UniversityHospital Heidelberg

Sichelzellkrankheit
Pathophysiologie, Genetik und Versorgung

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Die Anämie: meist das geringste Problem

Rees et al. Lancet 2010

Geschichte von Entdeckungen

	Discovery	Importance
1910	Sickled erythrocytes in Grenadan dental student[2]	First description of disease linked to abnormal erythrocytes
1924	Haemolysis in sickle-cell disease[3]	Explanation for anaemia, jaundice, and cholelithiasis
1924	Vaso-occlusion as cause of some pathological features[4]	Explanation for ischaemic tissue damage
1948	Abnormal electrophoretic mobility of sickle haemoglobin[5]	Identified pathophysiology to have a molecular basis
1948	No symptoms in infants noted[6]	Beneficial effects of high concentrations of fetal haemoglobin identified
1951	Characteristics of polymerisation of deoxygenated HbS[7]	Primary molecular mechanism identified
1980s	Value of penicillin in young children with sickle-cell anaemia[8,9]	Reduced mortality, role of neonatal screening
1984	Bone marrow transplant in child with sickle-cell anaemia and leukaemia[10]	Identified potential cure
1995	Efficacy of hydroxycarbamide[11]	Only disease-modifying drug identified
1998	Reduced stroke incidence in children with abnormal transcranial dopplers who were given blood transfusion[12]	Primary stroke prevention with fall in stroke occurrence

