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JOURNAL OF THE AMERICAN HEART ASSOCIATION

## **Urgent Clinical Challenges in Children With Ischemic Stroke: Analysis of 1065 Patients From the 1-800-NOCLOTS Pediatric Stroke Telephone Consultation Service**

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*Stroke* 2006;37;116-122; originally published online Dec 1, 2005;

DOI: 10.1161/01.STR.0000195044.44442.e0

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ISSN: 1524-4628

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# Urgent Clinical Challenges in Children With Ischemic Stroke

## Analysis of 1065 Patients From the 1-800-NOCLOTS Pediatric Stroke Telephone Consultation Service

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**Background and Purpose**—Clinical trials are lacking in pediatric stroke. As a result, physicians caring for children with stroke face significant challenges. The patient characteristics and specific nature of clinical challenges facing practicing clinicians can inform the design of and priorities for developing relevant clinical trials.

**Methods**—Physicians consulted the 1-800-NOCLOTS toll-free pediatric stroke telephone consultation service on children (birth to 18 years) with ischemic stroke. Pediatric neurologist or hematologists provided telephone consultation and documented caller and patient characteristics, antithrombotic treatments and callers' questions for entry into a computerized database. Children referred from January 1, 1995 to January 1, 2004, comprised the study cohort.

**Results**—Stroke consults were completed on 1065 children located predominantly in the United States (76%). Children had arterial ischemic stroke (AIS; 679; 64%) or cerebral sinovenous thrombosis (CSVT; 386; 36%) and were 54% male and 16% neonates. Risk factors and antithrombotic agents (none, aspirin, warfarin, and heparins) differed by stroke type. In 60% of patients, callers had not initiated antithrombotic therapy. Callers' questions for both stroke types usually concerned treatment selection (83%), but for AIS, questions more frequently ( $P < 0.0001$ ) concerned the selection and interpretation of etiological investigations.

**Conclusions**—Research is urgently needed in pediatric stroke to provide direction for management in “real-life” settings. Research efforts should address the unique challenges within different stroke types and include observational studies addressing investigation of the child with AIS. For AIS and CSVT, randomized controlled trials investigating the efficacy of antithrombotic treatment are urgently needed. (*Stroke*. 2006;37:116-122.)

**Key Words:** infants ■ child ■ sinus thrombosis ■ stroke, ischemic

Advances in the clinical recognition and radiographic diagnosis of pediatric arterial ischemic stroke (AIS) and cerebral sinovenous thrombosis (CSVT) have increased the frequency of these diagnoses. The lack of published clinical trials and a lack of experience in most institutions with large numbers of cases have resulted in significant challenges for clinicians who manage children with stroke. Only 1 randomized controlled trial (RCT) has been completed in childhood stroke: the STOP study of transfusion therapy in sickle cell disease. The clinician is thus forced to rely on anecdotal evidence or data obtained in adult trials in making clinical decisions when faced with children with stroke. Data from adult trials are not directly applicable to infants and children because of age-related differences in the coagulation, vascular, and neurological systems and major differences in the risk factors and outcomes from stroke.

The proven benefit of specialized care in adult stroke is attributable in part to the application of the “best available

evidence” to individual stroke patients by caregivers with expertise in stroke.<sup>1,2</sup> In adults, the use of “telestroke” consultation linking front-line physicians to physicians with stroke expertise has proven to be beneficial.<sup>3,4</sup> The 1-800-NOCLOTS pediatric stroke telephone consultation service was initiated in 1994 with 3 goals: first, to provide free telephone consultation to physicians requesting advice on the management of children with stroke based on the “best available evidence”; second, to document the patient characteristics and most urgent questions facing these physicians; and third, to make these data available for planning future clinical trials in pediatric stroke.

## Methods

### Study Design and Participants

This study involved prospective data collection on a consecutive referred sample of children with ischemic stroke in North America

Received May 18, 2005; final revision received August 16, 2005; accepted August 25, 2005.

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Stroke is available at <http://www.strokeaha.org>

DOI: 10.1161/01.STR.0000195044.44442.e0

and internationally. Children referred to the 1-800-NOCLOTS pediatric stroke telephone consultation service between January 1, 1995, and January 1, 2004, were included.

