REVIEW

Management of ac paediatric age grou

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INTRODUCTION

Stroke in neonates and children is a rare but serious condition with an annual incidence of 1–13 per 100 000 at risk (Schoenberg *et al*. 1978; Broderick *et al*. 1993; Fullerton *et al*. 1979–98; Kothari *et al*. 1995). There are few acute management protocols in the literature, and even fewer randomised trials in the paediatric age group. This is in contrast with adult stroke where numerous trials have been undertaken, culminating in the FDA approval of tissue plasminogen activator (TPA) for ischaemic stroke up to 3 h from symptom onset.

Given the contribution of genetic and congenital factors, the causes of stroke in paediatric patients only partially overlap with those of adult stroke. Among children, one would anticipate that certain cerebral responses might be affected differently depending on, for example, whether the fontanelles were open or closed, in the latter case strokes perhaps more resembling the pathophysiological situation in adults.

The first part of this article focuses on the acute management and work-up of ischaemic and haemorrhagic (intracerebral) stroke in children. Intraventricular haemorrhage of the premature/neonate, subarachnoid haemorrhage, and extra-axial (subdural, epidural) haematomas will not be included. The second part summarizes antithrombotic strategies for the common causes of paediatric ischaemic stroke.

ACUTE MANAGEMENT AND EVALUATION

The management of acute stroke is guided by knowing whether the stroke is ischaemic or due to intracerebral haemorrhage (ICH), differentiated by a noncontrast CT brain scan. Whereas ischaemic strokes are considerably more common than haemorrhagic strokes in adults, stroke types are more evenly split in paediatric patients (Earley *et al*. 1998).

Intracranial haemorrhage

Acute management

Control of the blood pressure is paramount while any haematological cause of bleeding is being investigated with platelet count, prothrombin time,

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partial thromboplastin time, bleeding time, and coagulation factors if necessary (Nishiyama *et al*. 2000; Puchstein *et al*. 1983). Although there are no controlled data to define the target blood pressure, it seems prudent to keep it lower than the 95th centile for age with an arterial line and using intravenous medications known not to increase intracranial pressure (ICP) such as:

- Labetalol (0.2–1 mg/kg every 10 min, maximum 20 mg each dose)
- Angiotensin converting enzyme inhibitors such as enalapril, 0.005–0.01 mg/kg every 8–24 h
- If not successful, an intravenous calcium channel blocker such as nicardipine (0.5–5 µg/kg/minute)

Even if the patient is not in frank respiratory failure, intubation should still be considered when the airway cannot be protected – due to impaired consciousness, or impaired gag, cough or swallow reflexes.

If there are signs of cerebral herniation or impending herniation, iv mannitol (0.25–1.0 g/kg over 20 min) should be administered and a neurosurgical consultation sought to possibly insert a ventriculostomy tube (Brott & Reed 1989). Hyperventilation to lower the paCO2 to 30–35 mmHg (at times even 25 mmHg) is another temporizing option (Brott 1989), although the effect starts wearing off within 24 h. Steroids are discouraged because they worsen outcome after haemorrhagic stroke (Broderick *et al*. 1999).

Close supervision in the ICU is required with frequent neurological assessments every hour during the first 12–24 h to watch for deterioration as a result of increasing ICP, or re-bleeding. As well as interfering with the neurological examination, heavy sedation should be avoided since it can drop the blood pressure enough to impair brain perfusion. Care should be taken to avoid cerebral perfusion pressure – the difference between mean arterial pressure and ICP – falling below 60 mmHg, when cerebral ischaemia might ensue (Strandgaard *et al*. 1973). If no rebleeding occurs, swelling around the haematoma peaks at 3–4 days following onset (Broderick *et al*. 1999).

