Handbook of Pediatric Neurological Emergency

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by

Muhammad Saeed

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DEDICATION

To my Loving family:

To my wife ***Dr. Saima Saeed***, My Son ***Muhammad Haider Saeed*** and My daughter ***Mahnoor Saeed*** every step of the way you have been there to support.

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PREFACE

Pediatric neurological problems or issues in pediatric emergency department constitute 20-30% of total pediatric emergency patients. This shows that child neurological diseases account for a large volume of pediatric emergencies. There is thus a great need for doctors to have access to updated knowledge helping in diagnosis and management of child neurological emergencies. However, I could not find any such book during my residency or afterwards or even in present day publications. Although there are many good books on the topic of pediatric emergency, they do not cover the pediatric neurology emergency topics sufficiently.

Considering the importance of child neurology, both in volume and in severity of child emergencies, and neurological consultations from general pediatricians and pediatric intensivists I decided to write a book on child neurology emergencies management.

This book covers the most common topics of child neurological issues comprehensively and should help the clinicians, Pediatric residents, Pediatric Neuorology residents, to recognize various child neurological problems and their management. This book is by no means an alternative to standards textbooks of Pediatrics Neurology and readers can use as quick practical guidelines in Pediatric neurology.

We urge the doctors to use this book as a guide but to always seek expertise as available and to use their best medical judgment, observation, and re-evaluation as appropriate to each clinical case.

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REVIEWS



Studying and managing Pediatric neurological emergencies is a challenge because of its complexity and ever-changing nature. With new research, evolving clinical experience, and an increase in the number of available medications, our knowledge in the management of pediatric neurological emergencies has been widening. This wonderful book is a bequest for pediatricians and neurologists managing emergencies. The author in this book provides a practical and concise, yet comprehensive review of management strategies in the diagnosis, workup, and treatment of such conditions. It is an invaluable reference for pediatricians. The information is synopsized for easy access providing assistance in quicker diagnostic strategies and the supplemented tables help greatly in devising a treatment plan.

This book benefits all physicians who work and manage pediatric patients with neurological conditions in the emergency rooms. The clear guidelines and practical approaches to various conditions will be useful to a wide variety of clinicians ranging from residents in training to the consultants.

Prof. Dr. Nadeem Shabbir
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This is a well-written reference for neurological emergencies in the emergency department. It would have been great if I had it when I started my career fifteen years ago in the pediatric emergency department. Still, with my experience I find myself referencing the tables and figures for quick facts during pediatric neurological emergencies. This book would be an asset for any resident or other practitioner working in any emergency department or urgent care setting.

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Chapter

01

Neonatal Seizures

STATUS EPILEPTICUS

Status epilepticus (SE) is a serious and often life-threatening medical emergency and requires prompt intervention. Although definitions vary, SE generally refers to a single unremitting seizure lasting longer than 30 minutes or frequent clinical seizures without an interictal return of consciousness or an ictal fraction greater than 50% on EEG and impending SE refers to seizures lasting longer than five minutes. In practice, treatment for SE should begin when impending SE is recognized. A precise definition of non-convulsive status epilepticus is (NCSE) is lacking.

TREATMENT

The treatment of neonatal seizures is related, at least in part, to an understanding of the underlying cause in each infant, and correction of identified metabolic derangements, along with ensuring adequate ventilation and support of circulation, should precede consideration of AED therapy.

Acute AED Therapy

- The ideal result in the acute treatment of electro-clinical seizures is the cessation of both the clinical and the electrical seizures. However, a typical response by electro-clinical seizures to acute AED therapy is the initial control of the clinical seizures with the persistence of the electrical seizure activity. With additional doses, the electrical seizures may be controlled. However, there are also instances in which the EEG seizures cannot be controlled despite increasing doses of the initial AED and addition of others.
- The role of continuous EEG monitoring in directing treatment is also debated.
- Current practice consists of acute AED therapy until clinical seizures are controlled, with the first AED given in doses to achieve serum levels in the high therapeutic range or to the maximum tolerated dose. This is followed by the second AED. A benzodiazepine may also be given if needed. If EEG is recorded during acute treatment, the same AED strategy is followed to treat the clinical seizures. However, if the clinical seizures are controlled and the electrical seizures persist, the AEDs are given in a high therapeutic range but no further drugs are added, since the electrical seizure discharges are most often resistant to further AED therapy. Additional drugs are not given, since they are likely to provide very limited additional benefit while increasing the chances of the occurrence of adverse effects.

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Chronic AED Therapy

- There are no well-defined criteria to determine which neonates require chronic AED therapy after acute seizures are controlled or the duration of such treatment.
- AED management is based on pathophysiology of the clinical seizures, seizure duration, and seizure frequency.
- Begin AED therapy with a first-line drug titrating to maximal tolerated dosages to control clinical seizures (if EEG is not available) or electrical seizures if EEG is available.
- Initiate second-line AED if first-line AED fails
- When chronic therapy is considered, maintenance doses of either, Phenobarbital or phenytoin are given (3 to 4 mg/kg per day for both drugs), and serum levels are monitored. Reported schedules for chronic AED treatment range from one week up to 12 months after the last seizure.
- If the infant is taking medication and seizures recur, increase the dose back to levels at which no seizures occurred, and then attempt to discontinue medications in 1 to 2 months.
- If repeated attempts to discontinue medications have been made with no success, the child may have epilepsy: attempt referral to a neurologist.
- Limited consensus exists concerning the duration of long-term AED therapy and controlling seizures. However, after medication is initiated and the seizures are controlled, AEDs can be discontinued gradually, decreasing medication dose weekly
- Currently utilized schedule is to withdraw AEDs two weeks after the infant's last seizure. This is often done just prior to the recording of an EEG that demonstrates no electrical seizure activity.

CONVULSIVE STATUS EPILEPTICUS

- Place IV line
- Administer O_2
- Monitor vital signs: pulse, BP, pulse oximeter
- Consider/obtain: electrolytes, blood glucose
- Treat metabolic derangements (hypoglycemia, hyponatremia)
- History
- Clinical examination

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Antiepileptic medications for the treatment of neonatal seizures

- Lorazepam 0.05 to 0.1 mg/kg (IV) (over 2-to 5-min period). Careful monitoring of cardiorespiratory status required
- Diazepam 0.25 mg/kg IV (bolus) 0.5 mg/kg (rectal)
- Phenobarbital (1st choice) 20 mg/kg IV/IM (≤40 mg/kg). Maintenance: 3–5 mg/kg/24 h divided every 12 h IV, IM, PO
- Phenytoin or Fosphenytoin (2nd choice, use if phenobarbital not available or not successful) 15 to 20 mg/kg IV (over 30 min period). Maintenance: 3–8 mg/kg/24 h divided every 8 to 12 h IV/PO

- Status epilepticus that had been refractory to conventional therapy, treatment with midazolam is recommended initial intravenous bolus of 0.06 to 0.15 mg/kg, followed by continuous infusion 0.1 to 0.4 mg/kg/hour, (1-7 mcg/kg/minute); maximum reported rate: 1.1 mg/kg/hour (18 mcg/kg/minute) until a favorable response.
- Lidocaine infusion can also be effective for treatment of refractory neonatal seizures, but concerns about cardiac toxicity have limited widespread adoption of this agent (with continuous cardiac monitoring, that the infusion be stopped if any cardiac arrhythmia develops, that it be used only for seizures that have not responded to phenobarbital and midazolam, and that it not be used in infants with congenital heart disease or prior treatment with phenytoin). A recent European study provided a detailed protocol that recommended a loading dose of 2 mg/kg in 10 minutes, followed by the continuous infusion of 6 mg/kg per hour for 6 hours, 4 mg/kg per hour for 12 hours, and finally 2 mg/kg per hour for 12 hours.
- The intravenous formulation of levetiracetam is gaining acceptance for rapid treatment of seizures and status epilepticus; there is insufficient information about pharmacokinetics and safety in neonates to recommend its utilization currently.
- Systematic assessment of AED efficacy for treatment of neonatal seizures is extremely challenging and very limited data are available. There is consensus that such studies need to incorporate continuous EEG monitoring, both for confirmation of the diagnosis and also for assessment of the efficacy of treatment.
- Newer antiepileptic for neonatal seizures: Bumetanide, Levetiracetam, Topiramate. Limited data and experience on safety and efficacy in newborns.

Metabolic Causes of Neonatal Seizures

Administration of pyridoxine is often considered in neonates with unexplained refractory seizures. Intravenous administration of 100 mg pyridoxine with continuous EEG and cardiac monitoring should result in a marked attenuation

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of epileptiform activity within 15 minutes in responders. (Rarely, treatment is associated with adverse effects, including onset of respiratory depression up to a day later). Usual maintenance dose: 50 to 100 mg/day.

- The novel strategy of antenatal pyridoxine supplementation in a pregnant woman with a family history of pyridoxine-dependent neonatal seizures
- Pyridoxal Phosphate responsive seizures; In an emergency situation always give pyridoxine, 100 mg iv, followed by pyridoxal phosphate 30 mg/kg/day (orally) for 3 days (max daily 200 mg), if ineffective add-on of folinic acid.
- Pyridoxal 5-phosphate dependent epilepsy; neonatal seizures unresponsive to pyridoxine and anticonvulsant treatment but responsive to pyridoxal phosphate (Pyridoxal phosphate 10-50 mg/kg/day).
- Folinic acid-responsive neonatal seizures, infants who respond preferentially to folinic acid (2.5–5 mg/day) have been described.
- GLUT-1(Glucose transporter -1) Deficiency. Defect of glucose transport. Treat with ketogenic diet.
- Deficiencies in Serine Synthesis. The diagnosis is made on the basis of decreased serine and glycine in plasma and more importantly in CSF and unrelated to the time of intake of diet. Treatment should start early with L-serine orally 500-700 mg/kg/day.
- Defect in biotinidase. Here the seizures start within the first 3 months of life but it can just start as an uncontrolled seizures. Treatment consists of life long Biotin 5-10 mg per day.

Treatment Algorithm for Recurrent Neonatal Seizures

Seizures suspected in high-risk neonate:

- Confirm seizures with EEG (where available) and start continuous EEG monitoring, if possible
- Check easily correctable causes: glucose, electrolytes
- Start antibiotics if febrile or high-risk for CNS infection
- LP as soon as seizures stabilized

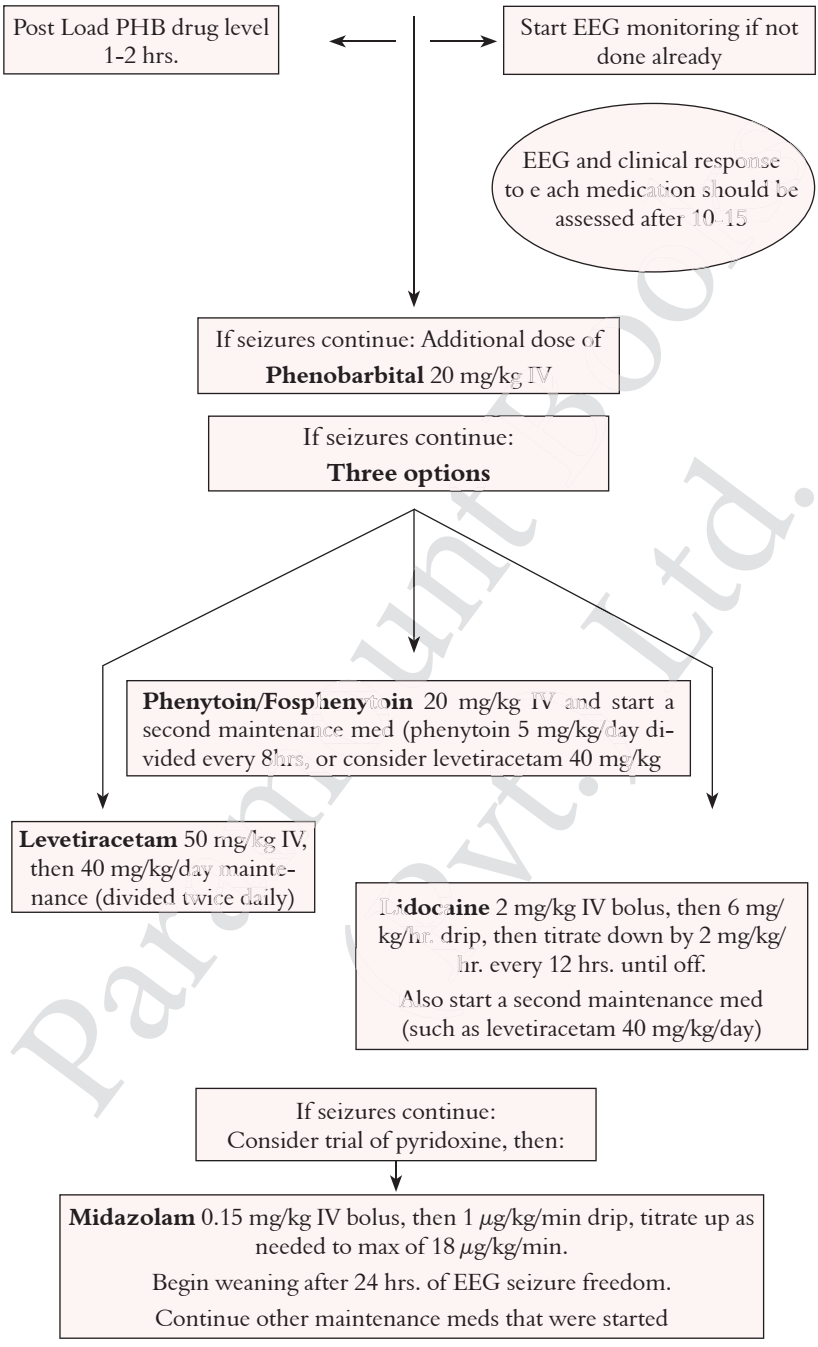
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Baby with a seizures more than 5 minutes or at least one EEG confirmed seizure and no immediately correctable cause:

Phenobarbital:

20 mg/kg IV and start PHB maintenance 5 mg/kg/day divided BID or Q day

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If seizures continue: Consider

Pentobarbital drip, or **Lidocaine** drip if not yet tried (unless phenytoin/fosphenytoin has been used)

When Seizures Cease:

- Monitor electrographically for at least 24hours of seizure freedom
- If on maintenance phenobarbital, check trough level in 4-5 days.
- Continue work-up to clarify seizure
- etiology; consider brain imaging (MRI whenever possible), LP for routine studies and/or metabolic disorders as indicated
- Attempt to wean to one maintenance seizure medication prior to discharge if possible
- Consider weaning all seizure medication prior to discharge if single or rare seizures, and if seizure-free for at least 48-72 hours, and risk of recurrence not felt to be unusually high.

KEY POINTS

- In the neonate, seizures may indicate the presence of a potentially treatable etiology and should prompt an immediate evaluation to determine cause and to institute etiology-specific therapy.
- Etiologic specific therapy (for metabolic disorders, central nervous system) is critical since it may prevent further brain injury. Also, neonatal seizures may not be effectively controlled with antiepileptic drugs (AEDs) unless their underlying cause is treated.
- Pyridoxine (100 mg IV) or pyridoxal phosphate (10 mg/kg IV) should be given to neonates with seizures unresponsive to conventional anticonvulsants. If there is no response to pyridoxine, folinic acid (leucovorin, 2.5 mg IV) may be administered for possible folinic acid responsive seizures.

References

1. Bok LA, Maurits NM, Willemsen MA, *et al*. The EEG response to pyridoxine-IV neither identifies nor excludes pyridoxine-dependent epilepsy. Epilepsia 2010; 51:2406.
2. Segal EB, Grinspan ZM, Mandel AM, Gospe SM Jr. Biomarkers aiding diagnosis of atypical presentation of pyridoxine-dependent epilepsy. Pediatr Neurol 2011; 44:289.
3. Stockler S, Plecko B, Gospe SM Jr, *et al*. Pyridoxine dependent epilepsy and antiquitin deficiency: clinical and molecular characteristics and recommendations for diagnosis, treatment and follow-up. Mol Genet Metab 2011; 104:48.
4. Gallagher RC, Van Hove JL, Scharer G, *et al*. Folinic acid-responsive seizures are identical to pyridoxine-dependent epilepsy. Ann Neurol 2009; 65:550.

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5. Mahajnah M, Corderio D, Austin V, *et al*. A Prospective Case Study of the Safety and Efficacy of Lysine-Restricted Diet and Arginine Supplementation Therapy in a Patient With Pyridoxine-Dependent Epilepsy Caused by Mutations in ALDH7A1. Pediatr Neurol 2016; 60:60.
6. Booth D, Evans DJ. Anticonvulsants for neonates with seizures. Cochrane Database Syst Rev 2004; :CD004218.
7. Slaughter LA, Patel AD, Slaughter JL. Pharmacological treatment of neonatal seizures: a systematic review. J Child Neurol 2013; 28:351.
8. Bartha AI, Shen J, Katz KH, *et al*. Neonatal seizures: multicenter variability in current treatment practices. Pediatr Neurol 2007; 37:85.
9. Glass HC, Kan J, Bonifacio SL, Ferriero DM. Neonatal seizures: treatment practices among term and preterm infants. Pediatr Neurol 2012; 46:111.
10. Hellström-Westas L, Boylan G, Ågren J. Systematic review of neonatal seizure management strategies provides guidance on anti-epileptic treatment. Acta Paediatr 2015; 104:123.
11. Mizrahi EM, Kellaway P. Characterization and classification of neonatal seizures. Neurology 1987; 37:1837.
12. Mizrahi, EM, Kellaway, P. The response of electroclinical neonatal seizures to antiepileptic drug therapy. Epilepsia 1992; 33:114.
13. Glass HC, Wirrell E. Controversies in neonatal seizure management. J Child Neurol 2009; 24:591.
14. Silverstein FS, Ferriero DM. Off-label use of antiepileptic drugs for the treatment of neonatal seizures. Pediatr Neurol 2008; 39:77.
15. Kilicdag H, Daglıoglu K, Erdogan S, *et al*. The effect of levetiracetam on neuronal apoptosis in neonatal rat model of hypoxic ischemic brain injury. Early Hum Dev 2013; 89:355.
16. Komur M, Okuyaz C, Celik Y, *et al*. Neuroprotective effect of levetiracetam on hypoxic ischemic brain injury in neonatal rats. Childs Nerv Syst 2014; 30:1001.
17. Abend NS, Gutierrez-Colina AM, Monk HM, *et al*. Levetiracetam for treatment of neonatal seizures. J Child Neurol 2011; 26:465.
18. van den Broek MP, Rademaker CM, van Straaten HL, *et al*. Anticonvulsant treatment of asphyxiated newborns under hypothermia with lidocaine: efficacy, safety and dosing. Arch Dis Child Fetal Neonatal Ed 2013; 98:F341.
19. Weeke LC, Toet MC, van Rooij LG, *et al*. Lidocaine response rate in aEEG-confirmed neonatal seizures: Retrospective study of 413 full-term and preterm infants. Epilepsia 2016; 57:233.
20. Lundqvist M, Ågren J, Hellström-Westas L, *et al*. Efficacy and safety of lidocaine for treatment of neonatal seizures. Acta Paediatr 2013; 102:863.
21. Pressler RM, Boylan GB, Marlow N, *et al*. Bumetanide for the treatment of seizures in newborn babies with hypoxic ischaemic encephalopathy (NEMO): an open-label, dose finding, and feasibility phase 1/2 trial. Lancet Neurol 2015; 14:469.
22. Dodson WE. Antiepileptic drug utilization in pediatric patients. Epilepsia 1984; 25 Suppl 2:S132.
23. Venkatesan C, Young S, Schapiro M, Thomas C. Levetiracetam for the Treatment of Seizures in Neonatal Hypoxic Ischemic Encephalopathy. J Child Neurol 2017; 32:210.

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24. Fitzgerald MP, Kessler SK, Abend NS. Early discontinuation of antiseizure medications in neonates with hypoxic-ischemic encephalopathy. Epilepsia 2017; 58:1047.
25. Shellhaas RA, Chang T, Wusthoff CJ, *et al*. Treatment Duration After Acute Symptomatic Seizures in Neonates: A Multicenter Cohort Study. J Pediatr 2017; 181:298.
26. Scheffer IE, Berkovic S, Capovilla G, *et al*. ILAE classification of the epilepsies: Position paper of the ILAE Commission for Classification and Terminology. Epilepsia 2017; 58:512.
27. Fisher RS, Cross JH, D'Souza C, *et al*. Instruction manual for the ILAE 2017 operational classification of seizure types. Epilepsia 2017; 58:531.
28. Fisher RS, Cross JH, French JA, *et al*. Operational classification of seizure types by the International League Against Epilepsy: Position Paper of the ILAE Commission for Classification and Terminology. Epilepsia 2017; 58:522.
29. Glass HC, Shellhaas RA, Wusthoff CJ, *et al*. Contemporary Profile of Seizures in Neonates: A Prospective Cohort Study. J Pediatr 2016; 174:98.
30. Harbison AL, Votava-Smith JK, Del Castillo S, *et al*. Clinical Factors Associated with Cerebral Metabolism in Term Neonates with Congenital Heart Disease. J Pediatr 2017; 183:67.
31. Shellhaas RA, Wusthoff CJ, Tsuchida TN, *et al*. Profile of neonatal epilepsies: Characteristics of a prospective US cohort. Neurology 2017; 89:893.
32. Mefford HC, Zemel M, Geraghty E, *et al*. Intragenic deletions of ALDH7A1 in pyridoxine-dependent epilepsy caused by Alu-Alu recombination. Neurology 2015; 85:756.
33. van Karnebeek CD, Tiebout SA, Niermeijer J, *et al*. Pyridoxine-Dependent Epilepsy: An Expanding Clinical Spectrum. Pediatr Neurol 2016; 59:6.
34. Al Teneiji A, Bruun TU, Cordeiro D, *et al*. Phenotype, biochemical features, genotype and treatment outcome of pyridoxine-dependent epilepsy. Metab Brain Dis 2017; 32:443.
35. Wilcken B. Treatments for rare diseases: molybdenum cofactor deficiency. Lancet 2015; 386:1924.
36. Glass HC, Shellhaas RA, Tsuchida TN, *et al*. Seizures in Preterm Neonates: A Multicenter Observational Cohort Study. Pediatr Neurol 2017; 72:19.
37. Uria-Avellanal C, Marlow N, Rennie JM. Outcome following neonatal seizures. Semin Fetal Neonatal Med 2013; 18:224.

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Chapter

02

Neurometabolic Crisis

ACUTE METABOLIC ENCEPHALOPATHY DUE TO INBORN ERROR OF METABOLISM (IEM)

- Acute metabolic encephalopathy is a condition of acute global cerebral dysfunction resulting in altered consciousness, behavior changes, or seizures, which is not due to primary structural brain disease (e.g. tumor or hemorrhage) or infection. Metabolic encephalopathy interferes with the function of the ascending reticular activating system and/or its projections to the cerebral cortex, thus leading to impairment of arousal and/or awareness, and/or seizures.
- The presentation of this condition in the newborn, infant, or child may be subtle and not easily recognized. Metabolic encephalopathy is often reversible and interruption of neuronal activity in the developing brain can have a long-lasting effect, prompt recognition and treatment is important

CLINICAL FEATURES

Most clinical features of acute metabolic encephalopathy are nonspecific and do not reliably identify a particular etiology.

Mental Status

The initial presentation may be subtle and include shortened attention span, disturbed cognitive function, and personality changes. Cognitive dysfunction may include impaired memory, perceptual deficits, and difficulty processing new information. Worsening brain dysfunction results in progressive disturbance of the level of consciousness from lethargy to obtundation, stupor, and coma.

Seizures

Seizures caused by inborn error of metabolism (IEM) usually present early and are refractory to standard anticonvulsant medications. The conditions that present most commonly with seizures include:

- Organic acidemias
- Urea cycle disorders and amino acid metabolism disorders
- Gangliosidosis
- Disorders of pyruvate metabolism
- Paroxysmal disorders

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- Mitochondrial disorders
- Pyridoxine and pyridoxal-5-phosphate-responsive seizures
- Biotinidase deficiency/holocarboxylase synthetase deficiency
- Nonketotic hyperglycinemia
- Molybdenum cofactor deficiency and isolated sulfite oxidase deficiency
- Disorders of copper metabolism
- Neuronal ceroid lipofuscinoses
- Disorders of creatine metabolism
- Purine and pyrimidine metabolism disorders

SIDS and ALTE

The following are the most common IEM that can cause sudden infant death syndrome (SIDS) or an apparent life-threatening event (ALTE):

- Fatty acid oxidation defects, the most common of which is medium chain acyl-CoA dehydrogenase (MCAD) deficiency.
- Disorders of amino acid metabolism and urea cycle disorders
- Organic acidemias

Motor Examination

- Many of them have abnormal tone; persistent hypotonia or hypertonia can be seen. These abnormalities typically are diffuse and symmetric. Generalized or focal seizure activity occurs commonly.
- Abnormal movements, including myoclonic jerks, fine tremors, and asterixis (difficulty with postural maintenance, often seen as a coarse, flapping tremor of the hands), may occur.
- Primitive reflexes, such as suck or grasp responses, may be elicited on examination.
- Other common features include brisk deep tendon reflexes and extensor plantar responses.
- In severely obtunded subjects, decorticate and decerebrate posturing may occur.
- Subtle movements generated by brainstem activity (including nystagmus, posturing, or sucking movements) may be seen in neonatal seizures.

Respiratory Abnormalities

Hyperventilation caused by metabolic and/or respiratory acidosis or hypoventilation causing respiratory acidosis or caused by metabolic alkalosis can result from a variety of metabolic abnormalities.

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BASIC WORK-UP

Basic work-up in all cases of an acute encephalopathy includes:

- Blood glucose, electrolytes, and serum concentrations of blood urea nitrogen (BUN), CRP, creatinine, calcium, magnesium, and phosphate.
- Liver enzymes (aspartate aminotransferase (AST) and alanine aminotransferase (ALT), coagulation studies.
- Serum concentrations of ammonia and Lactate.
- Blood gas (arterial or venous).
- Store plasma for amino acids or other.
- Store filter paper with dried blood spots (acylcarnitines, enzymes, DNA etc).
- Obtain urine sample; perform standard strip; store sample for organic acids, orotic acid, or amino acids at-20°.

INTERPRETATION OF METABOLIC DISTURBANCES

Hypoglycemia

- Definition: Hypoglycemia as a plasma glucose value of ≤40 mg/dL (2.22 mmol/L) regardless of age but in new born most widely accepted definition of hypoglycemia is blood glucose < 30 mg /dl, and 20 mg/dl in preterm.
- Hypoglycemia typically occurs in disorders of ketogenesis, fatty acid oxidation disorders (such as medium chain acyl-CoA dehydrogenase deficiency), some glycogen storage diseases (GSD), disorders of gluconeogenesis, and hereditary fructose intolerance (HFI). It also may occur in amino acid disorders, organic acidemias, and mitochondrial disorders.
- The hypoglycemia in glycogen storage diseases and organic acidemias is usually accompanied by ketosis, whereas no ketosis or inappropriately low ketone body production is more typical of disorders of ketogenesis (such as HMG-CoA lyase and 3-ketothiolase deficiency) and fatty acid oxidation disorders in which fatty acids cannot be converted to ketoacids in the liver. Patients with glycogen storage diseases may also have increased plasma concentrations of lactate, pyruvate, triglycerides, and uric acid.
- Additional evaluation for metabolic causes of hypoglycemia should be performed while the patient is hypoglycemic (or on samples that were obtained at the time of presentation and appropriately stored).

Additional evaluation includes:

- Plasma acylcarnitine profile and quantitative plasma carnitine levels (free, total, and acyl). Low carnitine levels are seen in primary carnitine deficiency or in secondary carnitine deficiency associated with organic acidemias or mitochondrial disorders.
- Measurements of lactate, triglycerides, uric acid, and creatine kinase may assist in the diagnosis of certain GSD.

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Acid-base Disorder

- Metabolic acidosis is characterized by: Ph < 7.20, HCO_3 < 10 mmol, $PaCO_2$ < 25 mmHg. In case of metabolic acidosis one should always study the anion gap: $(Na^+)–(Cl^- + HCO_3^-)$ which is normally 7-16 mmol/L.
- Metabolic acidosis due to an IEM is usually associated with an increased anion gap. The anion gap results from the presence of abnormal metabolites, such as ketoacids, lactic acid, or methylmalonic acid.
- The urine pH is helpful in determining the cause of metabolic acidosis. The appropriate physiologic response to metabolic acidosis is increased urinary acid excretion, with the urine pH usually falling below 5. A urine pH > 5 is more suggestive of metabolic acidosis due to renal tubular acidosis rather than an IEM.
- Respiratory alkalosis usually accompanies hyperammonemia in urea cycle disorders. The respiratory alkalosis is caused by hyperpnea that is induced by the elevated ammonia level. Among patients with an otherwise unexplained acid-base disorder, additional evaluation should include:
- Plasma lactate and pyruvate levels, Quantitative plasma amino acid analysis Quantitative urine organic analysis.

Hyperammonemia

- Hyperammonemia is defined as a plasma ammonia concentration above 90 micromol/L and above 110 micromol/L for the neonate and suspicion for a metabolic disease is > 200 micromol/L.
- Hyperammonemia is a characteristic feature of the urea cycle defects and organic acidemias, particularly propionic and methylmalonic acidemias.
- It also may occur in other amino acid disorders (such as lysinuric protein intolerance) and fatty acid oxidation defects.
- Ammonia concentrations tend to be highest in urea cycle disorders (300 to 1000 micromol/L and only moderately elevated or normal in organic acidemias.
- Ammonia can be normal in urea cycle disorders when the patient is not acutely ill. Modest elevations of ammonia occur rarely in mitochondrial disorders or with hepatic dysfunction.
- The ammonia concentration is usually normal in disorders of carbohydrate metabolism, lysosomal storage disorders, or peroxisomal disorders.

ACUTE NEUROMETABOLIC CRISIS

IMMEDIATE MANAGEMENT

- When suspected metabolic encephalopathy/crisis of unknown source of metabolic acidosis, hyperammonemia, or coma, start treatment before the confirmation of diagnosis.

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- Immediate management to prevent further acute deterioration and long-term sequelae. Appropriate and aggressive treatment before confirmation of the diagnosis may be life-saving or prevent or reduce the long-term neurologic sequelae of some of these conditions.
- Stop protein, fat, galactose and fructose.
- Remove metabolites, hyperammonemia: immediate dialysis (HD) for coma, ventilator dependency, or signs of cerebral edema.
- Organic academia: Vitamin B_{12} (1 mg) IM for B_{12} responsive form of methylmalonic academia. Biotin (10 mg) PO or NGT for biotin-responsive carboxylase deficiency. May need HD or peritoneal dialysis if coma.
- Urea cycle defect: 6 cc/kg of 10% arginine HCL. IV over 90 min.
- Prevent catabolism: IV glucose (calories needed to keep euglycemia) D10 150 cc/kg/dw/electrolytes.

Acidosis

- Although there is controversy regarding the use of sodium bicarbonate in the treatment of acute metabolic acidosis, but it is generally recommend bicarbonate therapy to correct severe acidosis in children with a pH less than 6.9 to 7.0. The balance between the potential benefits and adverse effects of bicarbonate therapy must be carefully weighed in newborns and older children with metabolic acidosis.
- Dosage should be based on the following formula if blood gases and pH measurements are available: Infants and Children: HCO_3-(mEq) = 0.3 x weight (kg) x base deficit (mEq/L) or HCO_3-(mEq) = 0.5 x weight (kg) x [24 - serum HCO_3-(mEq/L)]. Usual dosage in neonate is 1-2 mEq/kg/dose.
- If acid-base status is not available: Dose for older Children and Adults: 2-5 m Eq/kg IV infusion over 4-8 hours; subsequent doses should be based on patient's acid-base status.

Hypoglycemia

- **Do not delay** treatment if symptomatic hypoglycemia is suspected.
- Altered mental status: Give an initial IV bolus of glucose of 0.25 grams/kg of dextrose (maximum single dose 25 grams). The volume and concentration of glucose bolus is infused slowly at 2 to 3 mL per minute. 2.5 mL/kg of 10 percent dextrose solution (D10W) in infants and children up to 12 years of age (10 percent dextrose is 100 mg/mL).
- 1 mL/kg of 25% dextrose (D25W) or 0.5 mL/kg of 50 percent dextrose (D50W) in adolescents (25 percent dextrose is 250 mg/mL; 50 percent dextrose is 500 mg/mL).

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Hyperammonemia

The initial approach to treatment consists of the following:

- Rehydrate and maintain good urine output without over hydration
- Remove nitrogen (ammonia) from the body using medications and/or hemodialysis.
- Stop protein intake and minimize catabolism.
- Stimulate anabolism and uptake of nitrogen precursors by muscle.
- Patients with respiratory failure should receive assisted ventilation because increased work of breathing results in higher caloric demands, leading to increased catabolism and nitrogen accumulation.
- Intravenous access, preferably via a central catheter, for blood sampling and for the administration of fluids and medications. Intravenous fluids should consist of 10 percent dextrose in water.
- Excessive ammonia is removed by hemodialysis and medications. Hemodialysis is the quickest and most efficient method and should be used if ammonia is rapidly increasing, the acute hyperammonemia is resistant to initial drug therapy, and/or the ammonia is persistently above the range of 350 to 400 micromol.
- Pharmacologic therapy of hyperammonemia consists of administration of a combination preparation of sodium phenylacetate and sodium benzoate.
- For patients who weigh ≤20 kg, we use a loading dose of 500 mg/kg (250 mg/kg of each drug) in a volume of 25 to 35 mL/kg of 10 percent dextrose solution infused over 90 minutes. For patients who weigh >20 kg, dosing is based upon body surface area. The loading dose is 11 g/m2 (i.e. 5.5 g/m2 of each drug). Drug levels could be monitored in this circumstance to avoid toxicity, including death.

References

1. Champion MP. An approach to the diagnosis of inherited metabolic disease. Arch Dis Child Educ Pract Ed 2010; 95:40.
2. Weiner DL. Metabolic emergencies. In: Textbook of pediatric emergency medicine, 5th ed, Fleisher GR, Ludwig S, Henretig FM (Eds), Lippincott, Williams and Wilkins, Philadelphia 2006. p.1193.
3. Calvo M, Artuch R, Macià E, *et al*. Diagnostic approach to inborn errors of metabolism in an emergency unit. Pediatr Emerg Care 2000; 16:405.
4. Ficicioglu C, Bearden D. Isolated neonatal seizures: when to suspect inborn errors of metabolism. Pediatr Neurol 2011; 45:283.
5. Dhamija R, Patterson MC, Wirrell EC. Epilepsy in children--when should we think neurometabolic disease? J Child Neurol 2012; 27:663.
6. Gkampeta A, Pavlou E. Infantile spasms (West syndrome) in children with inborn

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errors of metabolism: a review of the literature. J Child Neurol 2012; 27:1295.

7. Saudubray JM, Chappentier C. Clinical phenotypes: Diagnosis/algorithms. In: Metabolic and molecular bases of inherited disease, Scriver CR, Beaudet AL, Sly WS, Valle D (Eds), McGraw-Hill, New York 2001. p.1327.
8. Ogier de Baulny H. Management and emergency treatments of neonates with a suspicion of inborn errors of metabolism. Semin Neonatol 2002; 7:17.
9. Nasser M, Javaheri H, Fedorowicz Z, Noorani Z. Carnitine supplementation for inborn errors of metabolism. Cochrane Database Syst Rev 2012; :CD006659.
10. Kamboj M. Clinical approach to the diagnoses of inborn errors of metabolism. Pediatr Clin North Am 2008; 55:1113.
11. Roe CR, Ding J. Mitochondrial fatty acid oxidation disorders. In: Metabolic and molecular bases of inherited disease, 8th ed, Scriver CR, Beaudet AL, Sly WS, Valle D (Eds), McGraw-Hill, New York 2001. p.2297.
12. Pfeffer G, Majamaa K, Turnbull DM, *et al*. Treatment for mitochondrial disorders. Cochrane Database Syst Rev 2012; :CD004426.
13. Platt FM. Sphingolipid lysosomal storage disorders. Nature 2014; 510:68.
14. Woods AG, Woods CW, Snow TM. Congenital disorders of glycosylation. Adv Neonatal Care 2012; 12:90.
15. Sadat MA, Moir S, Chun TW, *et al*. Glycosylation, hypogammaglobulinemia, and resistance to viral infections. N Engl J Med 2014; 370:1615.

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Chapter

03 Increased Intracranial Pressure

Elevated Intracranial Pressure (ICP) is a potentially devastating complication of neurologic injury. Early recognition of elevated ICP can prevent neurologic sequelae and/or death.

Current pediatric data support an ICP >20 mm Hg as threshold to define intracranial hypertension requiring treatment. Sustained ICP values of greater than 40mm Hg indicate severe, life threatening intracranial hypertension.

CAUSES OF INTRACRANIAL HYPERTENSION

- Traumatic brain injury/intracranial hemorrhage
- Subdural, epidural, or intraparenchymal hemorrhage
- Ruptured aneurysm
- Diffuse axonal injury
- Arteriovenous malformation or other vascular anomalies
- Central nervous system infections (e.g. encephalitis, meningitis, abscess)
- Ischemic stroke
- Cerebral sinus thrombosis
- Neoplasm
- Vasculitis
- Hydrocephalus
- Idiopathic intracranial hypertension (pseudotumor cerebri)
- Idiopathic

CLINICAL FEATURES

Symptoms

Symptoms of raised ICP are not specific. Global symptoms of elevated ICP include headache. Focal symptoms may be caused by local effects in patients with mass lesions or herniation syndromes. Infants may present with less specific symptoms, such as irritability and a bulging fontanel, or may have lethargy, a flat affect, and poor feeding. Any infant or child with any of the above complaints plus focal physical weakness or loss of coordination is of particular concern.

Headache is one of the earliest symptoms of increased ICP. Headache features that are associated with elevated ICP include:

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- Nocturnal awakening
- Worsening by cough, micturition, or defecation
- Recurrent and localized
- Progressive increase in frequency or severity

Historical features that suggest non-traumatic etiologies for elevated ICP in children who have headache include:

- Growth abnormalities
- Nuchal rigidity, torticollis
- Blurred vision, double vision,
- Focal neurologic deficit
- Persistent vomiting
- Known risk factor for intracranial pathology (e.g. neurocutaneous syndrome, macrocephaly, hormonal abnormalities)
- Lethargy
- Personality change

Extracranial Symptoms Due to Increased ICP

- Increased BP and bradycardia as in Cushing's triad
- Neurogenic pulmonary edema can be caused a sudden increased ICP resulting in an increased alveolar and permeability and edema. This is an emergency state with high risk of upcoming herniation of the brain, requiring both symptomatic and causative treatment.

Signs

The physical examination may help confirm the presence of intracranial hypertension, but a normal examination does not rule it out.

- Papilledema if present can confirm the diagnosis. However, papilledema may be absent in acute ICP elevations because it takes several days to become apparent, and is not invariably present in patients with intracranial hypertension.
- Retinal hemorrhages may be present in patients with increased intracranial pressure, and should raise the suspicion of abusive head trauma.
- Infants with elevated ICP may develop macrocephaly, split sutures or a bulging fontanel.
- With hydrocephalus, a "sun setting" appearance of the eyes appears.
- Children of any age may have a dilated pupil, usually on the side of the lesion.
- Cranial nerve palsies of the third, fourth, and sixth cranial nerves can occur, with third nerve palsy being most common. Cranial nerve palsies may cause double vision or abnormal head posture.

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- The level of consciousness can range from irritability to obtundation or coma.
- Hemiparesis, hyperreflexia, and hypertonia are late signs.
- The constellation of systemic hypertension, bradycardia, and respiratory depression (Cushing triad) is another late sign, and may be a preterminal event.
- Herniation: The earliest clinical signs of transtentorial herniation include headache and altered level of consciousness, followed by pupillary changes; bradycardia is another early sign in children.
- Patients with foramen magnum herniation may have downbeat nystagmus, bradycardia, bradypnea, and hypertension; these findings may be exacerbated by neck flexion and improve with neck extension.
- Clinical features of subfalcine herniation include unilateral or bilateral weakness, loss of bladder control, and coma. Retro-alar herniation results in hemiplegia, coma, and death due to compression of the anterior and middle cerebral arteries.

EVALUATION

- **Neuroimaging**: In the acute or emergency setting, computed tomography (CT) scan of the brain (without contrast) is the radiographic study of choice in children in whom intracranial hypertension is suspected on the basis of history or physical examination. The question we are asking here is "is there a surgical cause of raised ICP that necessitates immediate neurosurgery".
- Head CT may demonstrate the underlying etiology of elevated ICP (e.g. mass lesion, hemorrhage) or findings consistent with elevated ICP (e.g. midline shift, effacement of the basilar cisterns, and/or effacement of the sulci). However, patients without these findings on initial CT may have elevated ICP.
- **Lumbar puncture**: Lumbar puncture, if necessary, should be deferred until after head CT scan in any patient in whom intracranial hypertension is suspected. This is because of the possibility of precipitating herniation across the tentorial notch or into the foramen magnum by increasing the pressure gradient between compartments. The patients in whom central nervous system infection is a strong consideration, deferral of lumbar puncture should not delay the initiation of empiric antibiotic therapy.

MANAGEMENT

Initial Stabilization

- The treatment of intracranial hypertension depends upon the condition of the child and the etiology of the increased pressure.
- The first goal is stabilization of the cardiopulmonary status according to

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standard pediatric advanced life support protocols. Once the child is stable, head computed tomography (CT) scan without contrast should be performed.

- Maintenance of adequate ventilation and blood pressure are the cornerstones of management of elevated intracranial pressure. Maintenance of adequate ventilation and normal $PaCO_2$ prevents the vasodilation that occurs in response to hypercapnia.
- Maintenance of blood pressure is necessary to prevent cerebral ischemia since CPP is the difference between MAP and ICP.

Airway: A definitive airway must be established. Indications for endotracheal intubation in children with elevated ICP include:

- Refractory hypoxia
- Hypoventilation
- Glasgow coma score of ≤ 8
- Loss of airway protective reflexes
- Acute herniation requiring controlled hyperventilation
- Need for endotracheal administration of resuscitation medications
- Intubation, if necessary, should be undertaken by someone who has experience performing this procedure in children. Adequate oxygenation should be maintained before and during the procedure.
- Cervical spine stabilization must be maintained in patients with potential cervical spine injury.
- Precautions must be taken during endotracheal intubation to minimize elevations in ICP that are associated with this procedure. Awake intubation is contraindicated. Rapid sequence intubation (RSI) should be performed.

The following points should be considered when choosing medications for RSI for patients who may have elevated ICP:

- Lidocaine may be used intravenously, or as a local anesthetic, to prevent ICP surges.
- Etomidate is generally favored as a sedative because of its rapid onset of action and minimal side effects, particularly in the multi trauma patient with hemodynamic instability.
- Short-acting barbiturates are classically recommended for patients with elevated ICP who are hemodynamically stable. However, they cause cardiac suppression and vasodilatation, leading to decreased MAP and should be used with caution for patients who may develop hemodynamic instability.
- Midazolam provides some cerebral protective effects, but it can also cause hypotension in the dose required for RSI. In addition, its onset of action is slower and less reliable than short-acting barbiturates. Midazolam should be considered for sedation for RSI for the patient who is actively seizing and is hemodynamically stable.
- Ketamine may increase MAP and ICP.