### Telephone Consultation Methods

The 1-800-NOCLOTS line is a toll-free (for North America) physician consultation service available 24 hours per day. Beginning in 1994, the availability of the 1-800-NOCLOTS service was announced at international scientific conferences and in published childhood stroke treatment protocols.<sup>5</sup> Pediatric hematologists, neurologists, and other specialists throughout North America and previously caring for children (birth to 18 years) with ischemic stroke requested consultation via the 1-800-NOCLOTS service. The pediatric stroke telephone consultation service operated in parallel with a service for children with noncerebral thrombosis reported previously.<sup>6</sup>

Physicians accessing the 1-800-NOCLOTS line accepted a recorded legal disclaimer to reach the answering service. The answering service paged the appropriate physician ("responder") with the caller's name and contact telephone number. The responding physician made telephone contact with the calling physician within minutes or hours of the consult, discussed the patient, and provided relevant information from published and ongoing research studies and from institutional experience managing several hundred children with stroke. During 1995 to 1998 and 2001 to 2004, the initial responder was a pediatric neurologist (G.d.) who consulted with the on-call pediatric hematologist for complex thrombosis issues. During 1998 to 2001, the initial responder was 1 pediatric hematologist (M. Andrew) who consulted with the pediatric neurologist (G.d.) as needed.

### Investigation and Treatment Protocols

Annually updated and published protocols for the investigation and management of pediatric stroke<sup>5</sup> were followed and provided to calling physicians along with reprints of pertinent published studies. These "best practices protocols" were developed and published by the authors as a reasonable approach to the management of pediatric stroke patients in the absence of RCTs.

### Data Collection

For each call, the physician responders entered data onto standardized data sheets, including date, caller surname, subspecialty, and institution, patient location, stroke type (AIS or CSVT), age, gender, risk factors (cardiac, other systemic diseases, acute illnesses, vasculopathies, and prothrombotic states), radiographic diagnostic method (computerized tomography [CT], magnetic resonance imaging [MRI], CT venography [CTV], magnetic resonance venography [MRV], and vascular imaging consisting of magnetic resonance angiography [MRA] or conventional angiogram), vascular territory of stroke, therapy initiated by caller (none, aspirin, anticoagulant, or other), caller questions (investigations, treatment, other), and investigations or antithrombotic treatment options presented to the caller. Stroke type was defined as AIS if the onset was sudden, and CT or MRI showed a lesion with characteristics of arterial infarction within a known cerebral artery territory consistent in location and age with the clinical presentation. CSVT required clear visualization of thrombosis within dural sinuses or veins on MRI, CTV, or MRV. Children with unclassifiable radiographic lesions or primary cerebral hemorrhage not associated with AIS or CSVT were excluded. Infants with hemiparesis noted later in infancy and subsequent imaging showing a remote AIS were classified as having "presumed prenatal or perinatal AIS," as defined previously.<sup>7</sup> Risk factors were classified as: congenital heart disease, chronic diseases (renal or autoimmune disease, leukemia, brain tumor, or other), acute illnesses (sepsis, localized infection, dehydration, trauma, or other), vasculopathies, prothrombotic states (laboratory defined or L-asparaginase or oral contraceptive treatment), other, and unknown.

No identifiable patient data (name, initials, birth date, and contact information) were recorded. No patient-specific outcomes were pursued because patient identifiers were not obtained. Research

assistants entered these data into a computerized database (Microsoft Access). The host institutions, Hospital for Sick Children (Toronto, Canada), Children's Hospital at Chedoke McMaster (Hamilton, Canada), and Stollery Children's Hospital (Edmonton, Canada), supplied funding for the operation of the 1-800 service, including telephone service and long distance charges, pagers, and administrative staff. The database was funded by Baxter BioScience of California. The physician responders volunteered their time.

