Sickle Cell Anemia (SCA)

Background:

Transcranial Doppler (TCD) is used to detect children with sickle cell anemia (SCA) who are at risk for stroke, and transfusion programs significantly reduce stroke risk in patients with abnormal TCD. Two independent studies have demonstrated that the risk of stroke in children with SCD increases with TCD velocity (STOP and STOP II).

Literature:

Magnetic resonance imaging/angiography and transcranial Doppler velocities in sickle cell anemia: results from the SWiTCH trial.

Author	Helton KJ, Adams RJ, Kesler KL, Lockhart A, Aygun B, Driscoll C, Heeney MM, Jackson SM, Krishnamurti L, Miller ST, Sarnaik SA, Schultz WH, Ware RE;SWiTCH Investigators.
Content/Summary Abstract	The Stroke With Transfusions Changing to Hydroxyurea (SWiTCH) trial compared standard (transfusions/chelation) to alternative (hydroxyurea/phlebotomy) treatment to prevent recurrent stroke and manage iron overload in children chronically transfused over 7 years before enrollment. A novel MRA vasculopathy grading scale demonstrated frequent severe baseline left/right vessel stenosis (53%/41% ≥Grade 4); 31% had no vessel stenosis on either side. Baseline parenchymal injury was prevalent (85%/79% subcortical, 53%/37% cortical, 50%/35% subcortical and cortical). Most children had low or uninterpretable baseline middle cerebral artery TCD velocities, which were associated with worse stenoses (incidence risk ratio [IRR] = 5.1, P ≤ .0001 and IRR = 4.1, P < .0001) than normal velocities; only 2% to 12% had any conditional/abnormal velocity. Patients with adjudicated stroke (7) and transient ischemic attacks (19 in 11 standard/8 alternative arm subjects) had substantial parenchymal injury/vessel stenosis. At exit, 1 child (alternative arm) had a new silent infarct, and another had worse stenosis. SWiTCH neuroimaging data document severe parenchymal and vascular abnormalities in children with SCA and stroke and support concerns about chronic transfusions lacking effectiveness for preventing progressive cerebrovascular injury. The novel SWiTCH vasculopathy grading scale warrants validation testing and consideration for use in future clinical trials. This trial was registered at www.clinicaltrials.gov as #NCT00122980.
Comment	Trial study
Doppler-device	Not known

Quantification	Standardized brain magnetic resonance imaging/magnetic resonance angiography (MRA) and transcranial Doppler (TCD) exams were performed at entry and exit, with a central blinded review.

Physician attitude, awareness, and knowledge regarding guidelines for transcranial Doppler screening in sicklecell disease.

Author	Reeves SL[1], Fullerton HJ[2], Dombkowski KJ[3], Boulton ML[3], Braun TM[3], Lisabeth LD[3].
Content/Summary Abstract	OBJECTIVE: We explored factors that may influence physician adherence to transcranial Doppler (TCD) screening guidelines among children withsickle cell disease. METHODS: Pediatric hematologists, neurologists, and primary care physicians (n = 706) responded to a mailed survey in May 2012 exploring factors hypothesized to influence physician adherence to TCD screening guidelines: physician (internal) barriers and physician-perceived external barriers. Responses were compared by specialty using chi-square tests.
Comment	Among 276 physicians (44%), 141 currently treated children with sickle cell disease; 72% recommend screening. Most primary care physicians (66%) did not feel well informed regarding TCD guidelines, in contrast to neurologists (25%) and hematologists (6%, P < .0001). Proportion of correct answers on knowledge questions was low (13%-35%). Distance to a vascular laboratory and low patient adherence were external barriers to receipt of TCD screening.
Doppler-device	Not known
Quantification	Additional research regarding physicians' lack of self-efficacy and knowledge of recommendations could help clarify their role in recommendation of TCD screening.

Sickle cell disease: reference values and interhemispheric differences of nonimaging transcranial Doppler blood flow parameters.

Author	(Arkuszewski, Krejza, u. a., 2011)
Content/Summary	Respective reference limits for left-to-right velocity ratios were the following: 0.72 to 1.25 cm/s for the MCA; 0.62 to 1.39 cm/s for the ACA, and 0.69 to 1.27 cm/s for the tICA. Flow velocities in major arteries were inversely related to age and Hct or Hgb.
Comment	Reference limits of blood flow parameters were established on the basis of a consecutive cohort of 56 children (mean age, 100 ± 40 months; range, 29-180 months; 30 females) free of neurologic deficits and intracranial stenosis detectable by MRA,
Doppler-device	Pioneer TC 8080; Nicolet Vascular, Madison, Wisconsin
Quantification	The study provides reference intervals of TCD flow velocities and their interhemispheric differences and ratios that may be helpful in identification of intracranial arterial stenosis in children with SCD undergoing sonographic screening for stroke prevention.