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- Rocuronium is preferred for paralysis in patients with brain tumors because succinylcholine may cause increases in ICP. In children with brain injury, there is no definitive evidence that succinylcholine causes a rise in ICP. Factors that must be considered in choosing between succinylcholine and rocuronium in injured patients include the risk of succinylcholine for children with undiagnosed neuromuscular conditions and the longer duration of paralysis with rocuronium for those who may have a difficult airway.
- **Breathing**: Hyperventilation ($PaCO_2$ <35 mmHg) may cause cerebral ischemia as the result of decreased cerebral blood flow. Consequently, $PaCO_2$ should be maintained between 35 and 40 mmHg unless there are signs of impending herniation.
- **Circulation**: Cerebral perfusion must be maintained to prevent secondary ischemic injuries. Hypovolemia should be treated with isotonic fluids with a goal of attaining a state of normal, rather than excess, volume. Excess intravascular volume may exacerbate the development of cerebral edema. The administration of hypotonic fluids, such as D5W, should be avoided because they deliver too much free water, which may exacerbate cerebral edema and cellular destruction
- The goals of therapy are to minimize ICP elevation and maintain adequate Cerebral Perfusion Pressure (CPP) to prevent secondary ischemic injury.
- The best therapy for elevated ICP is resolution of the underlying cause. Regardless of the cause, Intracranial Hemorrhage (ICH) is a medical emergency, and treatment should be undertaken as expeditiously as possible.
- Early neurosurgical consultation should be obtained to assist with management decisions regarding the excision of mass lesions, ICP drainage, and ICP monitoring.
- Therapy usually follows a stepwise progression of interventions that have an increasing risk of adverse effects.

General Measures

Some general measures of therapy for elevated ICP have a low risk of adverse effects and can be used in all patients. These measures include:

- Rapid treatment of hypoxia, hypercarbia, and hypotension, since even brief derangements in these parameters can adversely affect outcome. Isotonic fluids [e.g. 0.9 percent (normal) saline] should be administered to patients to maintain adequate MAP; if this fails infusions of dopamine or norepinephrine can be initiated.
- Elevation of the head of the bed from 15 to 30 degrees; mild head elevation can lower ICP.
- Aggressively treating fever with antipyretics and cooling blankets, since hyperpyrexia increases cerebral metabolism and increases CBF, further elevating ICP.

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- Controlling shivering in intubated patients with muscle relaxants (e.g. vecuronium, rocuronium).
- Administering prophylactic anticonvulsants (e.g. levetiracetam, phenytoin, or phenobarbital) to patients who are at high risk of developing seizures (e.g. those who have parenchymal abnormalities, depressed skull fractures, or severe traumatic brain injuries). Seizures are associated with increases in ICP.
- Breakthrough seizures are best treated with benzodiazepines.

SPECIFIC TREATMENT

Mannitol

- Mannitol has a rapid onset of action and maintains its effect for a period of hours. Settings in which mannitol can be used to decrease ICP and improve CPP include acute herniation, acute elevation of ICP, and ICP elevation that does not respond to other therapies.
- Mannitol is prepared as a 20 percent solution. The recommended dose is 0.25 to 1 g/kg IV bolus. Repeat doses can be administered every six to eight hours to increase serum osmolarity to 300 to 310 mOsm/L.
- Mannitol administration has the potential side effects of hyperosmolarity, hypovolemia, electrolyte imbalance, and acute renal failure. These adverse effects are more common with chronic or high-dose administration, and patients who receive mannitol in this manner should be monitored carefully.
- Serum osmolarity, serum electrolytes, and renal function should be measured at least every six to eight hours, preferably before administration of the next dose.

Hypertonic Saline

- Intravenous hypertonic saline, alone or in combination with dextran or hydroxyethyl starch, has been shown to decrease ICP and increase CPP in adult and pediatric patients with elevated ICP that is refractory to conventional therapy.
- Rebound increased ICP has occurred after hypertonic saline administration. Theoretical complications, such as hyperosmolality, osmotic demyelination syndrome (formerly called central pontine myelinolysis), and heart failure have not been reported. However, renal insufficiency is associated with serum osmolality >320 mOsm/L. The current pediatric TBI guidelines recommend that serum osmolality should be maintained <360 mOsm/L.
- A commonly used dosing regimen consists of 3% saline administered as an initial bolus of 2 to 6 mL/kg. Continuous infusion of 3% saline at rates of 0.1 to 1 mL/kg per hour adjusted to maintain ICP <20 mmHg have also been described.

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Hyperventilation

- Because of the risk of cerebral ischemia, aggressive hyperventilation is reserved for episodes of acute brain herniation or ICP elevation that fail to respond to the previously mentioned therapies.
- When hyperventilation is used to manage refractory ICP elevation, cerebral oxygenation should be monitored to prevent exacerbation of cerebral ischemia.
- $PaCO_2$ should be maintained between 35 and 40 mmHg unless there are signs of impending herniation.

CSF Drainage

In cases of uncontrolled intracranial hypertension, an intracranial drain can be placed to remove cerebrospinal fluid (CSF) and monitor ICP.

Barbiturate Coma

- Barbiturates are used to treat intracranial hypertension that is refractory to other modalities
- It works by decreasing the cerebral metabolic rate, which causes a reduction in CBF and thus, in ICP. It may also provide some protective effect for the brain tissue during periods of hypoxia or hypoperfusion.
- Barbiturates produce cardiac suppression, which may result in hypotension. This should be anticipated and treated promptly with fluids and with inotropic support if necessary.
- Thiopental is given in a loading dose of 5 mg/kg over 30 minutes (monitor for hypotension) followed by infusion of 1-5 mg/kg hour until the electroencephalogram shows a burst suppression pattern. The mechanism of ICP reduction by barbiturates is unclear.

Corticosteroids

- Corticosteroids are not useful in the management of elevated ICP from infarction, hemorrhage, or head trauma.
- They may be helpful in the management of vasogenic edema associated with mass lesions (e.g. tumors and abscesses).
- If indicated, dexamethasone (0.25 to 0.5 mg/kg) is administered every six hours, with a maximum dose of 16 mg per day

KEY POINTS

- Signs of impending herniation include bradycardia or tachycardia with hypertension, altered mental status, and focal neurologic findings.
- Increased ICP is most often a complication of traumatic brain injury; it may also occur in children who have hydrocephalus, brain tumors, or intracranial infections

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- Treatment of increased ICP is formulated to maintain adequate cerebral perfusion pressure.
- Children whose intracranial hypertension is refractory to general measures may need treatment with osmotic therapy, cerebrospinal fluid (CSF) drainage, or barbiturates to decrease intracranial pressure (ICP).
- Aggressive hyperventilation (pCO_2 <35 mmHg) should be reserved for patients with signs of herniation.

References

1. Avery RA. Interpretation of lumbar puncture opening pressure measurements in children. J Neuroophthalmol 2014; 34:284.
2. Cartwright C, Igbaseimokumo U. Lumbar puncture opening pressure is not a reliable measure of intracranial pressure in children. J Child Neurol 2015; 30:170.
3. Stevens RD, Shoykhet M, Cadena R. Emergency Neurological Life Support: Intracranial Hypertension and Herniation. Neurocrit Care 2015; 23 Suppl 2:S76.
4. Jenkins LW, Kochanek PM. Developmental Neurobiology, Neurophysiology, and the PICU. In: Rogers' Textbook of Pediatric Intensive Care, 5th ed, Nichols DG, Shaffner DH (Eds), Lippincott Williams & Wilkins, Philadelphia 2015. p.861.
5. Aylward SC, Aronowitz C, Roach ES. Intracranial Hypertension Without Papilledema in Children. J Child Neurol 2016; 31:177.
6. Xu W, Gerety P, Aleman T, *et al*. Noninvasive methods of detecting increased intracranial pressure. Childs Nerv Syst 2016; 32:1371.
7. Bennett TD, DeWitt PE, Greene TH, *et al*. Functional Outcome After Intracranial Pressure Monitoring for Children With Severe Traumatic Brain Injury. JAMA Pediatr 2017; 171:965.
8. Tasker RC, Aboy M, Graham A, Goldstein B. Neurologic monitoring. In: Rogers' Textbook of Pediatric Intensive Care, 5th ed, Nichols DG, Shaffner DH (Eds), Wolters Kluwer, Philadelphia 2016. p.907.
9. Seder DB, Jagoda A, Riggs B. Emergency Neurological Life Support: Airway, Ventilation, and Sedation. Neurocrit Care 2015; 23 Suppl 2:S5.
10. Shah AK, Fuerst D, Sood S, *et al*. Seizures lead to elevation of intracranial pressure in children undergoing invasive EEG monitoring. Epilepsia 2007; 48:1097.
11. Brophy GM, Human T, Shutter L. Emergency Neurological Life Support: Pharmacotherapy. Neurocrit Care 2015; 23 Suppl 2:S48.
12. Shein SL, Ferguson NM, Kochanek PM, *et al*. Effectiveness of Pharmacological Therapies for Intracranial Hypertension in Children With Severe Traumatic Brain Injury--Results From an Automated Data Collection System Time-Synched to Drug Administration. Pediatr Crit Care Med 2016; 17:236.
13. Skippen P, Seear M, Poskitt K, *et al*. Effect of hyperventilation on regional cerebral blood flow in head-injured children. Crit Care Med 1997; 25:1402.
14. Hutchinson PJ, Kolias AG, Timofeev IS, *et al*. Trial of Decompressive Craniectomy for Traumatic Intracranial Hypertension. N Engl J Med 2016; 375:1119.

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Chapter 04 Idiopathic Intracranial Hypertension (Pseudotumor Cerebri)

- Idiopathic Intracranial Hypertension (IIH) is also commonly called pseudotumor cerebri. The etiology is not well understood, but is thought to be an impaired reabsorption of CSF.
- It is a disorder defined by clinical criteria that include symptoms and signs isolated to those produced by increased intracranial pressure (e.g. headache, papilledema, and vision loss), elevated intracranial pressure with normal cerebrospinal fluid composition, and no other cause of intracranial hypertension evident on neuroimaging or other evaluations.
- The headache is usually diffuse and pounding quality that worsens with Valsalva or recumbent position and can be progressive in severity.
- Symptoms can include diplopia, transient visual obscurations, and pulsatile tinnitus.
- Risk Factors: Obesity, endocrinopathies (hypothyroidism, Addison disease), use of medication (hormones, tetracyclines, vitamin A, steroids, Polycystic ovarian disease, Anemia, systemic lupus erythematosus, chronic kidney disease, and sleep apnea.
- It is more common in female.

EXAMINATION

The most common signs in IIH are:

- Papilledema: Papilledema is the hallmark sign of IIH
- Visual field loss or change in visual acuity
- Sixth nerve palsy

EVALUATION

- Increased intracranial pressure should be suspected in a patient with headache and papilledema.
- Urgent neuroimaging is required to exclude secondary causes of intracranial hypertension. If the neuroimaging study reveals no structural etiology for intracranial hypertension, a lumbar puncture (LP) is performed to document an opening pressure and to exclude other conditions.
- Ophthalmologic evaluation is required to document the severity of optic nerve involvement and monitor response to treatment.
- The diagnosis of IIH may be suspected prior to the evaluation, on the basis of a history and examination that reveals conditions or medications that are associated with IIH.
- Neuroimaging and LP are still required to exclude other conditions.

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Diagnostic Criteria

- There are established criteria called modified Dandy Walker Criteria (Table 4.1).
- Brain imaging is often unrevealing, but can show subtle findings of slit like ventricles or "empty sella sign" (flattening of the pituitary gland).
- LP shows elevated pressure on lumbar puncture of > 25 cm of H_2O obtained in lateral decubitus position with extended legs.
- For patients require sedation, propofol is recommended over ketamine. Propofol is known to decrease ICP and hence is considered safer, but can cause a falsely lower opening pressure. Ketamine is known to increase ICP.
- In fluoroscopically guided LP, the prone position used can increase opening pressure by a mean of 2.7 cm of H_2O.

Table 4.1: Modified Dandy-Walker Criteria.

- Symptoms of raised ICP (headache, nausea, vomiting, transient visual obscurations, or papilledema)
- No localizing signs with the exception of abducens (6^{th}) nerve palsy
- Patient is awake and alert
- Normal CT/MRI findings without evidence of thrombosis
- LP opening pressure of > 25 cm of H_2O and normal biochemical and cytological composition of CSF
- No other explanation for the raised intracranial pressure

TREATMENT

- The treatment of IIH has two major goals: the alleviation of symptoms (usually headache) and the preservation of vision.
- Some patients with normal vision and minimal symptoms require no treatment other than monitoring.
- The diagnostic tap can also be therapeutic, and sometimes, repeated lumber puncture are needed.
- **Fulminant IIH**: A subset of individuals with IIH have a more malignant or fulminant course with rapid development of vision loss within a few weeks of symptom onset. This is generally apparent at presentation. To limit the severity of permanent vision loss, more aggressive surgical treatment measures are considered at the outset, often with temporizing measures (e.g. serial lumbar punctures, lumbar drain, and/or corticosteroids) employed until surgery can be performed.
- **Carbonic anhydrase inhibitors (Acetazolamide)**: Carbonic anhydrase inhibitors are believed to reduce the rate of cerebrospinal fluid production. Acetazolamide is the usual first line treatment for IIH.
- In young children, the recommended starting dose is 25 mg/kg per day with a maximum dose of 100 mg/kg or 2 g per day. The sustained release

formulation (Diamox sequels) may be better tolerated by patients who are intolerant of generic acetazolamide.

- Furosemide and topiramate are considered second line drugs. Furosemide (1 to 2 mg/kg per day in children) may be a useful adjunctive therapy to acetazolamide in IIH.
- **Corticosteroids**: Although corticosteroids (e.g. prednisone) have been recommended in the past for IIH, now day's physicians avoid the use of corticosteroids in IIH for the following reasons.
- Corticosteroids can cause weight gain that might worsen IIH. Steroid withdrawal can cause severe rebound intracranial hypertension associated with marked visual loss.
- In the setting of acute visual loss, a short course of intravenous corticosteroids may be useful as a temporizing measure prior to surgical intervention in IIH.
- **Serial lumbar punctures**: Although serial lumbar punctures have been advocated for the treatment of IIH, we do not generally recommend this treatment for the following reasons.
- CSF reforms within six hours unless there is a CSF leak, making any treatment benefit of short-term duration only.
- Lumbar punctures are uncomfortable for most patients and painful for many.
- Lumbar punctures can produce complications (e.g. low pressure headaches, CSF leak, CSF infection, intraspinal epidermoid tumors).
- In obese patients, lumbar punctures are often technically difficult.
- However, serial lumbar punctures can be a useful temporizing measure as a prelude to surgery.
- **Surgery**: Patients with IIH have intractable headache or progressive visual loss appear to benefit from surgical intervention. Potential indications for surgical therapy include:
- Worsening visual field defect despite medical therapy.
- Presence of visual acuity loss attributed to papilledema.
- Intractable headache.
- **Shunting**: CSF shunting procedures include Ventriculoperitoneal (VPS) or Lumboperitoneal Shunt (LPS). Uncontrolled observations report that these can relieve headache, diplopia, papilledema, and visual loss in patients with IIH.
- Optic nerve sheath fenestration: Optic Nerve Sheath Fenestration (ONSF) can stabilize or improve visual loss due to papilledema in IIH.

References

1. Friedman DI, Jacobson DM. Diagnostic criteria for idiopathic intracranial hyper-

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tension. Neurology 2002; 59:1492.

2. Galvin JA, Van Stavern GP. Clinical characterization of idiopathic intracranial hypertension at the Detroit Medical Center. J Neurol Sci 2004; 223:157.
3. Bruce BB, Kedar S, Van Stavern GP, *et al*. Atypical idiopathic intracranial hypertension: normal BMI and older patients. Neurology 2010; 74:1827.
4. Wall M, Kupersmith MJ, Kieburtz KD, *et al*. The idiopathic intracranial hypertension treatment trial: clinical profile at baseline. JAMA Neurol 2014; 71:693.
5. Genizi J, Lahat E, Zelnik N, *et al*. Childhood-onset idiopathic intracranial hypertension: relation of sex and obesity. Pediatr Neurol 2007; 36:247.
6. Distelmaier F, Sengler U, Messing-Juenger M, *et al*. Pseudotumor cerebri as an important differential diagnosis of papilledema in children. Brain Dev 2006; 28:190.
7. Per H, Canpolat M, Gümüş H, *et al*. Clinical spectrum of the pseudotumor cerebri in children: etiological, clinical features, treatment and prognosis. Brain Dev 2013; 35:561.
8. Salpietro V, Chimenz R, Arrigo T, Ruggieri M. Pediatric idiopathic intracranial hypertension and extreme childhood obesity: a role for weight gain. J Pediatr 2013; 162:1084.
9. Blethen SL. Complications of growth hormone therapy in children. Curr Opin Pediatr 1995; 7:466.
10. Fraser CL, Biousse V, Newman NJ. Minocycline-induced fulminant intracranial hypertension. Arch Neurol 2012; 69:1067.
11. Dotan G, Goldstein M, Stolovitch C, Kesler A. Pediatric Pseudotumor Cerebri Associated With Low Serum Levels of Vitamin A. J Child Neurol 2013; 28:1370.
12. Biousse V, Bruce BB, Newman NJ. Update on the pathophysiology and management of idiopathic intracranial hypertension. J Neurol Neurosurg Psychiatry 2012; 83:488.
13. Riggeal BD, Bruce BB, Saindane AM, *et al*. Clinical course of idiopathic intracranial hypertension with transverse sinus stenosis. Neurology 2013; 80:289.
14. Ooi LY, Walker BR, Bodkin PA, Whittle IR. Idiopathic intracranial hypertension: can studies of obesity provide the key to understanding pathogenesis? Br J Neurosurg 2008; 22:187.
15. Wall M. Idiopathic intracranial hypertension (pseudotumor cerebri). *Curr Neurol Neurosci Rep*. 2008 Mar. 8(2):87-93.
16. Portelli M, Papageorgiou PN. An update on idiopathic intracranial hypertension. *Acta Neurochir (Wien)*. 2017 Mar. 159 (3):491-499.
17. Mollan SP, Ali F, Hassan-Smith G, Botfield H, Friedman DI, Sinclair AJ. Evolving evidence in adult idiopathic intracranial hypertension: pathophysiology and management. *J Neurol Neurosurg Psychiatry*. 2016 Sep. 87 (9):982-92.
18. Ameli PA, Madan M, Chigurupati S, Yu A, Chan SL, Pattisapu JV. Effect of acetazolamide on aquaporin-1 and fluid flow in cultured choroid plexus. *Acta Neurochir Suppl*. 2012. 113:59-64.
19. Baykan B, Ekizoğlu E, Altıokka Uzun G. An update on the pathophysiology of idiopathic intracranial hypertension alias pseudotumor cerebri. Agri. 2015. 27 (2):63-72.
20. Matthews YY, Dean F, Lim MJ, Mclachlan K, Rigby AS, Solanki GA, *et al*. Pseudotumor cerebri syndrome in childhood: incidence, clinical profile and risk factors in

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a national prospective population-based cohort study. *Arch Dis Child*. 2017 Aug. 102 (8):715-721.

21. Digre KB, Bruce BB, McDermott MP, Galetta KM, Balcer LJ, Wall M, *et al*. Quality of life in idiopathic intracranial hypertension at diagnosis: IIH Treatment Trial results. *Neurology*. 2015 Jun 16. 84 (24):2449-56.
22. Ottridge R, Mollan SP, Botfield H, Frew E, Ives NJ, Matthews T, *et al*. Randomised controlled trial of bariatric surgery versus a community weight loss programme for the sustained treatment of idiopathic intracranial hypertension: the Idiopathic Intracranial Hypertension Weight Trial (IIH:WT) protocol. *BMJ Open*. 2017 Sep 27. 7 (9):e017426.

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Chapter

05

Seizures and Status Epilepticus in Childhood

The International Classification of Epileptic Seizures defines status epilepticus (SE) as a seizure that lasts for 30 minutes or longer in most studies or is repeated frequently enough that the individual does not regain consciousness between seizures.

- The 30 min. duration is meant to demarcate the transition point when SE becomes established and also when seizures induced neuronal injury begins to occur.
- However, more recently there has been a move towards an "operational definition" of CSE (Convulsive status epilepticus), and the clinicians around the world agree that the patients with a seizure lasting for longer than 5 min should be treated as if they were in established CSE.
- The majority of generalized seizures last for less than 5 min and seizures lasting for more than 5-10 min are less likely to self-terminate.
- Another distinguishing feature of CSE is time dependent development of pharmacoresistance.
- CSE is considered to be refractory if an episode continues after the administration of one first line and one or two second line drugs or if a seizure lasts longer than 1-2 h.
- There is growing evidence that prolonged seizures result in neuronal injury and increase the risk of epilepsy and adverse cognitive and behavioral outcomes.

STAGES OF CSE

Based on the duration of the seizures, CSE can be divided into sequential stages. The knowledge of the stage of CSE is useful in guiding management of prolonged seizures:

- **Incipient CSE** — seizure duration less than 5 min.
- **Impending or early CSE** — seizure duration between 5 and 30 min.
- **Established or late CSE** — seizure duration between 30 and 60 min.
- **Refractory CSE** — seizure duration more than 60 min.

MANAGEMENT

The management of a child with CSE can be broadly divided into:

a. Initial stabilization and evaluation
b. Seizure termination
c. Diagnosis and treatment of underlying cause

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a. Initial Stabilization and Evaluation

- A brief physical examination should assess respiratory and circulatory status. An adequate airway should be established immediately if there is respiratory compromise, and supportive therapy (e.g. oxygen, mechanical ventilation) should be instituted as needed.
- A secure intravenous catheter should be placed for sampling of blood and administration of medications.
- Ongoing monitoring of vital signs should be initiated.
- A rapid neurologic examination should then be performed to provide a preliminary classification of the type of Status Epilepticus (SE).
- A history obtained from a parent or caregiver may help to determine the cause or precipitants of the seizures.

b. Seizures Termination

- The goal of treatment for CSE is to terminate all seizures activity as soon as possible, prevent the recurrence of seizures, and treat complications both of CSE and of the treatment administered.
- Ideally this is achieved by using a drug that is easy to administer, has immediate onset of action and long half-life, has no serious adverse effects on cardiorespiratory function, and has minimal effect on level of consciousness.
- Unfortunately, none of the currently available drugs fulfills all these criteria.

c. Diagnosis and Treatment of Underlying Cause

Laboratory studies in a child with Status Epilepticus for the diagnosis of underlying cause:

All Patients:

- Serum electrolytes
- Serum calcium, phosphate, and magnesium
- Brain imaging (CT or MRI)
- EEG

Epilepsy Patients Maintained on Anticonvulsants:

Anticonvulsant level

Febrile Patients:

- Blood culture
- Urinalysis, urine culture
- CSF culture (once seizures stopped and if brain imaging excludes increased intracranial pressure)
- CBC with differential

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Suspected or Poisoned Patient:

- Urine screen for cocaine, amphetamines, and PCP (Phencyclidine)
- Aspirin level
- Venous or arterial pH and pCO_2
- EKG once seizures stop

Infants <6 Months of Age:

- Blood gas and PH
- Plasma ammonia
- Plasma amino acids
- PT, PTT
- Serum AST, ALT, LDH, Alkaline phosphatase
- Blood lactate and pyruvate
- Urinalysis
- Urine for reducing substances
- Urine organic acids
- Urine amino acids
- Check newborn urine screening results if infant from country where instituted

Table 5.1: Drugs Commonly Used in the Treatment of CSE in Children (Pre-Hospital/Out of Hospital Treatment).

First Line Treatment			
Drug	**Route**	**Dose**	**Common Adverse Effects**
Lorazepam	Intravenous (IV)	0.1 mg/kg	Sedation/Respiratory depression
Diazepam	Intravenous (IV)	0.2-0.3 mg/kg	Sedation/Respiratory depression
Midazolam	Intravenous (IV)	0.15-0.2 mg/kg	Sedation/Respiratory depression
Midazolam	Buccal/ Intranasal/IM	Buccal and nasal 0.15-03 mg/kg IM 0.2 mg/kg	Sedation/Respiratory depression
Diazepam	Rectal	0.5 mg/kg	Sedation/Respiratory depression
Lorazepam	Intranasal	0.1 mg/kg	Sedation/Respiratory depression

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Second Line Treatment			
Drug	**Route**	**Dose**	**Common Adverse Effect**
Phenytoin	IV (Intravenous)	20 mg/kg (rate 1 mg/kg/min, a repeat dose of 10 mg/kg may be considered	Cardiac arrhythmias, hypotension
Fosphenytoin	IV	15-20 mg/kg (rate 2 mg/kg/min)	Cardiac arrhythmias, hypotension
Phenobarbital	IV	15-20 mg/kg (rate 2 mg/kg/min)	Sedation, respiratory depression, hypotension
Sodium Valproate	IV	20-40 mg/kg (rate 5 mg/kg/min	Hepatoxicity, encephalopathy, avoid in metabolic disorders
Levetiracetam	IV	30-60 mg/kg (rate 5 mg/kg/min) High dose 150 mg/kg/day	Consider in liver disease/ metabolic disorder

Treatment of Refractory CSE

Table 5.2:

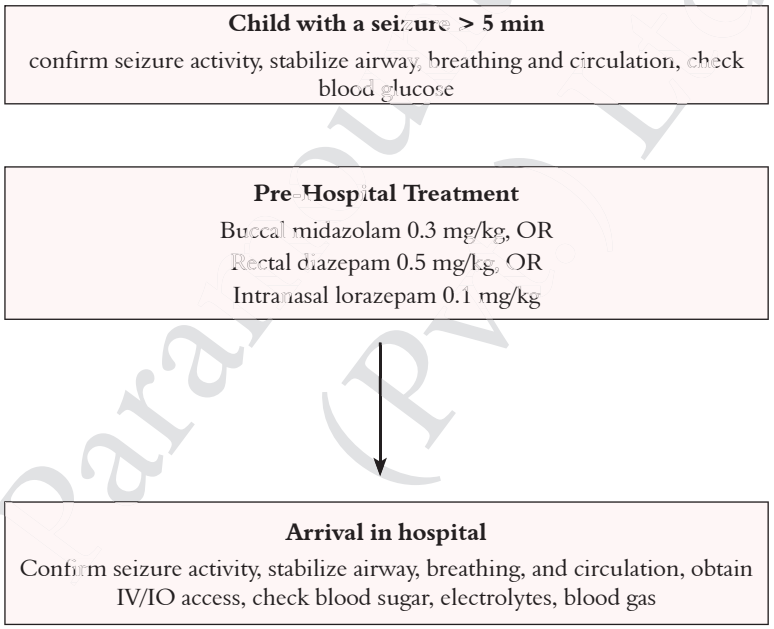
Drug	Route	Dose	Common Adverse Effects
Midazolam	Intravenous (IV)	Bolus 0.2 mg/kg, f/b infusion at 0.05-2 mg/kg/h	Respiratory depression, hypotension, Breakthrough seizures
Very High Dose of Phenobarbital	IV	Bolus 20 mg/kg, dose increased to reach a blood level of 70-344 microgram/ml	Respiratory depression, hypotension
Thiopental	IV	Bolus 5 mg/kg, f/b infusion at 3-5 mg/kg/h	Respiratory depression, hypotension, cardiopulmonary arrest, ileus, immunosuppression, Prolonged ventilation
Pentobarbital	IV	Bolus 5-15 mg/kg, f/b infusion at 0.5-5 mg/kg/h	Respiratory depression , hypotension, cardiopulmonary arrest, ileus, immunosuppression, Prolonged ventilation

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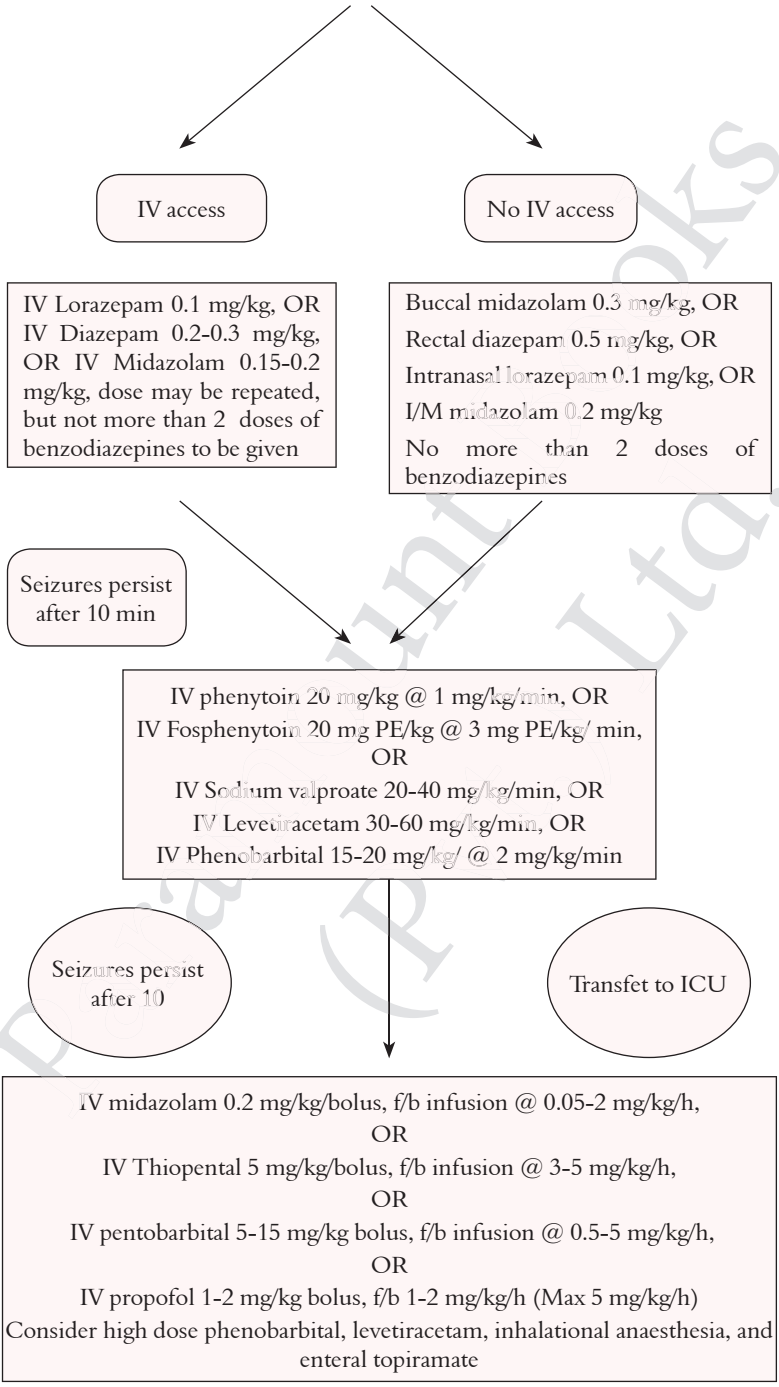
Propofol	IV	Bolus 1-2 mg/kg, f/b 1-2 mg/kg/h (Max. 5 mg/kg/h)	Avoid in children under the age of 16 years due to risk of Propofol infusion syndrome
Isoflurane/ Desflurane	Inhalation	1-5%	Respiratory depression, hypotension, Seizures recurrence dueing tapering

Immunomodulatory Therapy

Immunomodulatory therapy (corticosteroids, adrenocoricotrophic hormone, (ACTH), IV immune globulin, and plasmaphoresis) should be considered early in CSE due to suspected inflammatory conditions such as anti-NMDA receptors antibody encephalitis, Hashimoto encephalopathy, Rasmussen encephalitis, and limbic encephalitis with antibodies to GABAB receptors, GAD, or VGKC.



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IV access
No IV access
IV Lorazepam 0.1 mg/kg, OR IV Diazepam 0.2-0.3 mg/kg, OR IV Midazolam 0.15-0.2 mg/kg, dose may be repeated, but not more than 2 doses of benzodiazepines to be given
Buccal midazolam 0.3 mg/kg, OR
Rectal diazepam 0.5 mg/kg, OR
Intranasal lorazepam 0.1 mg/kg, OR
I/M midazolam 0.2 mg/kg
No more than 2 doses of benzodiazepines
Seizures persist after 10 min
IV phenytoin 20 mg/kg @ 1 mg/kg/min, OR
IV Fosphenytoin 20 mg PE/kg @ 3 mg PE/kg/ min, OR
IV Sodium valproate 20-40 mg/kg/min, OR
IV Levetiracetam 30-60 mg/kg/min, OR
IV Phenobarbital 15-20 mg/kg/ @ 2 mg/kg/min
Seizures persist after 10
Transfet to ICU
IV midazolam 0.2 mg/kg/bolus, f/b infusion @ 0.05-2 mg/kg/h,
OR
IV Thiopental 5 mg/kg/bolus, f/b infusion @ 3-5 mg/kg/h,
OR
IV pentobarbital 5-15 mg/kg bolus, f/b infusion @ 0.5-5 mg/kg/h,
OR
IV propofol 1-2 mg/kg bolus, f/b 1-2 mg/kg/h (Max 5 mg/kg/h)
Consider high dose phenobarbital, levetiracetam, inhalational anaesthesia, and enteral topiramate

Special consideration:

- IV Pyridoxine 100 mg in children less than 2 years without a clear cause of Seizures
- Rectal Paraldehyde after 2 doses of benzodiazepines if no IV access
- Immunomodulatory therapy if autoimmune inflammatory cause suspected
- IV antibiotics in suspected CNS infection
- IV mannitol/hypertonic saline in suspected raised Intracranial pressure
- Urgent neuroimaging in suspected acute CNS pathology to exclude neurosurgical emergency

References

1. Riviello JJ Jr, Ashwal S, Hirtz D, *et al*. Practice parameter: diagnostic assessment of the child with status epilepticus (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. Neurology 2006; 67:1542.
2. Chin RF, Neville BG, Peckham C, *et al*. Treatment of community-onset, childhood convulsive status epilepticus: a prospective, population-based study. Lancet Neurol 2008; 7:696.
3. Tay SK, Hirsch LJ, Leary L, *et al*. Nonconvulsive status epilepticus in children: clinical and EEG characteristics. Epilepsia 2006; 47:1504.
4. Abend NS, Arndt DH, Carpenter JL, *et al*. Electrographic seizures in pediatric ICU patients: cohort study of risk factors and mortality. Neurology 2013; 81:383.
5. Singh RK, Stephens S, Berl MM, *et al*. Prospective study of new-onset seizures presenting as status epilepticus in childhood. Neurology 2010; 74:636.
6. Yoong M, Madari R, Martinos M, *et al*. The role of magnetic resonance imaging in the follow-up of children with convulsive status epilepticus. Dev Med Child Neurol 2012; 54:328.
7. Glauser T, Shinnar S, Gloss D, *et al*. Evidence-Based Guideline: Treatment of Convulsive Status Epilepticus in Children and Adults: Report of the Guideline Committee of the American Epilepsy Society. Epilepsy Curr 2016; 16:48.
8. Gaínza-Lein M, Sánchez Fernández I, Jackson M, *et al*. Association of Time to Treatment With Short-term Outcomes for Pediatric Patients With Refractory Convulsive Status Epilepticus. JAMA Neurol 2018; 75:410.
9. Sánchez Fernández I, Abend NS, Agadi S, *et al*. Time from convulsive status epilepticus onset to anticonvulsant administration in children. Neurology 2015; 84:2304.
10. McTague A, Martland T, Appleton R. Drug management for acute tonic-clonic convulsions including convulsive status epilepticus in children. Cochrane Database Syst Rev 2018; 1:CD001905.
11. Chamberlain JM, Okada P, Holsti M, *et al*. Lorazepam vs diazepam for pediatric status epilepticus: a randomized clinical trial. JAMA 2014; 311:1652.
12. Alshehri A, Abulaban A, Bokhari R, *et al*. Intravenous Versus Nonintravenous Benzodiazepines for the Cessation of Seizures: A Systematic Review and Meta-analysis of Randomized Controlled Trials. Acad Emerg Med 2017; 24:875.

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13. Rai A, Aggarwal A, Mittal H, Sharma S. Comparative efficacy and safety of intravenous valproate and phenytoin in children. Pediatr Neurol 2011; 45:300.
14. Kim JS, Lee JH, Ryu HW, *et al*. Effectiveness of intravenous levetiracetam as an adjunctive treatment in pediatric refractory status epilepticus. Pediatr Emerg Care 2014; 30:525.
15. İşgüder R, Güzel O, Ceylan G, *et al*. A Comparison of Intravenous Levetiracetam and Valproate for the Treatment of Refractory Status Epilepticus in Children. J Child Neurol 2016; 31:1120.
16. Chen J, Xie L, Hu Y, *et al*. Nonconvulsive status epilepticus after cessation of convulsive status epilepticus in pediatric intensive care unit patients. Epilepsy Behav 2018; 82:68.
17. Tasker RC, Goodkin HP, Sánchez Fernández I, *et al*. Refractory Status Epilepticus in Children: Intention to Treat With Continuous Infusions of Midazolam and Pentobarbital. Pediatr Crit Care Med 2016; 17:968.
18. Gaspard N, Foreman B, Judd LM, *et al*. Intravenous ketamine for the treatment of refractory status epilepticus: a retrospective multicenter study. Epilepsia 2013; 54:1498.
19. Cobo NH, Sankar R, Murata KK, *et al*. The ketogenic diet as broad-spectrum treatment for super-refractory pediatric status epilepticus: challenges in implementation in the pediatric and neonatal intensive care units. J Child Neurol 2015; 30:259.
20. O'Connor SE, Ream MA, Richardson C, *et al*. The ketogenic diet for the treatment of pediatric status epilepticus. Pediatr Neurol 2014; 50:101.
21. Trinka E, Cock H, Hesdorffer D, *et al*. A definition and classification of status epilepticus--Report of the ILAE Task Force on Classification of Status Epilepticus. Epilepsia 2015; 56:1515.
22. Chin RF, Neville BG, Peckham C, *et al*. Treatment of community-onset, childhood convulsive status epilepticus: a prospective, population-based study. Lancet Neurol 2008; 7:696.
23. Zhang T, Ma J. Focal Status Epilepticus-Related Unilateral Brain Edema: Magnetic Resonance Imaging Study of Children in Southwest China. Pediatr Neurol 2019; 92:60.
24. Raspall-Chaure M, Chin RF, Neville BG, *et al*. The epidemiology of convulsive status epilepticus in children: a critical review. Epilepsia 2007; 48:1652.
25. Singh RK, Stephens S, Berl MM, *et al*. Prospective study of new-onset seizures presenting as status epilepticus in childhood. Neurology 2010; 74:636.
26. Berg AT, Shinnar S, Testa FM, *et al*. Status epilepticus after the initial diagnosis of epilepsy in children. Neurology 2004; 63:1027.
27. Watemberg N, Segal G. A suggested approach to the etiologic evaluation of status epilepticus in children: what to seek after the usual causes have been ruled out. J Child Neurol 2010; 25:203.
28. Kramer U, Chi CS, Lin KL, *et al*. Febrile infection-related epilepsy syndrome (FIRES): pathogenesis, treatment, and outcome: a multicenter study on 77 children. Epilepsia 2011; 52:1956.
29. van Baalen A, Vezzani A, Häusler M, Kluger G. Febrile Infection-Related Epilepsy Syndrome: Clinical Review and Hypotheses of Epileptogenesis. Neuropediatrics 2017; 48:5.

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30. Hirsch LJ, Gaspard N, van Baalen A, *et al*. Proposed consensus definitions for new-onset refractory status epilepticus (NORSE), febrile infection-related epilepsy syndrome (FIRES), and related conditions. Epilepsia 2018; 59:739.
31. Khawaja AM, DeWolfe JL, Miller DW, Szaflarski JP. New-onset refractory status epilepticus (NORSE)--The potential role for immunotherapy. Epilepsy Behav 2015; 47:17.
32. Kravljanac R, Jovic N, Djuric M, *et al*. Outcome of status epilepticus in children treated in the intensive care unit: a study of 302 cases. Epilepsia 2011; 52:358.
33. Jafarpour S, Hodgeman RM, De Marchi Capeletto C, *et al*. New-Onset Status Epilepticus in Pediatric Patients: Causes, Characteristics, and Outcomes. Pediatr Neurol 2018; 80:61.
34. Fisher RS, Cross JH, D'Souza C, *et al*. Instruction manual for the ILAE 2017 operational classification of seizure types. Epilepsia 2017; 58:531.
35. Fisher RS, Cross JH, French JA, *et al*. Operational classification of seizure types by the International League Against Epilepsy: Position Paper of the ILAE Commission for Classification and Terminology. Epilepsia 2017; 58:522.
36. Aaberg KM, Gunnes N, Bakken IJ, *et al*. Incidence and Prevalence of Childhood Epilepsy: A Nationwide Cohort Study. Pediatrics 2017; 139.
37. Fogarasi A, Tuxhorn I, Hegyi M, Janszky J. Predictive clinical factors for the differential diagnosis of childhood extratemporal seizures. Epilepsia 2005; 46:1280.

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Chapter

06 Emergent Evaluation and Management of Headache

- The terms "primary" and "secondary" may be used to describe headaches. Primary headaches (migraine, tension-type, or cluster headaches) are typically self-limited and diagnosed based on symptom profiles and patterns of headache attacks.
- Secondary headaches have identifiable etiologies. Although the vast majority of secondary headaches in children have benign etiologies (viral infections), the goal of the emergent evaluation of children with headaches is to identify as a first priority those with serious or life-threatening causes.
- This can generally be accomplished with a careful history and physical examination and occasional selected ancillary testing
- The majority of children who are evaluated emergently for headaches are diagnosed with viral illnesses or migraine headaches.
- The challenge for the emergency clinician is to identify patients with secondary headaches who require urgent diagnosis and treatment.

WORRISOME SIGNS

- Any acute headache located in the back of head (posterior fossa mass or hemorrhage).
- Early morning headache that awakes child, with or without nausea /vomiting (brain mass).
- Headache that worsens during Valsalva, exercise, coughing, laughing, defecating (increased ICP, Chiari 1 malformation).
- Optic disc edema (increased ICP).
- Changes in the mental status (intracranial bleed, CNS infection and midline shift)
- History of trauma (SDH, epidural hemorrhage, midline shift and parenchymal bleed).
- Dental pain (brain abscess).
- Meningismus (meningitis, SAH).
- Any focal neurological deficit.
- Elevated Blood pressure (arterial hypertension), if associated with bradycardia (increased ICP).

EVALUATION

- Patients with underlying conditions, such as ventriculoperitoneal shunts or immunodeficiencies, who develop headaches must receive thorough

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evaluations in accordance with specialized protocols developed for those conditions.

- For most other children requiring emergent evaluation for acute headache, the combination of history and physical findings, with selective laboratory testing and neuroimaging, generally identifies those with significant underlying conditions (meningitis or intracranial pathology).

