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Protocols and Guidelines for Stroke in Children: Point and Counterpoint

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Cerebrovascular diseases create a heavy burden of disease in children with consequences that last a lifetime.[1] Perinatal stroke causes most hemiparetic cerebral palsy with additional nonmotor consequences affecting diverse aspects of development and quality of life.[2] Stroke during childhood is also associated with broad neurodevelopmental disabilities and morbidity. Among a myriad of potential pathophysiologic mechanisms, few are directly treatable, and prevention strategies are the exception rather than the rule.[3,4] The ability of clinicians to recognize and manage children with stroke toward optimal outcomes are currently hindered by many factors including delayed diagnosis, limited understanding of disease mechanisms, and treatment strategies predominantly based on the theory and extrapolation from adult stroke rather than original evidence.

In an effort to address these difficult clinical challenges, multiple guidelines and protocols have emerged over the past 20 years. Comprehensive early guidelines from a UK working group have recently been updated.[5] The original American Heart Association pediatric stroke guideline of 2008[6] is now being revised as a scientific statement. The chest guidelines for antithrombotic therapy in children remain highly relevant.[7] Pediatric content has also been increasingly included in leading content-specific adult stroke guidelines including the American Heart Association and Canadian Stroke Best Practices Guidelines.[8] More focused guidelines for acute stroke management in children were recently developed in Australia.[9] An approach to acute neonatal stroke has been suggested in European guidelines.[10,11] Progress in specific elements of pediatric stroke care has also facilitated protocol development within institutions and across investigational groups, most notably the creation of acute care pediatric stroke centers stemming from the first thrombolysis trial in children.[12,13]

Although the issues identified within these protocols and guidelines are highly overlapping, the relative priority placed on different elements varies widely. Additional discrepancy exists between the recommendations provided by the different guidelines. These have been discussed and contrasted in the past,[14] but a lack of clarity remains.

Where does this leave the clinician caring for a child with stroke? The reasons for and against the protocolized approach to

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pediatric stroke were recently debated at a special gathering of international pediatric stroke experts in April 2018. The arguments made are reviewed here followed by suggestions of the balance that might exist between them, both currently and toward improved management and outcomes for affected children in the future.

Question

Do protocols improve the diagnosis, management, and outcomes of children with stroke?

Arguments for the protocolized approach to pediatric stroke

There is little doubt that protocolized medicine has improved outcomes in adult stroke. Such compliance appears to beget further compliance, potentially amplifying effects over time.[15] Broad implementation of stroke center certification and "Get With the Guidelines" initiatives serve as a tangible example of how effective the development of guideline and systematic implementation can be in stroke. There are many different metrics by which this can be measured, but the simplest outcomes may best demonstrate the positive effects. The degree of compliance of a stroke center with established guidelines has been repeatedly shown to improve numerous measurable outcomes including lower levels of disability and mortality.[16] One original study of the first million patients within the Get With the Guidelines program quantified large effects on broad outcomes including mortality, length of stay, and chances of discharge home with cumulative effects increasing over time.[17]

Such convincing demonstration of benefit in adult stroke creates a compelling rationale for applying the same approach in pediatric stroke. As outlined previously, a varied combination of pediatric stroke guidelines has been developed from multiple nations and organizations, some spanning most aspects of stroke care, others being more specific. What they share in common, and generally acknowledged in a similar fashion, is a relative lack of evidence to strongly support most recommendations. With this reality to consider, the value of such guidelines becomes all that much greater. Clinicians caring for children with stroke, whether they are expert or novice, cannot turn to readily available high-powered randomized trials to tell them what to do. Instead, they require a reasoned consideration of the available evidence interpreted by experienced professionals who can in turn offer the balanced consideration of the relative risks and benefits required to make good clinical decisions. This decision making is the most tangible and immediate benefit of having pediatric stroke guidelines.

Incorporation of pediatric elements into existing adult guidelines provides further potential benefit.[8] The value of having adult experts in critical areas of stroke care liaise with their pediatric colleagues to expand such protocols is potentially powerful. Whether adding pediatric considerations alongside each specific issue within such protocols brings the same benefit to children with stroke is not proven but seems a reasonable assumption. The many challenges of performing larger scale cohort studies and clinical trials in children need to be considered (see subsequently); simply demanding the same powerful evidence in populations where it cannot be obtained is not a strong counter argument to the benefit of such guidelines.