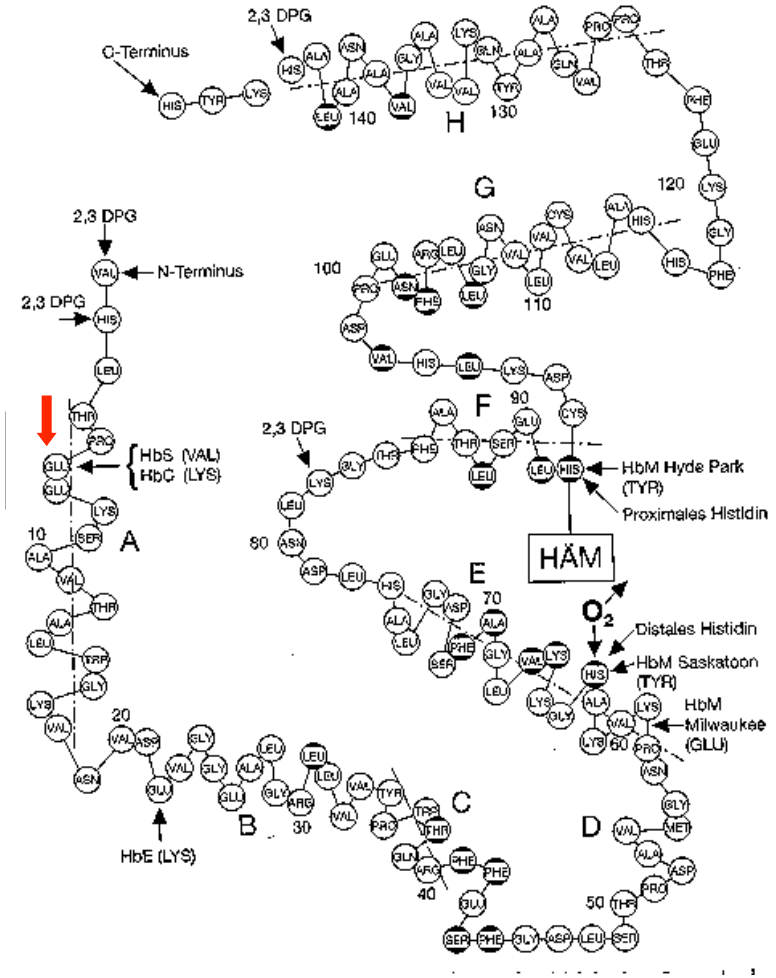
Rees et al. Lancet 2010

	Characteristics
Severe sickle-cell disease	
HbS/S (β6Glu>Val/β6Glu>Val); sickle-cell anaemia	The most common form of sickle-cell disease
HbS/β^0 thalassaemia	Most prevalent in the eastern Mediterranean region and India[14]
Severe HbS/β^+ thalassaemia	Most prevalent in the eastern Mediterranean region and India; 1–5% HbA present[14]
HbS/OArab (β6Glu>Val/β121Glu>Lys)	Reported in north Africa, the Middle East, and the Balkans; relatively rare[14]
HbS/D Punjab (β6Glu>Val/β121Glu>Gln)	Predominant in northern India but occurs worldwide[14]
HbS/C Harlem (β6Glu>Val/β6Glu>Val/β, β73Asp>Asn)	Electrophoretically resembles HbSC, but clinically severe; double mutation in β-globin gene; very rare[15]
HbC/S Antilles (β6Glu>Lys/β6Glu>Val, β23Val–Ile)	Double mutation in β-globin gene results in severe sickle-cell disease when co-inherited with HbC; very rare[16]
HbS/Quebec-CHORI (β6Glu>Val/β87Thr>Ile)	Two cases described; resembles sickle-cell trait with standard analytical techniques[17]
Moderate sickle-cell disease	
HbS/C (β6Glu>Val/β6Glu>Lys)	25–30% cases of sickle-cell disease in populations of African origin[13]
