MANAGEMENT OF NEUROLOGIC COMPLICATIONS IN PEDIATRIC PATIENTS

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Stroke subtype by age

- **Ischemic stroke**
  - 54% of CVAs
  - Highest in 1st decade and after 30 years
  - Peak at 2–5 years

- **Hemorrhagic stroke**
  - Highest during second decade
  - Risk factors: low Hb, high WBC, hypertension and steroid use

- **Silent stroke**
  - Radiological findings consistent with white-matter disease
  - 10–30% (not characterized as age-dependent)
  - Associated with cognitive deficiencies and further stroke risk

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WBC = white blood cell
# Risk factors for infarctive stroke

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior TIA</td>
<td>56</td>
</tr>
<tr>
<td>Anemia</td>
<td>1.85</td>
</tr>
<tr>
<td>Recent ACS</td>
<td>7</td>
</tr>
<tr>
<td>ACS rate</td>
<td>2.39</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.41</td>
</tr>
<tr>
<td>Silent infarcts</td>
<td>14</td>
</tr>
<tr>
<td>Nocturnal hypoxia (per 1% drop in SaO₂)</td>
<td>0.85</td>
</tr>
</tbody>
</table>

*Updated data from Ohene-Frempong K et al. Blood 1998;91:288–294.*

SaO₂ = oxygen saturation  
TIA = transient ischemic attack
CVAs in SCD

Age at first CVA and cumulative incidence of CVA

CVAs occurred earlier and more frequently with age in patients with Hb SS


CVA = cerebrovascular accident
Hb = hemoglobin; SCD = sickle cell disease
Management of stroke and prevention of recurrence

- Ischemic stroke is treated with emergent simple or exchange blood transfusion.
- Without transfusion, 70% will recur within 2–3 years.
- With chronic transfusion, risk of recurrence is reduced by 90%.

Management of stroke: initial simple vs initial exchange transfusion

All children received scheduled chronic blood transfusion therapy for at least 5 years after the first stroke and initial therapy.

Initial exchange transfusions were associated with significantly lower risk of stroke than simple transfusion therapy.

Prophylaxis of recurrent stroke: why not use hydroxyurea?

2 small prospective studies showed that HU and phlebotomy may be effective in decreasing the rate of stroke recurrence in patients in SCD

Similar results have recently been reported in a retrospective study from Jamaica

This was evaluated prospectively in the SWiTCH study

Ware RE et al. Blood 1999 Nov 1;94:3022-6;
Ware RE et al. J Pediatr 2004;145:346-52;

SWiTCH = stroke with transfusions changing to hydroxyurea.
SWiTCH: aims and study design

Aim: to compare 30 months of HU and phlebotomy (alternative) with transfusions and deferasirox (standard) for the prevention of secondary stroke and reduction of transfusional iron overload

161 pediatric patients with sickle cell anemia (83 male, 78 female), documented stroke, and iron overload enrolled in SWiTCH (US10)

134 patients randomized 1:1

Alternative arm
67 patients
HU + phlebotomy

Standard arm
67 patients
Transfusions + deferasirox

Prediction: increased occurrence of recurrent stroke events in alternative arm counterbalanced by better management of iron overload with phlebotomy

Ware RE & Helms RW. Blood 2012;119:3925–3932. HU = hydroxyurea
SWiTCH stroke recurrence higher with hydroxyurea than with transfusions

Study was terminated early as a result of the marked increase in secondary stroke risk with HU compared with transfusion therapy.

<table>
<thead>
<tr>
<th>Stroke incidence</th>
<th>Treatment arm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Transfusions + deferasirox</td>
</tr>
<tr>
<td>Estimated, %</td>
<td>6</td>
</tr>
<tr>
<td>Actual, n/N (%)</td>
<td>0/66 (0)</td>
</tr>
</tbody>
</table>

Transfusion remains the gold standard treatment for secondary stroke prevention in pediatric SCD patients.

Ware RE & Helms RW. Blood 2010;116(21):abst 844.
Intervention and outcome of 43 survivors of first clinical stroke in Jamaica

1st stroke  
N = 43

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>HU n = 10</td>
<td>No re-stroke n = 9</td>
</tr>
<tr>
<td></td>
<td>Re-stroke* n = 1 (10%)</td>
</tr>
<tr>
<td>No HU n = 33</td>
<td>No re-stroke n = 13</td>
</tr>
<tr>
<td></td>
<td>Re-stroke* n = 20 (60.6%)</td>
</tr>
<tr>
<td></td>
<td>Died n = 1</td>
</tr>
<tr>
<td></td>
<td>HU, n = 3 1 re-stroke</td>
</tr>
<tr>
<td></td>
<td>No HU, n = 16 7 re-stroke (2 died)</td>
</tr>
</tbody>
</table>