Perhaps the most demonstrable benefit today of protocol development in pediatric stroke is the emergence of the pediatric stroke center.[13] This initiative grew from the Thrombolysis in Pediatric Stroke trial, a multicentre dose-escalation study of tissue plasminogen activator for acute childhood stroke.[12] Although the trial was stopped early because of lack of recruitment, it succeeded in establishing 25 acute pediatric stroke centers in North America. Although clearly modeled on adult stroke, pediatric-specific issues were carefully identified and considered. The resulting development of acute care algorithms alone has likely tackled some of the largest issues in childhood stroke including the delay to diagnosis and options for emergency recanalization.[18] The result is the establishment of critical pathways for emergency pediatric stroke management, achieved with expert consensus and extrapolation of relevant adult evidence and not the clinical trials or large-scale studies that may never be possible in pediatric stroke. Similar utility can occur in other elements of stroke care, including neuroimaging and rehabilitation. With the vast majority of tertiary pediatric centers globally lacking access to a pediatric stroke expert, the value of such guidelines to patient care should not be underestimated.

Where pediatric guidelines may be most relevant, given the current evidence base, is to highlight the important differences between children and adults, possibly advising *against* the direct application of adult recommendations in the pediatric population where they may not apply or even be contraindicated. That the presentations, risk factors, outcomes, and recovery mechanisms differ between children and adults are few facts that are well established and should be respected with consideration that adult protocols may not apply. For example, giving tissue plasminogen activator to a child with moyamoya syndrome presenting with stroke secondary to dehydration and hypoperfusion or discharging a child without atherosclerotic disease or hyperlipidemia on statins "per protocol" are approaches that are likely of little or no benefit and even potentially harmful. In the emergency setting, the assumption that children are suffering from "little adult" strokes, when they are not, could also be dangerous. Adult guidelines cannot serve as "default pathways," and pediatric guidelines are required to guide all elements of management from the specific perspective of the child with stroke.

Arguments against the protocolized approach to pediatric stroke

The primary reason that adult stroke protocols have been able to impact patient outcomes is the strong evidence base on which they rest. Carefully designed, fully powered, randomized, controlled trials and other rigorous methods continue to address more and more specific questions. Many of the most fundamental and common questions have been answered to a high degree of certainty. Often, these same questions are relevant in the pediatric stroke world where the stark difference in knowledge and evidence is immediately apparent. Two examples are noted here—choice of antithrombotic therapies and acute recanalization—as well as a third that is relatively unique to pediatric stroke—focal cerebral arteriopathy (FCA).

Much debate has circled around which antithrombotic approach should be applied in children with arterial ischemic stroke. Remarkably, early studies found that many children around the world were receiving no such treatment and retrospective evidence suggested an association with higher recurrence rates.[19] Accordingly, antithrombotic medication became a leading priority in early guidelines where, despite agreed on importance, the recommendations were inconsistent.[14] A similar lack of consistency in neonatal and childhood cerebral sinovenous thrombosis is apparent globally.[20] In fact, considering there were only three original guidelines and two fundamental choices for arterial stroke (antiplatelet versus anticoagulation), the lack of agreement was striking.[21] More than anything, this reflects the lack of evidence; no one really knew the answers and the experts were left with theory to back their recommendations. For example, many protocols argued for starting anticoagulation in children with dissection, based at the time on mostly theory from the young adult stroke world where disease pathogenesis is likely similar. More recent

evidence from a randomized trial has now shown no difference in recurrence rates between antiplatelet and anticoagulation strategies.[22] With a reasonable answer in place, whether this has changed pediatric stroke practice remains to be seen.

A second issue is acute thrombolysis and recanalization, where high-level evidence has revolutionized adult stroke care in recent years.[23] With clear clinical and imaging criteria, the ability to quickly and accurately select patients eligible for potential benefits with very large effect sizes is now reality. In contrast, evidence for both chemical thrombolysis and mechanical interventions is barely more than anecdotal in children.[12,24] This evidence remains the state of affairs despite large efforts to acquire even preliminary data toward establishing the safety of thrombolysis in childhood stroke.[12] In spite of virtually no pediatric-specific evidence, protocols have been published suggesting how such approaches might be undertaken.[25] Although the development of such protocols within trials brings clear benefits (see subsequently), there is also a danger that the uninitiated nonexpert (present at the vast majority of centers encountering children with acute stroke) could mistake such protocols for evidence of safety or efficacy as would be reflected in similar versions in adults where the levels of evidence are completely different and, in most ways, are not comparable.