Moderate HbS/β^+ thalassaemia	Most cases in the eastern Mediterranean region; 6–15% HbA present[14]
HbA/S Oman (β^A/β6Glu>Val, β121Glu>Lys)	Dominant form of sickle-cell disease caused by double mutation in β-globin gene; very rare[18]
Mild sickle-cell disease	
Mild HbS/β^{++} thalassaemia	Mostly in populations of African origin; 16–30% HbA present[14]
HbS/E (β6Glu>Val/β26Glu>Lys)	HbE predominates in southeast Asia and so HbSE uncommon, although frequency is increasing with population migration[19]
HbA/Jamaica Plain (β^A/β6Glu>Val, β68Leu/Phe)	Dominant form of sickle-cell disease; double mutation results in Hb with low oxygen affinity; one case described[20]
Very mild sickle-cell disease	
HbS/HPFH	Group of disorders caused by large deletions of the β-globin gene complex; typically 30% fetal haemoglobin[14]
HbS/other Hb variants	HbS is co-inherited with many other Hb variants, and symptoms develop only in extreme hypoxia

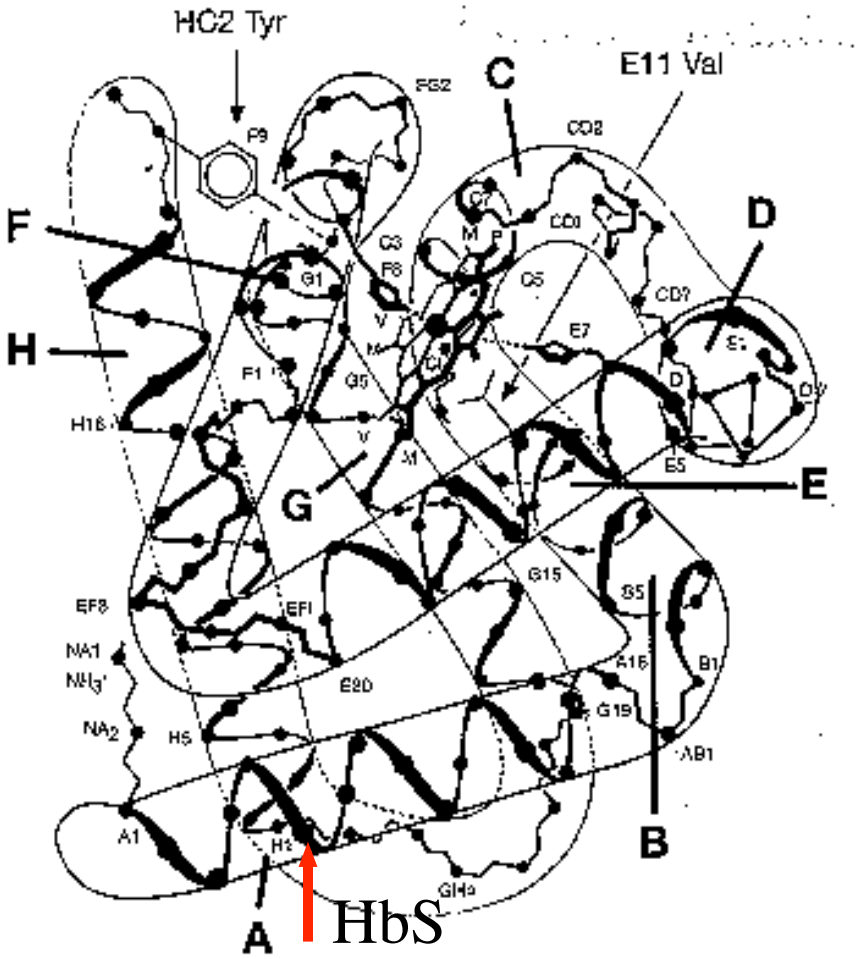
Genotypes that have been reported to cause sickle-cell disease are listed. All include at least one copy of the β^S allele, in combination with one or more mutations in the β-globin gene. HbS=sickle haemoglobin. HbA=haemoglobin variant A. HbE=haemoglobin variant E. Hb=haemoglobin.

