Keywords
Paediatric stroke, antithrombotic treatment

Summary
The past decade has seen a dramatic increase in pediatric stroke research. However few studies have addressed antithrombotic safety or effectiveness. Three paediatric stroke guidelines combining research data with expert consensus have been published in the past five years. For most patients treatment recommendations are consistent. Newborns with arterial ischaemic stroke (AIS) rarely require antithrombotic treatment given their extremely low risk of recurrence. In children with AIS a substantial recurrence risk means that antithrombotic treatment is required unless contraindicated. Anticoagulation (heparins, warfarin) is recommended for possible or established dissection and cardiogenic embolism. Antiplatelet treatment is recommended for other children with AIS. For neonatal cerebral sinus venous thrombosis (CSVT) most centers provide initial anti-coagulation in the absence of haemorrhagic contraindications, and otherwise, monitor for propagation. Children with CSVT, even with haemorrhagic infarction, more consistently receive anti-coagulation, as in adults. While more studies are necessary, current treatment guidelines offer an interim option for guiding the treatment of paediatric stroke.

Hämostaseologie 2009; 29: 88–90

A lack of strong evidence on which to base treatment hinders standardized care in paediatric stroke. The past decade has seen a dramatic increase in paediatric stroke research with cohort and case-control studies clarifying the mechanisms and outcome. However, few studies have addressed antithrombotic safety or effectiveness.

Treatment
Guidelines
Three evidence-based guidelines published in the past five years have combined accumulating research data with expert consensus to provide recommendations assisting the clinician in selecting therapies for the different subtypes of stroke (1–3). There are variations across the guidelines in scope, methodology and authorship. All were created within a framework previously set up for adult stroke or thrombosis guidelines, and all provide objective grades of evidence and strength ratings for each treatment recommendation. A recent review of the guidelines addresses the similarities and differences for treatment recommendations in the most frequently encountered subtype of stroke, children beyond the newborn period with AIS (4).

The American College of Chest Physicians’ Clinical Practice Guidelines on Antithrombotic Therapy in Neonates and Children focuses on anticoagulant and antiplatelet therapy among neonatal and childhood CSVT and AIS (1). The American Heart Association (AHA) Stroke Council’s paediatric stroke guideline was prepared by neurologists and neurosurgeons and focuses on diagnosis and management. It encompasses both ischaemic and haemorrhagic stroke across the paediatric age spectrum. Therapies for acute management and prevention of recurrence are the main focus, including but not limited to antithrombotic treatments (2). The AHA guidelines provide a mechanism-based approach to treatment selection with recommendations stratified by common causes including sickle cell disease, heart disease, vasculopathy, metabolic conditions, migraine and hypercoagulable states.

The management of the patient with an ischaemic or haemorrhagic stroke without an underlying condition is also discussed. Treatments for the major vasculopathies including arterial dissection, transient cerebral arteriopathy, moyamoya (sickle-cell related and non-sickle cell) and aneurysm and arteriovenous malformations are provided. Outcome and rehabilitation are also addressed.

The Royal College of Physicians (RCP) guidelines are similar in scope to the other guidelines, but provide a greater focus on stroke beyond the newborn period and on rehabilitation, and contain a handbook for parents and other care-givers of children with stroke (3).

Recommendations
Reflecting a paucity of clinical trials, some recommendations disagree. However for the majority of patients with pediatric ischemic stroke treatment recommendations are consistent across the three guidelines as summarized in the Table 1. Newborns with AIS without congenital heart disease rarely require antithrombotic treatment given their extremely low (<5%) risk of recurrent stroke. In children with AIS recurrence risk approaches 50% with no antithrombotic treatment. Therefore, antithrombotic treatment is required unless contraindicated. Anticoagulation (heparins, warfarin) is recommended for possible or established extra-cranial dissection and cardiogenic embolism. Antiplatelet treatment (aspirin, 2–5 mg/kg/day) is recommended for children with other underlying causes. For neonatal CSVT most centers provide initial anticoagulation in the absence of haemorrhagic contraindications, and if not, monitor for propagation. Children receive anticoagulation for CSVT more consistently, even in the presence of hemorrhagic venous infarction, modeling the approach in adult CSVT. While more studies are necessary, current treatment guidelines offer an interim option to maximize standardized care for pediatric stroke. Access to specialized care further supports decision-making in individual cases.
Paediatric stroke care

Specialized paediatric stroke care is recommended in all three sets of guidelines. The challenges for the clinician facing individual children with ischemic stroke cannot be adequately addressed with guidelines however detailed they are. Many children with ischaemic stroke fall between or overlap across the simple categories of etiologies, and each case presents unique challenges. These include a multiplicity of risk factors for stroke, and additional factors that increase the risks or benefits of a given treatment. One of the most effective interventions to improve outcome in adults with stroke has been the reorganization of services into specialist stroke services. Stroke units decrease morbidity and mortality from stroke (5). In contrast, stroke-specialized care is in its infancy and is only recently emerging as a subspecialty within paediatric neurology. Few paediatric stroke training programs exist, and at most centers stroke is still rare enough that extensive experience in managing newborns and children with stroke is uncommon. Given the importance of paediatric care for children with acute brain injury, especially those with complex paediatric illnesses, children with stroke under the age of 16–18 years of age should be managed in paediatric hospitals.