Some of the largest challenges in pediatric stroke remain virtually unaddressed by published guidelines. FCA is a leading cause of childhood arterial ischemic stroke, where associated clinical and investigational factors have led many to believe an inflammatory mechanism is the primary pathology. With a known high risk of rapid progression, stroke recurrence, and poor outcome, improved acute treatments are a leading priority in childhood stroke.[18] The use of acute corticosteroids is therefore a commonly considered (and hotly debated) topic, now leading to the development of two clinical trials, although these remain in development. In the interim, decision options remain limited to clinical reasoning and theory without even an adult correlate from which to extrapolate. Some would argue that the high risk situation with a highly suspect inflammatory mechanism and evidence that short course steroids have low risk of serious adverse events and do not worsen outcomes from adult stroke favors treatment. Despite such logic being explainable in a few sentences, the current largest pediatric stroke guidelines make no mention of the use of steroids in FCA. The lone exception is the Australian acute care guidelines, where the issue is acknowledged but no recommendations are made. The inability of so many guidelines to inform decision making for the most common and difficult scenarios of childhood stroke points clearly to their limited utility.

Additional limitations of protocolized medicine in pediatric stroke must also be considered. Most protocols are full of commonsense recommendations that are not particularly helpful. To say that a child with an unexplained arterial stroke should have an echocardiogram to look for heart disease could be surmised by the average medical student. Guidelines are difficult to keep current, with even the most recent versions lacking emerging evidence such as the role of thrombophilia testing in perinatal stroke.[26] Adopting a checklist mentality can also steer practitioners away from good clinical reasoning; a robotic, formulary approach to a complex problem like childhood stroke brings a risk of incorrect choices and potential harm.

Finally, two very important perspectives suggest that current pediatric stroke guidelines are missing the mark. First, in the age of patient and family centered care and research, input from families into the generation of guidelines has been minimal. Simple counseling of parents may have a major impact on long-term outcomes for the entire family,[11,27] yet such easy and economical recommendations are barely addressed. Second, the health care professionals most in need of guidance for the recognition and management of children with stroke have also been minimally involved in the development of guideline. Appropriately, they have begun to speak out, with some clearly articulating the relative shortcomings (if not overt failures) of the current guidelines to actually improve the care of patients in real clinical settings.[28]

Summary

Several things are clear regarding the role of guidelines and protocols in the care of children with stroke. Current guidelines lack evidence, and the strong evidence supporting adult guidelines is often not applicable in childhood stroke. There is no reasonable expectation that childhood stroke will acquire comparable levels of evidence to that found in adults for most major clinical decisions. These realities, however, should not preclude continuous efforts to improve and expand pediatric stroke knowledge, the clinical translation of which benefits from the use of protocols and guidelines.

To highlight that the direct application of adult guidelines to children may be inappropriate is in itself an important rationale toward optimizing the development and dissemination of pediatric stroke guidelines. Avoiding potential misapplication of adult protocols in emergency settings or where pediatric stroke expertise is limited is an important objective. The development of guideline may also help identify the most relevant clinical questions for further study. There are other routes to evidence generation besides randomized controlled trials. However, adult “Get with the guidelines registry” numbers over a million whereas the International Pediatric Stroke Study registry has only limited thousands so different approaches are required.

One example highlighting the need to not blindly apply evidence from adult stroke to children also demonstrates potential opportunities for new approaches to clinical research in pediatric stroke. The question of the initial antithrombotic treatment (aspirin versus heparin) for children with stroke is unanswered, continually debated, and inconsistently addressed in existing guidelines. In adults, evidence from the now venerable International Stroke Trial and others[29] showed that the potential benefit of heparin in prevention of progression or recurrence of stroke was offset by potential harm from increased hemorrhage. Although this precluded the routine use of initial anticoagulation in adult stroke, selective interpretation of segments of the evidence generated was used to suggest the opposite approach may be warranted in children.

Whether such extrapolated evidence is better than no evidence contributes to ongoing controversy. There remains clear clinical equipoise for the use of anticoagulation versus antiplatelet agents for the initial treatment of stroke in children with practice heterogeneity well documented across the world.[21] Similar equipoise exists for acute management strategies including steroids for FCA and endovascular therapies. With randomized trial feasibility extremely limited by many factors, comparative effectiveness or “natural experiment” approaches may provide an alternative. Protocols and guidelines may facilitate this, allowing pediatric stroke centers and even less experienced sites, to subscribe to specific practice patterns that could then be compared with estimate safety and efficacy of specific interventions. Only with such informed pragmatic approaches may the best practices of pediatric stroke care be defined.

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