*HR 9.4 (95% CI 1.3–70.6); p < 0.03

Children with SCD receiving regular blood transfusion therapy for secondary prophylaxis of strokes

- 53 children enrolled
- 13 children excluded
- 40 children met criteria for analysis
- No second overt strokes (n=33)
  - TIAs without new MRI lesions (n=1)
  - No new MRI lesions (n=21)
  - TIAs after silent infarct (n=1)
  - TIAs with silent infarct on next MRI (n=2)
- Second overt strokes (n=7)
- Silent infarcts (n=8)

Importance of TCD in SCD

Yearly stroke risk

- Baseline risk from CSSCD: ~0.5–1%\(^1\)
- If prior stroke: ~30%\(^2\)
- TIA, lower baseline Hb, prior and recent ACS (CSSCD study, no prior stroke), but yearly risk not quantified\(^1\)
- Abnormal TCD: 10–13% per year\(^3\)
- MRI silent lesions: ~2–3% per year\(^4\)
- Severe arterial lesions on angiography?
  - Assumed to be bad\(^5\), but yearly risk has not been quantified

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CSSCD = Cooperative Study of Sickle Cell Disease
MRI = magnetic resonance imaging
Stroke risk increases with increasing TCD flow rate

- Using imaging TCD the velocities are 10% lower
- Abnormal >185 cm/s

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STOP: Transfusion reduces the risk of a first stroke in children with SCD and abnormal TCD

After 2 TCDs ≥200 cm/s, children aged 2–16 years with SCD were randomized

Standard care (including occasional transfusion) (n=67)

Transfusion to Hb S <30% (n=63)

Endpoint: incidence of stroke (cerebral infarction or intracranial hemorrhage)

Number of strokes

<table>
<thead>
<tr>
<th>Standard care (n=67)</th>
<th>Transfusion (n=63)</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>1</td>
</tr>
</tbody>
</table>

Risk reduction 92%

P<0.001

STOP I study halted prematurely in 1997
NIH recommends all children with SCD should be screened for stroke risk using TCD; those at high risk should receive transfusion therapy


NIH = National Institutes of Health
With STOP protocol, transfusions are safe and complications manageable

- Alloimmunization limited by matching
- No evidence of infection
- Other salutary effects beyond preventing stroke
- Oral chelator now available
My recommendations

TCD

Repeat 1 year

Normal

Inadequate incomplete study

Repeat another examiner

Repeat as results indicate

Second inadequate incomplete consider MRI/MRA

Conditional

High conditional 185-199, <10 y

Repeat TCD after 6 weeks

Max velocity >220 cm/s

Confirmatory TCD within 1 week

Max velocity 200–219 cm/s

Confirmatory TCD within 2 weeks

Max velocity >200 cm/s

Max velocity <200 cm/s

Abnormal

Abnormal

Max velocity >200 cm/s

Place on chronic transfusion

TCD change after transfusions

Risk factors for persistent abnormal TCD

1. Lower initial Hb
2. Older age

Early TCD screening and intensification of transfusion therapy allows >5x reduction of stroke risk but not other abnormalities

Cumulative risks by 18 years of age

- Stroke: 1.9% (95% CI 0.6–5.9) compared with 11%
- Abnormal TCD 29.6% (95% CI 22.8–38), with a plateau at age 9 years
- Stenosis: 22.6% (95% CI 15.0–33.2)
- Silent stroke: 37.4% (95% CI 26.3–50.7) at age 14 years

Cumulating all events

- Early TCD and transfusions are effective in preventing strokes but not silent infarcts
- Most patients who develop silent infarcts have normal TCD
- Different strategies needed

Thus, early TCD screening and intensification therapy allowed the reduction of stroke risk by 18 years of age from 11% to 1.9%

In contrast, the 50% cumulative cerebral risk suggests the need for more preventive intervention

STOP II: Continuing transfusion therapy reduces risk of stroke

After ≥30 months of transfusion, 79 SCD patients with normalized TCD were randomized

Continued transfusion program (n=38)
Discontinued transfusion program (n=41)

Endpoint: stroke or reversion to abnormal TCD

STOP II study halted prematurely in 2004
NIH recommends that transfusions be continued indefinitely in children with SCD at high risk for stroke

Role of HU in primary stroke prevention

- HU decreases TCD velocity in patients with SCD
- Role of HU in preventing stroke in these patients is however not known
- This will be tested in the TWiTCH trial
- HU should only be used in this setting in patients who refuse transfusions or cannot be transfused

Proportion of SCD diagnoses among primary stroke patients

Ischemic strokes in pediatric patients

Overall strokes in adults

Silent infarcts: Prevalence and risk factors

Infants\(^1\)
- 3/23, 13% right frontal
- Risk factor: low Hb F

Young children <6 years\(^2\)
- 13/65, 20% developed new lesions over 1.8 years
  - Worst prevalence: 27.7%
- Risk factors: low rate of ACS, lower hemoglobin, stenosis by MRA not TCD, trend for Hb F