Central lines are not usually required for the stable patient unless peripheral access is difficult or multiple drugs and fluids have to be infused. Intravenous hydration should consist of normal saline, avoiding hypo-osmolar fluids since these can cause increased oedema of ischaemic tissue and thus an increase in ICP (Brott 1989). Also, intravenous dextrose should be avoided because a high serum glucose level is associated with a worse outcome (Mase *et al*. 1995; Song *et al*. 2003). Fever is preferably treated, using agents such as acetaminophen (paracetamol) and cooling blankets (Broderick *et al*. 1999). Therapeutic hypothermia (35–36 °C) is currently being studied in large clinical trials and could be seriously considered for patients with uncontrollably high ICP (Schwab *et al*. 1998a). Barbiturates such as thiopental are also beneficial in reducing ICP but are rarely resorted to (Hayashi *et al*. 1988).

The issue of patient nutrition and its route should be considered early, and feeding prefer-

ably not withheld beyond 24 h. In alert patients, and those who seem to have normal oropharyngeal reflexes, and if no surgical procedures are pending, supervised oral feeding can begin – preferably after examination by a swallow/speech specialist. Non-intubated neurologically compromised patients, and intubated patients, benefit from nasogastric tube feeding. Sucralfate or H2-blockers are commonly used to avoid gastritis and small intestinal ulceration (Cook 1995).

Diagnostic workup

Having stabilized the patient, the next concern is to discover the cause of the ICH. A physical examination will reveal syndromes such as Von Hippel-Lindau disease and Henoch–Schonlein purpura – both can be associated with ICH. In addition to coagulation tests to assess any bleeding diathesis (see above), a complete blood count may reveal idiopathic thrombocytopenic purpura or leukaemia. Magnetic resonance angiography (MRA) or catheter cerebral angiography may reveal a structural cause such as an arteriovenous malformation (AVM) or the moya moya syndrome – this syndrome causes both ischaemic and haemorrhagic strokes, and should be suspected in Down's syndrome, sickle cell disease and neurofibromatosis type 1 (Abram 1998; Kirkham 1999). Overall, about 30% of nontraumatic ICH in children is due to a bleeding diathesis or an AVM. Other causes include bleeds into tumours, cavernomas and rarely aneurysmal rupture. Further management is based on each particular underlying condition.

Ischaemic stroke

Any sudden change in neurological status requires a repeat noncontrast brain CT which will show any haemorrhagic transformation of the infarct.

Acute management

The acute management of nonhaemorrhagic stroke is slightly different, with particular care taken to rule out stroke mimics (Table 1). The history is helpful in this regard: a preceding viral illness is a clue for acute disseminated encephalomyelitis, and a past history of seizures might suggest the current deficits are due to transient postictal dysfunction (Todd's paralysis). To complicate matters, ischaemia (especially involving the cortex) can itself result acutely in seizures in up to 6% of cases with lobar infarction (Labovitz *et al.* 2001).

With a working diagnosis of ischaemic stroke, the immediate focus is stabilization of the respiratory and cardiovascular systems and to prevent stroke progression. Patients should be admitted to the ICU unless only a small stroke has occurred and is judged unlikely to recur or progress. Intubation should be performed if patients cannot protect their airway. It is imperative to avoid lowering the blood pressure acutely (unless at near-malignant levels) since higher pressures could be a compensation process to supply ischaemic tissue through collateral circulation (Powers 1993). Intra-arterial lines to measure blood pressure are not as critical as in the case of ICH, and the decision should be made on a case-by-case basis.

Like ICH, intravenous fluids should not be hypo-osmolar nor contain dextrose (Pulsinelli *et al.* 1983; Ropper & Shafran 1984; Parsons *et al.* 2002). Corticosteroids are not of proven benefit (Hofmeijer *et al.* 2003). Maximal brain swelling is expected at about 72 h from stroke onset (Hacke *et al.* 1996) but the use of mannitol is controversial and preferably limited to patients with signs of early or impending herniation (Adams *et al.* 2003). Hyperventilation is of transient benefit for patients with increased ICP. Although awaiting confirmation of benefit from large trials, hemicraniectomy can be a last resort in patients with early signs of herniation (Rieke *et al.* 1995; Schwab *et al.* 1998b). Not surpris-

Table 1 Potential stroke mimics (depending on specific circumstances such as patient age)