Effect of transfusion therapy on transcranial Doppler ultrasonography velocities in children with sickle cell disease

Author	(Janet L Kwiatkowski u. a., 2011)
Content/Summary	The median TCD velocity was lowered by 38 cm/sec within 3 months of initiating transfusions, followed by a more gradual decline then stabilization of velocities, although with significant individual variation. Factors associated with conversion to normal TCD included lower initial TCD velocity, younger age, and higher pre-transfusion hemoglobin level during transfusion therapy.
Comment	88 children with serial TCD data after starting transfusions
Doppler-device	Nicolet/EME Companion or Nicolet/EME Pioneer
Quantification	Younger children with higher pre-transfusion hemoglobin levels and lower abnormal TCD velocities are most likely to have rapid normalization of TCD on transfusions. Long-term follow-up of children with persistently abnormal exams or worsening velocities on transfusion is needed to determine if these children are at higher risk of stroke.

Impact of early transcranial Doppler screening and intensive therapy on cerebral vasculopathy outcome in a newborn sickle cell anemia cohort.

Author	(Bernaudin u. a., 2011) 20.10.2015 14:21:00
Content/Summary	Thus, early TCD screening and intensification therapy allowed the reduction of stroke-risk by age 18 from the previously reported 11% to 1.9%. In contrast, the 50% cumulative cerebral risk suggests the need for more preventive intervention.
Comment	Créteil newborn SCA cohort (n = 217 SS/Sβ(0)), who were early and yearly screened with TCD since 1992.
Doppler-device	Not known
Quantification	Early TCD is urgent!

Transcranial Doppler ultrasonography and prophylactic transfusion program is effective in preventing overt stroke in children with sickle cell disease.

Author	(Enninful-Eghan u. a., 2010)
Content/Summary	The incidence of overt stroke in the pre-TCD period was 0.67 per 100 patient-years, compared with 0.06 per 100 patient-years in the post-TCD period (P<.0001). Of the 2 strokes in the post-TCD period, 1 occurred in a child too young for the screening protocol, and 1 occurred in a child with high velocities solely in the anterior cerebral arteries. The program has been successful in reducing the rate of first overt stroke, but with increased use of transfusion. Additional modifications to screening might further reduce the risk of first stroke, and studies of alternative treatments may be beneficial.
Comment	475 patients observed in the 8-year period before instituting TCD screening with the rate in 530 children in the 8-year period after
Doppler-device	Not known
Quantification	Stroke rate could be reduced due to TCD guided infusion therapy.

Transcranial Doppler ultrasonography (TCD) in infants with sickle cell anemia: baseline data from the BABY HUG trial.

Author	(Pavlakis u. a., 2010)
Content/Summary	No patient had an abnormal TCD as defined in the older child (time averaged maximum mean TAMM velocity > or =200 cm/sec) and only four subjects (2%) had velocities in the conditional range (170-199 cm/sec). TCD velocities were inversely related to hemoglobin (Hb) concentration and directly related to increasing age. Determination of whether the TCD values in this very young cohort of infants with SCA can be used to predict stroke risk later in childhood will require analysis of exit TCD's and long-term follow-up, which is ongoing
Comment	TCD was performed on infants with SCA enrolled in the BABY HUG trial. Subjects were 7-17 months of age (mean 12.6 months).

Doppler-device	Nicolet Companion (EME) 2-MHZ
Quantification	Only few infants were screened with BFV higher than 170 cm/s. New baseline required?

Hydroxyurea or chronic exchange transfusions in patients with sickle cell disease: role of transcranial Doppler ultrasound in stroke prophylaxis.

Author	(Suliman u. a., 2009)
Content/Summary	The case demonstrates a pitfall when using hydroxyurea without monitoring intracranial cerebral vessels for vasculopathic changes
Comment	Case report
Doppler-device	Not known
Quantification	Transcranial Doppler is a crucial investigation that can reveal elevated cerebral arterial flow velocities

Primary stroke prevention for sickle cell disease in north-east Italy: the role of ethnic issues in establishing a Transcranial Doppler screening program.