### Statistical Analysis

Descriptive and univariate analyses were planned to compare major patient characteristics and caller questions between stroke types and risk factors and antithrombotic therapies between neonates (<1 month of age) and older infants and children (1 month to 18 years of age). We used the Mann-Whitney statistic for age comparison and Fisher's exact test for comparison of categorical variables (gender, risk factors, antithrombotic treatments, and caller questions). Instat 3 statistical software version 3.0a for Macintosh (Graphpad) was used.  $P < 0.05$  was considered statistically significant.

### Results

During the study 718 physicians placed 1131 stroke calls to 1-800-NOCLOTS on 1113 children. Multiple calls were placed by 203 physicians. The number of calls averaged 122 per year. Callers included pediatric hematologists (72%), neurologists (15%), neonatologists (4%), general pediatricians (2%), pediatric intensivists (2%), cardiologists (1%), and others. We removed 48 children from the analysis who had no ischemic stroke ( $n=25$ ) or cerebral infarction that could not be classified as AIS or CSVT ( $n=23$ ). For the remaining 1065 children with confirmed ischemic stroke, age, gender, risk factors, and initiated antithrombotic treatments are summarized below and in Table 1.

### Patient Characteristics

#### Geographic Location

The 1065 children were located primarily in the United States (76%) and Canada (14%), Europe, Australia/New Zealand, and South America. The 859 US-based patients were distributed in the Northeast (27%), Midwest (23%), West (16%), and South (34%) regions.

#### Stroke Type, Timing, and Associated Thromboses

There were 679 children with AIS and 386 with CSVT. These index events occurred within 7 days preceding the call in >90% of children. However, 27 infants had a presumed prenatal or perinatal AIS. At the time of the index AIS or CSVT, 94 (8.6%) children had concurrent thromboses within systemic arterial (21), systemic venous (62), or intracardiac (18) locations. In 102 (10%) children, the index AIS or CSVT events represented recurrent thromboses. These 102 children included 1 neonate, 13% of older children with AIS, and 7% of children with CSVT. The preceding thromboses were within cerebral (92 children) or systemic (5) locations.

#### Age and Gender

The median age at stroke was 6.2 years and was similar across stroke types. The most frequently affected age group was birth to 3 years of age (Figure). Neonates comprised 16% of patients and were more frequent in CSVT (23%) than AIS (12%;  $P < 0.0001$ ) stroke types. Gender was male in 54%.

**TABLE 1. Patient Characteristics**

Characteristic	Categories	All n=1065	AIS n=679	CSVT n=386	AIS vs CSVT Fisher's P Value
Age	Mean (SD)	6.2 (5.66)	6.1 (5.56)	6.4 (6.28)	Mann-Whitney 0.65
	Neonates n (%)	170 (16)	83 (12)	87 (23)	<0.0001
Gender n (%)	Male	536	345	191	0.70
	Female	456	289	167	
Risk factors n (%)	None	281 (26)	191 (28)	90 (23)	0.096
	Cardiac*	115 (11)	102 (15)	13 (3)	<0.0001
	Chronic disease	256 (24)	142 (21)	114 (30)	<0.01
	Acute illness	293 (28)	136 (20)	157 (41)	<0.001
	Vasculopathy*	...	93 (60)	...	
	Prothrombotic disorder†	218 (64)	157 (66)	61 (62)	0.53
Treatments before call n (%)	None	637 (60)	402 (59)	235 (61)	
	Aspirin	120 (11)	116 (17)	4	
	UFH	112 (10)	65 (10)	47 (12)	0.21
	LMWH	159 (15)	82 (12)	77 (20)	<0.01
	Warfarin	69 (6)	48 (7)	21 (5)	0.36
	TPA	5	0	5	

\*Includes 156 older children with AIS with vascular testing results available; †includes 338 children with prothrombotic laboratory testing results available.

UFH indicates unfractionated heparin; tPA, tissue plasminogen activator.

### Diagnostic Tests

The radiographic test diagnosing AIS or CSVT was documented in 573 and 364 patients, respectively. AIS was confirmed with MRI in 79% and CT alone in the remainder. CSVT was confirmed with MRI or MRV in 320 (88%) of children and CT and CTV alone in 39 (11%).