Rees et al. Lancet 2010

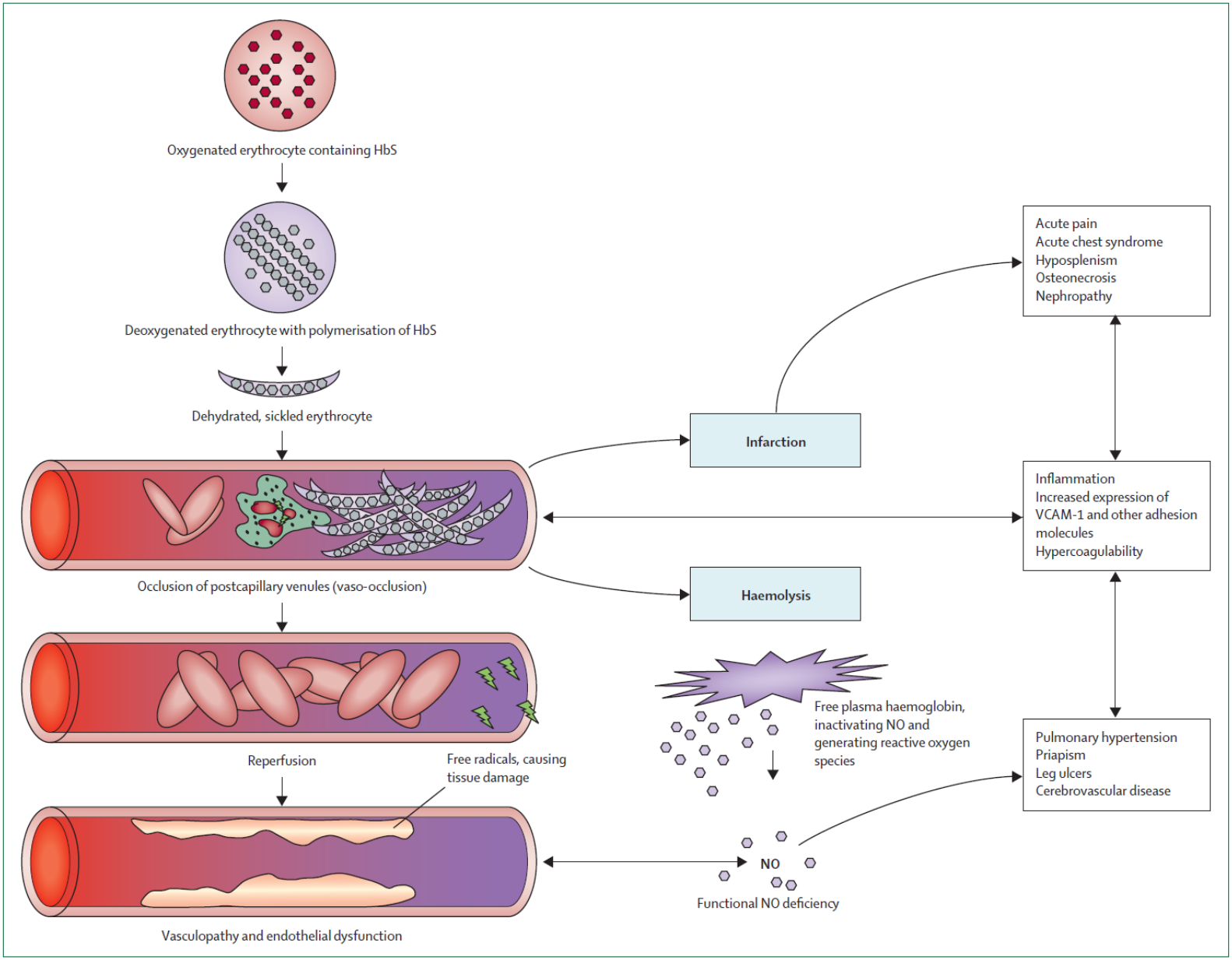
Die Sichelzellmutation



Huisman & Schröder, 1971



Kleihauer et al. 1996


Oxygenated erythrocyte containing HbS
Deoxygenated erythrocyte with polymerisation of HbS
Dehydrated, sickled erythrocyte
Occlusion of postcapillary venules (vaso-occlusion)
Reperfusion
Free radicals, causing tissue damage
Vasculopathy and endothelial dysfunction
Infarction
Haemolysis
Free plasma haemoglobin, inactivating NO and generating reactive oxygen species
NO
Functional NO deficiency
Acute pain