Neurologic Examination

- The vast majority of children with headaches who have serious neurologic conditions have abnormalities on neurologic examination.
- The following findings are significant for children with headaches:
- Altered mental status may be the result of encephalitis, intracranial hemorrhage, elevated intracranial (ICP), or hypertensive encephalopathy.
- Fundoscopic examination should be performed for all children who are being evaluated for headache. Papilledema, hemorrhages, exudates, and abnormal vessels are important manifestations of serious intracranial pathology, but the absence of these findings does not exclude significant conditions.
- Extraocular muscle palsies or nystagmus may be the result of elevated ICP or direct compression by a mass lesion.
- Motor asymmetry, gait disturbance, or difficulty with fine motor coordination suggests a focal intracranial lesion.
- Some children with migraine headaches develop focal neurologic abnormalities (ophthalmoplegia, motor weakness, or ataxia) as part of their migraine syndromes.
- Caretakers can generally confirm that the pattern is typical for the child's headaches.
- The majority of children with headache and normal neurologic examinations who are evaluated emergently do not require ancillary studies.

Neuroimaging

Experts suggest that neuroimaging in the emergency department is warranted for children with the following clinical features.

- Chronic progressive headache
- Worst headache/thunderclap headache
- Abnormal neurologic examination
- Skin lesions suggestive of neurocutaneous syndromes
- Age <3 years of age with unexplained severe headache
- Computed tomography (CT) is readily available and generally identifies any condition that requires immediate treatment.
- Some children may require subsequent magnetic resonance imaging (MRI) to provide clearer definition of abnormalities noted on CT or to

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identify lesions that may not be seen on CT (some infections, hemorrhagic processes, or cerebral venous thrombosis).

- Because CT can be performed quickly and safely, imaging should never be delayed in order to obtain an MRI for a child with a suspected space-occupying intracranial lesion.

Lumbar Puncture

The emergent evaluation of a child with headache should include a lumbar puncture in the following situations:

- Suspected non-focal infection (meningitis, encephalitis)
- Concern for subarachnoid hemorrhage not diagnosed on neuroimaging
- To measure opening pressure for suspected idiopathic intracranial hypertension (after neuroimaging).
- Most patients with focal neurologic examinations should have a CT performed before lumbar puncture. There is a risk of herniation syndrome when lumbar puncture is performed in patients with increased intracranial pressure.

Headache in Child with No Immunocompromise, No Shunt, and No Known Trauma

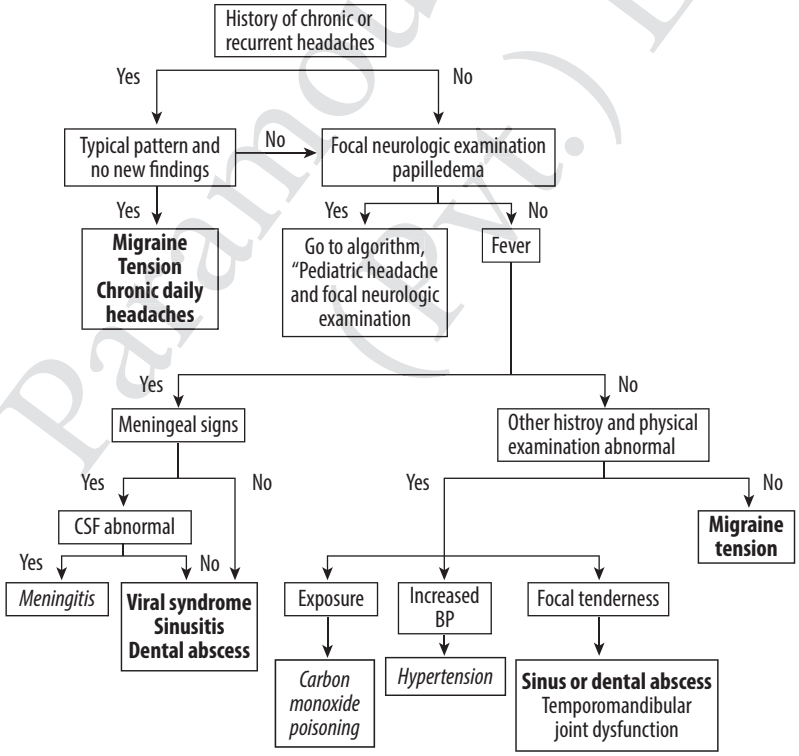


Fig. 6.1: CSF: cerebrospinal fluid; BP: blood pressure.

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Headache in Child with Focal Neurologic Examination or Papilledema

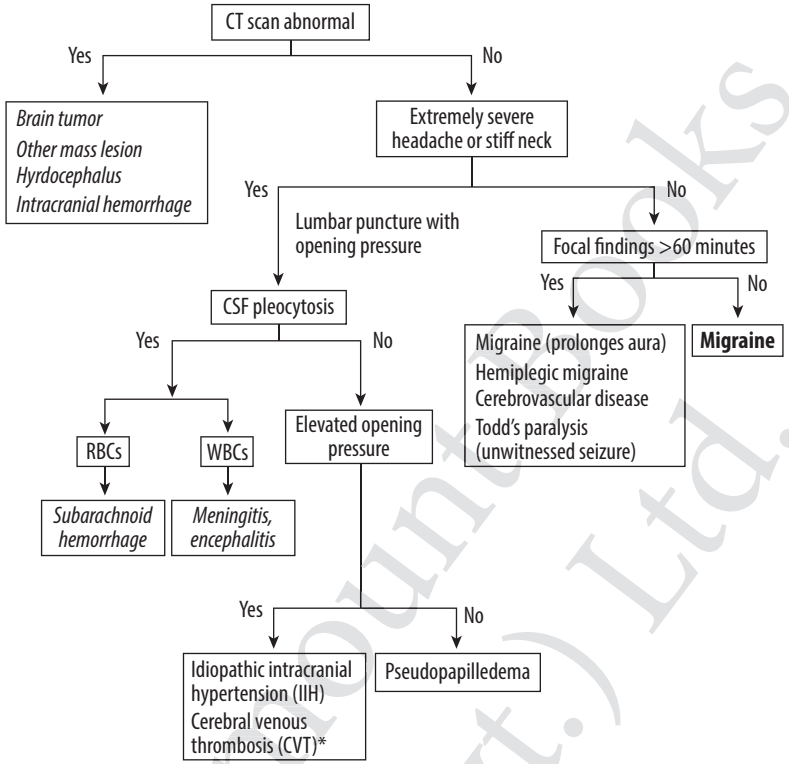


Fig. 6.2: CT: computed tomography; CSF: cerebrospinal fluid; RBCs: red blood cells; WBCs: white blood cells
⋆ Distinguish idiopathic intracranial hypertension from cerebral venous thrombosis by obtaining magnetic resonance imaging or magnetic resonance venogram.

Migraine

Features of migraine in children:

- Migraine is the most common acute and recurrent headache syndrome in children.
- It is characterized by periodic episodes of paroxysmal headache accompanied by nausea, vomiting, abdominal pain, and relief with sleep.

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ICHD-3: INTERNATIONAL CLASSIFICATION OF HEADACHE DISORDERS

Table 6.1: Diagnostic Criteria for Migraine.

Migraine without Aura
A. At least five attacks fulfilling criteria B through D
B. Headache attacks lasting 4 to 72 hours (untreated or unsuccessfully treated)
C. Headache has at least two of the following characteristics:
° Unilateral location
° Pulsating quality
° Moderate or severe pain intensity
° Aggravation by or causing avoidance of routine physical activity (e.g. walking or climbing stairs)
D. During headache at least one of the following:
° Nausea, vomiting, or both
° Photophobia and phonophobia
E. Not better accounted for by another ICHD-3 diagnosis
Migraine with Aura
A. At least two attacks fulfilling criterion B and C
B. One or more of the following fully reversible aura symptoms:
° Visual
° Sensory
° Speech and/or language
° Motor
° Brainstem
° Retinal
C. At least two of the following four characteristics:
° At least one aura symptom spreads gradually over ≥5 minutes, and/or two or more symptoms occur in succession
° Each individual aura symptom lasts 5 to 60 minutes
° At least one aura symptom is unilateral
° The aura is accompanied, or followed within 60 minutes, by headache
D. Not better accounted for by another ICHD-3 diagnosis, and transient ischemic attack has been excluded

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Migraine with Typical Aura	
A.	At least two attacks fulfilling criteria B through D
B.	Aura consisting of visual, sensory and/or speech/language symptoms, each fully reversible, but no motor, brainstem or retinal symptoms
C.	At least two of the following four characteristics:
	° At least one aura symptom spreads gradually over ≥5 minutes, and/or two or more symptoms occur in succession
	° Each individual aura symptom lasts 5 to 60 minutes
	° At least one aura symptom is unilateral
	° The aura is accompanied, or followed within 60 minutes, by headache
D.	Not better accounted for by another ICHD-3 diagnosis, and transient ischemic attack has been excluded

Migraine Variants

- **Hemiplegic familial migraine:** The hallmark of hemiplegic migraine is unilateral weakness that accompanies a migraine headache attack. The weakness is a manifestation of motor aura and occurs with other forms of aura that impair vision, speech, or sensation. This form of migraine with aura may occur either in families or only in one individual (sporadic).
- **Migraine with brainstem aura (basilar-type migraine):** Migraine with brainstem aura (MBA), previously called basilar-type migraine, is a rare form of migraine with aura wherein the primary signs and symptoms seem to originate from the brainstem, without evidence of weakness. In MBA, attacks of aura lasting 2 to 45 minutes, most often with unilateral or bilateral hemianopic visual disturbance, vertigo, ataxia, dysarthria, bilateral tingling, or numbness. The aura was typically followed by a throbbing occipital headache and nausea. Loss of consciousness lasting 2 to 30 minutes occurred in 25 percent of these individuals.
- **Retinal migraine:** Retinal migraine is a rare disorder. It is characterized by a sudden loss of vision or the perception of bright light (photopsia) or scintillations in one eye only. The aura spreads gradually and lasts 5 to 60 minutes. The headache is typically ipsilateral and periorbital. Visual symptoms may occur without headache. Vision usually recovers in this condition, although permanent visual loss may occur. Fundoscopic examination in this condition is abnormal. The retina appears pale and retinal vessels may be constricted.

EPISODIC SYNDROMES THAT MAY BE ASSOCIATED WITH MIGRAINE

Episodic syndromes that may be associated with migraine include: they are considered as potential precursors of migraine:

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- Cyclic vomiting syndrome
- Abdominal migraine
- Benign paroxysmal vertigo of childhood
- Benign paroxysmal torticollis

MANAGEMENT OF MIGRAINE HEADACHE IN CHILDREN

The management of migraine consists of general measures, abortive treatment, and prophylactic treatment.

General Measures

An AAN Practice Parameter has established the general principles for the management of migraine headache. Education of the family is important in management. Literature describing migraine in children should be provided. The family should be asked to document the occurrence of headaches on a calendar to clarify features of the attacks and to help evaluate the effectiveness of treatment.

- Precipitating factors for migraine should be identified. As an example, the use of caffeine may exacerbate migraine and should be eliminated.
- Sleep disturbances, such as snoring or frequent awakenings, may precipitate headache.
- Dehydration and missing meals are also possible precipitants of migraine.
- Stress caused by school or social situations may increase headache frequency.

Abortive Treatment

Status Migrainosus

- Headache lasting more than 72 h. Rescue medication: Sumatriptan, metoclopramide, prochlorperazine, valproic acid (10 mg/kg IV. Max 500 mg over 5 min, can be repeated x 1), magnesium sulphate (25 mg/kg, Max 1 Gm IV) and dexamethasone (0.3-0.6 mg/Kg IV, Max 8 mg).
- When symptoms develop, the child should rest and/or sleep in a quiet dark room with a cool cloth applied to the forehead.
- The initial treatment consists of an analgesic and may include an antiemetic.
- Improper chronic daily use of abortive headache medications should be avoided. Although they are thought to be benign, they may lead to a type of chronic daily headache known as medication overuse headache (previously termed analgesic rebound headache).
- For children with acute migraine headache, initial abortive treatment with an analgesic, either acetaminophen or ibuprofen, both of which have proven efficacy for migraine in children in randomized, controlled trials. The initial choice depends upon individual preference. If the patient does not respond to one, the other can be tried.

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- Ibuprofen is given in an initial dose of 10 mg/kg. This dose may be repeated in four to six hours if needed. No more than four doses should be given in 24 hours (maximum daily dose 40 mg/kg).
- Alternatively, acetaminophen can be given in a dose of 10 to 20 mg/kg (usually as one or two 325 mg tablets), with a maximum dose of 1000 mg. This may be repeated in two to four hours if symptoms persist but should not exceed three doses in 24 hours.
- Early use of an antiemetic may relieve symptoms and facilitate sleep if nausea and vomiting are prominent. For children with acute migraine who have nausea and vomiting, promethazine in a dose of 0.25 to 0.5 mg/kg rectally as needed at intervals of four to six hours.
- For children who have acute migraine headache without vomiting that is refractory to analgesics, we suggest initial treatment with oral triptans, oral sumatriptan starting at 25 mg, with a maximum dose of 50 mg. For children who do not respond to oral sumatriptan, alternatives include the oral disintegrating tablet formulations of rizatriptan (5 mg wafer) and zolmitriptan (2.5 or 5 mg), and almotriptan tablet (6.25 or 12.5 mg).
- For children who are unable to swallow pills or have early nausea or vomiting, we prefer the orally disintegrating tablet formulations of zolmitriptan and rizatriptan.
- For children and adolescents who have acute migraine headache without vomiting who do not respond to monotherapy with other abortive migraine medications, we suggest treatment with combination of oral sumatriptan and naproxen.
- In children at least five years of age, if analgesics do not provide relief or if persistent vomiting precludes the use of oral medications, including the orally disintegrating tablet (wafer) formulations of zolmitriptan and rizatriptan, we suggest a trial of sumatriptan nasal spray due to its proven efficacy in randomized, controlled trials in adolescents. In addition, it is generally more tolerable to children than an injection. We prefer to start with 5 mg and repeat once in four to six hours if initially effective but the headache returns. If there is no benefit, 10 mg nasal spray (two 5 mg units given together) may be tried. We suggest similar doses of nasal spray in older children, with a maximum daily dose of 20 mg. One drawback to nasal sumatriptan is the associated bad taste, which limits its acceptability in children. This problem can be mitigated by having children suck on a piece of hard candy.
- As alternative, zolmitriptan 5 mg nasal spray can be used, given the randomized clinical trial evidence cited earlier that this agent is safe and effective for the treatment of migraine in adolescents. In the clinical experience of some experts, zolmitriptan nasal spray has a less objectionable taste than sumatriptan nasal spray.

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Prophylactic Treatment Recommendations

- Prophylactic treatment is used when headaches are frequent (more than four times per month) or if severe and prolonged headache results in frequent school absences or prevents important daily activities.
- In the absence of better evidence from clinical trials, we suggest the following approach.
- In children younger than six years of age, we suggest cyproheptadine (Periactin) in a dose of 4 to 12 mg per day, given orally once at bedtime.
- In older children, we suggest propranolol in a starting dose of 1 mg/kg in three divided doses, with a maximum dose of 4 mg/kg per day. The heart rate should be >60 bpm after one minute of exercise. This drug is often discontinued by children who participate in strenuous physical activities.
- If propranolol is not well tolerated, we suggest valproate for prophylaxis. Valproate is given primarily to boys older than five years of age. We suggest not using this drug in adolescent girls because of concerns about weight gain, polycystic ovary syndrome. Prior to use, the potential side effects are discussed with the parents and child. Valproate is started in a dose of 10 to 15 mg/kg in two to three divided doses orally. The dose can be increased in increments of 15 mg/kg to a maximum dose of 60 mg/kg per day.
- If there is a mixed headache disorder or possible depression, we suggest amitriptyline, starting with a single daily 5 mg oral dose, given at night. If frequent headaches persist, the dose is advanced slowly by 5 mg increments, with at least two weeks between changes. The dose should rarely exceed 60 mg daily. An electrocardiogram should be obtained before using higher doses.

  Flunarizine 5 mg daily is a reasonable first line agent, but weight gain and drowsiness are significant side effects.

References

1. Abu-Arafeh I, Razak S, Sivaraman B, Graham C. Prevalence of headache and migraine in children and adolescents: a systematic review of population-based studies. Dev Med Child Neurol 2010; 52:1088.
2. Lateef TM, Merikangas KR, He J, *et al*. Headache in a national sample of American children: prevalence and comorbidity. J Child Neurol 2009; 24:536.
3. Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. Cephalalgia 2018; 38:1.
4. Slater SK, Powers SW, O'Brien HL. Migraine in children: presentation, disability and response to treatment. Curr Opin Pediatr 2018; 30:775.
5. Cuvellier JC, Couttenier F, Joriot-Chekaf S, Vallée L. Chronic daily headache in French children and adolescents. Pediatr Neurol 2008; 38:93.
6. Lewis DW, Koch T. Headache evaluation in children and adolescents: when to worry? When to scan? Pediatr Ann 2010; 39:399.

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7. Roth Z, Pandolfo KR, Simon J, Zobal-Ratner J. Headache and refractive errors in children. J Pediatr Ophthalmol Strabismus 2014; 51:177.
8. Linder SL. Understanding the comprehensive pediatric headache examination. Pediatr Ann 2005; 34:442.
9. Lewis DW, Ashwal S, Dahl G, *et al*. Practice parameter: evaluation of children and adolescents with recurrent headaches: report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. Neurology 2002; 59:490.
10. US Headache Consortium. Evidence-based guidelines in the primary care setting: Neuroimaging in patients with nonacute headache, 2000. www.aan.com/professionals/practice/pdfs/gl0088.pdf (Accessed on March 23, 2011).
11. Expert Panel on Pediatric Imaging:, Hayes LL, Palasis S, *et al*. ACR Appropriateness Criteria® Headache-Child. J Am Coll Radiol 2018; 15:S78.
12. Bear JJ, Gelfand AA, Goadsby PJ, Bass N. Occipital headaches and neuroimaging in children. Neurology 2017; 89:469.
13. Rho YI, Chung HJ, Suh ES, *et al*. The role of neuroimaging in children and adolescents with recurrent headaches--multicenter study. Headache 2011; 51:403.
14. Choosing Wisely. American Headache Society. Five things physicians and patients should question. www.choosingwisely.org/wp-content/uploads/2013/11/AHS-5things-List_112013.pdf (Accessed on December 08, 2013).
15. Taheri S. Effect of exclusion of frequently consumed dietary triggers in a cohort of children with chronic primary headache. Nutr Health 2017; 23:47.
16. Fisher E, Law E, Dudeney J, *et al*. Psychological therapies for the management of chronic and recurrent pain in children and adolescents. Cochrane Database Syst Rev 2018; 9:CD003968.
17. Gladstein J, Mack KJ. Common presentations of chronic daily headache in adolescents. Pediatr Ann 2010; 39:424.
18. Straube A, Heinen F, Ebinger F, von Kries R. Headache in school children: prevalence and risk factors. Dtsch Arztebl Int 2013; 110:811.
19. Abu-Arafeh I, Razak S, Sivaraman B, Graham C. Prevalence of headache and migraine in children and adolescents: a systematic review of population-based studies. Dev Med Child Neurol 2010; 52:1088.
20. Perry MC, Yaeger SK, Toto RL, *et al*. A Modern Epidemic: Increasing Pediatric Emergency Department Visits and Admissions for Headache. Pediatr Neurol 2018; 89:19.
21. Rossi R, Versace A, Lauria B, *et al*. Headache in the pediatric emergency department: A 5-year retrospective study. Cephalalgia 2018; 38:1765.
22. Kan L, Nagelberg J, Maytal J. Headaches in a Pediatric Emergency Department: Etiology, Imaging, and Treatment. The Journal of Head and Face Pain 2001; 40:25.
23. Gofshteyn JS, Stephenson DJ. Diagnosis and Management of Childhood Headache. Curr Probl Pediatr Adolesc Health Care 2016; 46:36.
24. Karsan N, Prabhakar P, Goadsby PJ. Characterising the premonitory stage of migraine in children: a clinic-based study of 100 patients in a specialist headache service. J Headache Pain 2016; 17:94.
25. Langdon R, DiSabella MT. Pediatric Headache: An Overview. Curr Probl Pediatr Adolesc Health Care 2017; 47:44.

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26. Massano D, Julliand S, Kanagarajah L, *et al*. Headache with focal neurologic signs in children at the emergency department. J Pediatr 2014; 165:376.
27. Lewis DW, Ashwal S, Dahl G, *et al*. Practice parameter: evaluation of children and adolescents with recurrent headaches: report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. Neurology 2002; 59:490.
28. American College of Radiology. ACR appropriateness criteria. Headache - child. http://www.acr.org/~/media/ACR/Documents/AppCriteria/Diagnostic/Headache-Child.pdf (Accessed on August 06, 2012).

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Chapter

07

The Child Who Suddenly Stops Walking

The child warrants immediate attention. Until the cause is determined, the child who lost the ability to walk or is experiencing severe difficulty in walking should be considered a potential neurological/neurosurgical emergency and urgent imaging may be required.

Historical Clues to the Etiology May Include

- Always specifically ask about bladder and bowel function to identify spinal pathology.
- Post-ictal: Todd paresis
- Post-migraine: hemiplegic migraine
- Preceding trauma: cord pathology causing compression, infarction, transection; stroke due to arterial dissection
- Recent inter-current illness: Guillain-Barre, Transverse myelitis
- Viral encephalitis
- Tic Bite: Lyme disease
- Semi-acute onset with bladder and bowel involvement: spinal tumor
- Chemotherapy: Vincristine, cisplatin
- Organophosphate or carbamate poisoning: exposure to insecticides
- Adolescent with history of IV drug abuse: wound botulism

Causes of Inability to Walk and Peripheral Weakness

Muscles

- **Myositis**: Transient acute myositis/myalgia with viral illness, Dermatomyositis
- **Useful early investigation**: Elevated CK; viral titers
- **Rhabdomyolysis**: Disorders of carbohydrate metabolism, disorders of fatty acid metabolism.
- **Useful early investigation**: Acyl carnitine profile when symptomatic, hyperkalemia
- **Periodic paralysis (AD Channelopathies)**: Familial hypokalemic periodic paralysis, Familial hyperkalemic periodic paralysis, Familial normokalemic periodic paralysis
- **Useful early investigation**: Serum K level

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Neuromuscular Junction

- **Autoimmune**: Myasthenia gravis
- **Useful early investigation**: Tensilon test, peripheral neurophysiology
- **Acquired**: Tick paralysis (North America), ICU weakness (Combination of neuromuscular blockade drugs, corticosteroid myopathy and depletion of myosin (usually presenting as failure to wean from ventilator)
- **Useful early investigation**: Peripheral neurophysiology

Peripheral Nerve

- Guillain-Barre syndrome
- **Useful early investigation**: Peripheral neurophysiology, CSF protein (late)
- **Metabolic**: Intermittent porphyria.
- **Toxic**: Vincristine, lead, mercury, arsenic

Anterior Horn Cell

- Poliomyelitis
- **Useful early investigation**: Peripheral neurophysiology

Spinal Cord

- Spinal cord compression
- **Epidural**: Metastasis(Leukemia, lymphoma, neuroblastoma), abscess, Hematoma (hemophilia, trauma), bony compression (Morquio syndrome, Down syndrome; fracture/ dislocation of vertebrae
- **Intradural**: Neurofibroma
- **Intramedullary**: Gioma, Ependymoma, Hydromyelia.
- Transversemyelitis
- **Vascular**: Anterior spinal artery occlusion (infarction of anterior portion of cord), Vascular malformation

EXAMINATION

- Purpose of examination is to locate the site(s) of pathology.
- Acute weakness will be due to cord, nerve root, peripheral nerve, neuromuscular junction or muscle weakness.
- Identify the pattern of weakness:
  - Proximal (myopathy?)
  - Peripheral (neuropathy?)
  - Symmetrical or asymmetrical?
- Are DTR present? Planter response?

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- What is the sensory distribution of any sensory disturbances? Is it consistent with spinal dermatome level, or a peripheral nerve pattern?
- What modalities of sensation are involved: selective loss of spinothalamic (pain and temperature) sensation with preservation of vibration and joint position sense seen in anterior spinal artery syndrome?
- Is there involvement of the sphincter :
  - Is anal sphincter closed tight or lax?
  - Is perianal sensation intact?
  - Is anal reflex (sphincter contraction in response to drawing point across perianal skin) preserved?

INVESTIGATIONS

- The main urgent decision is whether this child needs emergency MRI of the spine at appropriate level(s). This is required in any situation where examination locate these the lesion to the spinal cord.
- Organize urgent MRI when:
  - Back pain present (in contrast limb pain is common in, and consistent with Guillain Barre).
  - Weakness is in all muscle groups below a particular spinal root level.
  - A dermatomal pattern of sensory involvement is present (but not always seen).
  - Sphincter involvement typically implies intrinsic cord involvement and sphincter function may be preserved in situations of external cord compression.
- Establish whether this is a child who cannot move because of weakness; from a child who does not want to walk because of fear pain or fear (e.g. due to unsteadiness and fear of falling).
- Be persistent in cajoling and assisting the child to walk as much as possible in order to try to make this distinction.

GUILLAIN-BARRE SYNDROME

INTRODUCTION

The acute immune-mediated polyneuropathies are classified under the eponym Guillain-Barre syndrome (GBS), after the authors of early descriptions of the disease. Historically, GBS was considered a single disorder, but it is now known to be a heterogeneous syndrome with several variant forms. Most often, GBS presents as an acute monophasic paralyzing illness provoked by a preceding infection. In addition to the demyelinating form, which is the most common type, axonal forms of GBS are well-recognized.

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CLINICAL FEATURES

- Guillain-Barre Syndrome (GBS) is a syndrome with a number of variants. In patients with Acute Inflammatory Demyelinating Polyradiculopathy (AIDP), the most common form of GBS, two-thirds develop the neurologic symptoms two to four weeks after having what appears to be a benign febrile respiratory or gastrointestinal infection.
- The classic presentation of GBS begins with fine paresthesias in the toes and fingertips followed by lower extremity symmetric or modestly asymmetric weakness that may ascend over hours to days to involve the arms and, in severe cases, the muscles of respiration.
- The predominant symptoms of GBS at presentation in children are pain and gait difficulty. In preschool-aged children, the most common symptoms are refusal to walk and pain in the legs. Pain typically involves the back and the legs.
- The most frequent initial symptoms were gait unsteadiness, neuropathic pain, and inability to walk. By the peak of the illness, the frequency of symptoms appears as follows:
    - Neuropathic pain
    - Cannot walk
    - Autonomic dysfunction
    - Cranial nerve involvement
    - Cannot use their arms
    - May require mechanical ventilation to due respiratory muscles weakness
    - In those with cranial neuropathy, the facial nerve is most commonly affected, resulting some time in bilateral facial weakness.
- Autonomic dysfunction occurs in approximately one-half of children with GBS, and may include the following.
    - A variety of cardiac dysrhythmias (asystole, bradycardia, persistent sinus tachycardia, and atrial and ventricular tachyarrhythmias)
    - Orthostatic hypotension
    - Transient or persistent hypertension
    - Paralytic ileus
    - Bladder dysfunction
    - Abnormal sweating

SUBTYPES OF GUILLAIN-BARRE SYNDROME

- **Acute inflammatory demyelinating polyneuropathy:** Acute Inflammatory Demyelinating Polyneuropathy (AIDP) is the prototype of GBS, and is the most common form in North America, Europe and most of the developed world, where it accounts for about 85 to 90 percent of cases.

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- **Acute motor axonal neuropathy:** Acute Motor Axonal Neuropathy (AMAN) is a pure motor form of GBS. This disorder is distinguished from AIDP by its involvement of predominantly motor nerves and an electrophysiologic pattern suggesting axonal damage.
- **Acute motor-sensory axonal neuropathy:** Acute Motor-Sensory Axonal Neuropathy (AMSAN) Resembles The Motor Axonal Variant But Has More Sensory Symptoms. The course tends to be prolonged. The pathology is predominantly axonal lesions of both motor and sensory nerve fibers. This form of GBS is recognized infrequently in children. The infrequent diagnosis may be caused in part by the difficulty of performing sensory testing in children and because electrophysiologic studies often are not done.
- **Miller Fisher syndrome:** Miller Fisher Syndrome (MFS) is characterized by external ophthalmoplegia, ataxia, and muscle weakness with areflexia. Incomplete forms include acute ophthalmoplegia without ataxia, and acute ataxic neuropathy without ophthalmoplegia. Cerebrospinal fluid findings and electrophysiologic features are similar to those in acute inflammatory demyelinating polyneuropathy. Brainstem auditory evoked potentials demonstrate peripheral and central conduction defects.
- **Polyneuritis cranialis:** Patients with polyneuritis cranialis develop acute bilateral multiple cranial nerve involvement and severe peripheral sensory loss. They typically have bilateral facial weakness, dysphagia, and dysphonia with optic nerve sparing. Patients tend to be younger than those with other types.

DIAGNOSIS

- The initial diagnosis of Guillain-Barre Syndrome (GBS) is based upon the clinical presentation. The typical clinical features of GBS are progressive, mostly symmetric or modestly asymmetric muscle weakness and absent or depressed deep tendon reflexes. The weakness can vary from mild difficulty with walking to nearly complete paralysis of all extremity, facial, respiratory, and bulbar muscles. However, some GBS variants have atypical features, and the variable initial presentations can hinder early diagnosis.
- The diagnosis of GBS is confirmed if Cerebrospinal Fluid (CSF) and electrodiagnostic studies show characteristic abnormalities. Therefore, lumbar puncture and clinical neurophysiology studies are performed in all patients with suspected GBS.
- **Cerebrospinal fluid**: In patients with GBS, lumbar puncture often reveals an elevated Cerebrospinal Fluid (CSF) protein with a normal CSF white blood cell count. This finding, known as albuminocytologic dissociation, is present in 50 to 66 percent of patients with GBS in the first week after the onset of symptoms and ≥75 percent of patients in the third week. The elevated protein may be due to increased permeability of the blood-nerve-barrier at the level of the proximal nerve roots. A normal CSF

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protein is found in one-third to one-half of patients when tested earlier than one week after symptom onset.

- **Electrodiagnostic studies**: Electrodiagnostic studies are the most specific and sensitive tests for diagnosis of the GBS. They demonstrate a variety of abnormalities indicating evolving multifocal demyelination, including:
  - Partial motor conduction block
  - Slowed nerve conduction velocities
  - Abnormal temporal dispersion
  - Prolonged distal latencies
  - Evidence of conduction block usually is the earliest abnormality. Slowed nerve conduction velocities reflect the segmental demyelination. In the first days after the onset of weakness, some patients with acute inflammatory demyelinating polyneuropathy (AIDP) have a sural sparing pattern in which the sural nerve sensory response is normal, while median and ulnar nerve sensory responses are abnormal.
  - Absent H reflexes or abnormal prolonged F-waves indicate proximal nerve root involvement. The H-reflex was the single most sensitive test for early GBS, being absent in 97 percent tested within seven days of the onset of neurologic symptoms. Testing for the H-reflex requires electrical stimulation of the sciatic nerve.
  - A normal nerve conduction study occurring after several days of symptoms, particularly in the setting of severe weakness, renders the diagnosis of GBS unlikely. This finding should prompt a search for alternative explanations for the patient's illness.
  - Electromyogram abnormalities typically are delayed for two to three weeks. The motor units show denervation potentials, reflecting secondary axonal degeneration.
  - In the motor and motor-sensory variants of GBS, nerve conduction velocities are normal. In both forms, motor amplitudes in nerve conduction studies are less than 10 percent of normal, with severe denervation evident on follow-up needle examination. In the motor-sensory variant, sensory amplitudes also are decreased.
- **Magnetic resonance imaging:** Spinal MRI with administration of gadolinium frequently shows enhancement of the spinal nerve roots and cauda equina during the first weeks after the onset of GBS in children. The enhancement may be diffuse or predominantly involve the ventral (anterior) nerve roots, and less often the dorsal (posterior) roots. Evidence from uncontrolled retrospective studies suggests that the sensitivity of contrast-enhanced spinal MRI for the diagnosis of GBS is >90 percent. The diagnosis of GBS cannot be made by MRI alone.
- **Monitoring and supportive care:**
  - During the initial phase of GBS, all patients require close monitoring of motor, autonomic (i.e. blood pressure, heart rate and sphincter

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function), and respiratory function. Serial pulmonary function testing should be performed routinely. In most cases, pulmonary function monitoring (i.e. vital capacity and maximum inspiratory pressure) should be performed every four hours at the bedside. All children, particularly those who are too young to cooperate with pulmonary testing, should be closely monitored and observed for fatigue and other clinical signs of impending respiratory muscle failure, as discussed below.

- Patients should be electively intubated if clinical evaluation or pulmonary function tests suggest impending respiratory failure. Vigilance is essential since respiratory deterioration can occur rapidly.
- **Need for intensive care**: Children with any of the following problems should be admitted urgently to a pediatric intensive care unit.
- Flaccid quadriparesis
- Rapidly progressive weakness
- Reduced vital capacity (≤20 mL/kg)
- Bulbar palsy
- Autonomic cardiovascular instability
- **Need for assisted ventilation**: Approximately 10 to 20 percent of children with GBS require mechanical ventilation for respiratory failure..
- Children with a vital capacity approximately one-half the normal value for age or ≤20 mL/kg of body weight generally progress to require ventilatory support.
- The following parameters warn of impending respiratory arrest and are an indication for intubation.
- Vital capacity ≤20 mL/kg
- Maximum inspiratory pressure less negative than -30 cmH_2O (i.e. between -30 and 0 cmH_2O)
- Maximum expiratory pressure ≤40 cmH_2O
- Tidal volume <5 mL/kg
- Pulmonary testing and measuring vital capacity is difficult in children who cannot cooperate, typically those younger than six years of age. These patients should be closely monitored and observed for fatigue and other clinical signs of impending respiratory muscle failure. These signs include the following:
- A sustained increase of pCO_2 to ≥50 mmHg (normally 35 to 40 mmHg)
- An increasing respiratory rate
- An increased use of accessory muscles (e.g. sternocleidomastoid use, flaring of the ala nasae, intercostal retractions) and decreased or

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paradoxical diaphragm movements; these reflect restrictive lung-chest wall movement and low lung volumes

- Sweating about the head and neck, wide pulse pressure, and bounding pulses; these portend respiratory failure with CO_2 retention
- Children have less metabolic and muscle reserve than adults. They can deteriorate quite rapidly and become apneic or develop alveolar hypoventilation "right under your nose." Generally, it is wise to have a pediatric critical care specialist involved early in the clinical course.
- Sedation and neuromuscular blockade should be avoided in ventilated patients because they obscure the course of the illness. Providing scrupulous airway care and chest physiotherapy reduce the risk of pneumonia. Tracheostomy may need to be performed if prolonged ventilation is required.

- **Autonomic dysfunction**: Autonomic dysfunction is a well-recognized feature of GBS and is a significant source of mortality. Consequently, close monitoring of blood pressure, fluid status, and cardiac rhythm are essential to the management of these patients. Care must also be taken when vasoactive or sedative drugs are used, because the dysautonomia may exaggerate the hypotensive responses to these drugs.
- **Other supportive measures:**
  - Nutritional needs should be addressed early in the disease course. Orogastric tube feeding, gastrostomy, or parental nutrition often is necessary.
  - The patient's position should be changed frequently for comfort and to avoid skin breakdown.
  - Intermittent pressure leg boots and subcutaneous heparin treatment should be initiated to prevent deep vein thrombosis.
  - Physical therapy, occupational therapy, and social services should be involved early. Providing the patient with a method of communication is important if normal speech is not possible. Pencil and paper, a "magic slate" or a communication board can be given to those old enough to write.
- **Immunotherapies**:
  - The main modalities of therapy for GBS are intravenous immune globulin (IVIG) and plasma exchange (also called plasmapheresis). Treatment with IVIG or plasma exchange for children with severe GBS, in general agreement with guidelines from the American Academy of Neurology (AAN). IVIG is preferred to plasma exchange in children because of the relative safety and ease of administration, although there are no reliable data suggesting that one or the other is superior.
  - IVIG and plasma exchange for children with GBS should be reserved for those with any of the following indications:

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- Progressing weakness
- Worsening respiratory status or need for mechanical ventilation
- Significant bulbar weakness
- Inability to walk unaided

° IVIG and plasma exchange are not recommended for ambulatory children with GBS who have mild, non-progressive disease or for children whose symptoms have stabilized.

° Children who have rapid progression followed by stabilization of symptoms within the first or second week of GBS onset may still be considered candidates for treatment by some child neurologists.

° Time to treatment onset may be important in children although data are lacking.

° Glucocorticoids are not beneficial for GBS and have no role in its treatment

- **Intravenous immune globulin:**

° The total dose of IVIG for the treatment of GBS in children is 2 g/kg, given as 1 g/kg for two days or 400 mg/kg for five days. This dose is empiric and is based upon treatment of patients with immune deficiency disorders.

° However, there was no significant difference between the two-day and five-day regimens for the primary outcome measure, time to regain unaided walking. Given these data, we suggest using IVIG 400 mg/kg per day for five days when treating children with GBS.

° IVIG is preferred to plasma exchange in children because of the relative safety and ease of administration, although it has not been shown to have better results.

- **Plasma exchange:**

° The mechanism is thought to be removal of antibodies directed against nerves from the circulation. Increased muscle strength, earlier improvement, and a lower requirement for mechanical ventilation have been demonstrated, as discussed separately. Experience with plasma exchange in children with GBS is limited.

° Plasma exchange requires special equipment and trained personnel and can be performed only at centers with expertise in the treatment of children. Because of technical considerations, this procedure generally is not performed in children younger than two years of age. Younger children require placement of a central catheter, which increases the risks of developing thrombosis and infection. Complications of plasma exchange are uncommon but include hypotension, hypocalcemia, arrhythmias, and cardiac arrest.

° The procedure usually consists of four double-volume exchanges performed on alternate days over one week. Immunoglobulin levels may be decreased by 30 to 40 percent after plasma exchange.

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- Plasma exchange is recommended for those patients who have rapidly progressing weakness, worsening respiratory status, are unable to walk unaided, require mechanical ventilation, or have significant bulbar weakness. As a result of the cost, risk, and discomfort to the patient, plasma exchange generally is not used for ambulatory patients with mild disease or for patients whose symptoms have stabilized.
- Most of the physicians use plasma exchange in children who have had a previous adverse reaction to Intravenous Immune Globulin (IVIG) treatment and in those who do not respond to IVIG.

PROGNOSIS

- In general, the prognosis of GBS in children is thought to be better than adults but data are limited. In various reports, the following observations were noted:
- Mortality was 3 to 4 percent, and usually was secondary to respiratory failure or cardiac complications.
- An excellent long-term recovery (e.g. symptom-free or no disability despite residual symptoms) was observed in 85 to 92 percent of children.
- Approximately 88 percent or more of children were ambulatory within six months after onset, and nearly all walked within one year.
- Recurrence of GBS was reported in 2 to 5 percent.
- Although there are no firm prognostic indicators, some reports suggested that rapid progression of weakness during the acute phase of GBS was associated with long-term sequelae or that maximum disability correlated with outcome.

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Chapter

08

Transverse Myelitis

- Acute Transverse Myelitis (TM) is a rare acquired neuro-immune spinal cord disorder that can present with the rapid onset of weakness, sensory alterations, and bowel or bladder dysfunction.
- TM can occur as an independent entity, usually as a postinfectious complication, but TM also exists on a continuum of neuro-inflammatory disorders that includes acute disseminated encephalomyelitis, multiple sclerosis, and neuromyelitis optica.
- The clinical features, diagnostic work-up, and acute and chronic therapies differ between these forms of TM. It is important in the evaluation of patients with acute myelopathies to exclude compressive and noninflammatory causes of myelopathy as well as to distinguish various types of TM, since the prognosis, risk of recurrence, and treatment options may differ among these distinct entities.
- The immunopathogenesis of TM is varied and reflects the rather diverse spectrum of this disease from idiopathic to disease-associated myelitis.
- In 30 to 60 percent of the idiopathic TM cases, there is an antecedent respiratory, gastrointestinal, or systemic illness. Molecular mimicry and super antigen-mediated disease have also been described as potential mechanisms of autoimmunity.
- Idiopathic TM usually occurs as a postinfectious complication that appears to result from an autoimmune process. Alternatively, TM can be directly associated with infectious, systemic inflammatory, or multifocal central nervous system disease.
- Subtypes of TM are differentiated on the basis of the clinical severity and radiologic extent of the spinal cord lesion. These include acute partial TM, acute complete TM and Longitudinally Extensive TM (LETM).
    - Acute partial TM refers to spinal cord dysfunction that is mild or grossly asymmetric with an MRI lesion extending one to two vertebral segments
    - Acute complete TM refers to spinal cord dysfunction that causes symmetric, complete or near complete neurologic deficits (paresis, sensory loss, and autonomic dysfunction) below the level of the lesion with an MRI lesion extending one to two vertebral segments
    - Longitudinally Extensive Transverse Myelitis (LETM) refers to complete or incomplete spinal cord dysfunction with a lesion on MRI that extends three or more vertebral segments

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CLINICAL FEATURES

- The onset of TM is characterized by acute or subacute development of neurologic signs and symptoms consistent with motor, sensory and/or autonomic dysfunction.
- Motor symptoms include a rapidly progressing paraparesis that can involve the upper extremities, with initial flaccidity followed by spasticity. Most patients have a sensory level.
- Autonomic symptoms include increased urinary urgency, bladder and bowel incontinence, difficulty or inability to void, incomplete evacuation and bowel constipation.
- The onset of urinary retention may be the first sign of myelitis and should always raise the possibility of a myelopathy.

Diagnostic Criteria for Transverse Myelitis

The diagnosis of TM is suspected when there are acute or subacute signs and symptoms of motor, sensory and/or autonomic dysfunction that localize to one or more contiguous spinal cord segments in patients with no evidence of a compressive cord lesion. Thus, the diagnosis of TM requires exclusion of a compressive cord lesion, usually by MRI, and confirmation of inflammation by either gadolinium-enhanced MRI or lumbar puncture.

- Sensory, motor or autonomic dysfunction attributable to the spinal cord
- Bilateral signs and/or symptoms
- Clearly defined sensory level
- No evidence of compressive cord lesion
- Inflammation defined by cerebrospinal fluid pleocytosis

EVALUATION

- The diagnostic approach to acute myelopathy proposed here is based upon earlier work and emphasizes the determination of distinct entities that are likely to have different treatment options, risk of recurrence and prognoses.
- When myelopathy is suspected, emergent spinal imaging is warranted to exclude a compressive etiology. An MRI of the spine is the preferred diagnostic study, but a spine CT or CT myelogram are reasonable alternatives if an MRI cannot be obtained immediately.
- If a compressive myelopathy is ruled out, the clinician should determine whether the myelopathy is inflammatory or non-inflammatory. The best surrogate markers for inflammation cerebrospinal fluid with pleocytosis and/or an elevated IgG index or a 'hot' spinal MRI (i.e. with positive gadolinium enhancement).
- It is also necessary to evaluate for the presence of infection, systemic inflammation, and the extent and sites central nervous system inflammation.

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INVESTIGATIONS

The following investigations are recommended for the evaluation of all patients with suspected TM.