### Vascular Territory

The location of the infarct or thrombosis was available in 400 children. AIS infarcts were within the internal carotid artery territory in 329 (82%), vertebrobasilar territory in 50 (13%), and both in 21 (5%). Infarcts were left-sided in 48%, right in 40%, and bilateral in 12%. In children with CSVT, the thrombosis was within the superficial system in 167 (78%), the deep system in 33 (11%), and both in 11 children.<sup>8</sup> Thrombosis was within retinal (7) or internal jugular (5) veins in the remainder.

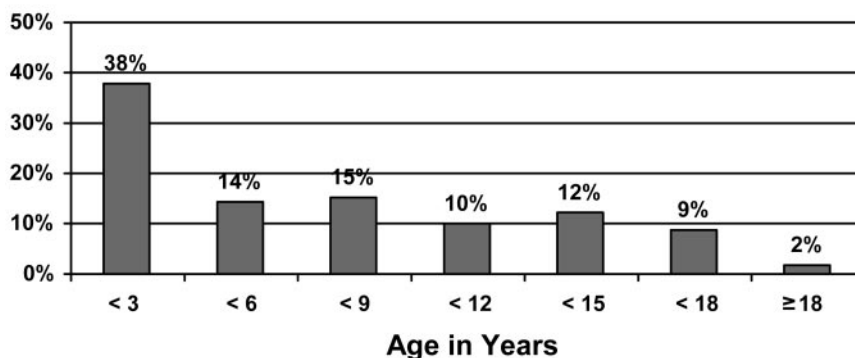
### Risk Factors

In 281 (26%) children, no risk factors were defined. In the remaining children, risk factors were multiple in 46% with AIS and 39% with CSVT. Risk factors were more frequently defined in older infants and children compared with neonates ( $P=0.01$ ; relative risk [RR], 1.49; CI, 1.1 to 1.9) and in children with CSVT compared with children with AIS ( $P=0.09$ ; RR, 1.1; CI, 0.99 to 1.2). Risk factors, summarized in Table 1, included cardiac disorders in 115 (11%) children, other chronic diseases in 256 (24%), acute illnesses in 293 (28%), vasculopathy in 60% of children with AIS, and prothrombotic disorders in 218 (64%).

### Cardiac Disorders

Echocardiography in 189 children (28 with CSVT and 161 with AIS) was normal in 39%. Cardiac disorders were present in 115 children (9% of neonates and 28% of older) and

## Age Groups Pediatric Stroke



Age distribution of 1065 children with ischemic stroke about whom physicians contacted the 1-800-NOCLOTS pediatric stroke telephone consultation service. Children <3 years of age predominated, and 16% of all patients were newborns.

included structural congenital heart disease in 85 children, in whom stroke was related to surgery or catheterization in 32 (38%). Isolated patent foramen ovale was present in 10 additional older children with AIS. Acquired heart disease was present in 20 children and included endocarditis, arrhythmia, cardiomyopathy, and intracardiac thrombus. Cardiac disorders were more frequent with AIS than with CSVT ( $P<0.0001$ ).

#### Other Chronic Diseases

There were 343 chronic diseases identified in 256 (24%) children (22 of 170 neonates and 227 of 824 older children). In neonates, these included chronic maternal diseases (7), other chronic prenatal conditions (3), or genetic syndromes (4). In older infants and children, they included malignancy (96), genetic syndromes (Down's in 15 and other in 24), hematological disorders (29), chronic infection (3), and hypertension (3). Additional chronic diseases involved head and neck structures (9), connective tissue (12), and endocrine (12), liver (6), gastrointestinal (5), or pulmonary (1) systems. Hematological conditions included sickle cell disease or trait (18), other anemias (5) and others (6). Systemic diseases were more frequent among children with CSVT ( $P<0.01$ ).

#### Acute Illnesses

There were 308 acute illnesses in 293 (28%) children consisting of infection (90), surgery (58), dehydration (57), trauma (49), perinatal complications (31), hypoxic-ischemic insults (12), hematological disorders (3), and other acute illnesses (8). Neonates had acute illnesses more frequently than older infants and children ( $P<0.0001$ ; RR, 2.1; CI, 1.65 to 2.82), especially dehydration (17% versus 2%) and hypoxic-ischemic injury (5% versus <1%). However, older infants and children were more likely than neonates to have trauma (29% versus 3%) or head and neck infections (5% versus <1%). Perinatal complications in 31 neonates included maternal eclampsia (2), complicated delivery (11), meconium aspiration syndrome (7), neonatal respiratory distress syndrome (6), and others. Acute illnesses were more frequent in children with CSVT than with AIS ( $P<0.01$ ).