Acute chest syndrome
Hyposplenism
Osteonecrosis
Nephropathy
Inflammation
Increased expression of VCAM-1 and other adhesion molecules
Hypercoagulability
Pulmonary hypertension
Priapism
Leg ulcers
Cerebrovascular disease

Die Sichelzellerkrankung ist eine Multiorgankrankheit

Blut
hämolytische Anämie
aplastische Krise

Milz
Sequestrationskrise
functionelle Asplenie

Knochen
Schmerzkrisen
Dactylitis
Osteomyelitis
aseptische Nekrose

Lunge
akutes Thoraxsyndrom
pulmonaler Hochdruck

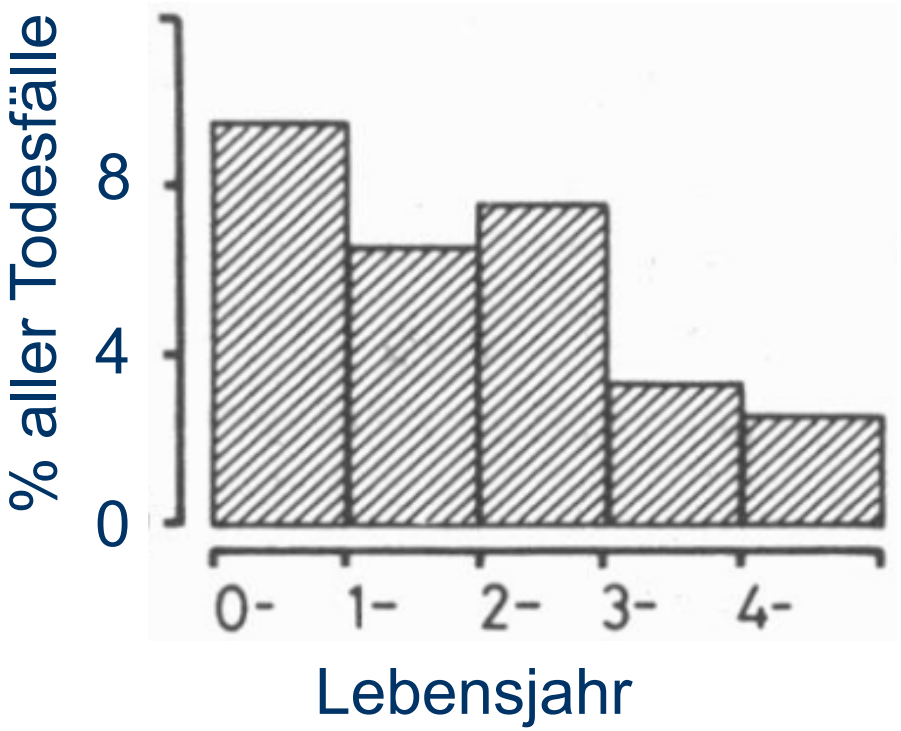
Darm
Gürtelsyndrom (paralytischer Ileus)