- MRI of the entire spine, with and without gadolinium, to evaluate for compressive versus noncompressive cord lesion(s)
- Brain MRI with and without gadolinium to evaluate for the presence of brain lesions suggestive of multiple sclerosis
- Cerebrospinal fluid analysis including cell count and differential, protein, glucose, VDRL, oligoclonal bands, immunoglobulin G index, and cytology

For patients with longitudinally extensive spinal cord lesions, the following tests are additionally recommended:

- Serum erythrocyte sedimentation rate, C reactive protein, antinuclear antibodies, antibodies to extractable nuclear antigen, rheumatoid factor, antiphospholipid antibodies, and antineutrophil cytoplasmic antibodies
- Chest CT to evaluate for evidence of sarcoidosis

TREATMENT OF ACUTE IDIOPATHIC TM

- Intravenous glucocorticoids have long been considered the standard of care and first-line therapy in acute idiopathic TM.
- Injection Methylprednisolone ("Pulse" therapy: IV (succinate): 30 mg/kg/dose once daily for 3 days; maximum dose: 1Gm daily) or dexamethasone IV: 0.08-0.3 mg/kg/day or 2.5-10 mg/m2/day in divided doses every 6-12 hours (200 mg daily) for three to five days. Continued treatment with glucocorticoids or more aggressive regimens is based upon the clinical course and radiologic parameters.
- Consider IVIG, plasma exchange, and alternate diagnosis (i.e. vascular) if not responsive.
- Plasma exchange may be effective for acute central nervous system demyelinating diseases that fail to respond to high-dose glucocorticoid treatment.
- Thus, in addition to high-dose glucocorticoid therapy, some neurologists suggest treatment with plasma exchange for patients who have acute TM with motor impairment. Some preferred regimen is five treatments, each with exchanges of 1.1 to 1.5 plasma volumes, every other day for 10 days.
- For patients with significant deficits, waiting until glucocorticoid treatments are completed is not necessary. Clinical judgment must be used and some patients may benefit from earlier intervention with plasma exchange.

PROGNOSIS

- Most patients with idiopathic TM have at least a partial recovery, which usually begins within one to three months, and continues with exercise and rehabilitation therapy.

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- Recovery can proceed over years. Some degree of persistent disability is common, occurring in about 40 percent.
- A very rapid onset with complete paraplegia and spinal shock has been associated with poorer outcomes.

KEY POINTS

- The onset of TM is characterized by acute or subacute development of neurologic signs and symptoms consistent with motor, sensory and/or autonomic dysfunction.
- Autonomic symptoms involve increased urinary urgency, bladder and bowel incontinence, difficulty or inability to void, incomplete evacuation and bowel constipation.
- The diagnosis of TM requires exclusion of a compressive cord lesion, usually by MRI, and confirmation of inflammation by either gadolinium-enhanced MRI or lumbar puncture.
- Most patients with idiopathic TM have at least a partial recovery, which usually begins within one to three months and continues with exercise and rehabilitation therapy.
- The majority of patients with TM experience monophasic disease. Recurrence has been reported in approximately 25 to 33 percent of patients with idiopathic TM. With disease-associated (secondary) TM, the recurrence rate may be as high as 70 percent.
- Patients presenting with acute complete transverse myelitis have a generally cited risk of multiple sclerosis of only 5 to 10 percent.

References

1. Jones HR Jr. Guillain-Barré syndrome: perspectives with infants and children. Semin Pediatr Neurol 2000; 7:91.
2. Yuki N, Hartung HP. Guillain-Barré syndrome. N Engl J Med 2012; 366:2294.
3. Sejvar JJ, Baughman AL, Wise M, Morgan OW. Population incidence of Guillain-Barré syndrome: a systematic review and meta-analysis. Neuroepidemiology 2011; 36:123.
4. Morris AM, Elliott EJ, D'Souza RM, *et al*. Acute flaccid paralysis in Australian children. J Paediatr Child Health 2003; 39:22.
5. Roodbol J, de Wit MC, Walgaard C, *et al*. Recognizing Guillain-Barre syndrome in preschool children. Neurology 2011; 76:807.
6. Lin JJ, Hsia SH, Wang HS, *et al*. Clinical variants of Guillain-Barré syndrome in children. Pediatr Neurol 2012; 47:91.
7. Arcila-Londono X, Lewis RA. Guillain-Barré syndrome. Semin Neurol 2012; 32:179.
8. McKhann GM, Cornblath DR, Griffin JW, *et al*. Acute motor axonal neuropathy: a

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frequent cause of acute flaccid paralysis in China. Ann Neurol 1993; 33:333.

9. Shahrizaila N, Yuki N. Bickerstaff brainstem encephalitis and Fisher syndrome: anti-GQ1b antibody syndrome. J Neurol Neurosurg Psychiatry 2013; 84:576.
10. Mulkey SB, Glasier CM, El-Nabbout B, *et al*. Nerve root enhancement on spinal MRI in pediatric Guillain-Barré syndrome. Pediatr Neurol 2010; 43:263.
11. Zuccoli G, Panigrahy A, Bailey A, Fitz C. Redefining the Guillain-Barré spectrum in children: neuroimaging findings of cranial nerve involvement. AJNR Am J Neuroradiol 2011; 32:639.
12. Baxter R, Lewis E, Goddard K, *et al*. Acute Demyelinating Events Following Vaccines: A Case-Centered Analysis. Clin Infect Dis 2016; 63:1456.
13. Beh SC, Greenberg BM, Frohman T, Frohman EM. Transverse myelitis. Neurol Clin 2013; 31:79.
14. Scott TF, Frohman EM, De Seze J, *et al*. Evidence-based guideline: clinical evaluation and treatment of transverse myelitis: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology 2011; 77:2128.
15. Wolf VL, Lupo PJ, Lotze TE. Pediatric acute transverse myelitis overview and differential diagnosis. J Child Neurol 2012; 27:1426.
16. Cortese I, Chaudhry V, So YT, *et al*. Evidence-based guideline update: Plasmapheresis in neurologic disorders: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology 2011; 76:294.
17. Bigi S, Banwell B, Yeh EA. Outcomes after early administration of plasma exchange in pediatric central nervous system inflammatory demyelination. J Child Neurol 2015; 30:874.
18. Agrawal S, Peake D, Whitehouse WP. Management of children with Guillain-Barré syndrome. Arch Dis Child Educ Pract Ed 2007; 92:161.
19. Patwa HS, Chaudhry V, Katzberg H, *et al*. Evidence-based guideline: intravenous immunoglobulin in the treatment of neuromuscular disorders: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology 2012; 78:1009.
20. Australian Department of Health and Ageing, 2013. Annual report of the Australian National Poliovirus Reference Laboratory, 2012.Communicable Diseases Intelligence 2013;37(2).
21. Australian Department of Health and Ageing, 2013. Australia's notifiable disease status, 2011: Annual report of the National Notifiable Diseases Surveillance System.
22. Australian Department of Health and Ageing, 2008. An Acute Flaccid Paralysis and Poliomyelitis Response Plan for Australia.
23. Australian Paediatric Surveillance Unit, 2008. Acute flaccid paralysis study protocol.
24. Heymann D (Ed), 2008. Control of Communicable Diseases Manual, 19th edition. American Public Health Association: Washington.

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Chapter

09 Vitamin-Responsive Epileptic Encephalopathies

Epileptic Encephalopathies (EEs) are conditions in which progressive cognitive and neuropsychological regression occurs, attributable to excessive ictal and interictal epileptogenic activity during brain maturation. The progression in such disorders is mostly relentless and leads to irreversible damage to the developing brain. Original classification of International League Against Epilepsy (ILAE) included only a few conditions under strict criteria of EE; however, in 2010, they extended the definition to any form of epilepsy that can cause encephalopathic effect. Most of these conditions are managed symptomatically with AEDs; very rarely do these conditions have treatable underlying causes, including genetic, metabolic, autoimmune, and nutritional causes. Treatment with a specific vitamin or vitamin derivative in these specific cases may halt such inexorable progression.

1. Pyridoxine Dependent Epilepsy (PDE)
2. Pyridoxal 5 phosphate dependent epilepsy
3. Folinic acid responsive epilepsies
4. Biotinidase deficiency
5. Vitamin B_{12} deficiency

1. Pyridoxine Dependent Epilepsy (PDE)

- It usually manifest in neonatal period. The affected neonates usually manifest within the first few hours after birth with seizures. The seizure evolves into status epilepticus despite adequate treatment with AEDs.
- An antenatal history of unusual fetal movements indicating intrauterine seizures may be present although this is not very common.
- The seizure semiology is quite variable with focal, generalized, myoclonic, epileptic spasms, and/or mixed seizure patterns. PDE can be easily confused with hypoxic ischemic encephalopathy or sepsis due to age of onset and frequent seizure manifestation.
- Rarely, the clinical manifestations may be delayed into the later part of infancy up to 2 months of age or beyond. Again, these children manifest with medically refractory epilepsy that can evolve into status epilepticus.

Investigations

- Urine L-Alpha Amniodipic, Semialdehyde (AASA) and CSF pipicolic acid level remain high even on treatment. However, AASA assay is not yet commercially available. Usually, these biochemical findings persist even after years of effective treatment.

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- There are no specific radiological findings unique to PDE. Infants with PDE often have variable degrees of brain atrophy, thinning of the corpus callosum, mega cisterna magna, progressive hydrocephalus, and focal cortical dysplasia.
- If treated early in the course, the brain MRI may become normal. MR spectroscopy may show decreased N acetylaspartate to creatine ratio in the cerebral cortex indicating neuronal loss.
- EEG findings are nonspecific and abnormalities range from a mildly slow background activity to burst-suppression pattern. In between these two extremes, one may find generalized and multifocal epileptiform activity, bursts of high voltage slow waves, and hypsarrhythmia. The paroxysmal events and seizures frequently are not associated with EEG changes indicating that not all the events are epileptic.
- Mutations in the ALDH7A1 gene have been proven to be the molecular cause of PDE.

Treatment

- Treatment is with an initial dose of 50 to 100 mg of IV pyridoxine which can result in dramatic seizure control and EEG improvement.
- Occasionally, some patients may require up to 500 mg in sequential dosing. These interventions should only be attempted in a controlled ICU setting, as intravenous pyridoxine is reported to cause rare instances of respiratory arrest.
- This should be followed by a maintenance dose of 15-18 mg/kg/day in two daily divided doses with a maximum daily dose of 500 mg.
- Although early diagnosis and treatment are very important, a wide variety of neurodevelopmental disabilities have been noted in patients with PDE irrespective of timing of initiation of treatment, indicating an underlying multifactorial etiology for developmental outcome. They range from expressive language deficits to cognitive dysfunction, obsessive compulsive disorder, and pervasive developmental disorder. There may be motor developmental delay with associated persistent mild reductions in tone.

2. Pyridoxal 5 Phosphate Dependent Epilepsy

Pyridoxal 5 Phosphate (P5P) dependent epilepsy is a different entity from PDE with distinct clinical features and neurophysiologic manifestations. Neonates born with PLP dependent epilepsy are invariably premature and have features that mimic organic acidemia immediately after birth. Hypoglycemia and lactic acidosis with intractable seizures are often seen. Antenatal history of fetal seizures is very common. The seizure semiology includes clonic or myoclonic jerks and complex ocular, facial, or orolingual movements. These infants are refractory to treatment with AEDs or pyridoxine. If untreated, these infants will die or have severe neurodevelopmental impairments. Affected patients respond gradually to pyridoxal 5 phosphate treatments.

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Investigations

- Plasma aminoacidogram will reveal elevated glycine and threonine.
- CSF neurotransmitter studies show elevated LDOPA and 3-methoxytyrosine; decreased homovanillic acid and 5-hydroxyindoleacetic acid.
- Interictal, EEG demonstrates a burst suppression pattern as seen in Ohtahara syndrome. Rarely, the EEG may be normal.
- Genetically, PLP dependent epilepsy is related to *PNPO* gene mutation located on chromosome 17 and is inherited in an autosomal recessive manner.

Treatment

- Treatment with pyridoxine has no impact on clinical or EEG characteristics. However, parenteral PLP results in significant improvement.
- The typical dose of PLP is 30–50 mg/kg/day in 3-4 divided doses as an enteral preparation.
- Early diagnosis and treatment is the most important predictor of outcome. Untreated cases have high mortality, and survivors are left with poor neurocognitive outcome.

3. Folinic Acid Responsive Epilepsies

i. Cerebral Folate Deficiency Syndrome

- Two forms-an inherited genetic syndrome due to mutations in the cerebral folate receptors gene FOLR1 (autosomal recessive); also described an infantile onset autoimmune disorder with autoantibodies to the folate receptor blocking folate uptake into CSF.
- Clinical features: onset at 4-6 months of age, marked irritability, developmental delay or regression, acquired microcephaly, cerebellar ataxia, lower limb pyramidal signs, dyskinesia; late epilepsy and autism.
- FOLR1 Gene Mutation. This condition is due to mutation in the FOLR1 gene located on the long arm of chromosome11. This leads to an impaired transport of folate to the central nervous system in turn causing disturbed myelin metabolism and neurodegeneration. In sharp contrast to the early presentation of autoimmune folate antibody EE, these children typically presented between late infancy to eight years of age.
- The affected children present with intractable myoclonic-astatic, myoclonic, and generalized tonic-clonic epilepsy. Other neurological manifestations include ataxia, developmental delay, hypotonia, and regression of developmental milestones. Children who present late in the second decade may exhibit features of severe polyneuropathy

ii. Folinic Acid Responsive Seizures

- Neonates with intractable seizures picture resembling pyridoxine-dependent

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epilepsy found serendipitously to respond folinic acid (and not to pyridoxine or pyridoxal).

- ALDH7A1 mutation has been identified (same gene responsible for pyridoxine dependent epilepsy), i.e. the conditions appear identical. The reason for the differential treatment responses is unclear.

Diagnosis

- Low CSF 5-MTHF but normal folate metabolism outside the central nervous system (normal serum and red folate, normal homocysteine level, normal hematological indices).
- Autoantibodies to folate are often present in serum.
- Neuroimaging findings are nonspecific and MRI of the brain may reveal supra- and infra-tentorial atrophy serum.
- EEG findings are nonspecific and vary from mild diffuse slowing, multifocal spike-wave discharges, and hypsarrhythmic background pattern to electrical status epilepticus in sleep. The most common findings on EEG are diffuse slowing of the background activity and multifocal spikes.
- These patients have almost undetectable levels of CSF 5 MTHF with a decrease in CSF MTHF concentration greater than 80% below the lower limit of the reference range.
- Brain MRI most frequently shows delayed myelination or hypomyelination of the cerebral white matter with mild cerebral atrophy and very pronounced cerebellar atrophy.

Treatment

Both of these conditions respond to folinic acid 3-5 mg/kg/d for 2 to 3 days or empiric trial of folinic acid 5 mg per dose for two weeks 6 h apart.

4. Biotinidase Deficiency

- Biotinidase deficiency is a biotin-responsive, autosomal recessive neurocutaneous metabolic disorder causing multiple carboxylase deficiency and presenting with seizures, hypotonia, visual/auditory symptoms, eczema, and alopecia. These carboxylases play an important role in fatty acid synthesis, amino acid catabolism, and gluconeogenesis. When biotinidase activity is 10–30% of normal, it is said to be a partial deficiency and when it is less than 10%, it is termed profound deficiency.
- The global incidence of biotinidase deficiency is 1 in 60,000 live Births. Untreated children usually have neurocutaneous features between 2 and 5 months of life although presentation can be in late adolescence or adulthood. The neurologic features in biotinidase deficiency are thought to result from aberrant myelination.
- The most common neurologic feature in untreated patients are seizures which occur in 70% of symptomatic children with severe biotinidase

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deficiency. These could take the form of tonic-clonic, myoclonic, or partial seizures or present as infantile spasms. Hypotonia is another frequent observation in infants with biotinidase deficiency. Presentation at a later age is with ataxia and developmental delay often with visual problems and hearing loss. When children remain asymptomatic till later childhood or adolescence, presentation can be with features such as rapid visual loss with scotomas, optic neuropathy, and spastic paraparesis, causing diagnostic confusion with juvenile multiple sclerosis.

- Cutaneous findings include atopic/seborrheic dermatitis, alopecia including loss of eyebrows and eyelashes, hypopigmentation of skin or hair, and fungal skin infections. Respiratory symptoms have also been described and include hyperventilation, laryngeal stridor, and apnea. Hyperventilation could be due to metabolic acidosis and can lead to coma and death. Laryngeal stridor is likely due to neurological involvement. Lactic acidosis is commonly, but not universally, seen in symptomatic children. Mild to moderate hyperammonemia is common, although this may not be present even in severely affected children.

Diagnosis

- Serum biotinidase level will be low and confirms the diagnosis.
- Organic acid metabolites are elevated in serum and urine due to mitochondrial carboxylase deficiency, most commonly 3-hydroxyisovalerate.
- Other organic acids elevated include 3-methylcrotonylglycine and methyl citrate suggesting the possibility of multiple carboxylase deficiency.
- CSF lactate and pyruvate may be elevated.
- Neuroimaging findings include cerebral atrophy with ventriculomegaly, enlarged CSF spaces, and diffuse white matter changes which may be related to dysmyelination.
- Recurrent encephalopathy with vasogenic edema in the bilateral putamen and caudate nuclei, infra- and supratentorial cortex, and brainstem and atrophy in chronic disease has been reported.
- MR spectroscopy can show decreased NAA peak, elevated lactate, and reversal of the choline/creatine ratio. These spectroscopic findings are similar to mitochondrial disorders such as Leigh disease or Alpers' disease.
- EEG findings in biotinidase deficiency include mild background slowing, attenuated background, multifocal spikes consistent with early infantile encephalopathy, burst suppression pattern, asynchrony, and hypsarrhythmia. EEG could be normal in affected children.
- ERG and VEP studies are normal, while BAEP can show findings consistent with sensorineural hearing loss.
- The biotinidase gene is localized to chromosome 3p25.

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Treatment

- Treatment with biotin can prevent symptoms if biotinidase deficiency is detected in neonatal screening. If symptomatic, improvement is seen often within a day of treatment. The seizures often do not respond to AEDs, but quickly respond to biotin supplementation.
- It has been suggested that, similar to pyridoxine trials, a trial of biotin should be considered in any child with poorly controlled seizures.
- Regardless of age or weight, a dose of 5–20 mg daily has been found to be effective and needs to be continued lifelong.

Biotin-responsive Basal Ganglia Disease (BBGD)

- Biotin responsive basal ganglia disease is an autosomal recessive neuro-metabolic disorder. It is characterized by sub-acute encephalopathy with confusion, seizure, dysarthria and dystonia following a history of febrile illness. If left untreated with biotin, the disease can progress to severe quadriparesis and even death.
- Defect is in the transport of biotin across the BBB; SLC19A3 gene mutation.
- Prognosis is very good if diagnosis made early and treated promptly
- Diagnosis; imaging shows bilateral head of caudate & putamen T2 hyper-intensity but definite diagnosis is by SLC19A3 mutation analysis.

Treatment

Biotin 5 to 10 mg/kg/day

5. Vitamin B_{12} Deficiency

- In infants, maternal Vitamin B_{12} deficiency is the most common cause and manifests in breast-fed infants between 4 and 8 months. The mothers are often vegan as the vitamin is absent in plants. The onset is more rapid in infants (over months) than in adults (over years), and the manifestation is mostly in the central nervous system.
- In infants, euro-developmental delay, regression of motor milestones, to thrive, irritability, apathy, hypotonia, hyperreflexia, tremor, choreoathetoid movements, and microcephaly can occur. Seizures with Vitamin B_{12} deficiency are rare but have been reported especially in infants including a case of West syndrome.
- The neurotoxic mechanisms of Vitamin B_{12} deficiency are not fully understood.
- Methylcobalamin is required in the central nervous system for myelin synthesis, and deficiency is thought to cause dysmyelination manifesting as diffuse white matter/axon sheath involvement leading to encephalopathy, myelopathy, peripheral neuropathy, and optic neuropathy.

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Diagnosis

- Vitamin B_{12} levels are in the low normal range, methionine and methylmalonic acid measurements may be more useful for diagnosis.
- Elevated urine methylmalonic acid is the most important laboratory test to diagnose Vitamin B_{12} deficiency at the tissue level.
- MRI of the spinal cord can show T2 hyperintensity in the posterior columns consistent with SCD (subacute cord degeneration).
- EEG shows slowing with encephalopathy. Patients with seizures can have epileptic discharges in the EEG which may be diffuse or focal. A modified hypsarrhythmia pattern can be seen in an infant presenting as West syndrome that did not respond to ACTH, but responded to B_{12} supplementation.
- Peripheral nerve involvement leads to a pattern of axonal neuropathy in the EMG

Treatment

- Vitamin B_{12} deficiency are also treated with weekly injections of 1000 mcg of hydroxocobalamin or cyanocobalamin for 3 months, followed by maintenance injections every 3 months.
- Lack of response in 3 months calls the diagnosis of B_{12} deficiency into question. Early treatment can prevent long-term sequelae and can even improve acute symptoms. About 90% of patients have improvement in symptoms of 50% or more, and up to 10% can have residual moderate to severe disability.

References

1. A. T. Berg, S. F. Berkovic, M. J. Brodie *et al.*, "Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005–2009," Epilepsia, vol. 51, no. 4, pp. 676–685, 2010. View at Publisher· View at Google Scholar· View at Scopus
2. P. B. Mills, E. J. Footitt, K. A. Mills *et al.*, "Genotypic and phenotypic spectrum of pyridoxine-dependent epilepsy (ALDH7A1 deficiency)," Brain, vol. 133, no. 7, pp. 2148–2159, 2010. View at Publisher· View at Google Scholar·
3. S. M. Gospe Jr., "Pyridoxine-dependent epilepsy and pyridoxine phosphate oxidase deficiency: unique clinical symptoms and non-specific EEG characteristics," Developmental Medicine and Child Neurology, vol. 52, no. 7, pp. 602–603, 2010.
4. B. Schmitt, M. Baumgartner, P. B. Mills *et al.*, "Seizures and paroxysmal events: symptoms pointing to the diagnosis of pyridoxine-dependent epilepsy and pyridoxine phosphate oxidase deficiency," Developmental Medicine and Child Neurology, vol. 52, no. 7, pp. e133–e142, 2010.
5. M. Gospe Jr., "Neonatal vitamin-responsive epileptic encephalopathies," Chang

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Gung Medical Journal, vol. 33, no. 1, pp. 1–12, 2010.

6. L. A. Bok, N. M. Maurits, M. A. Willemsen *et al*., "The EEG response to pyridoxine-IV neither identifies nor excludes pyridoxine-dependent epilepsy," Epilepsia, vol. 51, no. 12, pp. 2406–2411, 2010.
7. C. D. van Karnebeek, H. Hartmann, S. Jaggumantri *et al*., "Lysine restricted diet for pyridoxine-dependent epilepsy: first evidence and future trials," Molecular Genetics and Metabolism, vol. 107, no. 3, pp. 335–344, 2012. View at Google Scholar
8. L. A. Bok, F. J. Halbertsma, S. Houterman *et al*., "Long-term outcome in pyridoxine-dependent epilepsy," Developmental Medicine & Child Neurology, vol. 54, no. 9, pp. 849–854, 2012.
9. S. Stockler, B. Plecko, S. M. Gospe *et al*., "Pyridoxine dependent epilepsy and antiquitin deficiency. Clinical and molecular characteristics and recommendations for diagnosis, treatment and follow-up," Molecular Genetics and Metabolism, vol. 104, no. 1-2, pp. 48–60, 2011.
10. E. J. Footitt, S. J. Heales, P. B. Mills, G. F. G. Allen, M. Oppenheim, and P. T. Clayton, "Pyridoxal 5′-phosphate in cerebrospinal fluid; Factors affecting concentration," Journal of Inherited Metabolic Disease, vol. 34, no. 2, pp. 529–538, 2011.
11. B. Afroze and M. Wasay, "Biotinidase deficiency in Pakistani children; what needs to be known and done," Journal of the Pakistan Medical Association, vol. 62, no. 4, pp. 312–313, 2012.
12. B. Wolf, "The neurology of biotinidase deficiency," Molecular Genetics and Metabolism, vol. 104, no. 1-2, pp. 27–34, 2011.
13. B. Tabark, S. Al-Shafi, S. Al-Shahwan *et al*., "Biotin-responsive basal ganglia disease revisited: clinical, radiologic, and genetic findings," Neurology, vol. 80, no. 3, pp. 261–267, 2013.
14. Clayton PT, Surtees RAH, DeVile C, Hyland K, Heales SJR. Neonatal epileptic encephalopathy. Lancet 2003;361:1614.
15. Mills PB, Surtees RAH, Champion MP, Beesley CE, Dalton N, Scambler PK, Heales SJR, Briddon A, Scheimberg I, Hoffmann GF, Zschocke J, Clayton PT. Neonatal epileptic encephalopathy caused by mutations in the PNPO gene encoding pyridox(am)ine 5'-phosphate oxidase. Human Mol Genet 2005;14:1077-86.

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Chapter 10 Stroke

Stroke is defined by the World Health Organization (WHO) as "a clinical syndrome characterized by rapidly developing signs of focal or global disturbance of cerebral function, lasting more than 24 hours or death, with no apparent cause other than vascular origin."

The childhood vascular stroke syndromes include arterial ischemic stroke (AIS), Hemorrhage Stroke (HS), usually defined as primary nontraumatic cerebral subarachnoid or intraventricular hemorrhage and frequently secondary to underlying vascular malformation, and Cerebral Venous Sinus Thrombosis (CVST). Ischemic stroke has an incidence of 2.4 per 100,000 person years, while HS has an incidence of 1-4/100,000 children. The incidence of Cerebral Sinus Thrombosis (CVST) is at least 0.67/100,000 children per year.

Arterial Ischemic Stroke (AIS)

The most common etiologies and risk factors for ischemic stroke in children include cardiac abnormalities, vascular lesions, hematologic abnormalities, infection, head and neck trauma, and genetic conditions; the incidence of these factors varies greatly depending on the population being studied.

- **Cardiac**: Congenital heart disease is a risk factor for cardioembolic stroke, especially in the perioperative period or following catheterization or extracorporeal membrane oxygenation (ECMO).
- **Hematologic**: Sickle cell disease is the most common cause of stroke in children, with a rate approximately 300 times higher than that seen in children without SCD. The rate is highest in hemoglobin SS.
    - Numerous other inherited or acquired prothrombotic disorders have been associated with pediatric stroke in case series, case-control studies, and prospective cohorts. These include:
    - Anemia (particularly iron deficiency)
    - Antiphospholipid syndrome
    - Abnormal activated protein C resistance (usually related to the Factor V Leiden mutation)
    - Protein C deficiency
    - Protein S deficiency
    - Antithrombin III deficiency
    - Prothrombin gene mutation
    - Elevated lipoprotein(s)

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- Elevated homocysteine, often associated with homozygous mutation of the methylenetetrahydrofolate reductase (MTHFR) gene

- **Vasculopathy**: Abnormalities of the cerebral vasculature, whether inherited or acquired, predispose to AIS in the young. These can be divided into noninflammatory and inflammatory etiologies.
  - Focal cerebral arteriopathy of childhood
  - Primary or secondary moyamoya disease
  - Dissection
  - Vasculitis
  - Sickle cell disease arteriopathy
  - Postvaricella arteriopathy
  - Miscellaneous types
  - Unspecified
- **Metabolic disorders**: Several metabolic conditions are associated with AIS, generally through effects on the vessel wall.
  - Fabry disease
  - Homocystinuria
  - Menkes' disease
  - Deficiency of Adenosine Deaminase 2 (DADA2)
- **MELAS and disorders causing metabolic stroke**: Some metabolic conditions are associated with metabolic stroke rather than arterial stroke. This category includes the syndrome of Mitochondrial Encephalomyopathy with Lactic Acidosis and Stroke-Like Episodes (MELAS).

Other metabolic disorders associated with metabolic stroke typically present in neonates. These include:

- Organic acid disorders:
  - Methylmalonic academia
  - Propionic academia
  - Isovaleric academia
  - Glutaric aciduria types 1 and 2
  - Ornithine transcarbamylase deficiency

CLINICAL PRESENTATION

Infants with stroke may present with focal weakness, but are more likely than older children to present with seizures and altered mental status. Older children usually have hemiparesis or other focal neurologic signs such as aphasia, visual disturbance, or cerebellar signs, although seizures, headache, and lethargy are not uncommon. Neck pain can be associated with cervical artery dissection, and a Horner's syndrome may accompany carotid dissection.

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Early infarct signs, such as cortical effacement with loss of gray-white differentiation, loss of the insular ribbon, and hyperdense artery sign, may be observed on noncontrast head CT acutely, and within 24 hours hypodensity in an arterial territory may be appreciated.

EVALUATION

Urgent neuroimaging is important for confirming the diagnosis of acute arterial ischemic stroke because there are numerous conditions that can mimic ischemic stroke, particularly with regard to children.

- Clinicians should conduct a thorough investigation for possible cardiac, vascular, and hematologic risk factors in all patients. Stroke in children is a multifactorial disease, so the full diagnostic evaluation should be completed even if one risk factor is identified.
- **Neuroimaging**: In children, head CT is generally considered inadequate to diagnose stroke, since MRI may be required to reliably exclude stroke mimics. Brain MRI is more sensitive for acute ischemia than CT, particularly with use of diffusion weighted imaging in the hyperacute time period. In addition, brain MRI provides better visualization of the posterior fossa.
- Current UK guidelines from the Royal College of Physicians (RCP) recommend brain MRI for the investigation of children presenting with clinical stroke, and further suggest that brain MRI be obtained as soon as possible after admission. Head CT is considered an acceptable initial alternative only if brain MRI is not available within 48 hours of admission.

In addition to brain imaging, clinicians suggest the following neurovascular evaluation:

- Magnetic Resonance Angiography (MRA) of the head to evaluate the intracranial large arteries. Computed Tomography Angiography (CTA) can be substituted depending on availability and local expertise.
- MRA of the neck to evaluate the extracranial large arteries. CTA can be substituted depending on availability and local expertise.
- Axial T1 MRI of the neck with fat saturation to evaluate for dissection.

Laboratory Studies

The initial evaluation for stroke in children should include the following studies.

- Electrocardiogram
- Complete blood count including platelets
- Electrolytes, urea nitrogen, creatinine
- Serum glucose
- Prothrombin Time (PT) and International Normalized Ratio (INR)
- Partial Thromboplastin Time (PTT)

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- Oxygen saturation
- Transthoracic echocardiography with agitated saline study to evaluate for possible cardiac source of embolism, including right to left shunt
- Vasculitis evaluation
- Hemoglobin electrophoresis in patients with possible sickle cell disease
- Electroencephalogram if seizures are suspected
- Hemoglobin electrophoresis in patients with possible sickle cell disease

Hypercoagulable State Evaluation

Numerous prothrombotic conditions are risk factors for ischemic stroke in children. The following studies are suggested as part of the evaluation for a hypercoagulable state in children:

- Protein C functional
- Protein S free and total or protein S functional
- Antithrombin III activity
- Lipoprotein(s)
- Homocysteine
- Prothrombin gene mutations
- Factor V Leiden gene mutation
- Anticardiolipin antibodies (IgG and IgM)
- Beta 2-glycoprotein I antibodies (IgG and IgM)
- Lupus anticoagulant tests, including dilute Russell viper venom time and dilute activated PTT
- Factor VIII activity
- D-dimer

Vasculitis Evaluation

The following studies are suggested whenever there is clinical suspicion of vasculitis, inflammation, or infection as the cause of ischemic stroke in children:

- Cerebral digital subtraction angiography
- Erythrocyte sedimentation rate and C-reactive protein level
- Antinuclear antibody assay
- Varicella titers
- Lumbar puncture and Cerebrospinal Fluid (CSF) examination with cell count, differential, protein concentration, and acid-fast bacilli testing.

MELAS Evaluation

When the diagnosis of MELAS is suspected on clinical grounds, the evaluation includes, in part:

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- Lactate levels from serum and cerebrospinal fluid
- Molecular genetic testing (of blood leukocytes, cultured skin fibroblast, skeletal muscle, urine sediment and/or cheek mucosa)
- Muscle biopsy, particularly if genetic testing is nondiagnostic

These studies are not always abnormal in patients with MELAS because of heteroplasmy for mitochondrial mutations.

MANAGEMENT

Initial Management

No randomized controlled trials of treatment in acute childhood stroke have been performed. In general, treatment of pediatric stroke is largely adapted from treatment of adult stroke. However, the treatment of children with stroke diverges from that of adults with regard to the use of acute anticoagulation and the use of recombinant tissue plasminogen activator (t-PA or alteplase).

Supportive Measures

For most patients with suspected acute arterial ischemic stroke, the following supportive measures are recommended:

- Maintain Airway, Breathing, and Circulation (ABCs)
- Maintain normoglycemia and normothermia; start normal saline intravenously at maintenance rate
- Allow modest hypertension
- Perform frequent neurologic checks
- Begin respiratory and oxygen saturation monitoring, along with oxygen supplementation to keep oxygen saturation >95 percent
- Utilize cardiac monitoring for the first 24 hours after stroke onset to look for atrial fibrillation or other potentially serious cardiac arrhythmias
- Most patients with acute ischemic stroke should be positioned as flat as possible in bed for at least the first 24 hours from stroke onset, ideally with head-of-bed elevation kept between 0 and 15 degrees. Exacerbation of elevated Intracranial Pressure (ICP) may occur with flat head-of-bed positioning. Significant aggravation of elevated ICP is unlikely in the first 24 hours after ischemic stroke onset, but can occur after 24 hours. Thus, patients with large ischemic infarction of unknown onset or >24 hours since onset should be maintained at 30 degrees in bed, once hypovolemia has been excluded.

Thrombolysis: Alteplase (rt-PA) is not approved in the United States by the Food and Drug Administration for use in children less than 18 years of age with ischemic stroke.

Initial antithrombotic treatment: As noted above, there are no randomized controlled trials examining the effectiveness of antiplatelet or anticoagulation therapy for the treatment of acute arterial ischemic stroke in children.

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- Limited data suggest anticoagulation therapy in children has an acceptable safety profile, although efficacy remains uncertain.

Guidelines: There are differences among consensus guidelines regarding the initial treatment of children with acute arterial ischemic stroke.

- The American Academy of Chest Physicians (ACCP) recommends either unfractionated heparin or Low Molecular Weight Heparin (LMWH) or aspirin as initial therapy until dissection and embolic causes have been excluded.
- The American Heart Association Stroke Council guideline states that it may be reasonable to initiate anticoagulation with LMWH or unfractionated heparin in children with arterial ischemic stroke pending completion of the diagnostic evaluation.
- The Royal College of Physicians recommends initial therapy with aspirin

Acute Treatment for Specific Causes of Arterial Ischemic Stroke

There are no controlled trials or studies examining the effectiveness of specific treatments for different causes of arterial ischemic stroke in children. Thus, all of the recommendations that follow are based mainly upon extrapolation from studies involving adults, and the clinical experience of experts, as reflected in consensus guidelines.

- Although data are limited and consensus opinions conflicting, most of the clinicians suggest aspirin 3 to 5 mg/kg per day rather than anticoagulation as initial therapy for most children with acute arterial ischemic stroke of unknown etiology. However, in cases with a high clinical suspicion for either arterial dissection or cardioembolism as the etiology, we suggest short-term anticoagulation with low molecular weight heparin or unfractionated heparin until vascular imaging and echocardiography are obtained.
- Anticoagulation should then be stopped and aspirin initiated if no indication (e.g. a confirmed cardioembolic source or arterial dissection) is identified by these investigations. Exceptions to the use of any acute antithrombotic treatment (i.e. aspirin or anticoagulation) are children with sickle cell disease and those with evidence of intracranial hemorrhage. Children who are already anticoagulated at the time of ischemic stroke onset should not be treated acutely with aspirin.
- For children with arterial stroke due to a confirmed cardioembolic source, arterial dissection, or hypercoagulable state, experts suggest initial anticoagulation treatment (rather than aspirin) with intravenous unfractionated heparin (goal PTT 60 to 85) or subcutaneous low molecular weight heparin (e.g. enoxaparin [1 mg/kg dose every 12 hours] to achieve a goal anti-factor Xa level of 0.5 to 1.0 U/mL) for five to seven days, followed by treatment with low molecular weight heparin or warfarin. Aspirin (3 to 5 mg/kg per day) should be given if there is a contraindication to anticoagulation.

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- For children with acute ischemic stroke resulting from sickle cell disease, clinicians suggest urgent intravenous hydration, and further suggest hydration with normal saline rather than hypotonic saline to avoid the potential worsening of cytotoxic cerebral edema that may occur with infusion of hypotonic fluid. In addition, urgent exchange transfusion is also recommended in experienced centers with routine availability of this therapy to reduce the hemoglobin S fraction to <30 percent of total hemoglobin.
- Exchange transfusion rather than simple transfusion is recommended for acute emergencies in part because it avoids the risk of Transfusion-Associated Circulatory Overload (TACO) syndrome and associated pulmonary edema. In addition, exchange transfusion avoids the theoretical risk of increased blood viscosity associated with simple transfusion.
- UK guidelines, however, recommend urgent simple transfusion of packed red blood cells if the patient has severe anemia (i.e. in the setting of splenic sequestration or aplastic crisis) or if there will be a delay of greater than four hours to initiation of exchange transfusion.
- For children with arterial ischemic stroke related to vasculopathy (excluding dissection), lacunar disease, or cryptogenic etiology, we suggest treatment with aspirin (3 to 5 mg/kg per day) rather than anticoagulation. Immunosuppression may be indicated for confirmed inflammatory vasculitis.
- For children with large "malignant" middle cerebral artery territory stroke associated with mass effect, elevated intracranial pressure, midline shift, and deterioration of consciousness, physicians suggest decompressive hemicraniectomy. Published data for this procedure in children are limited but encouraging.

Secondary Prevention

As with acute treatment, there are no controlled trials or studies examining the effectiveness of specific treatments for the secondary prevention of arterial ischemic stroke in children. Thus, the recommendations for children that follow are based mainly upon extrapolation from studies involving adults, and the clinical experience of experts, as reflected in consensus guidelines.

- Antiplatelet therapy is a mainstay of secondary ischemic stroke prevention in children and adults. Once dissection and cardioembolic causes are excluded, the American College of Chest Physician (ACCP) guidelines for antithrombotic therapy in children suggest daily aspirin (1 to 5 mg/kg daily) for a minimum of two years. There is little clinical experience with combination aspirin-extended-release dipyridamole or with clopidogrel in childhood stroke.
- In children, limited data suggest that combined treatment with aspirin and clopidogrel is associated with an increased risk of intracranial bleeding.
- Given these data, we recommend avoiding the combined use of aspirin and clopidogrel in children.

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- Concern regarding the risk of Reye syndrome should not limit or preclude the use of aspirin therapy in children for stroke prevention, since there is insufficient evidence to establish that aspirin causes Reye syndrome.
- Nevertheless, guidelines from the American Heart Association (AHA) Stroke Council state that it is reasonable to verify the varicella vaccination status and to administer an annual influenza vaccine to reduce the risk of Reye syndrome in children treated with aspirin for stroke prevention. In addition, the AHA considers it reasonable to stop aspirin temporarily during suspected varicella or influenza infections.

KEY POINTS

- Most of the studies suggest MRI of the brain with diffusion weighted imaging rather than CT for children with suspected ischemic stroke. In addition, all children should have a complete investigation for cardiac, vascular, and hematologic risk factors.
- General supportive care is very important for children with ischemic stroke.
- For children with arterial ischemic stroke of unknown etiology, studies suggest initial therapy with aspirin (3 to 5 mg/kg per day) rather than anticoagulation.
- For children with acute arterial ischemic stroke due to a confirmed cardioembolic source, arterial dissection, or hypercoagulable state, clinicians suggest anticoagulation treatment with intravenous unfractionated heparin or subcutaneous low molecular weight heparin for five to seven days rather than aspirin, followed by treatment with low molecular weight heparin or warfarin. Aspirin (3 to 5 mg/kg per day) should be given if there is a contraindication to anticoagulation.

Cerebral Venous Sinus Thrombosis (CVST)

Cerebral vein and dural sinus thrombosis (CVT) is less common than most other types of stroke but can be more challenging to diagnose. Due to the widespread use of Magnetic Resonance Imaging (MRI) and rising clinical awareness, CVT is recognized with increasing frequency.

CLINICAL FEATURES

Cerebral vein and dural sinus thrombosis (CVT) has a highly variable clinical presentation. The onset can be acute, subacute, or chronic.

Symptoms and Signs

Symptoms and signs of CVT can be grouped in three major syndromes:

- Isolated intracranial hypertension syndrome (headache with or without vomiting, papilledema, and visual problems)

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- Focal syndrome (focal deficits, seizures, or both)
- Encephalopathy (multifocal signs, mental status changes, stupor, or coma)
- Less common presentations include cavernous sinus syndrome, subarachnoid hemorrhage, and multiple cranial nerve palsies

EVALUATION

Neuroimaging: The neuroimaging features of CVT include findings that suggest the primary underlying pathology of venous thrombosis and associated brain parenchymal lesions. These may include focal areas of edema or venous infarction, hemorrhagic venous infarction, diffuse brain edema, or (rarely) isolated subarachnoid hemorrhage.

- **MRI**: MRI using gradient echo T2* susceptibility-weighted sequences in combination with Magnetic Resonance (MR) venography is the most sensitive imaging method for demonstrating the thrombus and the occluded dural sinus or vein. The characteristics of the MRI signal depend on the age of the thrombus:
- **MR venography**: MR venography, usually performed using the Time-Of-Flight (TOF) technique, is useful for demonstrating absence of flow in cerebral venous sinuses.
- **Head CT**: Head CT is normal in up to 30 percent of CVT cases, and most of the findings are nonspecific. However, CT is often the first investigation to be performed in clinical practice, and it is useful to rule out other acute or subacute cerebral disorders.
- The dense triangle sign, seen on non-contrast head CT as a hyper-density with a triangular or round shape in the posterior part of the superior sagittal sinus caused by the venous thrombus.
- The empty delta sign (also called the empty triangle or negative delta sign), seen on head CT with contrast as a triangular pattern of contrast enhancement surrounding a central region lacking contrast enhancement in the posterior part of the superior sagittal sinus.
- The cord sign, usually seen on head CT with contrast as a curvilinear or linear hyperdensity over the cerebral cortex caused by a thrombosed cortical vein.
- **CT venography**: CT venography gives a good visualization of the major dural sinuses, is readily available, can be used for patients who have contraindications to MRI (e.g. pacemaker) and is quicker than MRI.
- However, its use may be limited because of low resolution of the deep venous system and cortical veins, the risk of contrast reactions, and radiation exposure.

Laboratory Tests

- Aside from neuroimaging, there is no simple confirmatory laboratory test that can confidently rule out CVT in the acute phase of the disease.