#### Prothrombotic Disorders

Laboratory testing results were available in 338 children (239 with AIS and 99 with CSVT), of whom 218 (64%) had laboratory-defined prothrombotic disorders. Factor V Leiden or activated protein C resistance were present in 81 children (24%) and antiphospholipid antibodies in 42 children (12%); elevated anticardiolipin antibodies in 35, lupus anticoagulant in 3, and unspecified in 5). The frequency of prothrombotic risk factors was similar for both stroke types and neonates (65%) and older children (66%). In addition, a family history of thrombotic events was present in 118 (14% of 815 with data) and prothrombotic medications in 48 (5%; asparaginase in 40; oral contraceptives in 8).

#### Vasculopathy

Vascular imaging in 156 children >1 year of age with AIS was abnormal in 93 (60%). Vasculopathies consisted of dissection (32), moyamoya (24), postvaricella angiopathy (18), vasculitis (12), other defined vasculopathies (2), and idiopathic vasculopathy (5).

**TABLE 2. Caller Questions**

Question Category	All n=1015	AIS n=649	CSVT n=366	AIS vs CSVT
Etiology and investigations	135 (13)	107 (16)	28 (8)	0.0001
Treatment advice	848 (84)	514 (79)	334 (91)	
Both	29 (3)	25 (4)	4	

#### Therapy Initiated By Caller

No antithrombotic therapy had been initiated in 60% of patients at the time of the call (Table 1). Neonates were more likely than older children to have no therapy initiated ( $P<0.001$ ; RR, 2.1; CI, 1.5 to 2.9). Aspirin (acetylsalicylic acid [ASA]) was initiated in 17% of AIS patients. Unfractionated heparin (10%) and warfarin (6%) were used at similar frequencies across stroke types, but low molecular-weight heparin (LMWH) was more frequent in children with CSVT than AIS ( $P<0.01$ ). Five children with CSVT and none with AIS had received tissue plasminogen activator.

#### Caller Questions and 1-800-NOCLOTS Responses

##### Caller Questions

Callers requested advice primarily regarding etiology and investigations (13%) or antithrombotic treatment (83%; Table 2). Questions regarding possible etiologies and investigations were twice as common in children with AIS (16%) compared with CSVT (8%;  $P=0.0001$ ) and were similar in neonates and children. Questions regarding antithrombotic treatment were frequent in both stroke types and were classified as general in 569 children or focused on antithrombotic treatment type (51), duration (93), or safety (71). Advice regarding lytic therapy was requested in 47 children (23 with AIS and 24 with CSVT).

##### 1-800-NOCLOTS Physician Responses

During each consultation, the responders provided general and individualized information regarding investigation and treatment options (Tables 3 and 4) based on published stroke protocols.<sup>5</sup> In all cases, the selection of final management strategies for individual children was left to the discretion of

**TABLE 3. 1-800-NOCLOTS Responses: Management Options**

Responses to Caller Questions	All n=973	AIS n=633	CSVT n=340
No change	88 (9)	55 (9)	33 (10)
No therapy	21 (2)	16 (3)	5 (1)
No tPA	45 (5)	23 (4)	22 (6)
Start/add therapy	288 (30)	182 (29)	106 (31)
Stop therapy	39 (4)	24 (4)	15 (4)
Change therapy type or dose	62 (6)	46 (7)	16 (5)
Duration therapy	102 (10)	56 (9)	46 (14)
Investigation	329 (34)	260 (41)	69 (20)
Etiology suggested	19 (2)	18 (3)	1
Therapy pending investigations	83 (9)	54 (9)	29 (9)
Other	47 (5)	24 (4)	23 (7)
Total	1123	758	365

tPA indicates tissue plasminogen activator.