Autoimmune
demyelinating disorders (multiple sclerosis, acute disseminated encephalomyelitis)
central pontine myelinolysis
sarcoidosis
myasthenia gravis
Infections
encephalitis
cerebritis, abcess
Metabolic
hypoglycaemia
electrolyte disorders e.g. (hyponatraemia)
Structural
neoplasm/metastasis
Migraine
Seizures (postictal)
Spinal cord lesions
Monoparesis due to local nerve or muscle pathology, joint or bone pathology (e.g. fracture, osteomyelitis, septic arthritis).

ingly, the type and size of the stroke help predict which patients are likely to progress to cerebral herniation – large middle cerebral infarcts.

Seizures occur in the setting of acute stroke, especially when the cortex is involved (So *et al*. 1996). When seizures are not clinically evident, an EEG may be helpful in suspected cases with fluctuating neurological status. Seizures are treated acutely with standard antiepileptic drugs, and the therapy should continue through the first few weeks post stroke and then be reassessed: acute seizures do not necessarily lead to epilepsy in the long term (So *et al*. 1996).

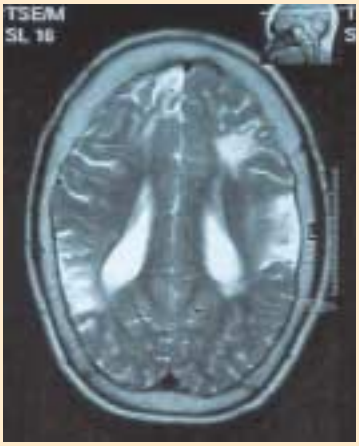
Given the association of fever with a worse outcome, pyrexia should probably be treated with acetaminophen (paracetamol) or with other measures such as cooling blankets. Therapeutic hypothermia is awaiting large clinical trials but could be beneficial in patients with uncontrollable raised ICP (Schwab *et al*. 1998; Schwab *et al*. 2001).

Any sudden change in neurological status requires a repeat noncontrast brain CT which will show any haemorrhagic transformation of the infarct.

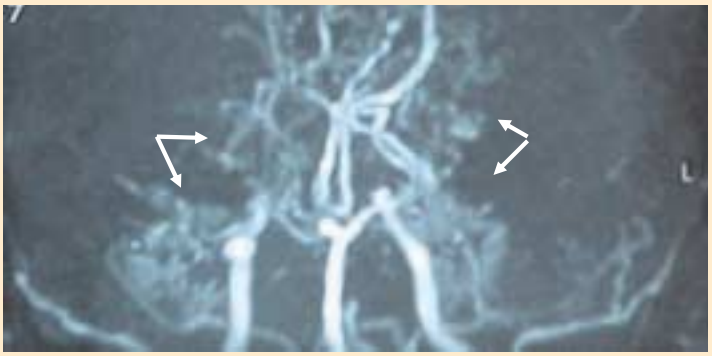
Patients with sickle cell disease should receive adequate oxygenation (Adams 2001). Hypotension is best avoided given the prevalence of vascular narrowing in this population. Blood transfusions are also commonly given, aiming to reduce sickle haemoglobin to less than 30% of total haemoglobin.

Diagnostic workup

Having stabilized the patient, the focus shifts to finding the cause of the ischaemic stroke. In the neonate, stroke is most often an embolic complication of congenital heart disease, perinatal asphyxia, or vascular injury (e.g. carotid dissection as a result of forceps application during a difficult delivery). For all patients, the cause and treatment can be influenced by knowing whether single or multiple strokes have occurred, and the approximate time of onset. This is helped by magnetic resonance imaging (Figs 1 and 2), preferably with perfusion and diffusion-weighting (Hunter 2002; Husson *et al*. 2002), to detect infarcts within the first few hours and differentiate recent from older infarcts (Tong & Albers 2000). MRI can also show signal abnormality in a dissected artery (Zuccoli *et al*. 2002), a situation seen usually but not exclusively following head and neck trauma (Ohkuma *et al*. 2003). MR angiography has also been used with some success to delineate vessel occlusion and stenosis (Hus-



