatric Emergency Care 2013;29:1055-1059.
22. Yasaka, Y., Khemani, R. G., Markovitz, B. P. Is shock index associated with outcome in children with sepsis/septic shock? Pediatric Critical Care Medicine 2013;14:e372-e379.
23. Kim, Y. A., Ha, E. J., Jhang, W. K., et al. Early blood lactate area as a prognostic marker in pediatric septic shock. Intensive Care Medicine 2013;39:1818-1823.
24. Surviving Sepsis Campaign. Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock. Critical Care Medicine 2013.

25. Dagan R, S. S., Philip M, Shahack E. Ambulatory care of febrile infants younger than 2 months of age classified as being at low risk for having serious bacterial infections. Journal of Pediatrics 1988;112:355-360.

26. Chiu C, L. T., Bullard M. Application of criteria odentifying febrile outpatient neonates at low risk for bacterial infections. Pediatric Infectious Disease Journal 1994;13(11):946-949.

27. Jaskiewicz J, M. C., Richardson A, et al. Febrile infants at low risk for serious bacterial infection -an appraisal of the Rochester criteria and implications for management. Paediatrics 1994;94(3):390- 396.

28. Chiu C, L. T., Bullard M. Identification of febrile neonates unlikely to have bacterial infections. Pediatric Infectious Disease Journal 1997;16(1):59-63. 53. Kuppermann N, F. G., Jaffe D. Predictors of occult pneumococcal bacteraemia in young febrile children. Annals of Emergency Medicine 1998;31(6):679-687.

29. Bachur R, H. M. Predictive model for serious bacterial infections among infants younger than 3 months of age. Pediatrics 2001;108(2):311-316.

30. Ayoola O, A. A., Osinusi K. Predictors of bacteraemia among febrile infants in Ibadan, Nigeria. J Health Popul Nutr 2002;20(3):223-229.

31. Byington C, E. R., Hoff C, et al. Serious bacterial infections in febrile infants 1 to 90 days old with and without viral infections. Paediatrics 2004;113(6):1662-1666.

32. Bang A, B. A., Reddy H, et al. . Simple clinical criteria to identify sepsis or pneumonia in neonates in the community needing treatment or referral. Pediatric Infectious Disease Journal 2005;24(4):335- 341.

33. National Institute of Clinical Excellence (2013). Feverish illness in children: Assessment and initial management in children younger than 5 years [CG160]

34. Advanced Life Support Group. Advanced Paediatric Life Support: The Practical Approach. BMJ Books. 2011.

35. National Institute of Clinical Excellence (2023). Head injury: Assessment and early management [NG232].

36. Best, J., Hughes, S. Evidence behind the WHO guidelines: Hospital care for children - What are the useful clinical features of bacterial meningitis found in infants and children? Journal of Tropical Pediatrics 2008;54(2):83-86.

37. Curtis, S., Stobart, K., Vandermeer, B., et al. Clinical features suggestive of meningitis in children: A systematic review of prospective data. Pediatrics 2010;126(5):952-960

38. BIMDG (2008). Hyperammonaemia due to transport defects: standard protocol.

39. BIMDG. Hyperammonaemia due to transport defects: A&E protocol. 2008.

40. BIMDG (2008). Undiagnosed hyperammonaemia – diagnosis and immediate management.

41. Association of British Neurologists and British Paediatric Allergy Immunology and Infection Group: Kneen R et al. Management of suspected viral infection in chidlren. Journal of Infectious Diseases 2011;64:449-472.

42. Skoldenberg B, A. K., Burman L, et al. Acyclovir verses vidarabine in Herpes simplex encephalitis. Randomised multicentre study in consecutive Swedish patients. Lancet 1984;2(8405):707-711.

43. Wintergerst, U., Kugler, K., Harms, F., et al. Therapy of focal viral encephalitis in children with aciclovir and recombinant beta-interferon - Results of a placebo-controlled multicenter study. European Journal of Medical Research 2005;10(12):527-531.

44. Tekkok I, E. A. Management of brain abscess in children: review of 130 cases over a period of 21 years. Childs Nervous System 1992;8(7):411-416.

45. National Institute of Clinical Excellence (2016). Tuberculosis [NG33], NICE.

46. National Institute of Clinical Excellence (2012). The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care [CG137].

47. Tonisson, M., Tillmann, V., Kuudeberg, A., et al. (2013). Acute alcohol intoxication characteristics in children. Alcohol and Alcoholism. 48: 390-395.

48. Patients in the emergency department. Academic Emergency Medicine 1998;5:607-612.

49. Royal College of Paediatrics and Child Health (2019). The management of children and young people with an acute decrease in conscious level. A nationally developed evidence-based Guideline for practitioners.