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- Current guidelines from the AHA/ASA recommend obtaining routine blood studies consisting of a complete blood count, chemistry panel, prothrombin time, and activated partial thromboplastin time for patients with suspected CVT. The findings from these tests may suggest the presence of conditions that contribute to the development of CVT such as an underlying hypercoagulable state, infection, or inflammatory process.
- **Lumbar puncture**: Lumbar puncture may be useful to exclude meningitis in patients with CVT who present with isolated intracranial hypertension, a syndrome that may account for up to 25 percent of all patients with CVT.
- **Evaluation for the cause of CVT**: Searching for a thrombophilic state, either genetic or acquired, should be done in all patients. Screening should include:
  - Antithrombin
  - Protein C
  - Protein S
  - Factor V Leiden
  - Prothrombin G20210A mutation
  - Lupus anticoagulant, anticardiolipin, and anti-beta2 glycoprotein-I antibodies

ACUTE ANTITHROMBOTIC TREATMENT

In children with CVST who are not treated with aniticoagulation, thrombus propagation is documented in approximately 25% and is associated with increasing brain infarction and worse clinical outcome. While the overall aim of treatment for Cerebral Venous Thrombosis (CVT) is to improve outcome, the immediate goals of antithrombotic treatment are:

- **Anticoagulation**: For children with CVT but without significant intracerebral hemorrhage, the American Academy of Chest Physicians (ACCP) recommends initial anticoagulation with unfractionated heparin or Low Molecular Weight Heparin (LMWH), followed by LMWH or Vitamin K antagonist treatment (i.e. warfarin) for a minimum of three months.
- Anticoagulation for an additional three months is suggested if there is still cerebral sinovenous occlusion or ongoing symptoms (the latter presumably meaning new venous infarcts or increased intracranial pressure) after three months of therapy.
- For children with CVT who have significant intracerebral hemorrhage, the ACCP suggests either initial anticoagulation as for children without hemorrhage, or radiologic monitoring of the thrombosis at five to seven days and anticoagulation if thrombus extension is noted at that time. The ACCP suggests thrombolysis, thrombectomy, or surgical decompression only in children with severe CVT in whom there is no improvement with initial anticoagulation therapy.

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- Guidelines from the American Heart Association (AHA) Stroke Council state that it is reasonable to institute either unfractionated heparin or LMWH in children with CVT, whether or not there is secondary hemorrhage. This is followed by warfarin therapy for three to six months.
- The 2011 AHA/ASA guidelines for the diagnosis and management of CVT conclude that, for children with acute CVT diagnosed beyond the first 28 days of life, it is reasonable to treat with full-dose LMWH even in the presence of intracranial hemorrhage, and that it is reasonable to continue LMWH or oral vitamin K antagonists for three to six months. For neonates with acute CVT, the guidelines state that treatment with LMWH or unfractionated heparin may be considered, and that continuation of LMWH for six weeks to three months may be considered.
- Finally most of the clinicians suggest initial anticoagulation with subcutaneous LMWH or unfractionated heparin for children with CVT with or without significant secondary hemorrhage.

ACUTE SYMPTOMATIC TREATMENT

- Elevated intracranial pressure and herniation
- Seizures

Stroke in the Newborn

Perinatal stroke may be defined as an acute neurologic syndrome with chronic sequelae due to cerebral injury of vascular origin occurring between 20 weeks gestation and 28 days postnatal life. These disorders include focal cerebral injury due to arterial ischemic stroke, cerebral venous thrombosis, and primary intracerebral hemorrhage. Perinatal stroke is a common cause of acute neonatal encephalopathy, and may manifest as seizures, altered mental status, and sensorimotor deficits. It is an important cause of chronic neurologic disability.

The incidence of perinatal stroke in North America for arterial ischemic stroke and intracerebral hemorrhage combined is 35 per 100,000 live births annually, or 1 per 2800. The frequency of each these may vary in terms infants compared to preterm infants.

Symptoms of Perinatal Stroke

- Among infants with acute perinatal arterial ischemic stroke, seizures are the presenting symptom in 48 to 85 percent.
- Focal seizures are typically contralateral to the affected hemisphere in neonates with unilateral cerebral infarction. Seizure onset typically occurs late (12-24h) after birth.
- Among newborns with seizures, infarction is one of the most common causes along with neonatal encephalopathy, intracranial infections, and intracranial hemorrhage.
- Most strokes that are clinically apparent affect the middle cerebral artery, the arm and face are likely to be more affected than the leg. The hemiparesis

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may appear as asymmetry of spontaneous movements. However, hemiparesis caused by perinatal stroke is first detected in infancy (median six months in one series) in some patients after a normal neonatal course.

- Infants with bilateral lesions typically have a mild quadriparesis. Primitive reflexes, such as Moro and tonic neck reflexes, may be exaggerated.
- Sensory deficits may occur if the parietal and occipital lobes are affected. Ischemic stroke in the territory of the posterior cerebral artery frequently results in a visual field defect such as a homonymous hemianopia or quadrantanopia.
- Diencephalic injury may result in disturbed temperature control and sleep-wake cycles.
- Border zone infarction — Watershed or border zone regions exist along the boundaries of major arterial territories in the parasagittal cortical regions of the term infant. These regions are prone to ischemia under conditions of global brain hypoperfusion or oxygen deprivation.

Diagnosis of Arterial Ischemic Stroke

Evaluation of perinatal stroke includes defining the lesion with imaging techniques and investigating potential underlying causes.

- **Imaging studies**: The diagnosis of ischemic stroke is confirmed by cranial MRI or CT. MRI is superior to CT, as it may detect small or early infarcts that are not apparent on CT
- Cranial ultrasonography, the primary imaging technique used to detect intraventricular hemorrhage and periventricular leukomalacia, is less useful for detecting ischemic stroke because of the peripheral location of most infarcts.
- Early infarction can be visualized with MRI using Diffusion-Weighted Imaging (DWI) before the lesion can be seen with conventional MRI or CT.
- Noninvasive neurovascular imaging, most often with Magnetic Resonance Angiography (MRA), is widely used in modern stroke evaluation in children and adults. However, the utilization of MRA is less widespread in neonatal stroke.
- MRA can identify congenital vascular anomalies of the intracranial vessels that would predispose to the occurrence of a stroke during birth.
- **Laboratory studies**: Most infants who are acutely symptomatic with stroke present with seizures. In these cases, a complete evaluation should be performed to exclude other etiologies of seizures, including systemic infection.
- Studies should include a complete blood count with leukocyte differential, examination of the Cerebrospinal Fluid (CSF), and cultures of the blood and CSF.

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- Serum concentrations of glucose, calcium, and electrolytes should be measured, and the urine should be screened for toxic substances. Studies to detect inborn errors of metabolism may be indicated in some circumstances (e.g. persistent seizures).
- Infants with ischemic stroke should be evaluated for prothrombotic disorders.
- **EEG**: Electroencephalogram (EEG) should be obtained in the newborn with seizures or other neurologic disturbance. The EEG may demonstrate a specific seizure focus. Changes in background activity may suggest more generalized brain involvement.
- **Echocardiogram**: Newborns with stroke should have an echocardiogram to detect structural heart disease with right-to-left shunt as a potential underlying etiology.

Hemorrhagic Stroke

Hemorrhagic stroke refers to acute neurologic syndromes resulting from intracranial hemorrhage of nontraumatic origin. The prevalence of perinatal hemorrhage stroke in this population was 6.2 in 100,000. It has two main forms:

- Hemorrhagic conversion of ischemic infarction of arterial or venous origin.
- Primary intraparenchymal hemorrhage from vascular anomalies (vascular malformations, and aneurysms) or from bleeding diatheses. Periventricular hemorrhagic infarction is particularly common in premature infants.

MANAGEMENT

Management of perinatal stroke is supportive:

- It should be directed at treatment of underlying conditions and preventing further injury. Adequate oxygenation and ventilation should be ensured. Dehydration and anemia should be treated.
- Metabolic disturbances, such as acidosis, hypoglycemia, hypocalcemia, or electrolyte disorders, should be monitored and corrected.
- Antibiotic treatment is started until culture results are available if infection is suspected.
- **Arterial ischemic stroke management:** Treatment of perinatal ischemic stroke with antiplatelet agents or anticoagulants is controversial. Except for the supportive care and treatment of seizures noted above, management in most cases consists of observation and monitoring. Because most thromboembolic strokes in infants do not recur or progress, this approach avoids the complications associated with anticoagulation.
- However, selected infants may benefit from treatment with aspirin, unfractionated heparin, or Low Molecular Weight Heparin (LMWH).
- Neonates with a first arterial ischemic stroke, the 2012 American College of Chest Physicians (ACCP) guidelines suggest supportive care rather than

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anticoagulation or aspirin therapy in the absence of a documented ongoing cardioembolic source.

- Neonates with a first arterial ischemic stroke and a documented cardioembolic source, the ACCP guidelines suggest anticoagulation with unfractionated heparin or LMWH.
- Neonates with recurrent arterial ischemic stroke, the ACCP suggests the use of anticoagulant or aspirin therapy.
- Guidelines from the American Heart Association (AHA) Stroke Council published in 2008 state that anticoagulation with LMWH or unfractionated heparin may be considered for neonates with severe thrombophilic disorders or multiple cerebral or systemic emboli.
- **Cerebral sinovenous thrombosis management**: The role of systemic anticoagulation for the treatment of acute perinatal Cerebral Sinovenous Thrombosis (CSVT) remains controversial.
- For neonates with CSVT without significant intracerebral hemorrhage, the American College of Chest Physicians (ACCP) guidelines suggest initial anticoagulation with unfractionated heparin or LMWH and subsequent anticoagulation with LMWH for a minimum of six weeks but no longer than three months.
- The American Heart Association guidelines state that anticoagulation with LMWH or unfractionated heparin may be considered for neonates with clinical or radiologic evidence of propagating CSVT despite supportive therapy.
- Given the available data, most clinicians suggest initial anticoagulation with unfractionated heparin or LMWH for neonates with acute CSVT with or without associated intracranial hemorrhagic infarction or parenchymal hemorrhage. Anticoagulation should be continued after the acute period for at least six weeks using LMWH. Repeat imaging with MRI and MRV at the targeted endpoint of therapy (six weeks) may be useful in guiding duration of therapy. For neonates who have not achieved clinically significant recanalization, clinicians suggest extending the duration of anticoagulation therapy for up to six months with the aim of attaining partial or full recanalization of thrombosed sinuses.

INTRACEREBRAL HEMORRHAGE MANAGEMENT

Guidelines from the American Heart Association (AHA) recommend the following measures for neonates with intracerebral hemorrhage:

- Correction of markedly low platelet counts.
- Replacement of deficient coagulation factors for neonates who have coagulation factor deficiency.
- Vitamin K administration for neonates who have Vitamin K-dependent coagulation disorders.

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- Ventricular drainage for those who develop hydrocephalus, followed by shunting if hydrocephalus persists.
- The AHA guidelines note that it is reasonable to evacuate an intraparenchymal brain hemorrhage to reduce elevated intracranial pressure, but it is not clear whether this intervention always improves outcome.

KEY POINTS

- Management of perinatal stroke is mainly supportive. Adequate oxygenation and ventilation should be ensured. Dehydration and anemia should be treated.
- Metabolic disturbances, such as acidosis, hypoglycemia, hypocalcemia, or electrolyte disorders, should be monitored and corrected.
- Antibiotic treatment is started until culture results are available if infection is suspected.
- Seizures should be treated with anticonvulsant medications.
- Neonates who have or may be at risk for recurrent arterial ischemic stroke due to documented systemic or cardiac risk factors for thromboembolic events, clinicians suggest treatment with antithrombotic therapy using aspirin, unfractionated heparin, or low molecular weight heparin.
- Neonates with acute CSVT, with or without significant secondary hemorrhage, anticoagulation therapy with unfractionated heparin or low molecular weight heparin are suggested.
- Neonates with intracerebral hemorrhage, we suggest interventions including the correction of severe thrombocytopenia, replacement of deficient coagulation factors, vitamin K administration for those who have Vitamin K-dependent coagulation disorders, and ventricular drainage for those who develop hydrocephalus, followed by shunting if hydrocephalus persists.

References

1. Shellhaas RA, Smith SE, O'Tool E, *et al*. Mimics of childhood stroke: characteristics of a prospective cohort. Pediatrics 2006; 118:704.
2. Stroke in childhood: Clinical guideline for diagnosis, management and rehabilitation (2017). Royal College of Paediatrics and Child Health. http://www.rcpch.ac.uk/stroke-guideline (Accessed on June 01, 2017).
3. Elbers J, Wainwright MS, Amlie-Lefond C. The Pediatric Stroke Code: Early Management of the Child with Stroke. J Pediatr 2015; 167:19.
4. Christy A, Murchison C, Wilson JL. Quick Brain Magnetic Resonance Imaging With Diffusion-Weighted Imaging as a First Imaging Modality in Pediatric Stroke. Pediatr Neurol 2018; 78:55.
5. Roach ES, Golomb MR, Adams R, *et al*. Management of stroke in infants and children: a scientific statement from a Special Writing Group of the American Heart Association Stroke Council and the Council on Cardiovascular Disease in the Young. Stroke 2008; 39:2644.

Paramount Books (P) Ltd.

6. Monagle P, Chan AK, Goldenberg NA, *et al*. Antithrombotic therapy in neonates and children: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012; 141:e737S.
7. Wilson JL, Eriksson CO, Williams CN. Endovascular Therapy in Pediatric Stroke: Utilization, Patient Characteristics, and Outcomes. Pediatr Neurol 2017; 69:87.
8. Demaerschalk BM, Kleindorfer DO, Adeoye OM, *et al*. Scientific Rationale for the Inclusion and Exclusion Criteria for Intravenous Alteplase in Acute Ischemic Stroke: A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke 2016; 47:581.
9. Cobb MIH, Laarakker AS, Gonzalez LF, *et al*. Endovascular Therapies for Acute Ischemic Stroke in Children. Stroke 2017; 48:2026.
10. Bigi S, Dulcey A, Gralla J, *et al*. Feasibility, safety, and outcome of recanalization treatment in childhood stroke. Ann Neurol 2018; 83:1125.
11. Greenham M, Gordon A, Anderson V, Mackay MT. Outcome in Childhood Stroke. Stroke 2016; 47:1159.
12. Fox CK, Glass HC, Sidney S, *et al*. Acute seizures predict epilepsy after childhood stroke. Ann Neurol 2013; 74:249.
13. Mallick AA, Ganesan V, Kirkham FJ, *et al*. Outcome and recurrence one year after paediatric arterial ischaemic stroke in a population-based cohort. Ann Neurol 2016.
14. Fullerton HJ, Wintermark M, Hills NK, *et al*. Risk of Recurrent Arterial Ischemic Stroke in Childhood: A Prospective International Study. Stroke 2016; 47:53.
15. deVeber GA, Kirton A, Booth FA, *et al*. Epidemiology and Outcomes of Arterial Ischemic Stroke in Children: The Canadian Pediatric Ischemic Stroke Registry. Pediatr Neurol 2017; 69:58.
16. Stacey A, Toolis C, Ganesan V. Rates and Risk Factors for Arterial Ischemic Stroke Recurrence in Children. Stroke 2018; 49:842. Powers WJ, Rabinstein AA, Ackerson T, *et al*. 2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke 2018; 49:e46.
17. Zonneveld TP, Nederkoorn PJ, Westendorp WF, *et al*. Hyperglycemia predicts post-stroke infections in acute ischemic stroke. Neurology 2017; 88:1415.
18. Bruno A, Durkalski VL, Hall CE, *et al*. The Stroke Hyperglycemia Insulin Network Effort (SHINE) trial protocol: a randomized, blinded, efficacy trial of standard vs. intensive hyperglycemia management in acute stroke. Int J Stroke 2014; 9:246.
19. Anderson CS, Arima H, Lavados P, *et al*. Cluster-Randomized, Crossover Trial of Head Positioning in Acute Stroke. N Engl J Med 2017; 376:2437.
20. Langhorne P, O'Donnell MJ, Chin SL, *et al*. Practice patterns and outcomes after stroke across countries at different economic levels (INTERSTROKE): an international observational study. Lancet 2018; 391:2019.
21. Woodhouse LJ, Manning L, Potter JF, *et al*. Continuing or Temporarily Stopping Prestroke Antihypertensive Medication in Acute Stroke: An Individual Patient Data Meta-Analysis. Hypertension 2017; 69:933.
22. FOCUS Trial Collaboration. Effects of fluoxetine on functional outcomes after acute stroke (FOCUS): a pragmatic, double-blind, randomised, controlled trial. Lancet 2019; 393:265.

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23. Neuhaus AA, Couch Y, Hadley G, Buchan AM. Neuroprotection in stroke: the importance of collaboration and reproducibility. Brain 2017; 140:2079.
24. Abbas Q, Merchant QU, Nasir B, *et al*. Spectrum of Intracerebral Hemorrhage in Children: A Report from PICU of a Resource Limited Country. Crit Care Res Pract 2016; 2016:9124245.
25. Gumer LB, Del Vecchio M, Aronoff S. Strokes in children: a systematic review. Pediatr Emerg Care 2014; 30:660.
26. Beslow LA, Licht DJ, Smith SE, *et al*. Predictors of outcome in childhood intracerebral hemorrhage: a prospective consecutive cohort study. Stroke 2010; 41:313.
27. Greenham M, Gordon A, Anderson V, Mackay MT. Outcome in Childhood Stroke. Stroke 2016; 47:1159.
28. Hawks C, Jordan LC, Gindville M, *et al*. Educational Placement After Pediatric Intracerebral Hemorrhage. Pediatr Neurol 2016; 61:46.
29. Smith SE, Vargas G, Cucchiara AJ, *et al*. Hemiparesis and epilepsy are associated with worse reported health status following unilateral stroke in children. Pediatr Neurol 2015; 52:428.
30. Lehman LL, Rivkin MJ. Perinatal arterial ischemic stroke: presentation, risk factors, evaluation, and outcome. Pediatr Neurol 2014; 51:760.
31. Miller V. Neonatal cerebral infarction. Semin Pediatr Neurol 2000; 7:278.
32. Martinez-Biarge M, Cheong JL, Diez-Sebastian J, *et al*. Risk Factors for Neonatal Arterial Ischemic Stroke: The Importance of the Intrapartum Period. J Pediatr 2016; 173:62.
33. Harteman JC, Groenendaal F, Kwee A, *et al*. Risk factors for perinatal arterial ischaemic stroke in full-term infants: a case-control study. Arch Dis Child Fetal Neonatal Ed 2012; 97:F411.
34. Ecury-Goossen GM, Raets MM, Lequin M, *et al*. Risk factors, clinical presentation, and neuroimaging findings of neonatal perforator stroke. Stroke 2013; 44:2115.
35. Cole L, Dewey D, Letourneau N, *et al*. Clinical Characteristics, Risk Factors, and Outcomes Associated With Neonatal Hemorrhagic Stroke: A Population-Based Case-Control Study. JAMA Pediatr 2017; 171:230.
36. Grunt S, Mazenauer L, Buerki SE, *et al*. Incidence and outcomes of symptomatic neonatal arterial ischemic stroke. Pediatrics 2015; 135:e1220.

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Chapter

11

Febrile Child with Neurological Symptoms

Fever is the cardinal feature of infection, but not all the children with CNS infection present with fever. A history of fever in the presence of neurological symptoms, which include many nonspecific features (e.g. vomiting, diarrhea, lethargy), should arouse the suspicion of CNS infection.

But seizures are the common neurologic presentation of infants and young children. In this chapter we will address only common CNS infections and febrile seizures.

CLINICAL FEATURES

Febrile seizures are the most common neurologic disorder of infants and young children. They occur in approximately 2 to 4 percent of children younger than five years of age, with a peak incidence between 12 and 18 months. Generally accepted criteria for febrile seizures include:

- A convulsion associated with an elevated temperature greater than 38°C
- A child older than three months and younger than six years of age
- Absence of central nervous system infection or inflammation
- Absence of acute systemic metabolic abnormality that may produce convulsions
- No history of previous afebrile seizures

Febrile seizures are further divided into two categories, simple or complex, based on clinical features.

- Simple febrile seizures, the most common type, are characterized by seizures that are generalized, last less than 15 minutes, and do not recur in a 24-hour period. Since most simple febrile seizures last less than five minutes, a cutoff of 10 minutes has been proposed as a more appropriate threshold for distinguishing between simple and complex.
- Complex febrile seizures are characterized by episodes that have a focal onset (e.g. shaking limited to one limb or one side of the body), last longer than 15 minutes, or occur more than once in 24 hours.
- **Risk factors**: Febrile seizures are an age-dependent phenomenon, likely related to a vulnerability of the developing nervous system to the effects of fever in combination with an underlying genetic susceptibility. Aside from age, the most commonly identified risk factors include high fever, viral infection, recent immunization, and a family history of febrile seizures.
- **Febrile status epilepticus**: Some patients present in Febrile Status Epilepticus (FSE), i.e. continuous seizures or intermittent seizures without

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neurologic recovery, lasting for a period of 30 minutes or longer. In up to one-third of cases of FSE, the actual seizure duration is underestimated in the emergency department. Important clinical clues that a seizure has ended include the presence of closed eyes and a deep breath. Children with persistently open and deviated eyes may still be seizing, even if convulsive motor activity has stopped.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of febrile seizure includes nonepileptic events or movements, provoked seizures from central nervous system infection (e.g. meningitis or encephalitis), and rare forms of genetic epilepsy in which seizures are particularly common with fever.

Shaking chills: Involuntary movements can occur in sick children and can be confused with seizures. Shaking chills are usually readily distinguished from seizures. Chills are common and are characterized by fine rhythmic oscillatory movements about a joint. They rarely involve facial or respiratory muscles, which frequently occur during febrile seizures. In addition, chills usually involve both sides of the body simultaneously and are not associated with loss of consciousness, in contrast to children with generalized seizures. Thus, bilateral manifestations without apparent unconsciousness strongly suggest that the movements are not epileptic. Any repetitive movements of concern should also be evaluated by touch, since seizures should not be suppressible.

Central nervous system infection: Provoked seizures from meningitis or encephalitis are the main concerns in a child presenting with fever and seizures. A thorough evaluation by an experienced clinician almost always will detect the child with meningitis.

Genetic epilepsies with febrile seizures: In some patients, the propensity for febrile seizures is an early manifestation of generalized epilepsy with febrile seizures plus (GEFS+), a genetic epilepsy for which a variety of causative mutations have been identified. The most common phenotype of GEFS+ consists of children who had seizures with fever in early childhood that, unlike typical febrile seizures, continue beyond six years of age or are associated with afebrile tonic-clonic seizures as well as other seizure types. The epilepsy typically remits by mid-adolescence but can persist into adulthood.

Severe myoclonic epilepsy of infancy (Dravet syndrome) is rare genetic epilepsy that can resemble complex febrile seizures in the first year.

EVALUATION

Febrile seizure is a clinical diagnosis, defined by the following features:

History

Key elements of the seizure history in a child presenting with a febrile seizure include seizure characteristics, duration of the seizure, and presence of focal features (e.g. shaking limited to one limb or one side of the body).

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- A witness to the seizure should be interviewed if possible, keeping in mind that seizures are frightening to many witnesses, and details of the seizure, including exact duration, may be difficult to elicit or unreliable.
- A careful history must identify any underlying medical or neurologic conditions that increase the child's risk of serious infection or underlying structural abnormality.
- The history should include an assessment of immunization status, personal or family history of seizure, and history of neurologic problems or developmental delay. A child with a known neurologic condition may be more likely to experience a seizure with fever, which would not be classified as a simple febrile seizure.

Physical Examination

- A general physical and neurologic examination should include attention to vital signs; level of consciousness; presence or absence of meningismus; a tense or bulging fontanels; and focal differences in muscle tone, strength, or spontaneous movements.
- The presence of any of these signs should prompt consideration such as meningitis or an underlying structural abnormality. Likewise, children with febrile seizures are typically well appearing, and post-ictal drowsiness usually resolves within five to ten minutes, depending upon the duration and type of seizure.
- Encephalopathy beyond this time period should prompt increased suspicion for possible central nervous system infection or severe systemic infection.
- Close attention may be necessary to detect ongoing or recurrent focal seizures in children presenting with complex febrile seizures, including febrile status epilepticus.

INVESTIGATIONS

Lumbar Puncture

The need for a Lumbar Puncture (LP) and Cerebrospinal Fluid (CSF) examination to exclude meningitis or encephalitis in children with a febrile seizure is based mainly on clinical signs.

Lumbar puncture is unnecessary in most well-appearing children who have returned to a normal baseline after a febrile seizure. The American Academy of Pediatrics (AAP) recommendations regarding the performance of LP in the setting of febrile seizures, which include the following:

- LP should be performed when there are meningeal signs or symptoms or other clinical features that suggest a possible meningitis or intracranial infection.

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- LP should be considered in infants between 6 and 12 months if the immunization status for Haemophilus influenzae type b or Streptococcus pneumoniae is deficient or undetermined.
- LP should be considered when the patient is on antibiotics because antibiotic treatment can mask the signs and symptoms of meningitis.

Laboratory Tests

- A complete blood count and measurement of serum electrolytes blood sugar, calcium, and urea nitrogen is of very low yield in patients with simple febrile seizures; these parameters should be measured only when the patient has a history of vomiting, diarrhea, and abnormal fluid intake, or when physical findings of dehydration or edema exist.
- If a decision to perform an LP has been made, blood culture and serum glucose testing should be performed concurrently.

Neuroimaging

- Neuroimaging with Computed Tomography (CT) or MRI is not required for children with simple febrile seizures. The incidence of intracranial pathology in children presenting with complex febrile seizures also appears to be very low.
- Urgent neuroimaging (CT with contrast or MRI) should be done in children with abnormally large heads, a persistently abnormal neurologic examination, particularly with focal features, or signs and symptoms of increased intracranial pressure.
- While not necessary in the emergent setting, high-resolution MRI is often obtained in the outpatient setting in children with focal or prolonged febrile seizures, particularly those with a history of abnormal development, since these children have a higher risk of developing afebrile seizures.

Electroencephalography

- Routine Electroencephalography (EEG) is not warranted, particularly in the setting of a neurologically healthy child with a simple febrile seizure.
- In children with complex febrile seizures, the need for an EEG depends on several factors and clinical judgment. A short, generalized seizure repeated twice in 24 hours is, by definition, complex but would not necessitate an EEG unless the neurologic examination were abnormal.
- A prolonged seizure, or one that has focal features, warrants an EEG and neurologic follow-up since the risk of future epilepsy (repeated afebrile seizures) is higher.
- The optimal timing of EEG is not well defined, but a study utilizing recordings performed within 72 hours of febrile status epilepticus suggest this may be a useful timeframe for prognostic purposes.

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TREATMENT

Acute Management

Emergency rescue therapy: The majority of febrile seizures have ended spontaneously by the time the child is first evaluated, and the child is rapidly returning to a normal baseline. In such cases, active treatment with benzodiazepines is not necessary. Fever should be treated symptomatically.

- As with afebrile seizures, febrile seizures that continue for more than five minutes should be treated. Intravenous benzodiazepines (diazepam 0.1 to 0.2 mg/kg or lorazepam 0.05 to 0.1 mg/kg) are effective in aborting seizure in many cases. If the seizure persists, an additional dose may be given.
- The child's respiratory and circulatory status should be monitored carefully and an advanced airway intervention (e.g. bag-mask ventilation, laryngeal mask airway, definitive artificial airway) undertaken if the ventilatory status becomes inadequate.
- When intravenous access is unavailable or cannot be achieved, buccal midazolam is an effective alternative a typical dose is 0.2 mg/kg, maximum dose 10 mg. Intranasal lorazepam is also an option.

Febrile Status Epilepticus

Febrile status epilepticus rarely stops spontaneously and often requires more than one medication to control.

- Patients with prolonged or repetitive seizures despite initial benzodiazepine administration (i.e. febrile status epilepticus) should be treated promptly with additional anticonvulsant medications, as are other patients with status epilepticus.
- The most commonly used drug in this setting is fosphenytoin (20 mg phenytoin equivalents [PE]/kg intravenously). Efforts should be made to lower fever with antipyretics and a cooling blanket. The management of status epilepticus in children is discussed in more detail separately.

DISCHARGING CRITERIA

- Most children with simple febrile seizures do not require hospital admission and can be discharged safely to home once they have returned to a normal baseline and parents have been educated about the risk of recurrent febrile seizures.
- Children with focal or prolonged seizures may require a more extended period of observation, particularly if there is delayed recovery to baseline or postictal focality. In addition, they are at higher risk of having multiple seizures within the index illness.
- Additional factors to consider when deciding whether to admit a child include the confidence with which outpatient follow-up can be arranged (for focal or prolonged seizures), comfort level of the parents, and severity of the underlying febrile illness (e.g. hydration status, ability to take oral fluids).

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- **Recurrent febrile seizures**: Children with febrile seizures are at risk for developing recurrent febrile seizures with future illnesses during early childhood. Risk factors for recurrence; The overall recurrence rate is approximately 30 to 35 percent.
- **Provision of home benzodiazepines**: In children with a history of prolonged febrile seizure, diazepam rectal gel (0.5 mg/kg) can be administered by parents at home if the episode lasts longer than five minutes. Parents can be taught to safely give the medication at home, and one dose administered rectally will not lead to respiratory depression.
- Prophylactic antiepileptic drugs can decrease the risk of recurrent febrile seizures, but given the benign nature of most seizures, the risks of side effects generally outweigh the benefits. Use of antipyretics at the first sign of fever does not prevent recurrent febrile seizures.
- A clinical practice guideline developed by the Committee on Quality Improvement, Subcommittee on Febrile Seizures of the American Academy of Pediatrics concludes that neither continuous nor intermittent anticonvulsive therapy is recommended for children with one or more simple febrile seizures, based on the risks and benefits of effective therapies. The guideline also recognizes that recurrent episodes of febrile seizures can create anxiety in some parents and their children and as such, appropriate educational and emotional support should be provided.
- Antipyretics: For children who have had febrile seizures, treatment with antipyretics at the time of a febrile illness may allay discomfort and be helpful in overall management, but it does not appear to affect the recurrence rate of febrile seizures.

Prognosis

The prognosis for children with febrile seizures is favorable. Neurologic sequelae, including new neurologic deficits, intellectual impairment, and behavioral disorder, are rare following febrile seizures. Subsequent epilepsy occurs more frequently in children who have had febrile seizures than in the general population. In a normal child with a simple febrile seizure, the risk is approximately 1 to 2 percent, only slightly above that of the general population. For children with complex febrile seizures, an abnormal developmental history, or a family history of epilepsy, the risk is closer to 5 to 10 percent.

BACTERIAL MENINGITIS IN CHILDREN OLDER THAN ONE MONTH

Meningitis is an inflammatory disease of the leptomeninges, the tissues surrounding the brain and spinal cord. The meninges consist of three parts: the pia, arachnoid, and dura mater. Meningitis reflects inflammation of the arachnoid mater and the Cerebrospinal Fluid (CSF) in both the subarachnoid space and in the cerebral ventricles. Suspected bacterial meningitis is a medical emergency, and immediate diagnostic steps must be taken to establish the specific

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cause so that appropriate antimicrobial therapy can be initiated. The mortality rate of untreated bacterial meningitis approaches 100 percent. Even with optimal therapy, morbidity and mortality may occur. Neurologic sequelae are common among survivors.

The organisms responsible for acute bacterial meningitis depend in part upon the route of acquisition and underlying host factors.

CLINICAL FEATURES

Acute bacterial meningitis has two patterns of presentation. In the first, meningitis develops progressively over one or several days and may be preceded by a febrile illness. In the second, the course is acute and fulminant, with manifestations of sepsis and meningitis developing rapidly over several hours. The rapidly progressive form is frequently associated with severe brain edema.

Most patients with bacterial meningitis present with fever and symptoms and signs of meningeal inflammation (nausea, vomiting, irritability, anorexia, headache, confusion, back pain, and nuchal rigidity). These findings are often preceded by symptoms of upper respiratory infection. However, the clinical manifestations of bacterial meningitis are variable and nonspecific; no single sign is pathognomonic. Previous receipt of oral antibiotics does not affect the clinical presentation of acute bacterial meningitis.

In older children, clinical manifestations may include fever, headache, photophobia, nausea, vomiting, confusion, lethargy, and/or irritability. In infants, manifestations may include fever, hypothermia, lethargy, respiratory distress, jaundice, poor feeding, vomiting, diarrhea, seizures, restlessness, and irritability.

Meningeal signs: Although meningeal signs are present at the time of admission in the majority of patients, they are not invariably present.

- Nuchal rigidity may not be elicited in comatose patients or those with focal or diffuse neurologic deficits.
- Nuchal rigidity is manifested by the inability to place the chin on the chest, limitation of passive neck flexion, and Kernig and Brudzinski signs.
- **Kernig sign**: Kernig sign is present if the patient, in the supine position with the hip and knee flexed at 90°, cannot extend the knee more than 135° and/or there is flexion of the opposite knee.
- **Brudzinski sign**: Brudzinski sign is present if the patient, while in the supine position, flexes the lower extremities during attempted passive flexion of the neck

Clinical Neurologic Findings

- **Altered consciousness**: The level of consciousness at the time of admission has prognostic significance; patients who are obtunded, semicomatose, or comatose at the time of admission are significantly more likely to have an adverse outcome than those who are lethargic or somnolent.

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- **Increased ICP**: Increased intracranial pressure may be manifest by complaints of headache in older children and bulging fontanel or diastasis of the cranial sutures in infants.
- Other signs of increased intracranial pressure that may occur in bacterial meningitis include palsies of the third, fourth, and sixth cranial nerves.
- Papilledema, which takes several days to become apparent, is an uncommon finding in acute bacterial meningitis. The finding of papilledema should prompt evaluation for venous sinus occlusion, subdural empyema, or brain abscess.
- **Seizures**: Seizures, typically generalized, occur before admission to the hospital or within the first 48 hours of admission in 20 to 30 percent of patients with meningitis. Focal neurologic findings 16 percent of patients overall and in 34 percent of those with pneumococcal meningitis (hemiparesis, quadriparesis, facial palsy, visual field defects) can occur at the same time.

Cutaneous Findings

Petechiae and purpura may occur with any of the bacterial pathogens but are most commonly seen in N. meningitides. The lesions are usually more pronounced on the extremities and can be preceded by an erythematous maculopapular eruption.

Complications

Complications that may occur during therapy for bacterial meningitis include seizures, increased ICP, cerebral edema, ischemia, infected subdural effusion, and disseminated illness (septic arthritis, pericarditis, etc). Arthritis is most common with meningococcal disease but may occur with other infections.

LABORATORY EVALUATION

- **Blood tests**: Initial blood tests should include a complete blood count with differential and platelet count and two aerobic blood cultures of appropriate volume. Serum electrolytes and glucose, blood urea nitrogen, and creatinine concentrations are helpful in determining the Cerebrospinal Fluid- (CSF) to-blood glucose ratio, and in planning fluid administration. Evaluation of clotting function is especially indicated if petechiae or purpuric lesions are noted.
- Blood cultures are positive in at least one-half of patients with bacterial meningitis.
- **CSF examination**: Analysis of the CSF is critical to the diagnosis of meningitis and the differentiation of bacterial from other etiologies. The threshold for CSF examination should be lower in high-risk patients. Contraindications to LP include cardiopulmonary compromise, signs of increased intracranial pressure, papilledema, altered respiratory effort, focal neurologic signs, and skin infection over the site for LP.

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- It is essential that antimicrobial therapy not be delayed if there is a contraindication to or inability to perform an LP, or if the LP is delayed by the need for cranial imaging. In any of these situations, blood cultures should be obtained and empiric antibiotics administered as soon as is possible (before the imaging study in children who require imaging).
- Examination of the CSF should include cell count and differential, glucose and protein concentration, Gram stain, and culture. Cytocentrifugation of CSF enhances the likelihood that laboratory personnel will detect bacteria on Gram-stained specimens.
- CSF cultures should be performed in all cases of suspected bacterial meningitis, regardless of the cell count. Early in the disease process, the CSF culture may be positive in the absence of pleocytosis.

Interpretation of CSF

- **Cell count**: The CSF White Blood Cell (WBC) count in acute bacterial meningitis is typically >1000 WBC/microL, with a predominance of neutrophils. However, early in the course, few or no WBCs may be present. A CSF WBC count >6/microL is considered abnormal in children older than three months of age, and >9 WBCs/microL is considered abnormal for infants 29 to 90 days.
- A traumatic LP can cause small amounts of bleeding into the CSF that can interfere with interpretation of the CSF cell count. Certain formulas can be used to aid in the interpretation of the cell count when the LP is traumatic. When the CSF is not grossly bloody, we subtract 1 WBC for every 1000 RBCs/microL. However, none of the formulas to "correct" the CSF WBC can be used with total confidence to exclude meningitis when the LP is traumatic.
- **Glucose and protein**: The CSF glucose in acute bacterial meningitis is <40 mg/dL in more than one-half of cases. In addition, the ratio of the CSF to blood glucose concentration is usually depressed (<0.6).
- The CSF protein in acute bacterial meningitis typically ranges from 100 to 500 mg/dL. The CSF protein concentration may be increased in children with traumatic LP because of the increased protein concentration in plasma and the release of proteins from lysed Red Blood Cells (RBC). In children with traumatic LP the CSF protein concentration may be corrected by subtracting 1 mg/dL for every 1000 RBCs/microL.
- **Gram stain**: The presence of an organism on CSF Gram stain can suggest the bacterial etiology one day or more before culture results are available. The absence of organisms on Gram stain does not exclude the diagnosis. The probability of visualizing bacteria depends upon the number of organisms present and is increased by cytocentrifugation.
- An organism is visualized on CSF Gram stain in approximately 90 percent of children with pneumococcal meningitis and 80 percent of children with meningococcal meningitis. In contrast, the Gram stain is positive in only

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one-half of patients with gram-negative bacillary meningitis and one-third of patients with listeria meningitis.

- **Culture**: Isolation of a bacterial pathogen from the CSF culture confirms the diagnosis of bacterial meningitis.
- **Rapid diagnostic tests**: Bacterial antigen tests should be reserved for cases in which the initial CSF Gram stain is negative and CSF culture is negative at 48 hours of incubation. Polymerase Chain Reaction (PCR) of CSF and blood is most helpful for documenting meningococcal disease in the patient with negative cultures.
- **Interpretation of CSF in pretreated patients**: Prior administration of antimicrobial agents, particularly oral antibiotics, tends to have minimal effects on CSF cytology. However, CSF chemistry results in pretreated patients must be interpreted with caution.

Although the use of antimicrobial therapy before LP affects the CSF culture and perhaps the Gram stain, conventional teaching has been that a pathogen still can be identified in the CSF in the majority of patients up to several hours after the administration of antibiotics.

Additional Cultures

Culture of other sites should be obtained as indicated.

- Gram stain and culture of petechial or purpuric lesions may identify the causative agent.
- Urine cultures should be obtained in infants (<12 months of age) who present with fever and nonspecific symptoms and signs of meningitis, since urinary tract infection may be the primary source of the meningitis pathogen in such patients.
- In patients with concomitant otitis media, Gram-stained smear of middle ear fluid (obtained by needle aspiration) may permit immediate identification of the likely pathogen and may be helpful if the Gram-stained smear of the CSF is equivocal.

Cultures of the nose and throat are not helpful in identifying the etiology of bacterial meningitis.

Other tests: Other tests for the diagnosis of bacterial meningitis have limited availability and/or undetermined utility for early diagnosis, as illustrated below.

- Despite its increasingly broad use, serum C-reactive protein is not a reliable indicator of severe infection.
- Elevated serum procalcitonin (>0.5 ng/mL) appears to be helpful in distinguishing bacterial from viral meningitis.

The presence of Tumor Necrosis Factor (TNF) may distinguish bacterial from viral meningitis but this assay is not generally available.

Imaging: It is not uncommon for Lumbar Puncture (LP) to be delayed while a Computed Tomographic (CT) scan is performed to exclude an intracranial

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process that would contraindicate an LP. Although concerns exist about herniation following LP in children, a review of the literature found that herniation was unlikely in children with bacterial meningitis unless they had focal neurologic findings or coma; furthermore, a normal CT does not absolutely exclude subsequent herniation.

Indications for imaging before LP in children with suspected bacterial meningitis include:

- Coma
- The presence of a Cerebrospinal Fluid (CSF) shunt
- History of hydrocephalus
- Recent history of CNS trauma or neurosurgery
- Papilledema
- Focal neurologic deficit (with the exception of palsy of cranial nerve VI [abducens nerve] or VII [facial nerve].

In children who require neuroimaging before LP, blood cultures should be obtained and empiric antibiotics administered before imaging. LP should be performed as soon as possible after neuroimaging provided that neuroimaging has not revealed any contraindications.

GENERAL PRINCIPLES OF MANAGEMENT

The most important initial issues are avoidance of delay in administering therapy and the choice of drug regimen. Delay in the administration of appropriate antibiotics can have a deleterious effect on outcome for patients who are deteriorating rapidly.

Antibiotic regimen: There are two general principles of antibiotic therapy for bacterial meningitis:

- The agent(s) used must be bactericidal against the infecting organism.
- The agent(s) used must be able to penetrate past the blood-brain barrier to reach a sufficient concentration in the CSF.

IMMEDIATE MANAGEMENT

Immediate management of children with suspected bacterial meningitis includes:

- Assurance of adequate ventilation and cardiac perfusion.
- Initiation of hemodynamic monitoring and support at the same time as obtaining appropriate laboratory studies (blood and cerebrospinal fluid)
- Establishment of venous access
- Administration of fluids as necessary to treat septic shock, if present
- Administration of dexamethasone if warranted after assessment of potential benefits and risks before or immediately after the first dose of antimicrobial

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- An appropriate empiric regimen (i.e. one that covers antibiotic-resistant S. pneumoniae, N. meningitidis, and Hib) includes high doses of a third-generation cephalosporin (e.g. cefotaxime, ceftriaxone) and vancomycin
- Cefotaxime 300 mg/kg per day intravenously (IV) (maximum dose 12 g/day) in 3 or 4 divided doses, or ceftriaxone 100 mg/kg per day IV (maximum dose 4 g/day) in 1 or 2 divided doses, **plus** Vancomycin 60 mg/kg per day IV (maximum dose 4 g/day) in 4 divided doses.
- Treatment of acidosis and coagulopathy if present.

Use of Dexamethasone

Issues related to neurologic sequelae after bacterial meningitis and the possible role of dexamethasone therapy to minimize these complications are discussed separately

The decision to use dexamethasone in children with suspected bacterial meningitis must be individualized. Factors to be weighed in this decision include:

- The etiologic agent
- The ability to administer dexamethasone before or within 1 hour of the first dose of antibiotic therapy
- The empiric antibiotic regimen
- The potential adverse effects

The American Academy of Pediatrics (AAP) Committee on Infectious Diseases suggests that dexamethasone therapy may be beneficial in children with Hib meningitis if given before or at the same time as the first dose of antimicrobial therapy. The AAP Committee on Infectious Diseases suggests that dexamethasone therapy be considered for infants and children older than six weeks with pneumococcal meningitis after weighing the potential risks and benefits.

If the decision is made to use dexamethasone, dexamethasone should be given before or concurrently with the first dose of the antimicrobial agent(s); it is probably of no benefit if given more than 1 hour later.

The regimen for dexamethasone is: Dexamethasone 0.15 mg/kg per dose every 6 hours for 2 to 4 days. Two days of dexamethasone appear to be as effective as and less toxic than longer courses.

Special Circumstances

The treatment of bacterial meningitis in children with immune deficiency, recent neurosurgery, anatomic defects, penetrating head trauma, CSF leak, and during epidemics requires consultation with an expert in pediatric infectious diseases.