French cohort\(^3\)
- 35/132
  - 28.2% by age 8 years
  - 37.4% by age 14 years
- Only boys had new silent infarcts after age 8 years
- Risk factors: only low Hb in multivariate analysis, no impact of TCD


MRA = magnetic resonance angiography
TCD = transcranial Doppler
Prevalence of silent infarcts in SCD

Neurocognitive outcomes associated with silent cerebral infaracts


FSIQ = full scale IQ
Association of high blood pressure and low Hb with silent infarcts

*SITT: Multicenter randomized trial evaluating the efficacy of blood transfusion for stroke and recurrent silent infarct prevention

Odds ratio

n=814; 30% had silent infarcts

Silent Cerebral Infarct Multi-Center Clinical Trial (SIT)

196 underwent randomization

99 were assigned to transfusion
90 received ≥1 transfusions
97 were assigned to observation
97 were observed
15 crossed over to observation
9 declined transfusion immediately after randomization
6 received transfusion and then crossed over to observation

199 were included in the analysis
2 were lost to follow-up or withdrew
1 had stroke
5 had new or enlarged silent cerebral infarcts

97 were included in the analysis
9 were lost to follow-up or withdrew
7 had strokes
5 had new or enlarged silent cerebral infarcts
2 had transient ischemic attacks only

This study showed a reduction in recurrence of cerebral infarcts (absolute RR 8%; relative RR 58%) among children with SCD whose HbS levels were kept below 30%

Risk factors for new events were younger age, recurring headaches and a higher steady-state reticulocyte count

Transfusion risks seem to be outweighed by the neurologic benefits

At study end, 3/37 (8.1%) patients in the continued-transfusion group developed new brain MRI lesions compared with 11/40 (27.5%) patients in the transfusion-halted group ($P=0.03$)

*One patient had no follow-up MRI.

†Three patients actually had a decrease in the number of lesions, one reverting to a normal scan.
In the multicenter Phase III TWiTCH trial, which treated children with SCA and abnormal TCD velocities but without severe MRA vasculopathy Hydroxyurea at MTD was non-inferior and possibly superior to chronic transfusions for maintaining TCD velocities.
Final TCD velocities (mean ± standard error) in the transfusion and hydroxyurea arms were 143 ± 1.6 and 138 ± 1.6 cm/sec, respectively.

Intention-to-treat analysis: p-value for non-inferiority = 8.82 x 10^{-16}

Post-hoc analysis the p-value for superiority = 0.046.

Among 29 new neurological events, all centrally adjudicated by masked reviewers, there were no strokes but 6 transient ischemic attacks (3 in each arm).

In the multicenter Phase III TWiTCH trial, which treated children with SCA and abnormal TCD velocities but without severe MRA vasculopathy, Hydroxyurea at MTD was non-inferior and possibly superior to chronic transfusions for maintaining TCD velocities.
Hydroxycarbamide versus chronic transfusion for maintenance of transcranial doppler flow velocities in children with sickle cell anaemia—TCD With Transfusions Changing to Hydroxyurea (TWITCH): a multicentre, open-label, phase 3, non-inferiority trial

Figure 1. Trial profile*Two participants were excluded for two reasons.
Figure 2. Laboratory parameters of the intention-to-treat population.
Results are shown for haemoglobin concentration (A); mean corpuscular volume (B); sickle haemoglobin (C); fetal haemoglobin (D); white blood cell count (E); absolute neutrophil count (F); abso...
Figure 3. Primary endpoint analysis of TCD velocities. TCD data are shown by use of mixed model statistical analysis (A); the curves are significantly different using the non-inferiority comparison ($p=8.82 \times 10^{-16}$) and also by post-hoc analysis for superiority (…
Approach to neurological complications in SCD

Overt stroke
Silent infarct on MRI
Abnormal TCD
Abnormal neuropsychology (↓FSIQ)

BMT (CBT)
Chronic transfusion
HU
Education support

SWiTCH trial
SITT trial

Intervention of proven value
Intervention of possible value
Efficacy of ‘intervention of possible value’ under investigation


BMT = bone marrow transplantation
CBT = cord blood transplantation
Conclusions

- Stroke is a significant cause of morbidity and mortality in children with SCD
- Chronic transfusion regimens are effective in preventing stroke recurrence as well as new strokes in pediatric patients with abnormal TCD
- The role of HU in preventing neurological complications in pediatric patients needs to be further evaluated
- Early transfusions seem effective in preventing development and progression of silent infarcts
- Risk factors such as high blood pressure, low Hb and nocturnal hypoxia may also need to be addressed
- Strokes are increasing in incidence among adults with SCD