(a)



(b)

Fig. 1 (a) Multifocal bilateral ischaemic strokes in a 14-year-old-shown as increased T2 signal in multiple frontal and parietal areas on MRI. At two years old, the patient had had left focal status epilepticus followed by a residual mild left hemiparesis and subsequent recurrent partial seizures and developmental delay.
(b) MR angiography shows the features of moya moya with complete obstruction of the internal carotids and the posterior and middle cerebral arteries more on the right, with collateral circulation resembling the typical 'puff of smoke' (arrows).

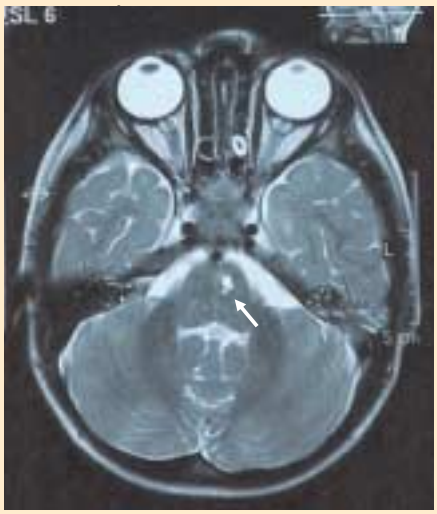


Fig. 2 MRI of a 2-year-old who presented with a right hemiplegia and right gaze preference showing a pontine ischaemic stroke (arrow) as a result of a presumed verterbral dissection.

son *et al*. 2002). Catheter angiography should be considered whenever a clinically suspected arterial lesion is still not detected by noninvasive imaging; this decision has to be based on the specifics of the case and on local expertise. It is recommended in most patients with no clear cause because MR angiography cannot exclude vasculitis, large vessel dissection, and the moya moya syndrome.

Hypercoagulable states

The list of prothrombotic disorders associated with childhood ischemic stroke is getting longer and longer (Bonduel *et al*. 1999; Goldenberg *et al*. 2004; Hanly 2003; Kurekci *et al*. 2003; Lanthier *et al*. 2000; Milionis Winder 2000; Strater *et al*. 2002; Vicente *et al*. 1999). These disorders seem to be a more common cause of venous than arterial infarction (see below), as is the case in adults (de Veber *et al*. 1998; Chan 2000). An underlying hypercoagulable state should be ruled out (Table 2) (if the patient is on warfarin protein C and S will be low so the child should be re- tested after the warfarin has been discontinued). If the child is receiving heparin, the tests are not affected. Haemoglobin electrophoresis will detect sickle cell disease (Francis 1991). The parents may need to be tested as well if there is any suspicion of an inherited coagulapathy. Longterm transfusion follow-up with transcranial dopler and possible hydroxyurea are used to manage patients with sickle cell disease associated strokes (Ware *et al*. 1999).

Table 2 Tests for evaluation of the hypercoagulable state (based on Hoppe *et al*. 2002).

Full blood count and platelet count
Prothrombin time
Protein C
Protein S (total and free)
Antithrombin III
Activated protein C resistance
Factor V (Leiden) mutation
Prothrombin gene 20210
Partial thromboplastin time
Lupus anticoagulant
Antiphospholipid antibodies
Factor VIII and D-dimer levels
Plasminogen
Thrombin time
Fibrinogen
Plasma homocysteine
Haemoglobin electrophoresis (sickle cell disease)
Urine proteins (nephrotic syndrome)
Heparin cofactor 2
Serum thrombomodulin
Tissue factor pathway inhibitor
Plasminogen activator inhibitor-1
Tissue plasminogen activator

Cardiac causes of stroke

An echocardiogram may reveal an underlying cardiac cause for ischaemic stroke (valvular disease, septal defect), and is better at showing a right-to-left shunt when a contrast agent is given (for example, agitated saline/bubble solution intravenously) and following cough or valsalva manoeuvres (Kronik *et al*. 1979). In contrast to young adults, previously undiagnosed cardiac disease, such as patent foramen ovale, appears to be uncommon in children (Ganesan *et al*. 2003). If a shunt is present, ultrasound of the legs to rule out deep venous thrombosis (DVT) should be performed, particularly if the child has been immobile for a while or has a hypercoagulable state (in fact it is not at all common for children without an underlying coagulopathy to develop DVT) (Rohrer *et al*. 1996).