Immune Deficiency

Vancomycin **plus** either cefotaxime or ceftriaxone given as described above are reasonable empiric coverage for most children with an underlying defect in

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host defense. If a Gram-negative rod is observed on Gram stain of the CSF, the addition of an aminoglycoside (e.g. gentamicin, amikacin) to these two agents is recommended.

- Gentamicin 7.5 mg/kg per day IV in 3 divided doses, **or**
- Amikacin 15 to 22. 5 mg/kg per day IV (maximum dose 1.5 g/day) in 3 divided doses.

T cell defects: S. pneumoniae and L. monocytogenes are the most likely causes of bacterial meningitis in patients with defective cell-mediated immunity it is particularly important to consider L. monocytogenes in renal transplant patients with suspected bacterial meningitis. To address these pathogens, the empiric regimen for children with defects in T cell immunity should include vancomycin **plus** either cefotaxime or ceftriaxone, dosed as recommended above, and high-dose ampicillin. The dose of ampicillin is as follows:

- Ampicillin 300 to 400 mg/kg IV per day (maximum dose 10 to 12 g/day) in 4 or 6 divided doses.

Recent neurosurgery: In addition to the usual nosocomial pathogens that may complicate any surgical procedure, coagulase-negative staphylococci (such as Staphylococcus epidermidis) and S. aureus are important causes of meningitis in patients who have had recent neurosurgery. Patients who undergo operations that involve a prosthetic device, such as a ventricular shunt or drain, are clearly at risk for developing infection. Patients who have undergone recent neurosurgery also are at increased risk for meningitis with enteric Gram-negative rods, such as E. coli and Klebsiella species, as well as P. aeruginosa. Empiric therapy in this setting usually consists of a combination of a third-generation cephalosporin and vancomycin. In addition, an aminoglycoside (e.g. gentamicin, amikacin) should be added if Gram-negative bacilli are noted on CSF Gram stain. Alternative regimens include:

- Vancomycin 60 mg/kg per day IV (maximum dose 4 g/day) in 4 divided doses, **plus**
- Cefepime 150 mg/kg per day IV (maximum dose 6 g/day) in 3 divided doses, **or** ceftazidime 150 mg/kg per day IV (maximum dose 6 g/day) in 3 divided doses, **or** meropenem 120 mg/kg per day IV (maximum dose 6 g/day) in 3 divided doses

The local antibiogram can help to guide which of the agents directed against Gram-negative organisms might be most appropriate (e.g. a high rate of resistance to ceftazidime suggests meropenem is a better choice).

Recent Placement of CSF Shunt

In infants and children who have had recent placement of a CSF shunt, vancomycin **plus** either cefotaxime or ceftriaxone are recommended.

Penetrating Head Trauma

Patients with penetrating head trauma are at risk for meningitis with S. aureus,

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coagulase-negative staphylococci (such as S. epidermidis), and aerobic Gram-negative bacilli, including P. aeruginosa.

Empiric therapy in this setting usually consists of a combination of vancomycin **plus** an extended-spectrum cephalosporin (cefepime or ceftazidime) or meropenem, **plus** an aminoglycoside;

- Vancomycin 60 mg/kg per day IV (maximum dose 4 g/day) in 4 divided doses, **plus**
- Cefepime 150 mg/kg per day IV (maximum dose 6 g/day) in 3 divided doses, **or** ceftazidime 150 mg/kg per day IV (maximum dose 6 g/day) in 3 divided doses, **or** meropenem 120 mg/kg per day IV (maximum dose 6 g/day) in 3 divided doses, **plus**
- Gentamicin 7.5 mg/kg per day IV in 3 divided doses or amikacin 15 to 22.5 mg/kg per day IV (maximum dose 1.5 g/day) in 3 divided doses.

Duration of therapy: The duration of antimicrobial therapy depends upon the causative organism and the clinical course.

Positive CSF culture: There is limited evidence from high-quality studies to guide the duration of treatment for bacterial meningitis. We suggest the following durations of therapy for uncomplicated meningitis caused by the following organisms:

- S. pneumonia: 10 to 14 days
- N. meningitides: 5 to 7 days
- H. influenzae type b (Hib): 7 to 10 days
- L. monocytogenes: 14 to 21 days
- S. aureus: at least 2 weeks
- Gram-negative bacilli: 3 weeks or a minimum of 2 weeks beyond the first sterile CSF culture.

Negative CSF culture: For children with negative CSF cultures at 48 to 72 hours, the duration of antibiotic therapy is individualized depending upon the remainder of the CSF evaluation, blood culture result, and clinical status:

- For those who have a normal CSF profile, and negative blood and CSF culture, discontinue antimicrobial therapy if cultures remain sterile after 48 to 72 hours of incubation.
- For those who have a CSF pleocytosis and positive blood culture, but negative CSF culture, treat for meningitis caused by the organism isolated from the blood culture (i.e. management is the same as if the CSF culture was positive for the same organism).

For those who have a CSF pleocytosis, negative blood culture, and negative CSF culture, individualize the duration of meningitic doses of antimicrobial therapy based on clinical parameters.

PROGNOSIS

Mortality: Case fatality rates for meningitis in children older than one month

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in the United States range from 0 to 15 percent, depending upon the infecting organism and when the survey was performed.

The mortality rate in developed countries varied by organism, ranging from 3.8 percent for H. influenzae type b (Hib) to 7.5 percent for N. meningitidis to 15.3 percent for S. pneumonia.

VIRAL CNS INFECTIONS

- Viral infection of the Central Nervous System (CNS) can involve the meninges (meningitis), the brain (encephalitis), the brainstem (rhombencephalitis), the spinal cord (myelitis), spinal roots (radiculitis), or combination of sites (meningoencephalitis, encephalomyelitis, or myeloradiculitis).
- Encephalitis is an acute, life-threatening emergency, requiring prompt intervention.
- Encephalitis is inflammation of the brain parenchyma, manifest by neurologic dysfunction (e.g. altered mental status, behavior, or personality; motor or sensory deficits; speech or movement disorders; hemiparesis; or paresthesias).
- However, in practice, most patients with encephalitis are diagnosed clinically. Clinical diagnosis of encephalitis requires evidence of neurologic dysfunction (e.g. depressed or altered level of consciousness, lethargy, personality change, seizure, ataxia, focal neurologic findings) and Central Nervous System (CNS) inflammation Cerebrospinal Fluid (CSF) pleocytosis; consistent neuroimaging or EEG findings).
- Encephalitis may occur during or after a viral infection (acute viral encephalitis and post-infectious encephalitis, respectively). Chronic encephalitis may be caused by a number of viruses (JC virus, BK virus, Simian virus 40, HIV) and prion diseases.
- A wide variety of viruses can cause encephalitis. Among those most commonly isolated are enteroviruses (e.g. poliovirus, echovirus, enterovirus, coxsackievirus A and B), parechoviruses, Herpes Simplex Virus (HSV) type 1 and 2, other Herpesviridae (e.g. Epstein-Barr, varicella zoster, cytomegalovirus, human herpesvirus 6), and arboviruses (e.g. La Crosse, West Nile, St. Louis, Eastern and Western equine encephalitis virus, Colorado tick fever, and yellow fever).
- Nonpolio enteroviruses and parechoviruses are a major cause of encephalitis in children. Enteroviruses have a clear seasonality, with 78 percent of cases in the United States occurring from June through October.

CLINICAL FEATURES

- Encephalitis causes neurologic dysfunction and has a broad range of presenting symptoms and signs. The clinical manifestations vary depending upon which portions of the Central Nervous System (CNS) are affected. Characteristic clinical features of viral infection at specific sites of the CNS are listed below.

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- Meningitis: Fever, headache, nausea, vomiting, photophobia, and stiff neck.
- Encephalitis: Fever, headache, nausea, vomiting, or altered level of consciousness, often with seizure and focal neurologic signs.
- Rhombencephalitis (brain stem encephalitis): Myoclonic jerks, tremor, ataxia, cranial nerve involvement, respiratory distress, shock, and coma.
- Myelitis: Muscle weakness, bladder dysfunction, flaccid paralysis, and reduced or absent reflexes.
- Radiculitis: Muscle weakness, shooting pain, dysesthesia, and diminished reflexes.
- **Neonates and young infants**: As with other infections in neonates (0 to 28 days) and young infants, the presentation of encephalitis can be nonspecific. Encephalitis should be considered in a neonate or young infant who has fever, seizure, poor feeding, irritability, lethargy, or decreased perfusion. Fever is a variable finding. Neonates who have viral illness, especially HSV and enterovirus, are at risk for severe CNS and systemic illness.
- **Children and adolescents**: In older children and adolescents, encephalitis can present with fever, psychiatric symptoms, emotional liability, movement disorder, ataxia, seizures, stupor, lethargy, coma, or localized neurologic changes (e.g. hemiparesis, cranial nerve defect, ataxia).
- **Complications**: Complications of acute viral encephalitis may include status epilepticus, cerebral edema, inappropriate secretion of antidiuretic hormone, cardiorespiratory failure, and disseminated intravascular coagulation.
- **Postinfectious encephalitis** (i.e. acute disseminated encephalomyelitis, ADEM) is a monophasic illness that is thought to be an autoimmune response to a preceding antigenic challenge (e.g. a febrile illness or immunization). Associated preceding illnesses may include measles, mumps, rubella, varicella zoster, Epstein-Barr virus, cytomegalovirus, herpes simplex virus, hepatitis A virus, influenza, and enterovirus. Associated immunizations may include anthrax, influenza, Japanese encephalitis virus, measles, rabies, smallpox, and yellow fever.
- The onset of postinfectious encephalitis is usually subacute and fever is typically absent at the time of neurologic manifestations. However, it can be difficult to distinguish postinfectious from acute encephalitis clinically. Characteristic magnetic resonance imaging findings of postinfectious encephalitis include multifocal white-matter lesions.

Autoimmune Encephalitis

- Anti-N-Methyl-D-Aspartate Receptor (NMDAR) and Voltage-Gated Potassium Channel Antibodies (VGKC Ab) are being increasingly recognized as causes of encephalitis in children.
- Anti-NMDAR encephalitis should be considered in children and

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adolescents who present with psychiatric symptoms, abnormal movements, seizure, autonomic instability, and hypoventilation. It is important to identify anti-NMDAR encephalitis because it may be associated with tumors (e.g. ovarian teratomas) and often responds to specific therapeutic interventions.

Examination

- The physical examination should include careful neurologic evaluation for focal findings. Neurologic evaluation should include assessment of the mental status and motor, sensory, cranial nerve, cerebellar, and reflex function. The Glasgow Coma Scale (GCS) score, although not validated in patients with nontraumatic brain injury, may be helpful in quantifying the level of consciousness and monitoring neurologic progression.
- Examination findings may suggest a possible etiologic agent. Examples include the vesicular rash that is present in approximately 60 percent of neonates with CNS Herpes Simplex Virus (HSV) disease, maculopapular rash in West Nile Virus (WNV) disease, the characteristic lesions of hand, foot, and mouth disease (coxsackieviruses A and B), and the rash of Rocky Mountain spotted fever, which typically does not appear until several days after the onset of fever.

LABORATORY EVALUATION

- Laboratory studies are performed to support the clinical diagnosis of encephalitis and establish an etiology, to assess for other conditions in the differential diagnosis, and to look for potential complications (e.g. inappropriate antidiuretic hormone secretion).
- **CSF evaluation**: Lumbar Puncture (LP) should be performed in all patients (unless contraindicated) with suspected encephalitis.
- Neuroimaging is required before LP in virtually all children with suspected encephalitis because they have altered levels of consciousness. Neuroimaging in patients with encephalitis may be normal or may demonstrate brain edema and inflammation of the cerebral cortex, gray-white matter junction, thalamus, or basal ganglia.
- MRI also detects other conditions that are in the differential diagnosis of encephalitis, such as Acute Disseminated Encephalomyelitis (ADEM), head trauma, intracranial hemorrhage, and tumor.
- Magnetic Resonance Imaging (MRI) is preferred, but it is not usually immediately available. In practice, many children undergo Computed Tomography (CT) before LP to make sure there are no contraindications to LP (e.g. mass lesion, shift) and MRI after LP because MRI is more sensitive and specific for encephalitis.
- An opening pressure should be documented (to provide a clue to conditions with elevated intracranial pressure that can mimic viral encephalitis.

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- Samples of Cerebrospinal Fluid (CSF) should be sent for cell count and differential, glucose, protein, Gram stain, bacterial culture, HSV PCR, and enterovirus PCR; additional tests should be done as indicated by epidemiology and clinical findings.
- Characteristic CSF findings in viral encephalitis are as follows:
  - CSF pleocytosis is present in approximately 60 percent of children with encephalitis. The CSF White Blood Cell (WBC) count typically ranges from 0 to 500 cells/microL with a lymphocytic predominance; however, a predominance of neutrophils can be seen during the first 24 to 48 hours of infection.
  - Red blood cells are usually absent (except in traumatic tap), but their presence can indicate HSV encephalitis.
  - Protein is usually slightly elevated (generally <150 mg/dL).
  - Glucose is usually normal and >50 percent of blood value. Moderate reduction in glucose can be seen with HSV and mumps.
- **Electroencephalogram**: Every patient with suspected encephalitis should undergo Electroencephalography (EEG) as soon as is feasible; however, EEG is not usually obtained as part of the initial evaluation in the emergency department or other acute care settings. EEG may help to differentiate encephalitis from nonconvulsive seizure activity (i.e. partial complex seizures, absence seizures).
- **Brain biopsy** should be the last resort. It may be indicated if a patient with encephalitis of unknown etiology continues to deteriorate neurologically despite acyclovir therapy.

OVERVIEW OF TREATMENT

Supportive Care

- Encephalitis is an acute, life-threatening emergency, requiring prompt intervention. Provision of empiric antimicrobial therapy and supportive care are the cornerstones of therapy for viral encephalitis in children and adolescents.
- Supportive care is a critical aspect of the treatment of encephalitis. Patients with severe encephalitis should be cared for in an intensive care unit with cardiorespiratory monitoring and careful attention to cardiorespiratory, fluid, and electrolyte status. Potential complications that must be anticipated include:
- Status epilepticus, which should be treated aggressively.
- Cerebral edema; repeat neuroimaging may be helpful in following comatose patients and may demonstrate cerebral edema before typical clinical indicators.
- Fluid and electrolyte disturbance e.g. the Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH).

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- Abrupt cardiac and respiratory arrest of central origin
- Gastrointestinal bleeding
- Disseminated intravascular coagulation
- Empiric acyclovir is recommend prompt initiation of Intravenous (IV) acyclovir for children (beyond the neonatal period) and adolescents with suspected encephalitis. The dose of acyclovir varies depending on age of the patient. The dose of acyclovir for all forms of neonatal HSV is 60 mg/kg per day intravenously divided every eight hours. The dose of acyclovir must be adjusted for neonates with renal failure. >28 days to <3 months – 20 mg/kg per dose every eight hours.
- ≥3 months to <12 years – 10 to 15 mg/kg per dose every eight hours; an increased dose (20 mg/kg per dose every eight hours) is approved by the US Food and Drug Administration for the treatment of HSV encephalitis in this age group, but the risk of nephrotoxicity may be increased. ≥12 years – 10 mg/kg per dose every eight hours.
- **Duration**: The duration of empiric acyclovir therapy depends upon laboratory results. If HSV is confirmed or probable (i.e. positive HSV Polymerase Chain Reaction [PCR] from Cerebrospinal Fluid [CSF] or other site), acyclovir should be continued for 21 days. Lumbar puncture should be performed near the end of acyclovir treatment to ensure that HSV PCR is negative; acyclovir therapy should be continued if CSF HSV PCR remains positive.
- Disseminated and Central Nervous System (CNS) disease should be treated for a **minimum** of 21 days. Because the persistence of HSV DNA in the CSF is associated with poor outcome, repeat lumbar puncture to obtain CSF HSV DNA PCR near the end of therapy is recommended to make sure that HSV DNA PCR is negative and that CSF parameters have returned to normal.
- **IV acyclovir not available**: In the event of a shortage of IV acyclovir, patients with HSV encephalitis are a priority group for existing supplies. However, if IV acyclovir is not available, in agreement with the American Academy of Pediatrics Committee on Infectious Diseases, clinicians suggest IV ganciclovir 6 mg/kg every 12 hours for patients ≤90 days of age and 5 mg/kg every 12 hours for patients >90 days of age. If ganciclovir cannot be given, we suggest IV foscarnet 60 mg/kg every 12 hours.

PROGNOSIS

- The prognosis of viral encephalitis varies depending upon the age of the patient, neurologic findings at the time of presentation, and the pathogen. Coma, convulsion, or focal neurologic findings in the acute phase; young age (<5 years); need for intensive care; and herpes simplex encephalitis are associated with worse outcome.
- The overall risk of death in childhood encephalitis ranges from 0 to 7 percent.

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References

1. McTague A, Martland T, Appleton R. Drug management for acute tonic-clonic convulsions including convulsive status epilepticus in children. Cochrane Database Syst Rev 2018; 1:CD001905.
2. Seinfeld S, Shinnar S, Sun S, *et al*. Emergency management of febrile status epilepticus: results of the FEBSTAT study. Epilepsia 2014; 55:388.
3. Wilmshurst JM, Gaillard WD, Vinayan KP, *et al*. Summary of recommendations for the management of infantile seizures: Task Force Report for the ILAE Commission of Pediatrics. Epilepsia 2015; 56:1185.
4. Hesdorffer DC, Shinnar S, Lax DN, *et al*. Risk factors for subsequent febrile seizures in the FEBSTAT study. Epilepsia 2016; 57:1042.
5. Offringa M, Newton R, Cozijnsen MA, Nevitt SJ. Prophylactic drug management for febrile seizures in children. Cochrane Database Syst Rev 2017; 2:CD003031.
6. Rosenbloom E, Finkelstein Y, Adams-Webber T, Kozer E. Do antipyretics prevent the recurrence of febrile seizures in children? A systematic review of randomized controlled trials and meta-analysis. Eur J Paediatr Neurol 2013; 17:585.
7. Hayakawa I, Miyama S, Inoue N, *et al*. Epidemiology of Pediatric Convulsive Status Epilepticus With Fever in the Emergency Department: A Cohort Study of 381 Consecutive Cases. J Child Neurol 2016; 31:1257.
8. Møller RS, Wuttke TV, Helbig I, *et al*. Mutations in GABRB3: From febrile seizures to epileptic encephalopathies. Neurology 2017; 88:483.
9. Guedj R, Chappuy H, Titomanlio L, *et al*. Do All Children Who Present With a Complex Febrile Seizure Need a Lumbar Puncture? Ann Emerg Med 2017; 70:52.
10. Olarte L, Barson WJ, Barson RM, *et al*. Impact of the 13-Valent Pneumococcal Conjugate Vaccine on Pneumococcal Meningitis in US Children. Clin Infect Dis 2015; 61:767.
11. Byington CL, Kendrick J, Sheng X. Normative cerebrospinal fluid profiles in febrile infants. J Pediatr 2011; 158:130.
12. Leber AL, Everhart K, Balada-Llasat JM, *et al*. Multicenter Evaluation of BioFire FilmArray Meningitis/Encephalitis Panel for Detection of Bacteria, Viruses, and Yeast in Cerebrospinal Fluid Specimens. J Clin Microbiol 2016; 54:2251.
13. Liesman RM, Strasburg AP, Heitman AK, *et al*. Evaluation of a Commercial Multiplex Molecular Panel for Diagnosis of Infectious Meningitis and Encephalitis. J Clin Microbiol 2018; 56.
14. Blaschke AJ, Holmberg KM, Daly JA, *et al*. Retrospective Evaluation of Infants Aged 1 to 60 Days with Residual Cerebrospinal Fluid (CSF) Tested Using the FilmArray Meningitis/Encephalitis (ME) Panel. J Clin Microbiol 2018; 56.
15. Hu R, Gong Y, Wang Y. Relationship of Serum Procalcitonin Levels to Severity and Prognosis in Pediatric Bacterial Meningitis. Clin Pediatr (Phila) 2015; 54:1141.
16. Bronstein DE, Shields WD, Glaser CA. Encephalitis and meningoencephalitis. In: Feigin and Cherry's Textbook of Pediatric Infectious Diseases, 7th ed, Cherry JD, Harrison GJ, Kaplan SL, *et al* (Eds), Elsevier Saunders, Philadelphia 2014. p.492.
17. Venkatesan A, Tunkel AR, Bloch KC, *et al*. Case definitions, diagnostic algorithms, and priorities in encephalitis: consensus statement of the international encephalitis consortium. Clin Infect Dis 2013; 57:1114.

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18. Liesman RM, Strasburg AP, Heitman AK, *et al*. Evaluation of a Commercial Multiplex Molecular Panel for Diagnosis of Infectious Meningitis and Encephalitis. J Clin Microbiol 2018; 56.
19. Ramanan P, Bryson AL, Binnicker MJ, *et al*. Syndromic Panel-Based Testing in Clinical Microbiology. Clin Microbiol Rev 2018; 31.
20. Bseikri MR, Barton JR, Kulhanjian JA, *et al*. Anti-N-methyl D-aspartate receptor encephalitis mimics viral encephalitis. Pediatr Infect Dis J 2012; 31:202.
21. Gable MS, Sheriff H, Dalmau J, *et al*. The frequency of autoimmune N-methyl-D-aspartate receptor encephalitis surpasses that of individual viral etiologies in young individuals enrolled in the California Encephalitis Project. Clin Infect Dis 2012; 54:899.
22. Papadopoulos KP, Romero RS, Gonzalez G, *et al*. Anti-Hu-Associated Autoimmune Limbic Encephalitis in a Patient with PD-1 Inhibitor-Responsive Myxoid Chondrosarcoma. Oncologist 2018; 23:118.
23. Matsuoka H, Kimura H, Koba H, *et al*. Nivolumab-induced Limbic Encephalitis with Anti-Hu Antibody in a Patient With Advanced Pleomorphic Carcinoma of the Lung. Clin Lung Cancer 2018; 19:e597.
24. Graus F, Dalmau J. Paraneoplastic neurological syndromes in the era of immune-checkpoint inhibitors. Nat Rev Clin Oncol 2019.
25. Dalmau J, Graus F. Antibody-Mediated Encephalitis. N Engl J Med 2018; 378:840.
26. Dalmau J, Lancaster E, Martinez-Hernandez E, *et al*. Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. Lancet Neurol 2011; 10:63.
27. Titulaer MJ, McCracken L, Gabilondo I, *et al*. Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. Lancet Neurol 2013; 12:157.
28. Gable M, Glaser C. Anti-N-Methyl-d-Aspartate Receptor Encephalitis Appearing as a New-Onset Psychosis: Disease Course in Children and Adolescents Within the California Encephalitis Project. Pediatr Neurol 2017; 72:25.
29. Dahm L, Ott C, Steiner J, *et al*. Seroprevalence of autoantibodies against brain antigens in health and disease. Ann Neurol 2014; 76:82.
30. Armangue T, Moris G, Cantarín-Extremera V, *et al*. Autoimmune post-herpes simplex encephalitis of adults and teenagers. Neurology 2015; 85:1736.
31. Armangue T, Spatola M, Vlagea A, *et al*. Frequency, symptoms, risk factors, and outcomes of autoimmune encephalitis after herpes simplex encephalitis: a prospective observational study and retrospective analysis. Lancet Neurol 2018; 17:760.
32. Nosadini M, Mohammad SS, Ramanathan S, *et al*. Immune therapy in autoimmune encephalitis: a systematic review. Expert Rev Neurother 2015; 15:1391.
33. Balu R, McCracken L, Lancaster E, *et al*. A score that predicts 1-year functional status in patients with anti-NMDA receptor encephalitis. Neurology 2019; 92:e244.
34. Van Sonderen A, Ariño H, Petit-Pedrol M, *et al*. The clinical spectrum of Caspr2 antibody-associated disease. Neurology 2016; 87:521.
35. Graus F, Titulaer MJ, Balu R, *et al*. A clinical approach to diagnosis of autoimmune encephalitis. Lancet Neurol 2016; 15:391.

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Chapter

12 Central Nervous System Tuberculosis

Central Nervous System (CNS) Tuberculosis (TB) includes three clinical categories: tuberculous meningitis, intracranial tuberculoma, and spinal tuberculous arachnoiditis. All three categories are encountered frequently in regions of the world where the incidence of TB is high and the prevalence of post-primary dissemination is common among children and young adults.

PATHOGENESIS

- During the bacillemia that follows primary infection or late reactivation Tuberculosis (TB), scattered tuberculous foci (tubercles) are established in the brain, meninges, or adjacent bone.
- The chance occurrence of a subependymal tubercle, with progression and rupture into the subarachnoid space, is the critical event in the development of tuberculous meningitis. The widespread and dense distribution of infectious foci seen in association with progressive miliary tuberculosis.
- Meningitis develops most commonly as a complication of post-primary infection in infants and young children and from chronic reactivation bacillemia in older adults with immune deficiency.
- The spillage of tubercular protein into the subarachnoid space produces an intense hypersensitivity reaction, giving rise to inflammatory changes that are most marked at the base of the brain. Three features dominate the pathology and explain the clinical manifestations:
    - Proliferative arachnoiditis, most marked at the base of the brain, eventually produces a fibrous mass that encases adjacent cranial nerves and penetrating vessels.
    - Vasculitis with resultant aneurysm, thrombosis, and infarction affects vessels that traverse the basilar or spinal exudate or are located within the brain itself. Multiple lesions are common and a variety of stroke syndromes may result, involving the basal ganglia, cerebral cortex, pons, and cerebellum. Intracranial vasculitis is a common feature of autopsy studies and a major determinant of residual neurologic deficits.
    - Communicating hydrocephalus results from extension of the inflammatory process to the basilar cisterns and impedance of cerebrospinal fluid circulation and resorption. Obstruction of the aqueduct develops less frequently, from contraction of exudate surrounding the brainstem or from a strategically placed brainstem tuberculoma.

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TYPES OF CNS TUBERCULOSIS

Tuberculous meningitis: Tuberculous meningitis accounts for about 1 percent of all cases of Tuberculosis (TB) and 5 percent of all extrapulmonary disease in immunocompetent individuals.

- Early recognition of tuberculous meningitis is of paramount importance because the clinical outcome depends greatly upon the stage at which therapy is initiated. Empiric antituberculous therapy should be started immediately in any patient with meningitis syndrome and Cerebrospinal Fluid (CSF) findings of low glucose concentration, elevated protein, and lymphocytic pleocytosis if there is evidence of TB elsewhere or if prompt evaluation fails to establish an alternative diagnosis. Serial examination of the CSF by acid-fast stain and culture is the best diagnostic approach. Smears and cultures will yield positive results even days after treatment have been initiated. Nucleic Acid Amplification (NAA) testing also may be helpful.

CLINICAL FEATURES

Typically, patients with tuberculous meningitis present with a subacute febrile illness that progresses through three discernible phases:

- The prodromal phase, lasting two to three weeks, is characterized by the insidious onset of malaise, lassitude, headache, low-grade fever, and personality change.
- The meningitic phase follows with more pronounced neurologic features, such as meningismus, protracted headache, vomiting, lethargy, confusion, and varying degrees of cranial nerve and long-tract signs.
- The paralytic phase supervenes as the pace of illness accelerates rapidly; confusion gives way to stupor and coma, seizures, and often hemiparesis. For the majority of untreated patients, death ensues within five to eight weeks of the onset of illness.

It is useful to categorize patients on presentation by the stage of illness, based upon the mental status and focal neurologic signs:

- Stage I patients are lucid with no focal neurologic signs or evidence of hydrocephalus.
- Stage II patients exhibit lethargy, confusion; they may have mild focal signs, such as cranial nerve palsy or hemiparesis.
- Stage III represents advanced illness with delirium, stupor, coma, seizures, multiple cranial nerve palsies, and/or dense hemiplegia.

About one-third of patients on presentation have underlying generalized (miliary) tuberculosis, in which case careful funduscopic examination often shows choroidal tubercles. These are multiple, ill-defined, raised yellow-white nodules (granulomas) of varying size near the optic disk. If present in a patient with meningitis, choroidal tubercles are a valuable clue to the etiologic diagnosis. Signs of active TB outside the Central Nervous System (CNS) are of diagnostic import if present but are often absent or nonspecific. Abnormalities on chest

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radiograph may be seen in half of cases, ranging from focal lesions to a subtle miliary pattern. A tuberculin skin test will be positive in the majority, although a negative result does not exclude the diagnosis.

Cases with atypical features that mimic other neurologic conditions are important to recognize. As an example, patients may present with an acute, rapidly progressive, meningitic syndrome suggesting pyogenic meningitis or with a slowly progressive dementia over months or even years characterized by personality change, social withdrawal, loss of libido, and memory deficits. Less common is an encephalitic course manifested by stupor, coma, and convulsions without overt signs of meningitis.

DIAGNOSIS

Diagnostic tools consist of cerebrospinal fluid examination (including culture and nucleic acid testing) and radiography.

Spinal Fluid Examination

The examination of cerebrospinal fluid specimens is of critical importance to early diagnosis of tuberculous meningitis. Typically, the CSF formula shows elevated protein and lowered glucose concentrations with a mononuclear pleocytosis. CSF protein ranges from 100 to 500 mg/dL in most patients; however, patients with subarachnoid block may show extremely high levels in the range of 2 to 6 g/dL, associated with xanthochromia. The CSF glucose is less than 45 mg/dL in 80 percent of cases. The usual CSF cell count is between 100 and 500 cells/microL.

Early in the course of illness, the cellular reaction is often atypical with only a few cells or with Polymorphonuclear Leukocyte (PMN) predominance. Such cases usually rapidly change to a lymphocytic cellular response on subsequent CSF examinations. Upon initiation of antituberculous chemotherapy, the CSF of some patients briefly reverts to a PMN cellular reaction, associated with transient clinical deterioration.

Culture and Sensitivity

The importance of repeated, careful examination and culture of CSF specimens for Mycobacterium tuberculosis cannot be overemphasized. In general, a minimum of three serial lumbar punctures should be performed at daily intervals, although empiric therapy need not be delayed during this time.

The sensitivity of the AFB smear of spinal fluid may be enhanced by attention to the following principles:

- It is best to use the last fluid removed at lumbar puncture, and recovery of the organism improves if a large volume (10 to 15 mL) is removed.
- Organisms can be demonstrated most readily in a smear of the clot or sediment. If no clot forms, the addition of 2 mL of 95 percent alcohol gives a heavy protein precipitate that carries bacilli to the bottom of the tube upon centrifugation.

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- 0.02 mL of the centrifuged deposit should be applied to a glass slide in an area not exceeding one centimeter in diameter and stained by the standard Kinyoun or Ziehl-Neelsen method.
- Between 200 and 500 high-powered fields should be examined (approximately 30 minutes), preferably by more than one observer.

Nucleic Acid Tests

Nucleic Acid Amplification Tests (NAATs) use Polymerase Chain Reaction (PCR) techniques. Sensitivity and specificity of PCR can be variable.

The assay MTBDRplus is a molecular probe capable of detecting rifampin and isoniazid resistance mutations (rpoB gene for rifampin resistance; katG and inhA genes for isoniazid resistance). The assay has been shown to be useful for detection of drug resistance for CSF samples that have a PCR-positive result.

The assay Xpert MTB/RIF may be an acceptable rule-in diagnostic tool for tuberculous meningitis in an endemic setting.

CSF specimens should be submitted for NAA testing whenever clinical suspicion is sufficiently high to warrant empiric therapy and AFB stains of the initial samples are negative. However, it is important to recognize that a negative result does not exclude the diagnosis or obviate the need for continued therapy.

Neuroimaging

Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) have greatly improved characterization and management of CNS infections. In patients with tuberculous meningitis, CT can define the presence and extent of basilar arachnoiditis, cerebral edema, infarction, and hydrocephalus.

The following observations can be derived from a review of selected clinical series:

- In a patient with compatible clinical features, CT or MRI evidence of basilar meningeal enhancement combined with any degree of hydrocephalus is strongly suggestive of tuberculous meningitis.
- The CT scan is normal in approximately 30 percent of cases with stage I meningitis, and patients with a normal scan nearly always recover completely on therapy.
- Hydrocephalus combined with marked basilar enhancement is indicative of advanced meningitic disease and carries a poor prognosis. Marked basilar enhancement correlates well with vasculitis and, therefore, with a risk for basal ganglia infarction.
- MRI is superior to CT in defining lesions of the basal ganglia, midbrain, and brainstem and for evaluating all forms of suspected spinal TB.

Tuberculoma

- Tuberculomas are conglomerate granulomatous foci within the brain

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parenchyma; they may be observed on histopathology or radiographic imaging. Centrally located lesions may reach considerable size without producing meningeal inflammation.

- Clinically silent single or multiple nodular enhancing lesions are commonly seen in the setting of meningitis; occasionally, they are seen in patients with miliary tuberculosis and no meningitis. These lesions generally disappear on therapy but may heal with calcification.
- Symptomatic intracranial mass lesions (clinical tuberculomas) are observed most frequently in individuals from areas where the prevalence of tuberculosis is high.
- Typically, a child or young adult presents with seizure or headache; occasionally, hemiplegia or signs of raised intracranial pressure are observed.
- On contrast CT imaging, early stage lesions are low density or isodense, often with edema out of proportion to the mass effect and little encapsulation. Later-stage tuberculomas are well encapsulated, isodense or hyperdense, and have peripheral ring enhancement.
- Symptoms of systemic illness and signs of meningeal inflammation are rarely observed.
- Lumbar puncture is usually avoided because of concern for raised intracranial pressure and risk of brainstem herniation; in the occasional reported case where cerebrospinal fluid has been examined, the findings are normal or nonspecific.
- The diagnosis is made in relation to clinical, epidemiologic, and radiographic features or by needle biopsy. Unless the location of the lesion threatens obstructive hydrocephalus or brainstem herniation, surgical intervention should be avoided as it may precipitate severe meningitis.

Spinal Tuberculous

- Spinal tuberculous arachnoiditis is observed most commonly in endemic areas. The pathogenesis is similar to that of meningitis, with focal inflammatory disease at single or multiple levels leading to gradual encasement of the spinal cord by a gelatinous or fibrous exudate.
- Symptoms develop and progress slowly over weeks to months and may culminate with a meningitis syndrome. Patients present with the subacute onset of nerve root and cord compression signs: spinal or radicular pain, hyperesthesia or paresthesias; lower motor neuron paralysis; and bladder or rectal sphincter dysfunction. Vasculitis may lead to thrombosis of the anterior spinal artery and infarction of the spinal cord. Other forms include extradural or intradural tuberculoma and epidural abscess.
- The diagnosis of spinal tuberculous arachnoiditis is based on findings of elevated cerebrospinal fluid protein levels and MRI findings of nodular arachnoiditis combined with tissue biopsy.
- The treatment for this form of disease is the same as for tuberculous meningitis.

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TREATMENT

Specific antituberculous chemotherapy should be initiated on the basis of strong clinical suspicion and should not be delayed until bacteriologic proof has been obtained. The clinical outcome depends greatly on the stage at which therapy is initiated; much more harm results from delay, even for only a few days, than from inappropriate therapy as long as efforts are continued to confirm the diagnosis.

General Approach

- Treatment begins with an "intensive phase" that consists of a four-drug regimen that includes isoniazid, rifampin, pyrazinamide, and a fourth drug, either a fluoroquinolone (moxifloxacin or levofloxacin) or an injectable aminoglycoside, administered daily for two months.
- This is followed by a "continuation phase" that consists of isoniazid and rifampin alone (if the isolate is fully susceptible) administered daily or three times a week. Ethambutol penetrates poorly into even inflamed meninges and can be replaced in standard treatment regimens with a fluoroquinolone (moxifloxacin or levofloxacin). Aminoglycoside penetration is optimized during acute inflammation and its value beyond initial treatment is not clear.
- In general, treatment consists of an initial 2 month period of intensive therapy (with four drugs) followed by a prolonged continuation phase (with isoniazid and rifampin) lasting 9 to 12 months, depending on the clinical response and drug sensitivity of the isolate. The regimen for tuberculoma generally warrants treatment duration of 18 months. The nature and duration of treatment may require adjustment depending on individual patient circumstances.
- Isoniazid, rifampin, and pyrazinamide are bactericidal, can be administered orally, penetrate inflamed meninges, and achieve Cerebrospinal Fluid (CSF) levels that exceed the inhibitory concentration needed for sensitive strains. Isoniazid has excellent CNS penetration and is more active against rapidly dividing than semidormant organisms. Rifampin is active against both rapidly dividing organisms and semidormant subpopulations of organisms. Pyrazinamide readily penetrates the CSF and is highly active against intracellular mycobacteria. Likewise, moxifloxacin and levofloxacin exhibit good CNS penetration.
- In the past, streptomycin (15 mg/kg per day Intramuscularly (IM) in adults to a maximum dose of 1 g; 20 to 40 mg/kg per day in children) was added to isoniazid in order to enhance sterilization and to reduce the risk of clinical relapse from resistant organisms. With the availability of rifampin and pyrazinamide, reliance upon streptomycin or other drugs of its class is generally limited to regions of the world with high prevalence of isoniazid resistance.

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Doses of First-line Antituberculosis Drugs

- **Isoniazid**: 5 mg/kg (300 mg) Daily (Tablets (50 mg, 100 mg, 300 mg); elixir (50 mg/5 mL); aqueous solution (100 mg/mL) for intravenous or intramuscular injection)
- **Rifampin**: 10 mg/kg (600 mg) Daily (Capsule (150 mg, 300 mg); powder may be suspended for oral administration; aqueous solution for intravenous injection)
- **Rifabutin**: 5 mg/kg (300 mg) Daily (Capsule (150 mg)
- **Rifapentine**: 5 mg/kg (300 mg)-Tablet (150 mg, film coated)
- **Pyrazinamide** Tablet (500 mg), Daily therapy: 15-30 mg/kg/day (maximum: 2 g/day), Twice weekly Directly Observed Therapy (DOT): 50 mg/kg/dose (maximum: 2 g/dose)
- **Ethambutol** Tablet (100 mg, 400 mg), Daily therapy: 15-20 mg/kg/day (maximum: 1 g/day); Twice weekly directly observed therapy (DOT): 50 mg/kg (maximum: 2.5 g/dose).
- **Drug resistance**: There are no definitive guidelines for the duration of therapy in patients with multidrug-resistant infection. In such cases, it may be advisable to extend the duration of therapy to 18 to 24 months, taking into account the severity of illness, rate of clinical response, and the patient's immune status.
- The prevalence of CNS infection caused by strains resistant to one or more first-line drugs is increasing. Those at greatest risk for drug-resistant disease include individuals from areas of the world where Tuberculosis (TB) is endemic, those with a history of previous antituberculous treatment, homeless individuals, and those with exposure to source patients harboring drug-resistant organisms.
- **Glucocorticoids**: Urgent warning signs that warrant prompt initiation of glucocorticoids include:
  - Patients who are progressing from one stage to the next at or before the introduction of chemotherapy
  - Patients with an acute encephalitis presentation, especially if the CSF opening pressure is ≥400 mmH_2O or if there is clinical or Computed Tomographic (CT) evidence of cerebral edema
  - Patients who demonstrate "therapeutic paradox" an exacerbation of clinical signs (e.g. fever, change in mentation) after beginning antituberculous chemotherapy.
  - Spinal block or incipient block (CSF protein >500 mg/dL and rising)
  - Head CT evidence of marked basilar enhancement (portends an increased risk for infarction of the basal ganglia) or moderate or advancing hydrocephalus
  - Patients with intracerebral tuberculoma, where edema is out of proportion to the mass effect and there are any clinical neurologic signs (altered mentation or focal deficits)

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- The regimen consists of dexamethasone or prednisone, as follows: Dexamethasone – Children <25 kg: 8 mg/day for two weeks, then taper gradually over four to six weeks. Adolescents and adults >25 kg: 0.3 to 0.4 mg/kg/day for two weeks, then 0.2 mg/kg/day week three, then 0.1 mg/kg/day week four, then 4 mg per day and taper 1 mg off the daily dose each week; total duration approximately eight weeks.
- Prednisone – Children: 2 to 4 mg/kg per day. Adolescents and adults: 60 mg/day. Administer initial dose for two weeks, then taper gradually over the next six weeks (i.e. reduce daily dose by 10 mg each week); total duration approximately eight weeks.

Surgery

Patients with hydrocephalus may require surgical decompression of the ventricular system in order to effectively manage the complications of raised intracranial pressure. In such patients with clinical stage II disease, the combination of serial lumbar puncture and steroid therapy may suffice while judging the early response to chemotherapy. However, surgical intervention should not be delayed in patients with stupor and coma or when the clinical course of therapy is marked by progressive neurologic impairment.

Unlike other CNS mass lesions, medical management is preferred for clinical tuberculomas unless the lesion produces obstructive hydrocephalus or compression of the brainstem. In the past, surgical resection was often complicated by severe, fatal meningitis.

References

1. World Health Organization. Global Tuberculosis Report 2018. http://www.who.int/tb/publications/global_report/en/ (Accessed on October 01, 2018).
2. Centers for Disease Control and Prevention. Slide Set— Epidemiology of Pediatric Tuberculosis in the United States, 1993-2016. https://www.cdc.gov/tb/publications/slidesets/pediatrictb/default.htm (Accessed on October 01, 2018).
3. American Academy of Pediatrics. Red Book: 2018 Report of the Committee on Infectious Diseases, 31st ed, Kimberlin DW, Brady MT, Jackson MA, Long SS (Eds), American Academy of Pediatrics, Itasca, IL 2018.
4. World Health Organization. WHO treatment guidelines for drug-resistant tuberculosis: 2016 update. WHO, Geneva 2016. http://www.who.int/tb/MDRTBguidelines2016.pdf?ua=1 (Accessed on May 17, 2016).
5. Centers for Disease Control and Prevention. Provisional CDC guidelines for the use and safety monitoring of bedaquiline fumarate (Sirturo) for the treatment of multidrug-resistant tuberculosis. MMWR Recomm Rep 2013; 62:1.
6. World Health Organization. The use of delamanid in the treatment of multidrug-resistant tuberculosis in children and adolescents: Interim policy guidance. Available at: http://apps.who.int/iris/bitstream/handle/10665/250614/9789241549899-eng.pdf;jsessionid=044DF19E602AD56EC47E859FCBE93AEB?sequence=1 (Accessed on June 05, 2018).

Paramount Books (Pvt.) Ltd.

7. Bourgi K, Fiske C, Sterling TR. Tuberculosis Meningitis. Curr Infect Dis Rep 2017; 19:39.
8. Centers for Disease Control and Prevention. Reported tuberculosis in the United States, 2013. US Department of Health and Human Services, Atlanta, GA 2014.
9. Lewinsohn DM, Leonard MK, LoBue PA, *et al*. Official American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention Clinical Practice Guidelines: Diagnosis of Tuberculosis in Adults and Children. Clin Infect Dis 2017; 64:e1.
10. Nahid P, Dorman SE, Alipanah N, *et al*. Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis. Clin Infect Dis 2016; 63:e147.
11. Heemskerk AD, Nguyen MTH, Dang HTM, *et al*. Clinical Outcomes of Patients With Drug-Resistant Tuberculous Meningitis Treated With an Intensified Antituberculosis Regimen. Clin Infect Dis 2017; 65:20.