**TABLE 4. 1-800-NOCLOTS Responses: Antithrombotic Treatments**

Medication Type	ALL n=1018	AIS n=644	CSVT n=374
No medication	275 (27)	189 (29)	86 (23)
Aspirin	127 (13)	127 (20)	0
UFH	71 (7)	37 (6)	34 (9)
LMWH	444 (44)	232 (36)	212 (57)
Warfarin	104 (10)	56 (9)	48 (13)
tPA	4	2	2
Plavix	1	1	0
Type unspecified	52 (5)	24 (4)	28 (8)

UFH indicates unfractionated heparin; tPA, tissue plasminogen activator.

the calling physician based on their preference, comfort level, and results of pending investigations.

Further investigations discussed in 260 children included MRI (67), cardiac echo (58), prothrombotic tests (38) conventional angiogram (27), and others. Responses to treatment questions included no antithrombotic agents in 275 (27%) children, including children with intracranial hemorrhage, and 70% of neonates with AIS based on a negligible risk of recurrent stroke.<sup>9,10</sup> In 396 patients, the initiation of antithrombotic agents or modification of treatment type, dose, duration, or monitoring was discussed.<sup>5</sup> In children with AIS, either initial ASA, or in children with possible or confirmed dissection, cardiac embolism or major prothrombotic disorders, initial LMWH followed by ASA or warfarin were suggested. In 18 children, either treatment of persistent intracranial hypertension in CSVT or revascularization surgery in moyamoya was discussed. In 43 children, the 1800 physicians consulted with other specialists (neurosurgeons, rheumatologists, and adult stroke neurologists) and recontacted the caller.

## Discussion

Our study represents the first systematic use of a stroke telephone consultation service for children. We provide data on the largest number of children with ischemic stroke reported to date and the most significant clinical challenges facing physicians managing children with stroke in "real world" settings, which consisted of determining treatments and etiological investigations.

Antithrombotic treatments were initiated in only 40% of children at the time of consultation, and in 83% of calls, questions regarded treatment. These findings emphasize the major uncertainty of clinicians managing children with stroke in the absence of RCT evidence and the desire for specialized input on treatment decision. The selection of etiological investigations was the second major category of caller questions in our study. Defining the risk factors underlying pediatric AIS and CSVT in individual cases is important because it influences treatment selection. The basic mechanisms of thrombosis underlying AIS likely differ in children with cardiac, vasculopathic, and prothrombotic conditions.<sup>11,12</sup> The majority of calls were made at the time of initial diagnosis of stroke reflecting the real-life situation in which treatment decisions must frequently be made before

the availability of all etiological results. In our study, there was an emphasis on etiology and investigation questions in children with AIS compared with CSVT. This reflects an increased complexity of etiological investigations in AIS, including the need for selective cardiac testing and cerebral angiography. In CSVT, clinically evident acute illnesses or chronic systemic diseases comprised the major risk factors. Prothrombotic disorders were prominent among children tested; however, they may have been transient because they were assessed in the acute phase in most children.<sup>13–15</sup> The presence of diverse etiologies in childhood stroke reinforces the need for more research on the basic mechanisms of vascular occlusion in pediatric stroke conditions to guide selection of appropriate therapies targeting platelet, coagulation, and other systems for RCT studies.

The 1-800-NOCLOTS stroke consultation system represents the first systematic use of a stroke telephone consultation service for children. In adults, "telestroke" consultation has effectively linked geographically remote treating physicians and stroke specialists.<sup>16</sup> Videolinkage of the clinical and imaging findings enhances patient selection for tissue plasminogen activator.<sup>3</sup> Simple telephone consultation is also a successful method of telestroke care delivery<sup>4</sup> that is safe, effective, convenient, and cost-effective.<sup>17</sup> Both methods yield "expertise gained by healthcare professionals through the interaction with a remote expert."<sup>16</sup> During our study, the 1-800-NOCLOTS pediatric stroke consultation system provided continuous free and rapid access to pediatric neurologist and hematologists, with a combined perspective on cerebral thrombosis. In the absence of clinical trials, the 1-800-NOCLOTS physicians could not provide truly evidence-based recommendations. Patient-specific support was provided through the application of annually updated published pediatric stroke protocols. These were based on clinical and research experience with large numbers of children with stroke,<sup>8,9,13,18–23</sup> the selective extrapolation of evidence-based treatments for adult stroke, and emerging data from cohort and case-control pediatric stroke studies clarifying potential risk factors,<sup>7–9,11–15,19,20–22,24,25</sup> risks for recurrent stroke,<sup>7–12,18,22</sup> and safety and dosing guidelines for antithrombotic treatments in children with stroke.<sup>5,23,26–33</sup> Although pediatric stroke guidelines can support clinicians, they are based on limited data, and RCTs are urgently needed to achieve truly evidence-based guidelines.<sup>34</sup>