Table 3 Tests for metabolic disorders that predispose to stroke (based on the Canadian Stroke Protocol Guidelines 2002)

Mitochondrial disease
Serum and CSF lactate and pyruvate
Peripheral blood DNA analysis.
Homocystinuria
Plasma homocysteine
Fabry's disease
Urinary ceramide trihexoside
Leucocyte Alpha galactosidase
Other
Hyperlipidaemia
Fasting serum cholesterol
Triglycerides
Urea cycle enzyme defects
Postprandial plasma ammonia
Amino acid chromatography.

'Metabolic' causes of ischaemic stroke

If still no cause is found, and if there are muscu-

Unfortunately, almost half the children with stroke have no known cause, a similar proportion as in adults.

loskeletal or other neurological abnormalities, mitochondrial diseases (e.g. MELAS, Leigh's syndrome) should be considered, particularly if the infarct does not follow a typical vascular distribution. Other metabolic disorders can cause arterial or venous strokes (Table 3).

Other causes

- In adolescents a urine toxicology screen for drugs like cocaine that can cause a vasospastic vasculopathy is warranted (Konzen *et al*. 1995).
- If there is any suspicion of central nervous system infection or inflammatory/infectious vasculitis, then a lumbar puncture should be done.
- Iron deficiency and migraine may be important in cryptogenic stroke in children (Hartfield *et al*. 1997; Couch & Hassanein 1997; Tietjen 2000). In addition to an association of haemolytic and iron deficiency anaemias with intracranial venous thrombosis (see below), nearly one quarter of children with arterial stroke had evidence of iron deficiency in a recent series (Ganesan *et al*. 2003).
- Children who are HIV positive have an increased risk of stroke which may be associated with an increased prevalence of antiphospholipid antibodies (Visudtibhan *et al*. 1999; Narayan *et al*. 2002).

Unfortunately, almost half the children with stroke have no known cause, a similar proportion as in adults (Williams *et al*. 1997).

Intracranial venous thrombosis

Intracranial venous thrombosis should be considered in a child with a history of otitis or sinusitis, or in those with a hypercoagulable state (e.g. nephrotic syndrome, polycythaemia due to cyanotic heart disease, etc.) (de Veber & Andrew 2001). Venous thrombosis also seems to be a common cause of neonatal strokes (de Veber & Andrew 2001). Suspicion is heightened if the arterial system is normal and the infarct is haemorrhagic and not in a recognizable arterial territory. Intracranial venous thrombosis can be diagnosed with magnetic resonance venography, though involvement of the superior saggital sinus can sometimes be seen as a hyperdensity on noncontrast CT or as a nonfilling gap on a contrast CT scan (delta sign).

SHORT AND LONG-TERM ANTITHROMBOTIC THERAPY FOR ISCHAEMIC STROKE

Thrombolytic agents

Tissue plasminogen activator is the only FDA approved thrombolytic treatment for acute ischaemic stroke in adults, but has not been tested systematically in children (Furlan 1999). The few reported cases seem to have had a fairly successful outcome (Thirumalai & Shubin 2000; Carlson *et al*. 2001). Its use in paediatric practice is limited by the low incidence of paediatric stroke that in itself so often causes diagnostic uncertainty and thus delay, and by the possibility of stroke mimics that require time for investigation.

Anticoagulants

These are used for (Hyers *et al*. 2001; Klement *et al*. 1996):

- Acute 'bridging' therapy before initiating long-term anticoagulation
- DVT prophylaxis is seldom needed in children given their low risk.