Author	(Colombatti u. a., 2009)
Content/Summary	Pulsatility index and depth values in both the MCA and the Basilar Artery (BA) were similar at TCD and TCCS evaluation in the three groups while time-average maximum velocities (TAMM), peak systolic velocity and diastolic velocity in the MCA and BA were higher in the patients' group on both TCD and TCCS evaluation.
Comment	TCD and TCCD were performed in all patients.
Doppler-device	TCD and TCCS were performed using a 2 MHz pulsed Doppler ultrasonograph (EME TCD 2000/S) and a ATL HDI 3000/S Echo Doppler system respectively.
Quantification	Ethnic background does not seem to influence TCD velocity and internationally accepted reference values already validated in African-American SCD pediatric patients can be used, but long prospective trials are needed to verify their efficacy in defining stroke risk in our setting.

A critical assessment of transcranial Doppler screening rates in a large pediatric sickle cell center: opportunities to improve healthcare quality.

Author	(Raphael u. a., 2008)
Content/Summary	The average yearly screening rate for eligible patients was 45%. The average yearly cancellation rate by patients was 20%. Patient with private insurance were three times more likely to be compliant with ordered screenings than patients with Medicaid (P = 0.0077).
Comment	
Doppler-device	Not known
Quantification	Determination of whether the TCD values in this very young cohort of infants with SCA can be used to predict stroke risk later in childhood will require analysis of exit TCD's and long-term follow-up, which is ongoing.

The natural history of conditional transcranial Doppler flow velocities in children with sickle cell anaemia.

Author	(Hankins u. a., 2008)
Content/Summary	Fifty-four patients (20%) had conditional TAMV either on initial screening or a subsequent examination. The 18-month cumulative incidence of conversion from conditional to abnormal TAMV was 23%
Comment	In 2003, our centre initiated universal TCD screening, targeting all children (aged 2-16 years) with SCA. TCD examinations were repeated at intervals based on initial results. To determine rates and risk factors for TCD conversion, we reviewed all examinations since 2003, excluding patients receiving hydroxycarbamide (hydroxyurea) or transfusions.
Doppler-device	Not known
Quantification	Children without treatment need TCD-Screening because of 23% conversation to abnormal BFV within 18 months.

A simple index using age, hemoglobin, and aspartate transaminase predicts increased intracerebral blood velocity as measured by transcranial Doppler scanning in children with sickle cell anemia.

Author	(D. C. Rees u. a., 2008)
Content/Summary	This detected a time-averaged mean of the maximum velocity of >170 cm/second with 100% sensitivity and 58% specificity. The index was validated on the second data set and again showed 100% sensitivity with 73% specificity.
Comment	Routinely collected clinical and laboratory data were correlated with transcranial Doppler measurements on children with sickle cell anemia seen in a single institution in 2006.
Doppler-device	Not known
Quantification	This simple index has the potential to identify children who are at higher risk of cerebrovascular disease to allow them to be prioritized for transcranial Doppler scanning and other intracerebral imaging.

Evaluation of a comprehensive transcranial Doppler screening program for children with sickle cell anemia.

Author	(McCarville u. a., 2008)
Content/Summary	Eighteen strokes occurred in Period 1, 22 in Period 2 and three in Period 3. The first stroke incidence was significantly lower in Period 3 compared to Periods 1 and 2 (P = 0.047).
Comment	We evaluated the efficacy of our program by comparing the number of patients screened per year and incidence of first stroke across three periods defined by TCD usage: (1) pre-dating TCD screening, (2) sporadic TCD screening, and (3) comprehensive TCD screening.
Doppler-device	Not known
Quantification	It is possible to perform TCD screening of most children with SCA. TCD screening is effective in reducing first stroke incidence in these children

Preventing stroke among children with sickle cell anemia: an analysis of strategies that involve transcranial Doppler testing and chronic transfusion.

Author	(Mazumdar u. a., 2007)
Content/Summary	For a hypothetical cohort of 2-year-old children, the optimal strategy was transcranial Doppler ultrasonography screening annually until age 10 with children at high risk receiving monthly transfusions until age 18. The optimal strategy would prevent 32% of strokes predicted to occur without intervention. The optimal strategy led to benefits similar to more intensive screening and transfusion strategies but resulted in fewer adverse events.
Comment	Our goals were to (1) compare the projected benefits and risks of 6 primary stroke-prevention strategies, (2) estimate the optimal frequency of screening, and (3) identify key assumptions that influence the risk/benefit relationship.
Doppler-device	Not known
Quantification	The optimal stroke-prevention strategy was projected to be annual transcranial Doppler ultrasonography screening until age 10 with transfusion for children at high risk until age 18

Big strokes in small persons.