ZNS
Schlaganfall
Retinopathie

Urogenital
Chronisches Nierenversagen
Hyposthenurie
Priapismus

Haut
Ulcera cruris

Wann stirbt der Sichelzellpatient?



aus: Thomas et al. 1982, Br Med J **285**(6342): 633-635

Woran stirbt der Sichelzellpatient?

Milzsequestration	10%
Sepsis/Meningitis	13%
Schlaganfall	7%
Thoraxsyndrom	25%

aus: Thomas et al. 1982, Br Med J **285**(6342): 633-635

Komplikationen der Sichelzellkrankheit sind vermeidbar.

Milzsequestration

Elternschulung senkt Risiko um 75%

(Emond et al. 1985, J Pediatr 107(2): 201-206)

Sepsis/Meningitis

Penicillinprophylaxe senkt Risiko um 85%

(Gaston et al. 1986, N Engl J Med 314(25): 1593-1599)

Schlaganfall

Transfusion von Risikopatienten senkt Risiko um 90%

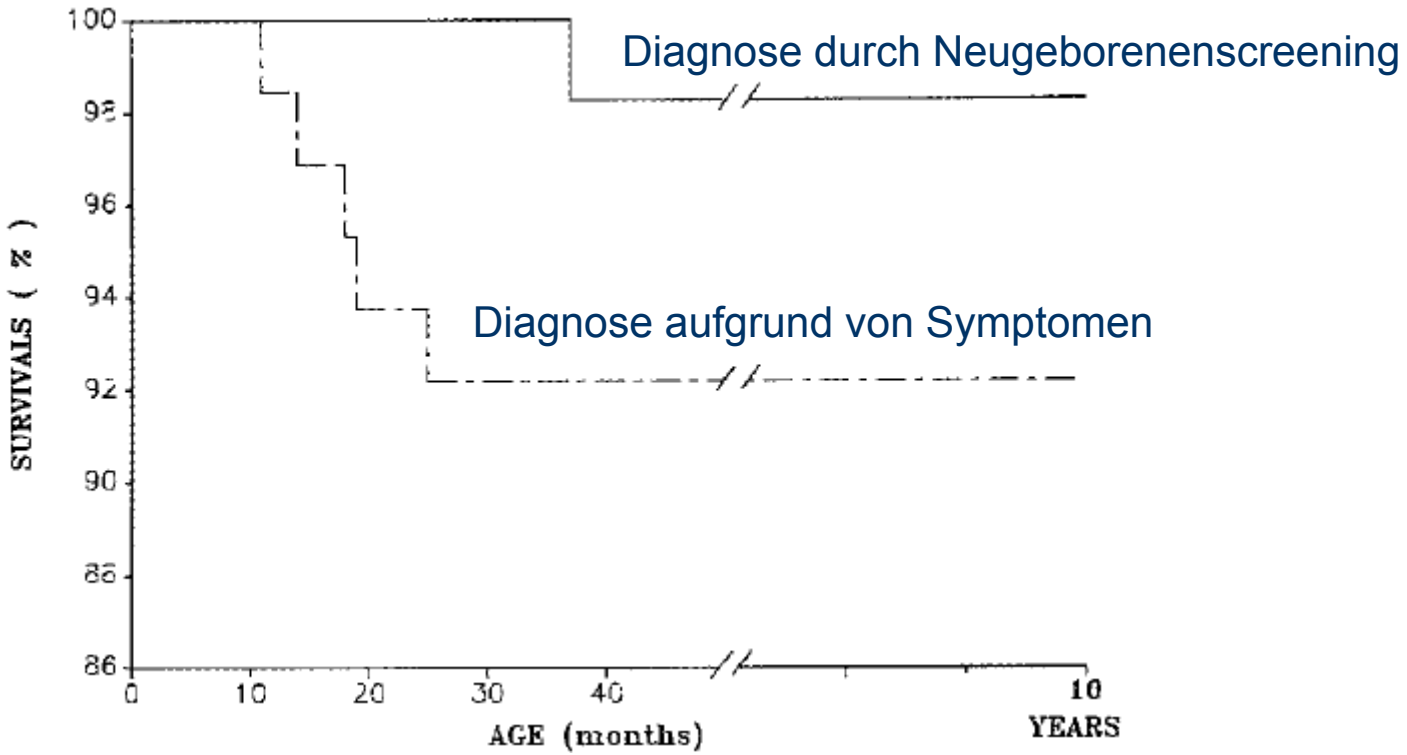
(Adams et al. 1992, N Engl J Med 326(9): 605-610)