Acute therapy

Care must be taken in the setting of a medium to large acute stroke when anticoagulants may transform the recent ischaemic infarct into a haemorrhagic one. There is no consensus as to what constitutes a 'medium' or 'large' stroke, though most experts would agree that any stroke less than 2 cm in diameter represents a 'small' stroke. Therefore, for the larger strokes, it is advisable to wait at least a week before start-

ing anticoagulants (Cerebral Embolism Study Group 1983).

Unfractionated heparin

Compared with adults, newborns and children have increased heparin clearance, greater plasma protein binding of heparin, and lower antithrombin concentrations – all of which necessitate relatively higher doses. As in adults adverse effects include increased risk of bleeding, heparin induced thrombocytopenia and – with chronic use – osteopenia (Saxon *et al*. 1999; Severin & Sutor 2001; Wilhelm *et al*. 1996).

Physicians should control the heparin dose so the activated partial thromboplastin time (APTT) is no more than twice the control value (or up to 65 s). Typical starting doses are 25 U/kg/ h for infants (age < 1 years) and 18 U/kg/ h for children > 1 years with the following guidelines:

- Do not administer a loading dose
- The maintenance dose is age related: children < 12 months of age, 28 units/kg/ h, children > 12 months of age, 20 units/kg/ h.
- Obtain antifactor Xa level within 48 of initiating therapy. If it and the APTT do not correspond, adjust the dose to maintain anti-Xa levels between 0.35 and 0.7 U/mL

Low molecular weight heparins (LMWH)

- Usually aim for an antiactivated factor Xa level of 0.5–1.0 U/mL in a blood sample taken 4–6 h after subcutaneous injection (Boneu 1994; Abbate *et al*. 1998; Massicotte *et al*. 1996; Massicotte *et al*. 1997; Severin *et al*. 2002)
- Enoxiparin (lovenox): 1.5 mg/kg sc every 12 h for children below 2 months, and 1.0 mg/kg sc every 12 h for age over 2 months (Monagle *et al*. 2001)
- Reviparin: 150 U/kg every 12 h for children weighing less than 5 kg and 100 U/kg every 12 h for those weighing over 5 kg (Monagle *et al*. 2001)
- Deltaparin: initial dose 129 units/kg every 24 h.
- Tinzaparin: 275 U/kg 0–2 months, 250 U/kg 2–12 months, 240 U/kg 1–5 years, 200 U/kg 5–10 years and 275 U/kg for 10–16 years

Again, if anticoagulation is going to be used in the first week after stroke, lowering the dose and aiming for Xa levels 10–20% lower than usual may avert haemorrhagic transformation, but anticoagulation is preferably withheld in the first week in the presence of a medium to large sized stroke.

Warfarin

Warfarin dosing for paediatric patients (Albers *et al*. 2001a; Albers *et al*. 2001b; Bauer 2003):

- Initial loading dose of 0.2 mg/kg orally (Michelson *et al*. 1995)
- The maintenance dose is 0.1 mg/kg daily
- Occasionally higher doses (between 0.4 and 0.55 mg/kg/day) may be required for patients with homozygous protein C or S deficiency (Bern *et al*. 1990; Gebara *et al*. 1995)
- Vitamin K antagonists are problematic and rarely used in newborns. This is because:
  - infant formula is supplemented with Vitamin K whereas breast milk has low concentrations of Vitamin K
  - they are only available in tablet form, and because of the rapidly changing physiological levels of vitamin K dependent proteins
- Older children require less warfarin per kg body weight compared to younger ones: children younger than 1 year of age require an average of 0.33 mg/kg as daily maintenance, compared to 0.09 mg/kg for those between 11 and 18 years (Andrew *et al*. 1994). Rare skin necroses has been reported
- Current therapeutic international normalized ratio (INR) ranges for children are directly extrapolated from recommendations for adult patients, being 2.5 (range: 2.0–3.0) for most conditions (Monagle *et al*. 2001). A higher INR target of 3.0 (range: 2.5–3.5) is recommended for patients with mechanical prosthetic valves (Monagle *et al*. 2001). Occa-

Compared with adults, newborns and children have increased heparin clearance, greater plasma protein binding of heparin, and lower antithrombin concentrations.