Author	(Adams, 2007)
Content/Summary	There are no evidence-based guidelines for the discontinuation of transfusion in children once they have been identified as having high risk based on TCD The current situation is undesirable because of the long-term effects of transfusion, including iron overload
Comment	Review
Doppler-device	Not known
Quantification	We can reduce many of the big strokes that occur in these small persons by aggressively screening patients at a young age (and periodically throughout the childhood risk period) and interrupting the process with regular blood transfusions.

Angle-corrected imaging transcranial Doppler sonography versus imaging and nonimaging transcranial Doppler sonography in children with sickle cell disease.

Author	(Krejza u. a., 2007)
Content/Summary	Two arteries were not found on TCDI compared with 15 not found on TCD. Average angle of insonation in the MCA, ACA, ICA, and PCA was 31 degrees , 44 degrees , 25 degrees , and 29 degrees , respectively. TCDI and TCD mean depth of insonation for all arteries did not differ significantly; however, individual differences varied substantially. TCD and angle-corrected TCDI velocities were not statistically different except for higher angle-corrected TCDI values in the left ACA and right PCA.
Comment	A total of 37 children (mean age, 7.8 +/- 3.0 years) without intracranial arterial narrowing determined with MR angiography, were studied with use of TCD and TCDI at the same session.
Doppler-device	Pioneer TC 8080; Nicolet Vascular
Quantification	TCD results are similar to TCDI results.

Treatment and prevention of stroke in children with sickle cell disease.

Author	
Content/Summary	The study showed a very significant 90% reduction in first stroke with transfusion (STOP). In STOP2, discontinuing transfusions after 30 months or more (even with normal TCD) resulted in a high rate of reversion to abnormal TCD values and stroke. TCD screening of all children with SCD, and initiation and maintenance of chronic transfusion to maintain hemoglobin S below 30% in the high-risk group, is the only proven prevention strategy for stroke in SCD. Bone marrow transplantation can be curative for SCD, and limited data support its use to prevent stroke in SCD.
Comment	Background information
Doppler-device	none
Quantification	General treatment of SCD is described

Transcranial Doppler ultrasonography in adults with sickle cell disease.

Author	(Valadi u. a., 2006)
Content/Summary	Adults with SCD had a higher mean time-averaged maximum mean velocity (110.9 +/- 25.7 cm/s) compared with healthy controls (71.1 +/- 12.0 cm/s), and the difference is approximately proportional to their anemia. No cases with velocities >/=200 cm/s (the threshold used in children for prophylactic treatment) were found in this sample.
Comment	The authors examined 112 adult patients from two convenience population samples with SCD and 53 healthy control subjects to compare velocities in adults to those reported in children with SCD and to evaluate the influence of age and hematocrit on TCD.
Doppler-device	TC2000 or Companion (Nicolet/EME)
Quantification	Transcranial Doppler velocities in adults with sickle cell disease (SCD) are lower than those in children with SCD. Velocity criteria used in children cannot be used to stratify risk of stroke in adults.

TCD in sickle cell disease: an important and useful test.

Author	(Adams, 2005)
Content/Summary	Currently, TCD is the only recommended method for treatment selection for primary-stroke prevention. TCD and TCDI offer an opportunity to apply an effective therapy for patients in this risk group and reduce many first-time strokes.
Comment	Background information
Doppler-device	Not known
Quantification	TCD screening is recommended for SCD patients to begin at 24 months of age and should be repeated every 6-12 months during early childhood.

Summary:

Early and regular TCD screening allows reduction of stroke rates in children. Screening should be started within two years und should be repeated at least once a year.
References values of children cannot be used in adults. Ethnic background does not seem to influence TCD velocity and internationally accepted reference values already validated in African-American SCD pediatric patients can be used.
It is possible to perform TCD screening of most children with SCA. TCD results are similar to TCDI results.