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Chapter

13

Peripheral Facial Nerve Palsy (Bell's Palsy)

- Bell's palsy is caused by the dysfunction of the ipsilateral facial nerve. The most common type of facial paralysis in children is Bell's palsy, which is defined as an acute, idiopathic, unilateral paralysis of the facial nerve without any associated disorders.
- Affected patients develop unilateral facial paralysis over one to three days with forehead involvement and no other neurologic abnormalities. Symptoms typically peak in the first week and then gradually resolve over three weeks to three months.

CLINICAL FEATURES

Patients with Bell's palsy typically present with the sudden onset of unilateral facial paralysis. Common findings include the eyebrow sagging, inability to close the eye, disappearance of the nasolabial fold, and drooping at the affected corner of the mouth, which is drawn to the unaffected side. Decreased tearing, hyperacusis, and/or loss of taste sensation on the anterior two-thirds of the tongue may help to site the lesion in the fallopian canal, but these findings are of little practical use other than as indicators of severity.

Peripheral versus Central Lesions

- Sparing of the forehead muscles on the affected side of the face is suggestive of a central (upper motor neuron) lesion because of bilateral innervation to this area. However, this finding does not exclude a peripheral site of pathology in all cases.
- A "peripheral" (lower motor neuron) pattern of facial weakness that involves the forehead is usually due to a lesion of the ipsilateral facial nerve, but also can be caused by a central (brainstem) lesion that involves the ipsilateral facial nerve nucleus or facial nerve tract in the pons.
- Accurate diagnosis begins with a thorough history and physical examination. The history should address the time of onset, rapidity of progression, associated symptoms (e.g. hyperacusis, lack of taste), and any systemic diseases such as diabetes mellitus or chronic otitis media.

Physical examination should include a careful assessment of facial musculature paralysis as well as careful examination of the ear, mastoid region, parotid gland, and neck. Examination of other cranial nerves, hearing, taste, salivation, and lacrimation may help localize the lesion.

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The Diagnosis of Bell's Palsy is Based Upon the Following Criteria

- A diffuse involvement of all of the distal branches of the facial nerve is present.
- Onset is acute, over a day or two; the course is progressive, reaching maximal clinical weakness/paralysis within three weeks or less from the first day of visible weakness; recovery of some degree of function usually occurs within six months.
- Associated prodrome, ear pain, or dysacusis may be reported.

TREATMENT

- The treatment of facial nerve palsy is guided by the etiology and the severity of the condition. In the case of idiopathic acquired facial palsy (i.e. Bell's palsy), treatment options include glucocorticoids with or without antivirals (e.g. acyclovir or valacyclovir).
- The treatment of facial nerve palsy due to a specific cause (acute otitis media) involves treatment of the underlying disorder.
- **Eye care**: Appropriate eye care is required to help avoid corneal abrasions if the patient with facial palsy is unable to close the eye. This care generally entails administration of artificial tears during the day with ophthalmic ointment and patching at night.
- Most clinicians recommend early treatment with oral glucocorticoids for all children with Bell's palsy. This recommendation is consistent with guidelines from the American Academy of Neurology. Treatment should preferably begin within three days of symptom onset. Our suggested regimen is prednisone 2 mg/kg daily (up to 60 to 80 mg) for five days, followed by a five-day taper.
- The two largest and most rigorous clinical trials have found no additional benefit for antiviral therapy and its use is no longer routinely recommended. However, there is no consensus among experts regarding the routine use of antivirals along with glucocorticoids to treat Bell's palsy. But if herpes infection is identified, then antiviral should be given.
- Until certainty is reached, some clinicians suggest early combined therapy with prednisone 2 mg/kg daily (up to 60 to 80 mg per day) plus Valacyclovir 20 mg/kg three times per day (up to 1000 mg three times daily) for one week for children with severe facial palsy.
- Patients with Ramsay-Hunt syndrome should be treated with prednisone plus acyclovir or valacyclovir.

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Refernces

1. Shargorodsky J, Lin HW, Gopen Q. Facial nerve palsy in the pediatric population. Clin Pediatr (Phila) 2010; 49:411.
2. Karalok ZS, Taskin BD, Ozturk Z, *et al*. Childhood peripheral facial palsy. Childs Nerv Syst 2018; 34:911.
3. Pitaro J, Waissbluth S, Daniel SJ. Do children with Bell's palsy benefit from steroid treatment? A systematic review. Int J Pediatr Otorhinolaryngol 2012; 76:921.
4. Zandian A, Osiro S, Hudson R, *et al*. The neurologist's dilemma: a comprehensive clinical review of Bell's palsy, with emphasis on current management trends. Med Sci Monit 2014; 20:83.
5. van der Veen EL, Rovers MM, de Ru JA, van der Heijden GJ. A small effect of adding antiviral agents in treating patients with severe Bell palsy. Otolaryngol Head Neck Surg 2012; 146:353.
6. Salinas RA, Alvarez G, Daly F, Ferreira J. Corticosteroids for Bell's palsy (idiopathic facial paralysis). Cochrane Database Syst Rev 2010; :CD001942.
7. Turgeon RD, Wilby KJ, Ensom MH. Antiviral treatment of Bell's palsy based on baseline severity: a systematic review and meta-analysis. Am J Med 2015; 128:617.
8. Baugh RF, Basura GJ, Ishii LE, *et al*. Clinical practice guideline: Bell's Palsy executive summary. Otolaryngol Head Neck Surg 2013; 149:656.

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Chapter

14 Acute Myasthenic Crisis

- Myasthenia gravis is an antibody-mediated autoimmune disease that affects the postsynaptic neuromuscular junction. Most commonly, it presents in a slowly progressive fashion. However, myasthenic crisis can occur, which can lead to respiratory failure.
- Transient neonatal myasthenia affects 10 to 15 percent of babies born to mothers with myasthenia gravis. It can lead to weakness, dysphagia, and occasionally, respiratory distress or failure.
- Neonatal myasthenia transplacental maternal anti-AchR antibody is an acute but rather benign condition. The infant is hypotonic and has weak cry and poor sucking effort. With prompt diagnosis and appropriate management, most newborns recover within a few weeks.
- Management: Ventilator support is sometimes is needed. Attention to the nutritional support is important and gavage feeding is often needed.
- The infant gradually recovers and can be weaned off these supports in 4-6 weeks.
- Anticholinesterase therapy may shorten the course and can be stopped after the infant becomes asymptomatic. Since the anti-AchR titer does not correlate well with clinical strength, there is no need to check the titer repeatedly.
- Children with generalized myasthenia are more susceptible to myasthenic crisis than those isolated ocular myasthenia. The cause of acute exacerbation of generalized weakness is often unknown but acute febrile illness, pregnancy, and sometime antibiotics use (aminoglycosides) were known to precipitate myasthenic crisis.
- During acute exacerbation patient has problem with dysartheria, hypophonia with nasal speech, ptosis, difficulty with swallowing, weak cough, and respiratory distress.
- Regular dose of treatment in infant and young children is 0.5-1 mg/kg/dose every 4-6 h. In older children, a total dose of 7 mg/kg/day of mestinon is given 3-5 doses.
- The management of acute exacerbation is often dependent on the severity of the weakness. Mild exacerbation may be managed as outpatient with adjusted dose of mestinon.
- In young children, the acute weakness associated with respiratory infection should be hospitalized for observation. In patients with respiratory distress, supportive care including endotracheal intubation should be provided in an intensive care unit.

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- Additional therapies such as high dose corticosteroids (2 mg/kg/day Max 60-80 mg), IVIG (total dose of IVIG is 2 g/kg, usually over two to five days (e.g. 400 mg/kg per day over five days), and plasmaphoresis are used to treat myasthenic crisis.
- In patients hospitalized for surgical procedures (such as thymectomy), the pyridostigmine can be given in IV from using 1/30 conversion rate from from oral dose (i.e. every 60 mg of oral dose can be given in 2 mg IV) given in the same interval.
- Bedside physical should be started as soon as possible to facilitate functional recovery.

References

1. Carr AS, Cardwell CR, McCarron PO, McConville J. A systematic review of population based epidemiological studies in Myasthenia Gravis. BMC Neurol 2010; 10:46.
2. Hansen JS, Danielsen DH, Somnier FE, *et al*. Mortality in myasthenia gravis: A nationwide population-based follow-up study in Denmark. Muscle Nerve 2016; 53:73.
3. Sanders DB, Wolfe GI, Benatar M, *et al*. International consensus guidance for management of myasthenia gravis: Executive summary. Neurology 2016; 87:419.
4. Jani-Acsadi A, Lisak RP. Myasthenic crisis: guidelines for prevention and treatment. J Neurol Sci 2007; 261:127.
5. Gajdos P, Chevret S, Toyka KV. Intravenous immunoglobulin for myasthenia gravis. Cochrane Database Syst Rev 2012; 12.
6. Mandawat A, Kaminski HJ, Cutter G, *et al*. Comparative analysis of therapeutic options used for myasthenia gravis. Ann Neurol 2010; 68:797.
7. Patwa HS, Chaudhry V, Katzberg H, *et al*. Evidence-based guideline: intravenous immunoglobulin in the treatment of neuromuscular disorders: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology 2012; 78:1009.

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Chapter

15 Infant Botulism

- Infant botulism results from intestinal colonization by Clostridium botulinum, which produces a neurotoxin that blocks presynaptic cholinergic transmission, affecting skeletal and smooth muscle and autonomic function. While infant botulism occurs worldwide, the disease occurs more commonly in areas where environmental conditions favor persistence of spores in the soil.
- Foodborne cases can result from ingestion of wild honey or home canned foods contaminated with C. botulinum spores. Young age and the absence of competitive bowel flora are factors that predispose to vulnerability. Colostrum in breast milk offers some protection, but breast fed infants may become susceptible during the transition to formula or solid foods.

CLINICAL FEATURES

The clinical features result from progressive neuromuscular blockade and range from mild to severe. Muscles innervated by the cranial nerves are affected first, followed by those of the trunk, extremities, and diaphragm.

- Infants typically present with constipation and poor feeding. This presentation is followed by progressive hypotonia, and weakness. Loss of deep tendon reflexes appears to occur more commonly in type B infection. Cranial nerve dysfunction is manifested by decreased gag and suck, diminished range of eye movement, pupillary paralysis, and ptosis. Autonomic signs include decreased tearing and salivation, fluctuating heart rate and blood pressure, and flushed skin.
- Infant botulism may present with or progress to life-threatening respiratory failure, and serious complications may develop during the course. In a clinical trial, most infants required intensive care and about half required mechanical ventilation. In atypical cases, infants may present with catastrophic collapse or rapid deterioration following brief periods of poor feeding but without the typical initial complaints of constipation, ptosis, or facial weakness.

DIAGNOSIS

- The diagnosis of infant botulism should be suspected in any infant with acute onset of weak suck, ptosis, inactivity, and constipation. However, infant botulism is a rare disorder, and the diagnosis is often missed.
- Serum samples for botulinum toxin are often negative in cases of infant botulism. The diagnosis is supported by the isolation of C. botulinum

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spores from the stool and is confirmed by the identification of botulinum toxin in stool samples. Anaerobic cultures often take up to six days for growth and identification of the organism, and initial detection of toxin requires one to four days.

TREATMENT

Any infant with clinical signs, symptoms, or history suspicious for botulism should be hospitalized immediately and meticulously monitored for signs of respiratory failure.

- Botulism immune globulin intravenous (Injection, powder for reconstitution Baby BIG: 100 mg, Initial: Begin at 25 mg/kg/hour (0.5 mL/kg/hour using the 50 mg/mL concentration) for the first 15 minutes; if well tolerated after 15 minutes, rate may be increased to the maximum infusion rate of 50 mg/kg/hour (1 mL/kg/hour using the 50 mg/mL concentration) to the end of the infusion (infusion should conclude within 4 hours of reconstitution unless infusion rate is decreased due to an adverse reaction), a human-derived botulinum antitoxin, is safe and effective therapy for infant botulism and should be administered as early as possible. Treatment should not be delayed while awaiting results of confirmatory tests. No serious adverse events were associated with BIG-IV therapy.
- Management of infant botulism is otherwise supportive and includes close monitoring to detect sudden worsening.
- Current guidelines state that antibiotics are not indicated for infants with suspected gastrointestinal botulism because of concern that lysis of intraluminal C. botulinum could increase the amount of toxin available for absorption. This recommendation is reasonable even though a single BIG-IV infusion should neutralize all botulinum toxin available for absorption for at least six months.
- Penicillin or metronidazole should be used to treat patients with wound botulism after antitoxin has been administered. Aminoglycosides should be avoided because they can potentiate the effects of the toxin.

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References

1. Dover N, Barash JR, Hill KK, *et al*. Molecular characterization of a novel botulinum neurotoxin type H gene. J Infect Dis 2014; 209:192.
2. Rao AK, Walters M, Hall J, *et al*. Outbreak of Botulism Due to Illicit Prison-Brewed Alcohol: Public Health Response to a Serious and Recurrent Problem. Clin Infect Dis 2017; 66:S85.
3. Fleck-Derderian S, Shankar M, Rao AK, *et al*. The Epidemiology of Foodborne Botulism Outbreaks: A Systematic Review. Clin Infect Dis 2017; 66:S73.
4. Peak CM, Rosen H, Kamali A, *et al*. Wound Botulism Outbreak Among Persons Who Use Black Tar Heroin - San Diego County, California, 2017-2018. MMWR Morb Mortal Wkly Rep 2019; 67:1415.

5. Adalja AA, Toner E, Inglesby TV. Clinical management of potential bioterrorism-related conditions. N Engl J Med 2015; 372:954.
6. Centers for Disease Control and Prevention. National Botulism Surveillance. https://www.cdc.gov/botulism/surveillance.html (Accessed on February 07, 2018).
7. Griese SE, Kisselburgh HM, Bartenfeld MT, *et al*. Pediatric Botulism and Use of Equine Botulinum Antitoxin in Children: A Systematic Review. Clin Infect Dis 2017; 66:S17.
8. Hodowanec A, Bleck TP. Clostridium botulinum (Botulism). In: Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, 8th ed, Bennett JE, Dolin R, Blaser MJ (Eds), Elsevier Saunders, Philadelphia 2015. p.2763.
9. O'Horo JC, Harper EP, El Rafei A, *et al*. Efficacy of Antitoxin Therapy in Treating Patients With Foodborne Botulism: A Systematic Review and Meta-analysis of Cases, 1923-2016. Clin Infect Dis 2017; 66:S43.
10. Schussler E, Sobel J, Hsu J, *et al*. Workgroup Report by the Joint Task Force Involving American Academy of Allergy, Asthma & Immunology (AAAAI); Food Allergy, Anaphylaxis, Dermatology and Drug Allergy (FADDA) (Adverse Reactions to Foods Committee and Adverse Reactions to Drugs, Biologicals, and Latex Committee); and the Centers for Disease Control and Prevention Botulism Clinical Treatment Guidelines Workgroup-Allergic Reactions to Botulinum Antitoxin: A Systematic Review. Clin Infect Dis 2017; 66:S65.

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Chapter

16

Acute Inflammatory Myopathies

Inflammatory myopathies in children are caused by autoimmune processes such as dermatomyositis and rarely, polymyositis and infection of the muscles by various microbes (Infectious myositis). Juvenile Dermatomyositis (JDM) and Juvenile Polymyositis (JPM) are rare autoimmune myopathies in childhood. JDM is primarily a capillary vasculopathy, whereas JPM involves direct T-cell invasion of muscle fibers similar to that seen in adult polymyositis. Juvenile Dermatomyositis (JDM) is the most common idiopathic inflammatory myopathy of childhood accounting for approximately 85 percent of cases.

CLINICAL FEATURE

Muscle weakness is the hallmark of Juvenile Dermatomyositis (JDM) and Juvenile Polymyositis (JPM). In addition, patients with JDM present with characteristic rashes. Children with JDM and JPM also may have constitutional symptoms (fever, weight loss, fatigue, and headache), which may be the initial finding prior to the onset of muscle weakness, and in patients with JDM, rash.

- **Cutaneous manifestations**: Cutaneous manifestations are common in children with JDM and include a characteristic heliotrope rash, Gottron's papules, nailfold capillary changes, calcinosis, and skin ulcerations.
- Heliotrope dermatitis is a reddish-purple rash on the upper eyelids, often accompanied by swelling of the eyelid. Malar and facial erythema may also be present. Gottron's papules are an erythematous, papulosquamous eruption over the dorsal surfaces of the knuckles. Similar lesions can occur over the extensor aspects of the elbows, knees, and medial malleoli, at times mimicking psoriasis.
- Nailfold capillary changes may be observed at the bedside or in clinic. These include capillary dilatation, tortuosity and dropout.
- Ulcerative skin disease is a serious and potentially life-threatening manifestation of JDM, as shown in panel E. Ulcers presumably reflect significant vasculopathy in the skin (with tissue hypoxia and necrosis), and may signal vasculopathy in other organs (especially the lungs and gut). Patients with ulcerative lesions have more severe disease and a worse prognosis.
- **Calcinosis**: Dystrophic calcification or calcinosis (soft tissue calcification) generally develops within a few years of diagnosis. Five distinct patterns of calcinosis have been described.
- **Amyopathic dermatomyositis**: The cutaneous manifestations of JDM may appear in the absence of clinically apparent muscle disease in a small number of children. Children with this presentation, termed amyopathic

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JDM, may never develop muscle weakness, but amyopathic JDM may reflect an early phase in the disease course before muscle weakness has yet developed.

- **Muscle weakness**: The inflammatory myopathies are characterized by symmetric, proximal muscle weakness. This may present with functional limitations, such as difficulty getting up from the floor, getting into and out of motor vehicles, or climbing stairs. Washing or grooming hair may pose a challenge, and severely affected children may not be able to feed themselves. In very young children, frequent falls may be an important symptom. A Gower's sign is frequently present.
- Weakness of the palate and cricopharyngeal muscle may result in problems swallowing, a nasal voice, tracheal aspiration, and reflux of food into the nasopharynx. Involvement of the upper esophagus can lead to dysphagia for solids and liquids.
- Arthritis; Non-erosive arthralgia and arthritis may be present at the time of diagnosis or during the disease course. Contractures may be seen but are usually related to muscle inflammation rather than arthritis.
- **Lipodystrophy**: Acquired lipodystrophy, JDM appears to be a common cause of lipodystrophy in children.
- **Classification and Diagnostic Criteria**: In 1975, Bohan and Peter proposed a classification schema and diagnostic criteria for the various forms of myositis including Juvenile Dermatomyositis (JDM).
- The diagnosis of Juvenile Dermatomyositis (JDM) is clinically based upon the presence of symmetric, proximal muscle weakness, and characteristic heliotrope rash and Gottron's papules. The diagnosis of Juvenile Polymyositis (JPM) is more challenging because of the lack of cutaneous manifestations.
- Polymyositis are usually associated with autoimmune disease such as juvenile Systemic Lupus Erythematosus (SLE). Infectious mysositis can be caused by viral, bacterial, fungal, and parasitic infection.

TREATMENT

There are several factors to consider in the treatment of a patient with Juvenile Dermatomyositis (JDM) or Juvenile Polymyositis (JPM):

- Initial treatment varies with the clinical presentation, which ranges from mild disease with muscle weakness and cutaneous manifestations to serious life-threatening weakness, internal organ damage, and ulcerative skin lesions. The intensity of initial therapy increases with increasing severity of the symptoms.
- Glucocorticoids: Glucocorticoids are the initial agents of choice in treating patients with JDM or JPM.
- Treatment of new onset or acute exacerbation of dermatomyositis usually starts with a course of high dose IV methylprednisolone at total dose of

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2 gm/kg/divided into 4-5 daily doses followed by tapering course of oral prednisolone starting with 2 mg/kg dose. While the goal is to bring the patients into remission and off steroid treatment, some patients may need a chronic low dose prednisolone given in every other day schedule is to maintain in remission.

- Other therapeutic modalities include IVIG who previously failed to respond treatment with glucocorticoids (usually given as a dose of 2 g/kg (maximum dose of 70 g) administered as a single dose or divided over two days. IVIG may be given every two weeks initially for five doses, and is then generally administered monthly for up to two years.
- The decision to begin IVIG typically occurs months into treatment when patients experience persistent or increasing symptoms as glucocorticoids are weaned, indicating steroid-resistance or steroid-dependence; however, in very severe cases of JDM, IVIG is often used earlier.
- **Cyclosporine**: Cyclosporine, a calcineurin inhibitor, has been primarily used in patients with refractory JDM and JPM. Small observational studies have shown that the addition of cyclosporine to patients with an inadequate response to glucocorticoid and other immunosuppressive agents was associated with clinical improvement (e.g. recovery of muscle strength), leading to a reduction in prednisone dose. The starting dose of cyclosporine is 3 to 5 mg/kg per day. The dose is adjusted depending upon the clinical response and the presence of cyclosporine toxicity (often earliest seen as a rising serum creatinine).
- **Cyclophosphamide**: Cyclophosphamide is generally reserved for severe and life-threatening JDM, particularly chronic ulcerative disease of the gastrointestinal tract or skin, or respiratory involvement.
- Biologic agents (Rituximab,Infliximab,Abatacept): Increasingly, biologic agents are being used in the treatment of autoimmune diseases. However, the use of these agents is limited in children with JDM and JPM.
- Treatment for polymyositis usually aims at treating the associated systemic autoimmune diseases. Treatment for infectious myositis includes using appropriate antibiotics for bacterial and parasitic infection and supportive and physical therapy.

Reference

1. Dalakas MC. Inflammatory muscle diseases. N Engl J Med 2015; 372:1734.
2. O'Connell MJ, Powell T, Brennan D, *et al*. Whole-body MR imaging in the diagnosis of polymyositis. AJR Am J Roentgenol 2002; 179:967.
3. Amato AA, Barohn RJ. Evaluation and treatment of inflammatory myopathies. J Neurol Neurosurg Psychiatry 2009; 80:1060.
4. Distad BJ, Amato AA, Weiss MD. Inflammatory myopathies. Curr Treat Options Neurol 2011; 13:119.

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5. van der Meulen MF, Bronner IM, Hoogendijk JE, *et al*. Polymyositis: an overdiagnosed entity. Neurology 2003; 61:316.
6. Uruha A, Nishikawa A, Tsuburaya RS, *et al*. Sarcoplasmic MxA expression: A valuable marker of dermatomyositis. Neurology 2017; 88:493.
7. Amato AA, Barohn RJ. Evaluation and treatment of inflammatory myopathies. J Neurol Neurosurg Psychiatry 2009; 80:1060.
8. Stringer E, Bohnsack J, Bowyer SL, *et al*. Treatment approaches to juvenile dermatomyositis (JDM) across North America: The Childhood Arthritis and Rheumatology Research Alliance (CARRA) JDM Treatment Survey. J Rheumatol 2010; 37:1953.
9. Ruperto N, Pistorio A, Oliveira S, *et al*. Prednisone versus prednisone plus cyclosporin versus prednisone plus methotrexate in new-onset juvenile dermatomyositis: a randomised trial. Lancet 2016; 387:671.
10. Deakin CT, Campanilho-Marques R, Simou S, *et al*. Efficacy and Safety of Cyclophosphamide Treatment in Severe Juvenile Dermatomyositis Shown by Marginal Structural Modeling. Arthritis Rheumatol 2018; 70:785.
11. Rider LG, Aggarwal R, Pistorio A, *et al*. 2016 American College of Rheumatology/European League Against Rheumatism Criteria for Minimal, Moderate, and Major Clinical Response in Juvenile Dermatomyositis: An International Myositis Assessment and Clinical Studies Group/Paediatric Rheumatology International Trials Organisation Collaborative Initiative. Arthritis Rheumatol 2017; 69:911.

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Chapter

17

Dystonia

- Dystonia is a movement disorder characterized by involuntary sustained or intermittent muscle contractions causing abnormal twisting, often repetitive (hyperkinetic), movements, postures, or both.
- Dystonic movements are typically patterned, twisting, and may be tremulous.
- Dystonia is often initiated or worsened by voluntary action and associated with overflow muscle activation.
- By definition, primary dystonia (formerly known as dystonia musculorum deformans or idiopathic torsion dystonia) was associated with no other neurologic impairment, such as intellectual, pyramidal, cerebellar, or sensory deficits. However, tremor that appears identical to essential tremor occurs in approximately 20 percent of patients with this condition.
- Cerebral palsy is probably the most common cause of acquired dystonia (t3 seen in children).

Classification of Dystonia (According to Body Distribution)

- Focal: involving a single body region
- Segmental: involving two or more contiguous body regions
- Multifocal: involving two noncontiguous or more (noncontiguous or not) body regions
- Generalized: involving the trunk and at least two other sites
- Hemidystonia: involving more regions restricted to one body side

Inherited or Acquired Causes of Dystonia

Inherited (Dystonia Forms of Proven Genetic Origin)

- Autosomal dominant
- Autosomal recessive
- X-linked recessive
- Mitochondrial disorders

Acquired (Dystonia Due to a Known Specific Cause)

- Cerebrovascular (infarction or hemorrhage)
- Perinatal brain injury
- Traumatic brain injury

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- Infection
- Drug
- Toxic
- Neoplastic
- Psychogenic

CLINICAL FEATURES

- The onset of involuntary movements occurs before age 20 in approximately 30 percent of patients with dystonia. The distribution of the affected muscle groups appears to depend upon age. The disorder typically begins distally in children and cranial-cervical distribution in adults. Childhood dystonia usually progresses to a generalized disorder, whereas adult dystonia usually remains focal or segmental.
- The range of severity of dystonia is variable and may depend upon the situation, like task-specific dystonias that occur only when they participate in certain activities, such as writing, typing, or playing the piano (musician's hands). As the dystonia worsens, it typically extends to adjacent muscles and eventually occurs even at rest. In rare cases, the spasms become severe and may cause cervical disc, nerve, or root problems. Muscle breakdown with myoglobinuria (dystonic storm) also can occur.
- No specific morphologic changes have been noted in neuropathologic examinations of patients with isolated dystonia. In the brains of a few patients, the norepinephrine concentration was markedly reduced in the posterior and lateral hypothalamus and increased in the red nucleus, suggesting a neurotransmitter abnormality.
- Dopa-responsive dystonia: Dopa-Responsive Dystonia (DRD) is an unusual form of inherited progressive dystonia that begins during the first decade after birth. The dystonia usually starts in the legs and becomes generalized. Some patients may also have hyperreflexia, rigidity, tremor, and other parkinsonian features, and less commonly, cerebellar signs. The most frequent form of DRD is autosomal dominant DYT5 dystonia.
- The hallmark of DRD is a clinically significant, sustained response to levodopa.
- Paroxysmal dyskinesia with dystonia: Several rare genetic forms of dystonia are characterized by paroxysmal dyskinesia.
    - Paroxysmal Nonkinesigenic Dyskinesia (PNKD) is characterized by spontaneous episodes of dystonia and/or choreoathetosis not triggered by exercise or activity. Alcohol, coffee, tea, fatigue, stress, or excitement may be precipitating factors. Episodes last minutes to hours and recur two or three times a month.
    - Paroxysmal kinesigenic choreoathetosis, also known as paroxysmal kinesigenic dyskinesia, is characterized by episodic choreoathetosis and

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dystonia brought on by voluntary movement. The disorder is genetically heterogeneous.

- Paroxysmal exertion-induced dyskinesia is an autosomal dominant disorder with reduced penetrance that begins in childhood with dyskinesia and dystonia induced by prolonged exertion (e.g. ≥15 minutes), fasting and stress. Associated features include absence and/or partial complex seizures.

- Neurodegeneration with brain iron accumulation: Neurodegeneration with Brain Iron Accumulation (NBIA) represents a group of disorders that includes pantothenate kinase-associated neurodegeneration, infantile neuroaxonal dystrophy, fatty acid hydroxylase-associated neurodegeneration, aceruloplasminemia, neuroferritinopathy, and other conditions.
- Other causes: Additional causes of paroxysmal or fluctuating dystonia in children include multiple sclerosis, thyrotoxicosis, metabolic disorders (e.g. Hartnup disease), paroxysmal dystonia in sleep (hypnogenic dystonia), "infectious torticollis", and the GLUT1 deficiency syndrome.

TREATMENT

- Appropriate treatment of dystonia depends upon an accurate diagnosis. Patients with atypical features, such as impaired intellect, seizures, neuroophthalmologic abnormalities, ataxia, corticospinal tract signs, sensory deficits, severe speech disturbance, and unilateral distribution of the dystonia, are more likely to have an underlying disorder that can be treated, such as Wilson disease.
- For pediatric patients with focal or generalized dystonia of unknown etiology, clinicians recommend a trial of levodopa to confirm or exclude the diagnosis of dopa-responsive dystonia.
- Patients with multifocal or generalized isolated dystonia who do not respond to levodopa can be treated with other oral medications, botulinum toxin injections, or deep brain stimulation in refractory cases.
  - Patients with debilitating generalized isolated dystonia that does not respond to a trial of levodopa, treatment with trihexyphenidyl is suggested.
  - For children with debilitating multifocal or generalized isolated dystonia who do not respond to pharmacologic therapy or botulinum toxin injections, experts suggest bilateral deep brain stimulation of the internal globus pallidus.

Status Dystonicus

Status dystonicus (also called dystonic storm) is a rare, life-threatening condition characterized by increasingly frequent or continuous severe generalized dystonic contractions that may be refractory to standard medical treatment. Status dystonicus can occur in children and adults as a result of progressive

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worsening in various types of dystonia. Commonly reported complications include bulbar weakness, progressive impairment of respiratory function leading to respiratory failure, exhaustion, pain, and metabolic derangements including rhabdomyolysis and acute kidney injury. Status dystonicus constitutes a neurologic emergency and requires urgent intervention. Management includes the following measures:

- Supportive care
- Intensive care unit admission
- Intravenous hydration
- Antipyretics and cooling blankets
- Pain control
- Monitoring for the development of rhabdomyolysis (e.g. creatine kinase, urinalysis, and renal function)
- Sedation with intravenous midazolam (0.03 to 0.1 mg/kg per hour)
- Possible mechanical ventilation

Specific measures to treat dystonia

Initial use of oral agents, often in combination:

- Trihexyphenidyl (0.05-2.6 mg/kg/day in three divided doses)
- Tetrabenazine (age more than 12 years Dose should be individualized; titrate slowly Initial: 12.5 mg once daily, may increase to 12.5 mg twice daily after 1 week not FDA approved for the use in children)
- Haloperidol (Children 3 to 12 years weighing 15 to 40 kg: Oral, Initial: 0.5 mg/day in 2 to 3 divided doses; may increase by 0.5 mg every 5 to 7 days to usual maintenance range of 0.05 to 0.075 mg/kg/day in 2 to 3 divided doses (i.e. a fixed dose of 0.75 to 3 mg/day in divided dose
- Baclofen(<2 years: 10-20 mg daily divided every 8 hours; titrate dose every 3 days in increments of 5-15 mg/day to a maximum of 40 mg daily 2-7 years: 20-30 mg daily divided every 8 hours; titrate dose every 3 days in increments of 5-15 mg/day to a maximum of 60 mg daily ≥8 years: 30-40 mg daily divided every 8 hours; titrate dosage as above to a maximum of 120 mg daily)

Acute Dystonic Reaction

An acute dystonic reaction, usually transient, is a recognized complication of the dopamine receptor-blocking drugs, such as the antipsychotics (e.g. haloperidol, chlorpromazine) and antiemetics (e.g. phenothiazines, metoclopramide). Dystonic reactions also can occur with levodopa, anticonvulsants, antidepressants (e.g. selective serotonin reuptake inhibitors), and ergots.

Life Threatening

- Oxygen administration

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- Diazepam: Orally/Rectally 5-10 mg, Lorazepam: Orally, IM, IV: 0.1 mg/kg Max. 4 mg as single dose
- Biperiden: Slowly IV. 0.05-0.1 mg/kg Max. 5 mg/6h

Severe

- Biperiden: Slowly IV, 0.05-0.1 mg/kg
- Promethazine: IV, 0.5-1 mg/kg

Treatment of acute dystonia with antihistamine or anticholinergic medications is usually rapidly effective.

- Parenteral diphenhydramine (1 to 2 mg/kg per dose, maximum dose 50 mg) is used most frequently and typically results in resolution of an acute dystonic reaction within minutes.
- Intravenous administration is preferred over oral administration for initiation of treatment because patients may have difficulty swallowing.
- Parenteral administration is required for life-threatening dystonia with associated laryngospasm or stridor. Diphenhydramine may also be given intramuscularly but the onset of action is delayed compared with intravenous administration.
- Once the acute dystonic reaction is treated, diphenhydramine is given orally (1.25 mg/kg per dose) every six hours for one to two days to prevent recurrence. The offending drug should be discontinued.

CHOOSING THERAPY

The choice of initial therapy depends on the type of dystonia requiring treatment

Oral Medication in Primary Generalized Dystonia

- Children with primary focal or generalized dystonia of unknown etiology, most experts recommend a trial of levodopa(Dopamine agonists), start with 1 mg/kg BW/day (Max 25 mg) and increase in 25 mg steps/week to maximum of 10 mg/kg divided into 3 doses/day (e.g. carbidopa-levodopa 25/100 mg three times daily, to confirm or exclude the diagnosis of dopa responsive dystonia.
- Patients with a clinically significant positive response (i.e. those with dopa-responsive dystonia) should continue levodopa. The dose is then adjusted to obtain the optimum response.
- Children with debilitating primary generalized dystonia that does not respond to a trial of levodopa, initial treatment with trihexyphenidyl (Anticholinergic) is a reasonable choice. High trihexyphenidyl doses may be necessary to achieve a clinically significant response. (Start with 0.5 mg and increase by 0.5 mg/week (more than 5 years of age use 1 mg steps) maintenance dose is 10-20 mg/day divided into 3-4 doses/day.

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- Baclofen: Start with 0.5 mg/kg divided into 3 doses, and increase weekly by 0.5 mg/kg. Maintenance: dose is 2-5 mg/kg day divided into 2-4 doses (Max 60mg/day).
- Experts suggest bilateral Deep Brain Stimulation (DBS) of the internal Globus Pallidus (GPi) for children with debilitating generalized primary dystonia who do not respond to or tolerate pharmacologic therapy or botulinum toxin, and who are appropriate candidates for the procedure.

Cervical Dystonia and Other Types of Focal Primary Dystonia

Initial treatment with oral agents for children with primary cervical dystonia or other types of primary focal dystonia, assuming secondary causes of dystonia have been evaluated and excluded. Reasonable choices are trihexyphenidyl and tetrabenazine. For children who fail oral therapy, experts suggest BoNT.

References

1. Albanese A, Asmus F, Bhatia KP, *et al*. EFNS guidelines on diagnosis and treatment of primary dystonias. Eur J Neurol 2011; 18:5.
2. Simpson DM, Hallett M, Ashman EJ, *et al*. Practice guideline update summary: Botulinum neurotoxin for the treatment of blepharospasm, cervical dystonia, adult spasticity, and headache: Report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology 2016; 86:1818.
3. Jinnah HA, Factor SA. Diagnosis and treatment of dystonia. Neurol Clin 2015; 33:77.
4. Marques RE, Duarte GS, Rodrigues FB, *et al*. Botulinum toxin type B for cervical dystonia. Cochrane Database Syst Rev 2016; :CD004315.
5. van Egmond ME, Kuiper A, Eggink H, *et al*. Dystonia in children and adolescents: a systematic review and a new diagnostic algorithm. J Neurol Neurosurg Psychiatry 2015; 86:774.
6. Singer HS, Mink JW, Gilbert DL, Jankovic J. Movement Disorders in Childhood, 2nd ed, Butterworth-Heinemann (Elsevier), Philadelphia 2015.
7. Thenganatt MA, Jankovic J. Treatment of dystonia. Neurotherapeutics 2014; 11:139.
8. Allen NM, Lin JP, Lynch T, King MD. Status dystonicus: a practice guide. Dev Med Child Neurol 2014; 56:105.
9. Honey CM, Malhotra AK, Tarailo-Graovac M, *et al*. GNAO1 Mutation-Induced Pediatric Dystonic Storm Rescue With Pallidal Deep Brain Stimulation. J Child Neurol 2018; 33:413.
10. Derinoz O, Caglar AA. Drug-induced movement disorders in children at paediatric emergency department: 'dystonia'. Emerg Med J 2013; 30:130.
11. Kanburoglu MK, Derinoz O, Cizmeci MN, Havali C. Is acute dystonia an emergency? Sometimes, it really is! Pediatr Emerg Care 2013; 29:380.
12. Rodrigues FB, Duarte GS, Prescott D, *et al*. Deep brain stimulation for dystonia. Cochrane Database Syst Rev 2019; 1:CD012405.

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Chapter

18

Traumatic Brain Injury

Traumatic Brain Injury (TBI) is the leading cause of death and disability in children. Pediatric TBI is associated with several distinctive characteristics that differ from adults and are attributable to age- related anatomical and physiological differences, pattern of injuries based on the physical ability of the child, and difficulty in neurological evaluation in children. Evidence suggests that children exhibit a specific pathological response to TBI with distinct accompanying neurological symptoms, and considerable efforts have been made to elucidate their pathophysiology. In addition, recent technical advances in diagnostic imaging of pediatric TBI has facilitated accurate diagnosis, appropriate treatment, prevention of complications, and helped predict long-term outcomes. The functional impact of TBI in children can be different than in adults deficits may not be immediately apparent because the pediatric brain is still developing. TBI in children is a chronic disease process rather than a one-time event, because symptoms may change and unfold over time. Severity of TBI may be categorized as mild, moderate, or severe, based on the extent and nature of injury, duration of loss of consciousness, posttraumatic amnesia (PTA; loss of memory for events immediately following injury), and severity of confusion at initial assessment during the acute phase of injury.

- **Mild TBI (mTBI)** — loss of consciousness for less than 30 minutes, an initial Glasgow Coma Scale (GCS) or Pediatric GCS of 13–15 after 30 minutes of injury onset, and PTA for not greater than 24 hours.
    - **Uncomplicated**: mTBI where there are no overt neuroimaging findings.
    - **Complicated**: mTBI where there are intracranial abnormalities (e.g., bruising or a collection of blood in the brain) seen on CT scan or MRI.
- **Moderate TBI** — loss of consciousness and/or PTA for 1–24 hours and a GCS of 9–12.
- **Severe TBI** — loss of consciousness for more than 24 hours and PTA for more than 7 days with a GCS of 3–8.

Concussion, a form of mTBI, is an injury to the brain characterized by the physical and cognitive sequelae of TBI. Concussion typically occurs as a result of a blow, bump, or jolt to the head, face, neck, or body that may or may not involve loss of consciousness. Concussion has received more attention in recent years, particularly with respect to sports injuries.

As the ICP continues to rise with subsequent ICH, herniation syndromes may develop, with classic clinical findings of the Cushing triad: irregular respirations, bradycardia, and systemic hypertension. Neurogenic posturing and

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seizures may also occur, in addition to changes in cranial nerve examination due to brainstem compression.

Signs of occult TBI in patients with no history of trauma include retinal hemorrhages on ophthalmologic examination. The presence of these signs suggest abusive or intentional head trauma, and they are commonly associated with subdural hematomas. Additionally, papilledema following unintentional or intentional trauma signifies ICH, necessitating emergent further evaluation.

Management of TBI

These Guidelines have been created in an attempt to create consistency in the management of head injuries in children with the following goals:

- Identification of at risk patients and utilization of early CT scanning
- Avoidance of Skull x-ray as diagnostic tool in head injury assessment
- Minimise secondary injury.
- Use of "discharge after Normal CT scanning" if clinically appropriate and carer available with access to phone and transport.
- Identification of infants at risk from abuse or neglect. In some series, child abuse accounts for 25% or more of admissions for head injury in children under 2 years.
- Magnetic Resonance Imaging (MRI) provides more detailed imaging than CT scanning and is used to confirm the diagnosis of traumatic brain injury. MRI also provides better visualization of posterior fossa lesions. However, MRI is not feasible in the initial stabilization and management of the patient in the emergency department and intensive care unit due to its lengthily time requirement, but it may provide useful information about the injury severity once the patient is stable.
- The Society of Critical Care Medicine and World Federation of Pediatric Intensive and Critical Care Societies published the second edition of the Guidelines for the Acute Management of Severe Traumatic Brain Injury for Infants, Children, and Adolescents in 2012 (the most recent edition to date), based on a review of the pediatric Traumatic Brain Injury (TBI) literature. A brief synopsis of the guidelines is discussed below, but the reader is urged to read the actual guidelines for complete details.

Initial intervention for patients with TBI focuses on the detection of the primary injury and prevention or treatment of secondary brain injury. The following treatable conditions can exacerbate secondary brain injury:

- Hypoxemia
- Hypotension
- Elevated Intracranial Pressure (ICP) leading to Intracranial Hypertension (ICH)
- Hypercarbia or hypocarbia
- Hyperglycemia or hypoglycemia

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- Electrolyte abnormalities
- Enlarging hematomas
- Coagulopathy
- Seizures
- Hyperthermia

Primary Survey

- Assess and secure airway whilst ensuring cervical spine immobilization
- Assess breathing and give high flow oxygen by mask
- Assess circulation, obtain IV access, and commence fluid resuscitation if indicated (signs of hypovolaemia)
- Determine conscious level using Pediatric Glasgow Coma Scale (PGCS) or AVPU scale (note any asymmetry in limb response), and examine pupil size, symmetry and reaction to light.
- Check blood glucose level, treat if low

Notes

- Good oxygenation and circulatory resuscitation are essential to avoid further brain injury (secondary brain injury). The presence of hypotension should be considered an emergency.
- If possible the neurological status should be reassessed following treatment of hypoxaemia and hypotension. The best GCS after resuscitation is used for classification of the severity of head injury.
- Intubation (after induction of anaesthesia) and mechanical ventilation may be required as part of primary steps during the Initial assessment. However, for the patient who has been brought in by ambulance unintubated there is almost always sufficient time (30 – 60 seconds) to assess their neurological status prior to intubation.
- Establishing the mechanism of injury is important in assessing the risk of head and/or spinal injury.

Pediatric Glasgow Coma Scale

The Glasgow Coma Scale (GCS) is used to describe the general level of consciousness in patients with Traumatic Brain Injury (TBI) and to define broad categories of head injury. The GCS is divided into 3 categories, eye opening (E), motor response (M), and verbal response (V). The score is determined by the sum of the score in each of the 3 categories, with a maximum score of 15 and a minimum score of 3, as follows:

GCS score = E + M + V

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Glasgow Coma Scale

Eye Opening			
Score	**Age 1 Year or Older**		**Age 0-1 Year**
4	Spontaneously		Spontaneously
3	To verbal command		To shout
2	To pain		To pain
1	No response		No response
Best Motor Response			
Score	**Age 1 Year or Older**		**Age 0-1 Year**
6	Obeys command		
5	Localizes pain		Localizes pain
4	Flexion withdrawal		Flexion withdrawal
3	Flexion abnormal (decorticate)		Flexion abnormal (decorticate)
2	Extension (Decerebrate)		Extension (Decerebrate)
1	No response		No response
Best Verbal Response			
Score	**Age >5 Years**	**Age 2-5 Years**	**Age 0-2 Years**
5	Oriented and converses	Appropriate words	Cries appropriately
4	Disoriented and converses	Inappropriate words	Cries
3	Inappropriate words; cries	Screams	Inappropriate crying/ screaming
2	Incomprehensible sounds	Grunts	Grunts
1	No response	No response	No response

Interpretation

Patients who are intubated are unable to speak, and their verbal score cannot be assessed. They are evaluated only based on eye opening and motor scores, and the suffix T is added to their score to indicate intubation. In intubated patients, the maximum GCS score is 10 T and the minimum score is 2 T. The GCS is often used to help define the severity of TBI. Mild head injuries are generally defined as those associated with a GCS score of 13-15, and moderate head injuries are those associated with a GCS score of 9-12. A GCS score of 8 or less defines a severe head injury. These definitions are not rigid and should be considered as a general guide to the level of injury.