Thoraxsyndrom

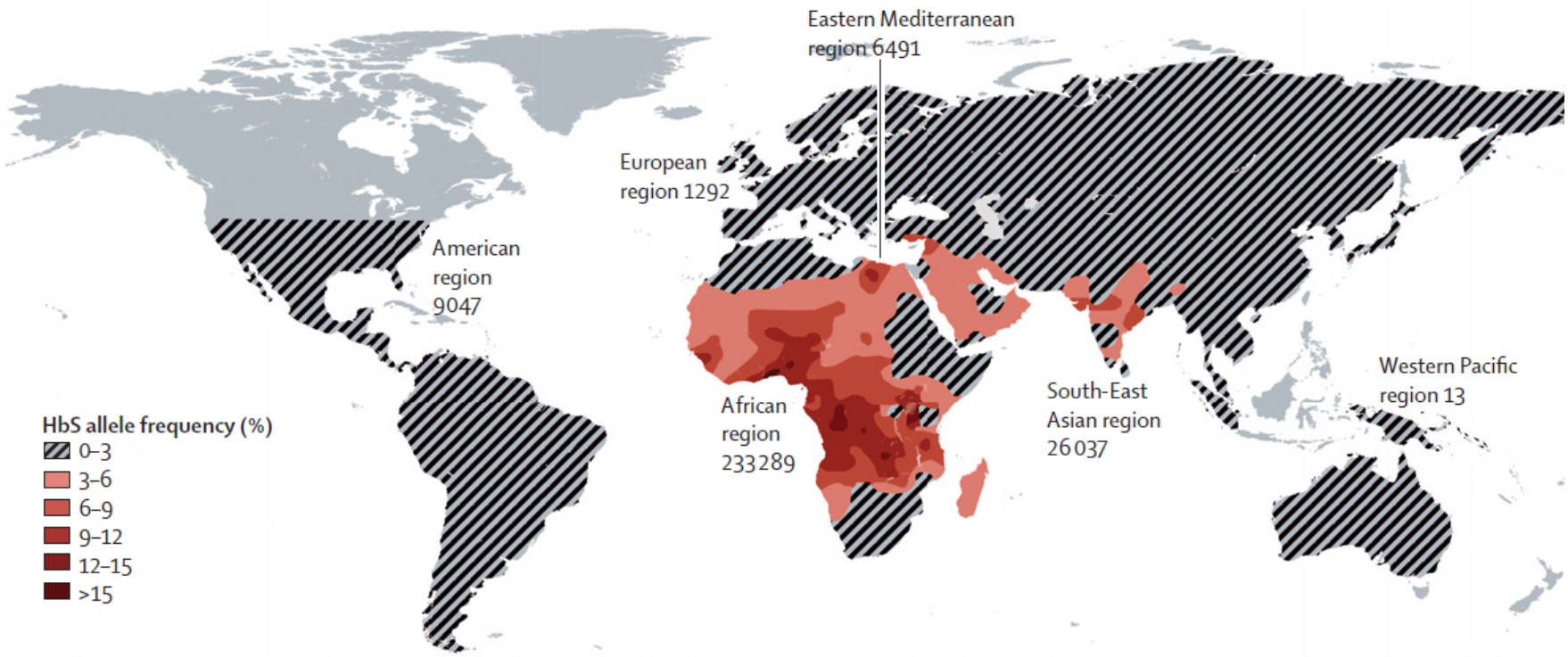
Hydroxycarbamid senkt Risiko um 64%

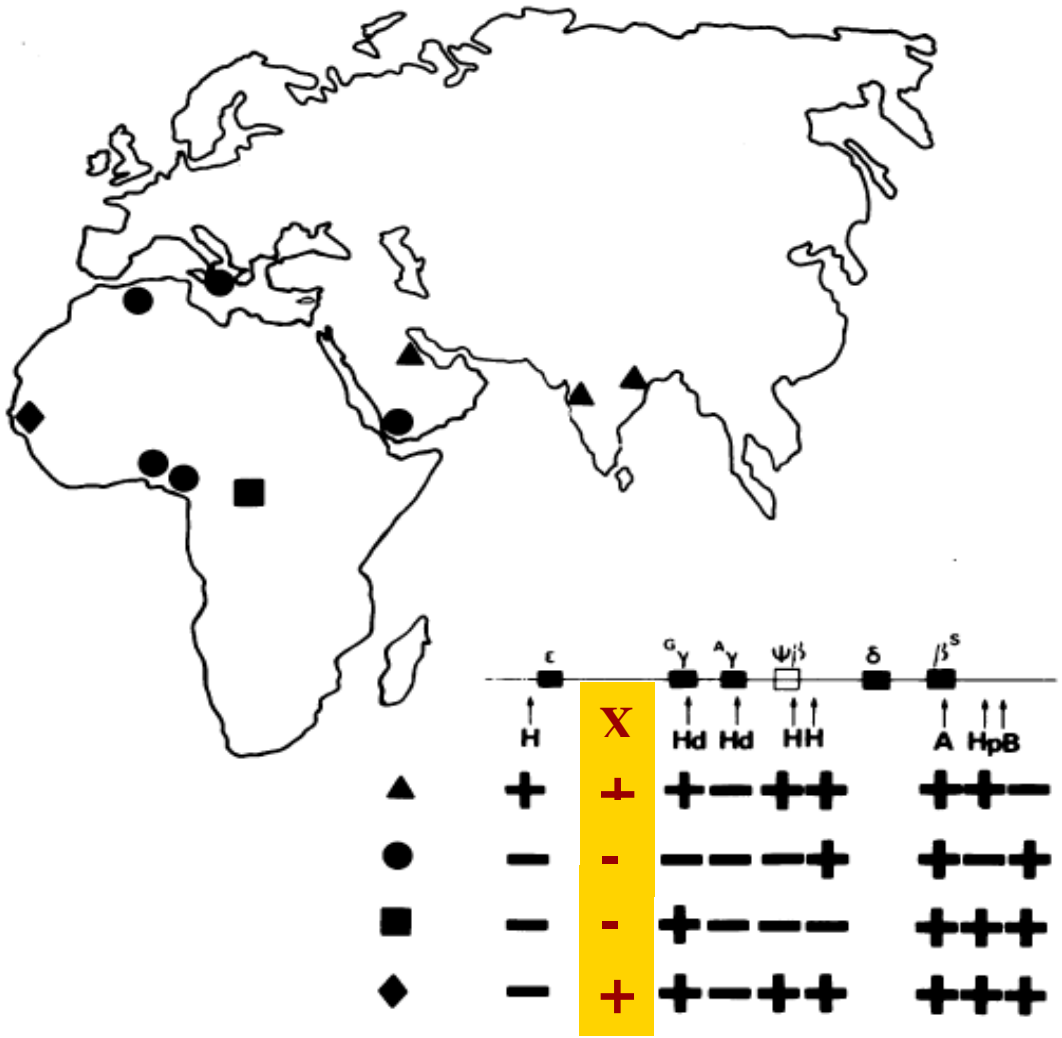
(Wang et al. 2011, Lancet 377(9778): 1663-1672)