Our study was neither funded nor designed as an epidemiological or outcome study. No outcomes were obtained, nor were they required to meet the major study objectives: to provide expertise for requesting physicians and determine clinical questions and patient characteristics presenting the greatest challenges in pediatric stroke. Our study population is unlikely to be representative of all children with stroke because it was a referred sample. During the final 7 years of the study, we received calls on 859 children in the United States. Based on population statistics for 2000 and an incidence for ischemic stroke of 2 per 100 000 children per year including neonates, we estimate that our study population represented  $\approx 7.5\%$  of children with incident strokes in the United States. The majority of callers in this study were pediatric hematologists who were consulted on the study patients by pediatric neurologists or neonatologists. Because

a pediatric hematologist (M. Andrew) initiated the 1-800-NOCLOTS service, awareness of the service was likely increased among pediatric hematologists. Despite these potential referral biases, the characteristics of these 1065 children facing physicians in real-world settings can inform the planning of research studies, including identifying children who present the greatest clinical challenges. Among patients referred for advice, we found that neonates were the most frequently affected age group, consistent with their increased risk for ischemic stroke.<sup>8,9</sup> We also noted recurrence or extensions of thrombosis in 10% of children emphasizing the need for more effective antithrombotic strategies in children with thrombotic events.

### Summary

Data from “real world” clinical settings are necessary for the design of relevant clinical trials. For clinicians managing children with stroke, the increasing numbers of children with this diagnosis and lack of evidence on which to base treatment result in specific clinical challenges that inform research priorities and clinical trial design in this field.

Analysis of the 1065 children referred to the 1-800-NOCLOTS stroke telephone consultation service provides relevant data on the characteristics of children with ischemic stroke and the management challenges facing their physicians. Future pediatric stroke research studies clearly need to evaluate neonates separately from older infants and children and AIS separately from CSVT. For pediatric AIS, the clarification of etiological investigations is a research priority that can be addressed with cohort and case-control studies. However, for pediatric AIS and CSVT, basic research on thrombotic mechanisms in various etiologies and RCTs is urgently needed.

### Acknowledgments

S.K. is a recipient of the Baxter BioScience pediatric hemostasis fellowship 2002/2003 at the Hospital for Sick Children, Toronto. L.M. was supported as a scholar of the Canadian Institutes of Health Research. G.d. is supported by a Research Scholarship from the Heart and Stroke Foundation of Canada. As stated in the manuscript, the operation of the 1-800 service, including telephone service and long distance charges, pagers, and administrative staff was funded by the host institutions: Hospital for Sick Children (Toronto, Canada), Children’s Hospital at Chedoke McMaster (Hamilton, Canada), and Stollery Children’s Hospital (Edmonton, Canada). The 1-800 database was funded by Baxter BioScience, California. We are indebted to Kim Lucid for administrative assistance with data entry and telephone triage. The 1-800-NOCLOTS service, initiated by M. Andrew in 1994, was the culmination of a career devoted to the care of children with thrombosis with the ultimate goal of making a difference in children’s lives. M. Andrew died unexpectedly August 28, 2001, leaving a permanent void. During the final 5 years of her life, she received >5000 calls, with a mean duration of 15 minutes, devoting many hours to the 1800 service. On behalf of the physicians and children who have benefited from this pioneering approach, the authors respectfully dedicate this article to her memory.

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