The development of paediatric stroke training and paediatric stroke clinical programs is necessary especially at larger paediatric centers where a critical mass of paediatric patients with stroke will be admitted. Meanwhile, most children require transfer to a centre with paediatric stroke experience. Other options to remotely access specialized advice including telestroke can be explored. However, there is limited experience with this approach and host institutions are increasingly reluctant to accept the risk of litigation associated with telephone advice (6).

Research considerations

While some consensus is now available for treatment of infants and children with ischaemic stroke, more treatment studies are urgently needed. It is important to recognize the rather flimsy nature of the evidence base for the majority of the recommendations, mainly dependant on consensus. Truly evidence-based treatment for paediatric stroke will rely heavily on future randomized controlled trials.

Is a randomized controlled study necessary for every candidate treatment in paediatric stroke?

Certainly, some strategies that are of proven benefit in adults can be selectively extrapolated into paediatric stroke care, including low-risk interventions based on an understanding of the pathophysiology of a subtype of paediatric stroke with a significant recurrence risk, for example antimicrobial or anti-inflammatory treatment for transient cerebral arteriopathy. However, with regard to antithrombotic treatments, the pathophysiology of the formation of occlusive thrombus that underlies paediatric arterial ischaemic stroke (AIS) and CSVT likely differs sufficiently from that in adult stroke that age-specific data are important. There are obvious and significant developmental differences in the coagulation, fibrinolytic, vascular and cerebrovascular systems. Risk factors causing stroke differ. For example atherosclerosis is not a cause for childhood AIS. The challenges of conducting clinical trials in paediatric stroke include the wide heterogeneity of paediatric stroke, relative rarity and consequent need for large numbers of centers to achieve adequate sample sizes, limited funding resources for paediatric stroke research.

As paediatric neurologists and haematologists link together in large collaborative groups the momentum, talent and sample sizes to design and conduct paediatric stroke studies is developing (7).

Conclusion

Paediatric stroke is emerging as an exciting new subspecialty and research in this area is at a rapidly emerging stage. The goal of developing evidence based treatments to reduce the adverse outcomes from paediatric stroke is closer than ever to becoming a reality.

Conflict or Interest

No conflict of interest to declare.

Tab. 1 Antithrombotic recommendations from paediatric stroke guidelines (1–3)

<table>
<thead>
<tr>
<th>subtype</th>
<th>acute treatment</th>
<th>chronic treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>neonatal AIS</td>
<td>general: none</td>
<td>cardiac: surgical connection</td>
</tr>
<tr>
<td></td>
<td>cardiac: ACT</td>
<td>cardias: if corrected, ASA, if not ACT</td>
</tr>
<tr>
<td>neonatal CSVT</td>
<td>no haemorrhage*: initial ACT (or, if no ACT monitor for subclinical propagation)</td>
<td>ACT duration 6 weeks if fully recanalized, otherwise 12 weeks</td>
</tr>
<tr>
<td></td>
<td>with haemorrhage: monitor for propagation, ACT if propagates</td>
<td>ACT duration 6 weeks if fully recanalized, otherwise 12 weeks</td>
</tr>
<tr>
<td>child AIS</td>
<td>general: ASA (or initial week ACT)</td>
<td>general: ASA long term</td>
</tr>
<tr>
<td></td>
<td>cardiac: ACT until corrected</td>
<td>cardiac: if corrected, ASA, if not ACT</td>
</tr>
<tr>
<td></td>
<td>dissection: ACT until artery normalizes or 3 months (intracranial dissection or with subarachnoid haemorrhage: APT)</td>
<td>dissection: &gt; 3 months ASA long term</td>
</tr>
<tr>
<td></td>
<td>severe prothrombotic Abn: ACT</td>
<td></td>
</tr>
<tr>
<td></td>
<td>recurrence on ASA: ACT</td>
<td></td>
</tr>
<tr>
<td>child CSVT</td>
<td>general: ACT</td>
<td>ACT duration 3 months if fully recanalized, otherwise 6 months</td>
</tr>
<tr>
<td></td>
<td>severe ICH: monitor for propagation then ACT</td>
<td></td>
</tr>
</tbody>
</table>

ACT: anticoagulation (heparin, warfarin, APT, antiplaquette (usually aspirin)), AICP: intracranial pressure; APT: antiplatelet (usually aspirin).

*ACCP recommends ACT, AHA no recommendation except ACT for propagation or thrombophilic disorders.
References

Correspondence to:
Dr. Gabrielle deVeber, M.H.Sc, M.D., FRCP(C)
Associate Professor, University of Toronto,
Director, Children’s Stroke Program
Division of Neurology, Hospital for Sick Children
Scientist, Child Health Evaluative Studies,
Hospital for Sick Children Research Institute
Tel. 416/813/77 21, Fax 416/813/63 34
E-mail: gabielle.dev@cogeco.ca,
gabrielle.deveber@sickkids.ca