RECOMMENDATIONS (MONAGLE *ET AL*. 2004)

- Neonates with intracranial venous thrombosis without large ischaemic infarcts or intracranial haemorrhage, use either unfractionated heparin or low molecular weight heparin for 5–7 days, followed by the latter for 3 months
- Neonates with intracranial venous thrombosis with large ischaemic infarcts, CT monitoring only; anticoagulants indicated – as above – only if extension occurs
- Neonates with noncardioembolic ischaemic stroke, do not use anticoagulation or aspirin
- Neonates with cardioembolic ischaemic stroke, use either unfractionated heparin or low molecular heparin for 3 months
- Children with intracranial venous thrombosis, use unfractionated heparin or low molecular weight heparin for 5–7 days, followed by the latter or warfarin for 3–6 months, even in the presence of a haemorrhagic infarct
- Children with acute arterial ischaemic stroke, use unfractionated heparin or low molecular weight heparin for 5–7 days until any cardioembolic cause or vascular dissection has been excluded
- Children with acute ischaemic cardioembolic stroke or vascular dissection, use 5–7 days unfractionated heparin or low molecular weight heparin followed by the latter or warfarin for 3–6 months
- For all children with acute arterial ischaemic stroke, long-term aspirin, 1–5 mg/kg/day is recommended after anticoagulation has been discontinued
- Children with sickle cell disease who have ischaemic stroke, give intravenous hydration and exchange transfusion to reduce haemoglobin S to levels < 30% total haemoglobin
- Hypercoagulable states such as protein C, S, or antithrombin III deficiency are an indication for long-term warfarin, which is often also used for patients with Factor V Leiden mutation or antiphospholipid antibodies

sionally, lower targets for the INR in patients with increased risk of bleeding are appropriate
- Being prone to falls, toddlers are a special group that requires careful consideration of anticoagulant intensity

Warfarin vs. heparin

The decision to use low molecular weight heparin instead of warfarin is taken after comparing the advantages of each strategy. Warfarin is less expensive, and being an oral medication is easier to administer. However heparin requires less monitoring due to the more predictable pharmacokinetics, and it is not affected by dietary factors; warfarin is affected by foods rich in vitamin K such as green vegetables, spinach sprouts, broccoli and cauliflower (Schmidt & Andrew 1992).

Compared to unfractionated heparin, low molecular weight heparin carries a lower risk of heparin-induced thrombocytopenia (Warkentin *et al*. 1995) and osteoporosis (Monreal *et al*. 1994).

While recommendations are published with variable levels of supporting evidence, common sense suggests that anticoagulation should be maintained for as long as the triggering cause of any thrombosis is present.

Antiplatelet agents

Aspirin

The most commonly used antiplatelet agent is still aspirin and doses in the range of 1–5 mg/kg/day have been suggested for children (Hathaway 1984). These relatively low doses seldom cause major adverse effects (Reye's syndrome being associated with doses of aspirin > 40 mg/kg).

Dipyridamole

The second most commonly used antiplatelet agent in children, dipyridamole, has also been used in combination with high aspirin doses in patients with valve prosthesis (dipyridamole dose ranging from 2 to 5 mg/kg/day in three divided doses) (El Makhlouf *et al*. 1987; Solymar *et al*. 1991; Le Blanc *et al*. 1993), but this is thought to be inferior to anticoagulation with warfarin for the prevention of embolic events (Stein *et al*. 2001; Mok *et al*. 1985). The combination may have a beneficial effect in adults for secondary prevention of stroke but there is no information in children.

Thienopyridines

Ticlopidine and clopidogrel have a similar structure and mechanism of action (inhibition of ADP-induced platelet aggregation). Clopidogrel has fewer adverse effects, especially thrombotic thrombocytopenic purpura, but there has been no reported use in children and dosage recommendations are unknown (Bennett *et al*. 1999).

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