Experts:

Adams
Kwiatkowski

Literature

Adams RJ. TCD in sickle cell disease: an important and useful test. Pediatr Radiol 2005; 35: 229-234.[zitiert 2011 Dez 20]

Adams RJ. Big strokes in small persons. Arch. Neurol. 2007; 64: 1567-1574.[zitiert 2011 Dez 20]

Arkuszewski M, Krejza J, Chen R, Kwiatkowski J L, Ichord R, Zimmerman R, u. a. Sickle cell disease: reference values and interhemispheric differences of nonimaging transcranial Doppler blood flow parameters. AJNR Am J Neuroradiol 2011; 32: 1444-1450.[zitiert 2011 Okt 29]

Bernaudin F, Verlhac S, Arnaud C, Kamdem A, Chevret S, Hau I, u. a. Impact of early transcranial Doppler screening and intensive therapy on cerebral vasculopathy outcome in a newborn sickle cell anemia cohort. Blood 2011; 117: 1130-1140; quiz 1436.[zitiert 2011 Okt 31]

Colombatti R, Meneghetti G, Ermani M, Pierobon M, Sainati L. Primary stroke prevention for sickle cell disease in north-east Italy: the role of ethnic issues in establishing a Transcranial Doppler screening program. Ital J Pediatr 2009; 35: 15.[zitiert 2011 Dez 20]

Enninful-Eghan H, Moore RH, Ichord Rebecca, Smith-Whitley K, Kwiatkowski Janet L. Transcranial Doppler ultrasonography and prophylactic transfusion program is effective in preventing overt stroke in children with sickle cell disease. J. Pediatr. 2010; 157: 479-484.[zitiert 2011 Okt 31]

Hankins JS, Fortner GL, McCarville MB, Smeltzer MP, Wang WC, Li C-S, u. a. The natural history of conditional transcranial Doppler flow velocities in children with sickle cell anaemia. Br. J. Haematol. 2008; 142: 94-99.[zitiert 2011 Nov 2]

Krejza J, Rudzinski W, Pawlak MA, Tomaszewski M, Ichord R, Kwiatkowski J, u. a. Angle-corrected imaging transcranial Doppler sonography versus imaging and nonimaging transcranial Doppler sonography in children with sickle cell disease. AJNR Am J Neuroradiol 2007; 28: 1613-1618.[zitiert 2011 Dez 20]

Kwiatkowski Janet L, Yim E, Miller S, Adams RJ. Effect of transfusion therapy on transcranial Doppler ultrasonography velocities in children with sickle cell disease. Pediatr Blood Cancer 2011; 56: 777-782.[zitiert 2011 Dez 20]

Mazumdar M, Heeney MM, Sox CM, Lieu TA. Preventing stroke among children with sickle cell anemia: an analysis of strategies that involve transcranial Doppler testing and chronic transfusion. Pediatrics 2007; 120: e1107-1116.[zitiert 2011 Dez 20]

McCarville MB, Goodin GS, Fortner G, Li C-S, Smeltzer MP, Adams R, u. a. Evaluation of a comprehensive transcranial Doppler screening program for children with sickle cell anemia. Pediatr Blood Cancer 2008; 50: 818-821.[zitiert 2011 Nov 2]

Pavlakis SG, Rees RC, Huang X, Brown RC, Casella JF, Iyer RV, u. a. Transcranial Doppler ultrasonography (TCD) in infants with sickle cell anemia: baseline data from the BABY HUG trial. Pediatr Blood Cancer 2010; 54: 256-259.[zitiert 2011 Dez 20]

Raphael JL, Shetty PB, Liu H, Mahoney DH, Mueller BU. A critical assessment of transcranial Doppler screening rates in a large pediatric sickle cell center: opportunities to improve healthcare quality. Pediatr Blood Cancer 2008; 51: 647-651.[zitiert 2011 Dez 20]

Rees DC, Dick MC, Height SE, O'Driscoll S, Pohl KRE, Goss DE, u. a. A simple index using age, hemoglobin, and aspartate transaminase predicts increased intracerebral blood velocity as measured

by transcranial Doppler scanning in children with sickle cell anemia. Pediatrics 2008; 121: e1628-1632.[zitiert 2011 Dez 20]

Suliman H, Wali Y, Al Saadoon M, Zechariah M, William RR, Gujjar A, u. a. Hydroxyurea or chronic exchange transfusions in patients with sickle cell disease: role of transcranial Doppler ultrasound in stroke prophylaxis. J. Pediatr. Hematol. Oncol. 2009; 31: 42-44.[zitiert 2011 Nov 2]

Valadi N, Silva GS, Bowman LS, Ramsingh D, Vicari P, Filho AC, u. a. Transcranial Doppler ultrasonography in adults with sickle cell disease. Neurology 2006; 67: 572-574.[zitiert 2011 Nov 14]

Blood. 2014 Aug 7;124(6):891-8. doi: 10.1182/blood-2013-12-545186. Epub 2014 Jun 9.

Clin Pediatr (Phila). 2015 Apr;54(4):336-45. doi: 10.1177/0009922814553429. Epub 2014 Oct 15.