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AVPU (A=ALERT, V= VOICE, P=PAIN, U= UNRESPONSIVE)

AVPU is a quick and simple assessment of neurological state. It is essentially the same as determining the motor response of the GCS. It may be useful in young (pre-verbal) children.

AVPU (for children under 2 years old)

Alert

Responds to **V**oice

Responds to **P**ain purposeful – localizes, non-purposeful – withdrawal, abnormal flexion or extension

Unresponsive

Secondary Survey

History

Detailed account of mechanism of injury including time of injury. Give children with appropriate verbal skills opportunity to tell you themselves as well as taking an eye witness account including:

- Fall. Height, surface, posture of fall, point of contact
- Motor vehicle collision. Speed, place in car, restraint, point of impact
- Loss of Consciousness (LOC) or altered level of consciousness at the scene or in transit
- Focal neurological signs at the scene or in transit
- Seizures document timing in relation to accident
- Vomiting
- Headache, visual disturbance or focal neurological symptoms
- Amnesia document duration of Post Traumatic Amnesia (PTA) and Retrograde Amnesia (RGA)
- Details of pre-hospital care
- Features that may suggest non-accidental injury (e.g. delayed presentation or inconsistent history). If the history does not appear to fit with the injury, it is important to do your best to ensure you have taken a clear history of the mechanism proposed.
- Document developmental level of child
- Past history especially previous head injury, neurological disease, developmental problems and haematological disorders
- Medication
- Allergies
- Immunisation status
- Last food or drink

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Examination

Always fully undress the child to look for occult injuries Head

- Scalp haematomas are highly significant and should be carefully looked for.
- Fractures: depressed, base of skull ("raccoon eyes", "Battles sign" (posterior auricular bruising), CSF leak, blood in the ear canal or behind the tympanic membrane)
- Check ears for pinna bruising (associated with inflicted injury)
- Head circumference should be measured in children under 1 year
- Face examination for facial fractures, intraoral injuries, frenulum tears (associated with inflicted injury)
- Neck immobilisation if injury cannot be excluded clinically
- Trunk and Limbs look for bruises, swelling, deformity, bony crepitus, burns
- Neurological examination, check cranial nerves and document neurology for all 4 limbs

Management of Moderate to Severe Head Injury

Treatment of severe TBI (Glasgow Coma Scale [GCS] score, 3-8) follows current trauma life-support guidelines. Stabilization begins with applying the basic elements of resuscitation: securing the airway, achieving adequate oxygenation and ventilation, and avoiding or rapidly treating hypotension.

Early airway management involves providing proper airway position, clearance of debris while maintaining cervical spine precautions, and orotracheal intubation. Hypercarbia and hypoxia must be avoided, because they are both potent cerebral vasodilators that result in increased cerebral blood flow and volume and, potentially, increased ICP and ICH. Orotracheal intubation allows for not only airway protection in patients who are severely obtunded but also for better control of oxygenation and ventilation.

In the initial resuscitation period, efforts should be made to maintain eucapnia at the low end of the normal reference range (partial pressure of carbon dioxide [$PaCO_2$] of 35-39 mm Hg) and prevent hypoxia (partial pressure of oxygen [PaO_2] <60-65 mm Hg) to prevent or to limit secondary brain injury. Nasotracheal intubation should be avoided because of the risk of cervical spine injury and direct intracranial injury, especially in patients with basilar skull fractures.

Special neuroprotective considerations must be given to the choice of medications used to facilitate endotracheal intubation. These considerations are as follows:

- Prevent elevated ICP
- Minimize the cerebral metabolic rate of oxygen consumption
- Avoid hypotension

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Common medications used in the intubation of patients with TBI include midazolam, fentanyl, etomidate, and/or lidocaine, along with neuromuscular blockade. Potential specific side effects of these medications include (but are not limited to) hypotension, chest wall rigidity, adrenal suppression, and myoclonus.

Other medications used to facilitate intubation include Propofol and Ketamine. Propofol increases the depth of sedation in a dose-dependent manner. Propofol reduces ICP and decreases the metabolic rate of cerebral oxygen consumption, but this agent is not recommended in hemodynamically compromised trauma patients as it can cause hypotension through myocardial depression and vasodilation. Also, it should not be used for prolonged sedation in children with TBI because of the risk of propofol infusion syndrome, which consists of cardiac failure, rhabdomyolysis, severe metabolic acidosis, and renal failure.

Ketamine is thought to have the potential for elevating ICP. However, a prospective, controlled, clinical trial of ketamine administration in intubated and mechanically ventilated children with elevated ICP from severe TBI revealed that ketamine effectively decreased ICP and prevented untoward elevation of ICP during potentially distressing interventions, without lowering the blood pressure and the Cerebral Perfusion Pressure (CPP). However, these patients were already on continuous infusions of Intravenous (IV) sedative medications, and some patients received hyperosmolar therapy or decompressive craniectomy prior to the administration of ketamine.

Every effort should be made to avoid hypotension in these patients, because hypotension has been shown to increase morbidity and mortality. Euvolemia should be maintained. Isolated TBI rarely leads to severe hypotension. Other causes of trauma-related hypotension include, but are not limited to:

- Intra-abdominal injuries
- Pericardial tamponade
- Hemothorax
- Pneumothorax
- Spinal cord injury causing spinal shock

Raising the head of the bed to decrease venous obstruction may help to control ICP. Traditionally, elevation of the head to 30° in the midline position is recommended, but titration of head elevation to achieve the lowest ICP would be optimal. Again, care of the cervical spine must always be a consideration when moving patients with TBI.

Posttraumatic hyperthermia (core body temperature 38.0°C-38.5°C [100.4°F-101.5°F]) is not uncommon in patients with TBI. Fever increases cerebral metabolic requirements and oxygen consumption, and it can promote ICH. Fever also decreases the seizure threshold. Consequently, efforts should be made to avoid hyperthermia. The patient should also be evaluated and treated for other etiologies of fever, such as infection and atelectasis.

Sedation and analgesia are also important adjuncts to minimize increases in

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ICP. Painful stimuli and stress increase metabolic demands and increase blood pressure and ICP. However, sedatives and analgesics must be judiciously selected to prevent unwanted side effects, such as hypotension. Short-acting and reversible analgesics, such as fentanyl, are commonly used. Short-acting benzodiazepines, such as midazolam, are also commonly used and they have the added benefit of increasing the seizure threshold.

Head Computed Tomography (CT) scanning should be performed after initial resuscitation in patients with severe TBI to establish a baseline and to assess the initial injury. Neurosurgeons will evaluate the potential need for surgical intervention, such as evacuation of a hematoma that could lead to ICH and herniation. Due to the potential for intracranial lesions to evolve, repeat CT scanning should be considered whenever neurologic deterioration or increased ICP persist despite medical interventions.

Treatment of Raised Intracranial Pressure

For patients with severe TBI or a GCS score of 8 or less and suspected ICH, either an intraparenchymal or intraventricular ICP monitor is placed, with the latter being advantageous for draining Cerebrospinal Fluid (CSF) in the case of ICH.

Intracranial hypertension is associated with poor neurologic outcome. In the intensive care unit, continuous ICP monitoring is predominantly used to help target therapies to maintain adequate CPP, which is equal to the mean Arterial Blood Pressure (MAP) minus either the ICP or the Central Venous Pressure (CVP), whichever is greater.

Although no randomized controlled trials have been conducted to assess the use of ICP monitoring in pediatric patients with severe TBI, it is widely accepted as an essential tool in major pediatric centers to guide therapies for the treatment of severe TBI. The exact threshold of pathologic ICP or ICH for a given age has not been established, but the general consensus is that treatment efforts should, at a minimum, attempt to keep ICP less than 20 mm Hg.

ICP can be measured using any of the following:

- External strain gauge transducer
- Catheter tip pressure transducer
- Catheter tip fiberoptic transducer

Clinical Signs of raised intracranial pressure include:

- Cushing's reflex (hypertension with bradycardia) (NB relative bradycardia alone can herald raised ICP before patient becomes hypertensive)
- Unilateral or bilateral pupillary dilatation
- Deteriorating GCS > 2 points
- Developing focal signs
- Extensor posturing

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This is an emergency and the child requires urgent CT scan and neurosurgical review. While these are being organised, do the following:

- Arrange PICU admission
- Ventilate to low normal $PaCO_2$ (4.5 – 5 kPa, 30-35 mm Hg) or hyperventilate while waiting for other treatments to take effect
- Treat hypotension with IV fluid boluses and vasopressors
- Provide adequate analgesia (morphine) and sedation (midazolam)
- Paralyse with muscle relaxants
- Mannitol 0.5-1 g/kg (2.5-5 ml/kg of 20% mannitol) by intravenous infusion over 20 min
- Consider hypertonic saline (3-5 mls/kg of 3% saline) intravenous bolus (if given rapidly may drop BP)
- Phenytoin 20 mg/kg should be given to prevent early post-traumatic seizures.
- Hyperthermia should be avoided (> 37.5°C).

The head of the bed should be elevated (without hip flexion). The child's head should be kept in the midline, neutral position (to avoid Hyperosmolar therapy)

Hypertonic saline has been shown to be an effective therapy for ICH in children with TBI. Hypertonic saline, typically 3% saline, increases serum osmolality, causing the shift of water from intracellular compartments to the intravascular space, with subsequent decrease in cellular edema. Additional theoretical benefits of hypertonic saline include improved vasoregulation, cardiac output, immune modulation, and plasma volume expansion.

Pediatric patients with severe TBI appear to tolerate a high osmolar load with the use of hypertonic saline, reaching serum osmolalities around 360 mOsm/L, although some of these patients developed reversible renal insufficiency. However, reversible renal insufficiency has been noted with the use of hypertonic saline when serum osmolality approached 320 mOsm/L; thus, caution should be used. Effective doses for acute use of 3% saline for ICH range from 6.5 to 10 mL/kg; continuous infusion of 3% saline ranges from 0.1 to 1 mL/kg/h administered on a sliding scale. The minimum dose needed to maintain an ICP of less than 20 mm Hg should be used. Serum osmolality should be maintained at less than 360 mOsm/L.

Risks of hypertonic saline administration include, but are not limited to, the following:

- Rebound ICH after withdrawal of therapy
- Central pontine myelinolysis with rapidly increasing serum sodium levels
- Subarachnoid hemorrhage due to rapid shrinkage of the brain and tearing of bridging vessels
- Renal failure

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- Hyperchloremic metabolic acidosis
- Hypervolemia
- Hypokalemia

Hypertonic saline may have an advantage over mannitol in hypovolemic patients. In such situations, hypertonic saline may increase intravascular volume and thus increase blood pressure in addition to decreasing ICP. However, mannitol has long been successfully used to treat ICH, especially following TBI in adults. Mannitol is an osmolar agent with a rapid onset of action via two distinct mechanisms.

The initial effects of mannitol result from a reduction of blood viscosity and a reflex decrease in vessel diameter to maintain cerebral blood flow through autoregulation. This decrease in vessel diameter contributes to decreasing total cerebral blood volume and ICP. Such a mechanism of action is transient (lasting about 75 min) and requires repeated dosing for prolonged effect. Mannitol exhibits its second mechanism of action through its osmotic effects. Although slower in onset, this mechanism lasts up to 6 hours.

Pitfalls of mannitol include the potential to accumulate in regions of injured brain if the blood-brain barrier is damaged, with subsequent reverse osmotic shift and worsening of ICP; this risk has been reported with continuous infusions. As a result, intermittent mannitol boluses are recommended. In addition, mannitol has been associated with renal failure at serum osmolality levels above 320 mOsm/L in adults. However, the literature supporting this finding is limited and was published at a time when dehydration therapy was common. A euvolemic hyperosmolar state generally is targeted with current care. Because mannitol is a potent diuretic, this effect is undesirable in hypotensive patients in whom the CPP is consequently decreased. Hypovolemia should be avoided by judicious fluid replacement (jugular venous compression and spinal cord injury).

Hyperventilation

Hyperventilation has the potential to reduce ICH via reflex vasoconstriction in the presence of hypocapnia. The vasoconstriction leads to decreased cerebral blood flow, decreased cerebral blood volume, and a subsequent decrease in ICP.

Hyperventilation is one of the fastest methods to lower ICP in a child with impending herniation. However, hyperventilation should only be considered as a temporizing measure for the reduction of ICP. In cases of refractory ICH despite all of the above treatments (sedation, analgesia, head elevation, CSF drainage, neuromuscular blockade, and hyperosmolar therapy), persistent mild hyperventilation ($PaCO_2$ of 30-35 mm Hg) may be beneficial in decreasing ICP.

The potential dangers associated with hyperventilation are related to the cerebral vasoconstriction and the subsequent risk for cerebral ischemia. Individual autoregulation of cerebral blood flow with respect to hypocapnia widely varies

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and is difficult to predict. Excessive hypocapnia may lead to ischemia secondary to insufficient cerebral blood flow. Ensuing respiratory alkalosis also shifts the hemoglobin-oxygenation dissociation curve to the left, making release of oxygen to tissues more difficult. As a result, avoidance of prophylactic severe hyperventilation to a $PaCO_2$ below 30 mm Hg may be considered in the initial 48 hours after injury.

Severe hyperventilation ($PaCO_2$ <30 mm Hg) may be necessary in emergencies such as impending herniation (e.g. a patient with the Cushing triad), but it should not be commonly used for prolonged therapy unless there is refractory ICH. If aggressive hyperventilation is used for an extended period, advanced neuromonitoring for cerebral ischemia (e.g. cerebral blood flow, brain tissue oxygen monitoring, jugular venous oxygen saturation, transcranial Doppler, near-infrared spectroscopy) is suggested.

Barbiturates

High-dose barbiturate therapy (e.g. with pentobarbital) is used for refractory ICH. This class of medications suppresses the cerebral metabolic rate, improves regional blood flow to metabolic demands, decreases cerebral blood volume, and inhibits excitotoxicity. With continuous Electroencephalographic (EEG) monitoring, barbiturate infusions may be titrated to achieve burst suppression.

The minimum dose required to control refractory ICH is recommended, as barbiturates may cause myocardial depression, decreased systemic vascular resistance, and hypotension. Furthermore, the ability to perform neurologic examination is lost when barbiturates are used to control ICP. Prolonged barbiturate therapy may result in immune suppression, leading to sepsis and ileus with subsequent feeding intolerance. When administering high-dose barbiturate therapy, continuous blood pressure monitoring and adequate cardiovascular support are required to maintain adequate CPP.

Temperature Control

Experimentally, hyperthermia (core body temperature ≥38.0°-38.5°C [100.4°-101.3°F] has been shown to exacerbate neuronal cell damage, whereas therapeutic hypothermia (core body temperature <35°C) has been shown to decrease many of the mechanisms associated with secondary brain damage, such as decreased inflammation, excitotoxicity, and cerebral metabolism.

The Cool Kids Trial involving a multicenter international study of children to determine if hypothermia (32°C-33°C [89.6°F -91.4°F]) initiated earlier and for a longer duration following injury, with a slower rewarming period, improves neurologic outcome following TBI was terminated due to futility. In the revised guidelines, the authors suggested that moderate hypothermia (32°-33°C [89.6°F -91.4°F]) beginning within 8 hours after severe TBI for up to 48 hours' duration should be considered to reduce ICH. If hypothermia is induced, rewarming at a rate faster than 0.5°C/h should be avoided. However, the authors stated that "the implications of this development (Cool Kids Trial)

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on the recommendations may need to be considered by the treating physician when details of the study are published".

Potential complications associated with hypothermia include, but are not limited to, increased arrhythmias, electrolyte abnormalities, bleeding risk, and increased susceptibility to infection or sepsis.

Antiseizure Prophylaxis

It is generally agreed that posttraumatic seizures should be aggressively treated, because they may contribute to hyperthermia and ICH. Prophylactic anticonvulsant administration of phenytoin may be a treatment option to prevent early posttraumatic seizures (occurring within 1 wk following injury) in infants and young children with severe TBI.

Decompressive Craniectomy

Decompressive craniectomy with duraplasty, leaving the bone flap out, may be considered for pediatric patients with TBI who show early signs of neurologic deterioration or herniation, or are developing ICH refractory to medical management during the early stages of their injury. Potential complications from decompressive craniectomy include, but are not limited to, hemorrhage and exacerbation of cerebral edema.

NOTE: Neurosurgical consultation is required prior to CT scan if patient deteriorating:

- Deteriorating GCS > 2 points
- Dilating pupil
- Developing focal signs
- Extensor posturing
- Further management dependent on CT findings: Operating Theatre / PICU

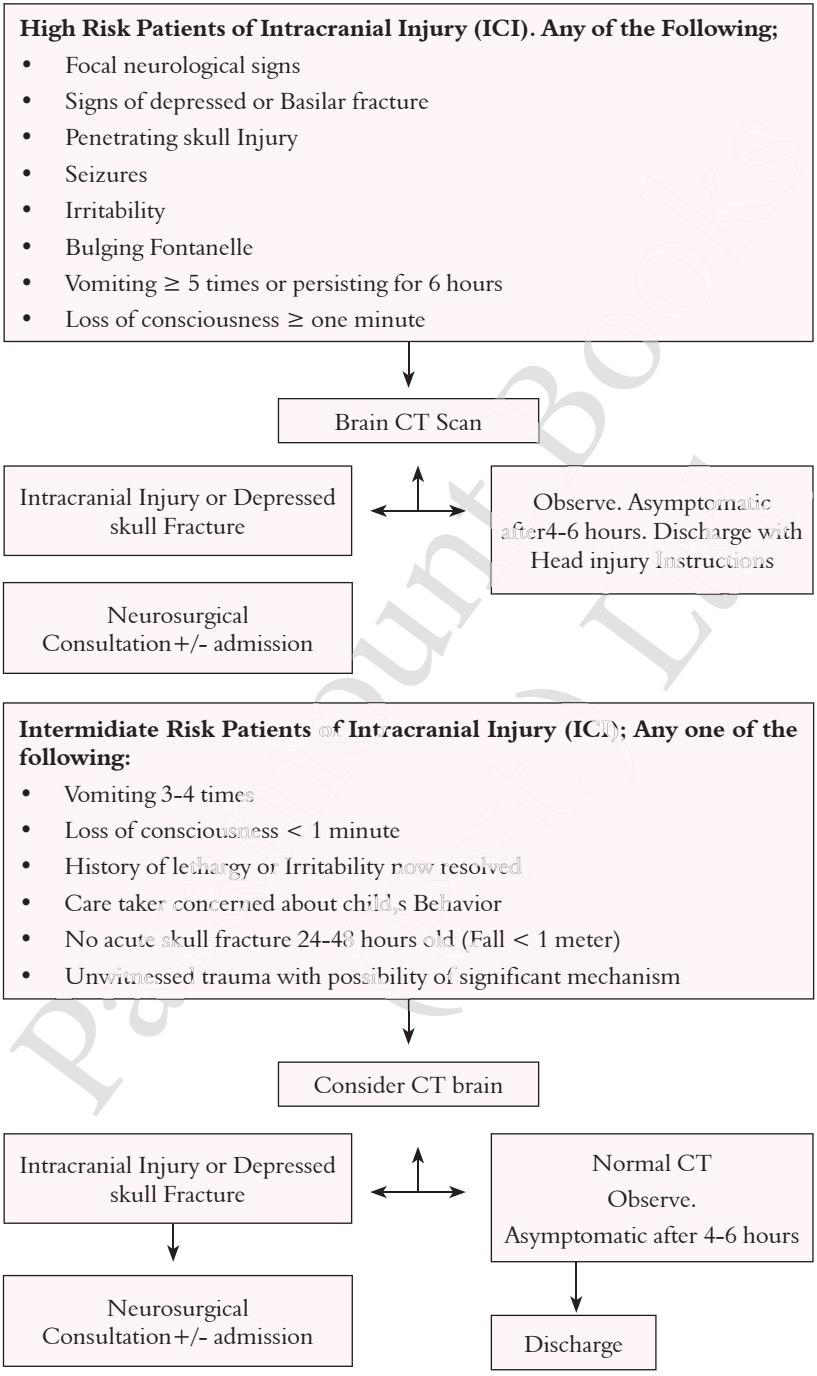
Minor Head Injury (GCS 14-15)

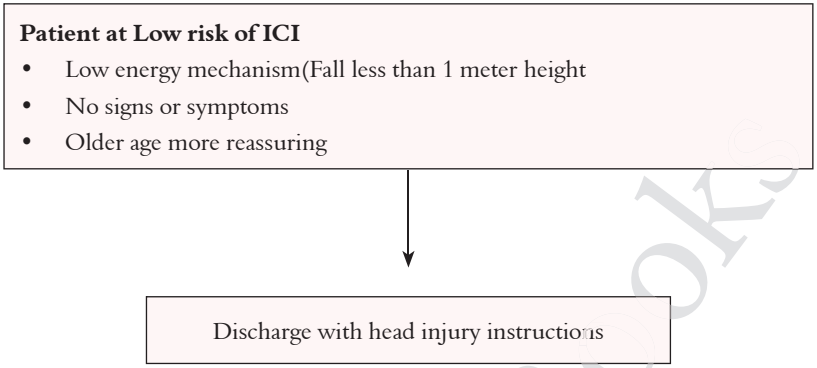
This is the largest group. Goals of management are to identify the small subgroup at risk of late deterioration particularly from intracranial bleeding, and to identify infants at risk from child abuse. This is achieved by good clinical assessment (including a meticulous approach to taking the history), and early management, selective CT scanning and (in the case of possible child abuse) appropriate referral for further investigation. A normal CT scan is the most accurate way of excluding intracranial injury and reducing the likelihood of late deterioration.

Minor Head Injury in Children < 2 Years of Age

Use this algorithm for an infant < 2 years with apparently minor head trauma who is alert or responds to voice or light touch. Exclusion criteria: Birth trauma, bleeding diathesis, VP shunt, multiple trauma, pre-existing neurologic disorder or significant concern regarding abuse/negligence on initial evaluation.

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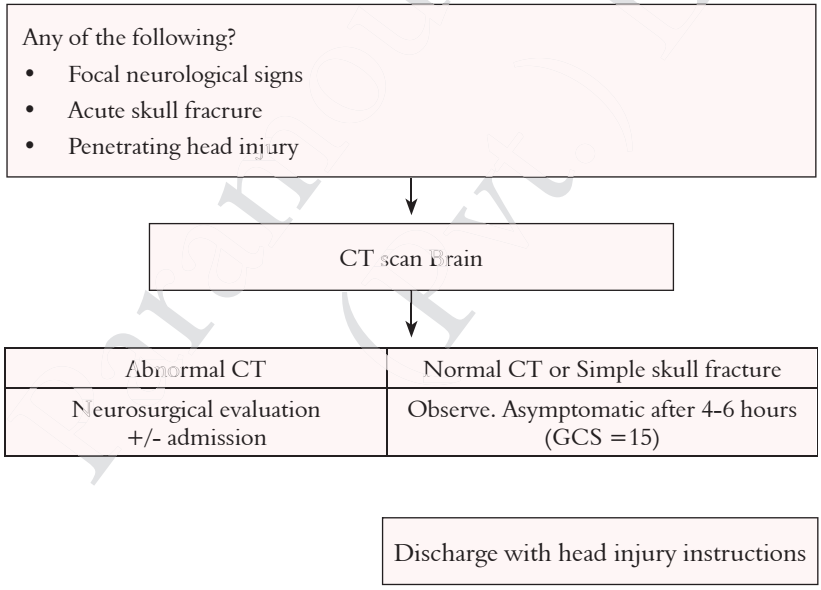

High Risk Patients of Intracranial Injury (ICI). Any of the Following;
• Focal neurological signs
• Signs of depressed or Basilar fracture
• Penetrating skull Injury
• Seizures
• Irritability
• Bulging Fontanelle
• Vomiting ≥ 5 times or persisting for 6 hours
• Loss of consciousness ≥ one minute
Brain CT Scan
Intracranial Injury or Depressed skull Fracture
Observe. Asymptomatic after4-6 hours. Discharge with Head injury Instructions
Neurosurgical Consultation+/- admission
Intermidiate Risk Patients of Intracranial Injury (ICI); Any one of the following:
• Vomiting 3-4 times
• Loss of consciousness < 1 minute
• History of lethargy or Irritability now resolved
• Care taker concerned about child,s Behavior
• No acute skull fracture 24-48 hours old (Fall < 1 meter)
• Unwitnessed trauma with possibility of significant mechanism
Consider CT brain
Intracranial Injury or Depressed skull Fracture
Normal CT
Observe.
Asymptomatic after 4-6 hours
Neurosurgical Consultation+/- admission
Discharge



Minor Head Injury in Children 2-15 Years of Age

Use this algorithm for children and young people 2-15 years of age with apparently minor head trauma and GCS 14-15.

Exclusion criteria: Bleeding diathesis, VP shunt, multiple trauma, pre-existing neurologic disorder or significant concern regarding abuse/ negligence on initial evaluation.



Observation Period in Emergency Department

Children with minor head injury may require a period of observation in CED (see algorithms above). This will usually be for a period of 4-6 hours with hourly neuro observations of GCS, pupil size and reactivity, power in limbs and

vital signs (BP, pulse, respirations). At the end of the observation period perform a full clinical assessment and re-categorise into risk group (as described in the algorithm) to determine the next step in management.

Criteria for Admission or Discharge

Indicators for Admission:

- GCS <15
- CT abnormality except simple uncomplicated fracture
- Delayed seizure
- Inadequate supervision / poor access to medical care
- Disabling symptoms
- Children may also be admitted at the discretion of the Starship ED Consultant
- All children with suspicion of child abuse require admission for assessment

All admissions should be discussed with the Neurosurgical Registrar.

Patients admitted during the day should be reviewed on the ward by the Paediatric Neurosurgical Registrar. After hours admissions will be reviewed by the Neurosurgical Registrar on call.

Requirements for Discharge

- Orientated in time and place (GCS 15)
- No focal neurological signs
- Mild / moderate headache only
- Normal CT scan with or without skull fracture
- A responsible person, with access to phone and transport, available to continue observation of patient
- Medical officer is satisfied that the mechanism was accidental

Require provision of discharge check list on when to return to hospital:

- Increasing headache
- Persistent vomiting
- Becomes restless or drowsy
- Seizure
- Provision of information regarding post concussion syndrome and where to seek assistance for this.

Inpatient Management of Mild Head Injury

- Hourly neurological observations
- Clear fluids orally for 6 hours, IV fluids if persistent vomiting (0.9% saline)
- Simple analgesia e.g. Paracetamol orally or PR

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- Consider discharge after 12 hrs if asymptomatic
- Neurological symptoms, declining GCS or persistent vomiting >4hrs after admission require reassessment +/- head imaging

Fluid Management in the Paediatric Head Injured Patient

Hyponatraemia

The most serious and frequently seen electrolyte abnormality is that of hyponatraemia (Na< 135mmol/L). Purported mechanisms include SIADH, cerebral salt wasting and overzealous fluid resuscitation.

The effects of hyponatraemia are those of cerebral oedema as fluid crosses the blood-brain-barrier into the cerebral parenchyma worsening cerebral swelling. Symptoms can include headache, anorexia, nausea, weakness, lethargy, confusion, disorientation, blurred vision, cramps, coma and seizure. Symptoms often mimic those of the head injury / concussion itself. The consequence of this can lead to extremely rapid neurological decline and has been associated with death or worsened neurological outcome.

Although the head injured child may have associated pulmonary and gastrointestinal injuries that may complicate electrolyte homeostasis, our experience suggests that:

All paediatric head injured patients that require intravenous fluid for maintenance or resuscitation MUST receive 0.9% NaCl +/- 10mmol KCL/500mL.

- This has been shown on numerous occasions to be the most important prophylactic measure to prevent the development of hyponatraemia.
- **Avoid hypotonic solutions**, e.g. 0.18% Sodium Chloride and 4% Dextrose or 5% Dextrose, which may impair cerebral compliance.
- Infants require blood glucose checks 4 hourly as there is a significant risk of hypoglycaemia and subsequent seizure.
- Serum sodium and potassium need assessment 12 hourly when in the Neurosurgical High Dependency Unit (HDU) ie Moderate–Severe Head Injuries. This can be changed to daily if parenteral fluids are still required when the patient is on the ward.
- If the serum sodium remains low despite parenteral 0.9% NaCl then:
- A thorough review of fluid status is warranted
- Reduce fluid intake
- Check serum and urine sodium and osmolality

Guidelines on Drug Usage

i. Raised Intracranial Pressure

Indications for medication:

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- Deteriorating GCS > 2
- Dilating pupil
- Developing focal signs
- Extensor posturing
- Cushing's reflex (hypertension, bradycardia)
- Prior to transfer with GCS < 9. Mannitol. Dose: 0.25 - 1g /Kg/dose (= 1.25-5ml/kg of 20%) repeated if necessary. Given as 20% solution, run in over 20 minutes (20g/100ml) e.g.: for 20 Kg child, 25-50 ml over 20 minutes

ii. Seizures

- Immediate post traumatic seizures (<1 hour) do not have the same pathological significance as those occurring after 1 hour.
- Treatment with anticonvulsants in the first 10 days can make management during the initial critical periods easier, but does not change incidence or severity of late post traumatic epilepsy.
- Diazepam. Give ongoing seizure > 3minutes, 0.25 mg/kg/dose IV
- Phenytoin. Give to stop and prevent further seizures 20 mg / Kg, slow IV injection or infusion. Maintenance 5 mg/kg/day (as single or divided doses)
- Monitor for side effects: rash, hepatitic picture, ataxia, nystagmus, slurred speech, nausea, vomiting, constipation

Note: Some Neurosurgeons choose to administer Phenytoin to all patients with severe head injury for a period of 10 days.

iii. Analgesia

- Paracetamol: 20 mg/kg stat then 15 mg/kg/dose 4hrly (max 90 mg/kg/day). Use lower doses in infants less than 3 months o f age.
- Morphine: May be cautiously used at the lowest dose noting that even slight respiratory depression raises intracranial pressure.

Post Traumatic Seizure

Post traumatic seizure is a relatively frequent clinical manifestation of head injury. The temporal sequence of seizure, in combination with the degree of intra-cranial injury, is the most important prognostic indicator for determining ongoing treatment requirements.

Seizures are classically separated into immediate, early and late.

Immediate Seizure

Usually occur within seconds of injury and are thought to be represent traumatic depolarisation of neuronal elements. These patients do not require epilepsy work-up if they are normal on presentation to the Emergency Department.

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These seizures are not thought to increase the susceptibility to later, unprovoked, seizures and treatment with anti-epileptic medication is not indicated.

Early Seizure

Early Seizure is commonly defined as a seizure occurring within 1 week of head injury. Early seizures are more frequent in the paediatric population in comparison with late seizures, with the majority occurring within the first 24 hours. Younger children (< 7 yrs) are at increased risk of both early and late seizures, and are also at higher risk of status epilepticus.

The risk of early seizure increase with the severity of brain injury:

- Mild head injury - 1.0% risk
- Moderate head injury - 1.1% risk
- Severe head injury - 30.5% risk

Treatment for early seizures is recommended with either phenytoin or carbamazepine.

Late Seizure

Late seizures are defined as seizures occurring after 7 days from time of initial head injury. Younger children appear more at risk of developing late seizures.

The incidence increases with severity of head injury:

- Mild head injury - 0.2%
- Moderate head injury - 1.6%
- Severe head injury - 7.4%

The greatest risk factors for the development of late seizures are degree of brain contusion, subdural haematoma and age.

There is no evidence for the use of prophylactic treatment utilising anti-epileptic drugs with any severity of head injury, but the recommendation is for active treatment of epilepsy (2 or more seizures) as identified.

Post Concussion Syndrome

The number of people that sustain post concussion symptoms following mild head injury has been reported to be almost 50%. The most frequent symptoms are those of headache, nausea and

lethargy. Other symptoms include dizziness, fatigue, poor memory, poor concentration, irritability, depression, sleep disturbance, blurred vision and photophobia.

Whilst most of these symptoms resolve within 1-2 weeks, 8% of people are reported to have persistent symptoms at 1 year.

There has been great debate as to whether the symptoms are of organic or psychological origin. Although MRI, cerebral blood flow anomalies and histopathological studies have clearly shown evidence suggesting organic

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abnormalities, it seems likely that both organic and psychological factors are involved in an interplay determining the symptoms. In the acute hospital setting, the main concern is the appropriate management of the patient with ongoing concussive symptoms. The main factors to consider are:

1. Normal neurological examination
2. Normal electrolyte profile and fluid intake
3. Adequate analgaesic and anti-emetic requirements.

If the child who has sustained a mild to moderate head injury, has ongoing symptoms, and a CT scan has not been performed, then this should be requested.

If a CT scan has been performed, and there is no deterioration in GCS, then a repeat CT scan is not indicated. The child should be managed with careful fluid intake (oral or parenteral), daily electrolyte analysis, correct analgaesia (ensuring no allergies) and adequate anti-emetics. If the symptoms persist and are relatively mild, the child may be discharged as per the discharge policy.

If parenteral fluids, or high levels of analgesic/anti-emetic are required, then the child should remain in hospital until these are readily controlled.

References

1. Lenzlinger PM, Saatman K, Raghupathi R, *et al*. Overview of basic mechanisms underlying neuropathological consequences of head trauma. Miller LP, Hayes RL, eds. Head Trauma-Basic, Preclinical, and Clinical Directions. Wiley-Liss; 2001. 3-36.
2. Vavilala MS, Muangman S, Tontisirin N, *et al*. Impaired cerebral autoregulation and 6-month outcome in children with severe traumatic brain injury: preliminary findings. Dev Neurosci. 2006. 28(4-5):348-53.
3. Vavilala MS, Muangman S, Waitayawinyu P, *et al*. Neurointensive care; impaired cerebral autoregulation in infants and young children early after inflicted traumatic brain injury: a preliminary report. J Neurotrauma. 2007 Jan. 24(1):87-96.
4. Oshio K, Watanabe H, Song Y, Verkman AS, Manley GT. Reduced cerebrospinal fluid production and intracranial pressure in mice lacking choroid plexus water channel Aquaporin-1. FASEB J. 2005 Jan. 19(1):76-8.
5. Tong KA, Ashwal S, Holshouser BA, *et al*. Diffuse axonal injury in children: clinical correlation with hemorrhagic lesions. Ann Neurol. 2004 Jul. 56(1):36-50.
6. Neurological recovery after traumatic brain injury. J Head Trauma Rehabil. 2005 Jan-Feb. 20(1):76-94.
7. Huh JW, Widing AG, Raghupathi R. Midline brain injury in the immature rat induces sustained cognitive deficits, bihemispheric axonal injury and neurodegeneration. Exp Neurol. 2008 Sep. 213(1):84-92.
8. Osteen CL, Moore AH, Prins ML, Hovda DA. Age-dependency of 45calcium accumulation following lateral fluid percussion: acute and delayed patterns. J Neurotrauma. 2001 Feb. 18(2):141-62.
9. Schneier AJ, Shields BJ, Hostetler SG, Xiang H, Smith GA. Incidence of pediatric traumatic brain injury and associated hospital resource utilization in the United States. Pediatrics. 2006 Aug. 118(2):483-92.

Paramount Books Pvt. Ltd.

10. Duhaime AC, Christian CW, Rorke LB, Zimmerman RA. Nonaccidental head injury in infants--the "shaken-baby syndrome". N Engl J Med. 1998 Jun 18. 338(25):1822-9.
11. Aldrich EF, Eisenberg HM, Saydjari C, Luerssen TG, Foulkes MA, Jane JA. Diffuse brain swelling in severely head-injured children. A report from the NIH Traumatic Coma Data Bank. J Neurosurg. 1992 Mar. 76(3):450-4.
12. Duhaime AC, Durham S. Traumatic brain injury in infants: the phenomenon of subdural hemorrhage with hemispheric hypodensity ("Big Black Brain"). Prog Brain Res. 2007. 161:293-302.
13. Suh DY, Davis PC, Hopkins KL, Fajman NN, Mapstone TB. Nonaccidental pediatric head injury: diffusion-weighted imaging findings. Neurosurgery. 2001 Aug. 49(2):309-18; discussion 318-20.
14. Ichord RN, Naim M, Pollock AN, Nance ML, Margulies SS, Christian CW. Hypoxic-ischemic injury complicates inflicted and accidental traumatic brain injury in young children: the role of diffusion-weighted imaging. J Neurotrauma. 2007 Jan. 24(1):106-18.
15. Schneier AJ, Shields BJ, Hostetler SG, Xiang H, Smith GA. Incidence of pediatric traumatic brain injury and associated hospital resource utilization in the United States. Pediatrics. 2006 Aug. 118 (2):483-92.
16. Corrigan JD, Selassie AW, Orman JA. The epidemiology of traumatic brain injury. J Head Trauma Rehabil. 2010 Mar-Apr. 25 (2):72-80.
17. Taylor CA, Bell JM, Breiding MJ, Xu L. Traumatic brain injury-related emergency department visits, hospitalizations, and deaths - United States, 2007 and 2013. MMWR Surveill Summ. 2017 Mar 17. 66 (9):1-16.
18. Coronado VG, Xu L, Basavaraju SV, *et al*. Centers for Disease Control and Prevention (CDC). Surveillance for traumatic brain injury-related deaths--United States, 1997-2007. MMWR Surveill Summ. May 2011. 60(5):1-32.
19. ATLS Subcommittee, American College of Surgeons' Committee on Trauma, International ATLS working group. Advanced trauma life support (ATLS): the ninth edition. J Trauma Acute Care Surg. 2013 May. 74 (5):1363-6.
20. [Guideline] Society of Critical Care Medicine. Guidelines for the acute medical management of severe traumatic brain injury in infants, children, and adolescents. Pediatr Crit Care Med. 2012 Jan. 13(1 Suppl):S1-82.
21. Bar-Joseph G, Guilburd Y, Tamir A, Guilburd JN. Effectiveness of ketamine in decreasing intracranial pressure in children with intracranial hypertension. J Neurosurg Pediatr. 2009 Jul. 4(1):40-6.
22. Cohen L, Athaide V, Wickham ME, Doyle-Waters MM, Rose NG, Hohl CM. The effect of ketamine on intracranial and cerebral perfusion pressure and health outcomes: a systematic review. Ann Emerg Med. 2015 Jan. 65 (1):43-51.
23. Badjatia N. Hyperthermia and fever control in brain injury. Crit Care Med. 2009 Jul. 37(7 Suppl):S250-7.
24. Stiefel MF, Udoetuk JD, Storm PB, Sutton LN, Kim H, Dominguez TE, *et al*. Brain tissue oxygen monitoring in pediatric patients with severe traumatic brain injury. J Neurosurg. 2006 Oct. 105 (4 Suppl):281-6.
25. Narotam PK, Burjonrappa SC, Raynor SC, Rao M, Taylon C. Cerebral oxygenation in major pediatric trauma: its relevance to trauma severity and outcome. J Pediatr Surg. 2006 Mar. 41 (3):505-13.

Paramount Books (Pvt.) Ltd.

26. Stippler M, Ortiz V, Adelson PD, Chang YF, Tyler-Kabara EC, Wisniewski SR, *et al*. Brain tissue oxygen monitoring after severe traumatic brain injury in children: relationship to outcome and association with other clinical parameters. J Neurosurg Pediatr. 2012 Nov. 10 (5):383-91.
27. Schrieff-Elson LE, Thomas KG, Rohlwink UK, Figaji AA. Low brain oxygenation and differences in neuropsychological outcomes following severe pediatric TBI. Childs Nerv Syst. 2015 Dec. 31 (12):2257-68.
28. Khanna S, Davis D, Peterson B, *et al*. Use of hypertonic saline in the treatment of severe refractory posttraumatic intracranial hypertension in pediatric traumatic brain injury. Crit Care Med. 2000 Apr. 28(4):1144-51.
29. Coritsidis G, Diamond N, Rahman A, *et al*. Hypertonic saline infusion in traumatic brain injury increases the incidence of pulmonary infection. J Clin Neurosci. 2015 Aug. 22(8):1332-7.
30. Tasker RC, Vonberg FW, Ulano ED, Akhondi-Asl A. Updating Evidence for Using Hypothermia in Pediatric Severe Traumatic Brain Injury: Conventional and Bayesian Meta-Analytic Perspectives. Pediatr Crit Care Med. 2017 Apr. 18 (4):355-362.
31. Crompton EM, Lubomirova I, Cotlarciuc I, Han TS, Sharma SD, Sharma P. Meta-Analysis of Therapeutic Hypothermia for Traumatic Brain Injury in Adult and Pediatric Patients. Crit Care Med. 2017 Apr. 45 (4):575-583.
32. Webster DL, Fei L, Falcone RA, Kaplan JM. Higher-volume hypertonic saline and increased thrombotic risk in pediatric traumatic brain injury. J Crit Care. 2015 Dec. 30(6):1267-71.
33. Taylor CA, Bell JM, Breiding MJ, Xu L. Traumatic brain injury-related emergency department visits, hospitalizations, and deaths - United States, 2007 and 2013. MMWR Surveill Summ. 2017 Mar 17. 66(9):1-16.
34. Schneier AJ, Shields BJ, Hostetler SG, Xiang H, Smith GA. Incidence of pediatric traumatic brain injury and associated hospital resource utilization in the United States. Pediatrics. 2006 Aug. 118(2):483-92.
35. Cohen L, Athaide V, Wickham ME, Doyle-Waters MM, Rose NG, Hohl CM. The effect of ketamine on intracranial and cerebral perfusion pressure and health outcomes: a systematic review. Ann Emerg Med. 2015 Jan. 65(1):43-51.e2.
36. Lloyd O, Ownsworth T, Fleming J, Zimmer-Gembeck MJ. Development and preliminary validation of the Paediatric Awareness Questionnaire for children and adolescents with traumatic brain injury. Child Neuropsychol. 2018 Jul. 24 (5):702-22.
37. Konigs M, Beurskens EA, Snoep L, Scherder EJ, Oosterlaan J. Effects of timing and intensity of neurorehabilitation on functional outcome after traumatic brain injury: a systematic review and meta-analysis. Arch Phys Med Rehabil. 2018 Jun. 99 (6):1149-59.e1.
38. Narayan V, Mohammed N, Savardekar AR, Patra DP, Notarianni C, Nanda A. Noninvasive intracranial pressure monitoring for severe traumatic brain injury in children: a concise update on current methods. World Neurosurg. 2018 Jun. 114:293-300.
39. Reisner A, Chern JJ, Walson K, *et al*. Introduction of severe traumatic brain injury care protocol is associated with reduction in mortality for pediatric patients: a case study of Children's Healthcare of Atlanta's neurotrauma program. J Neurosurg Pediatr. 2018 May 25. 1-8.
40. Jennett B, Teasdale G, Braakman R, *et al*. Prognosis of patients with severe head injury. Neurosurgery 1979; 4:283.

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