Sichelzellscreening verringert die Mortalität



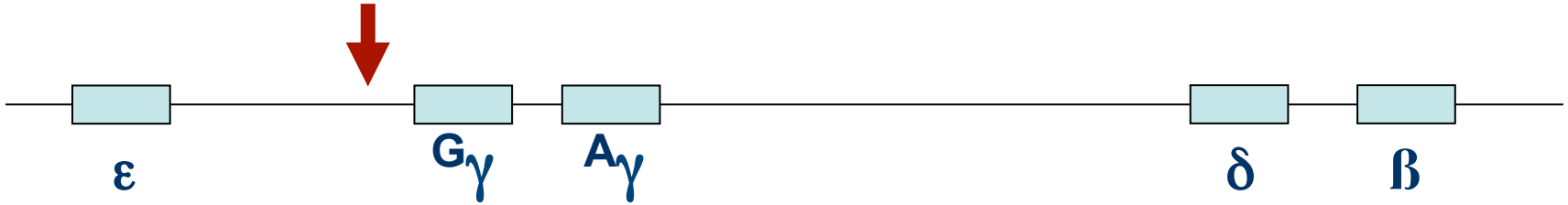
Vichinsky et al. 1988, Pediatrics 81(6) 749-755


Eastern Mediterranean region 6491
European region 1292
American region 9047
African region 233 289
South-East Asian region 26 037
Western Pacific region 13
HbS allele frequency (%)
0–3
3–6
6–9
9–12
12–15
>15



Kulozik et al. Am. J. Hum. Genet. 1986

$^{G}\gamma$ -158 C → T



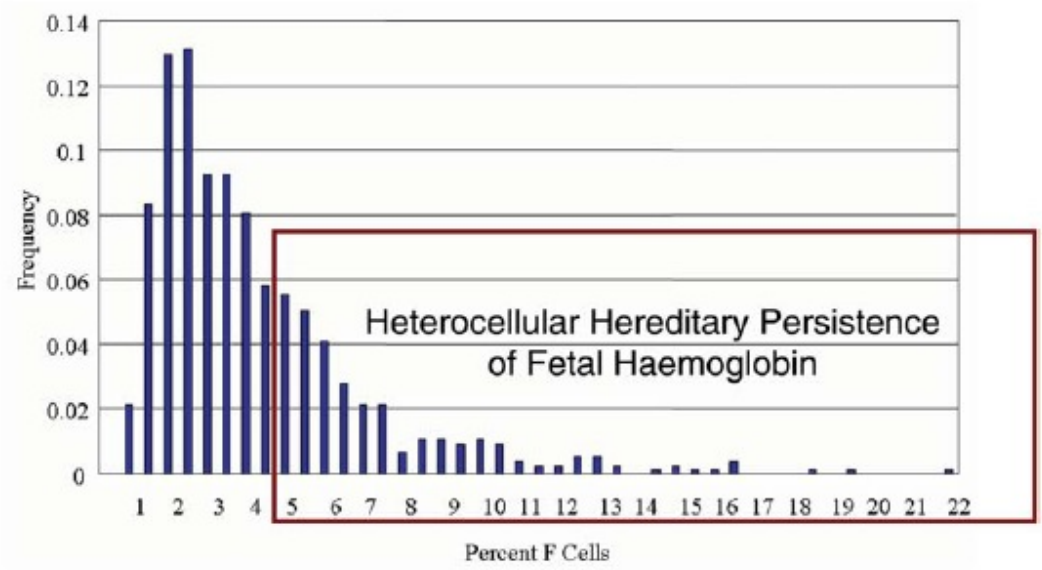
HbF 12-22 %
85 % $^{G}\gamma$-chains

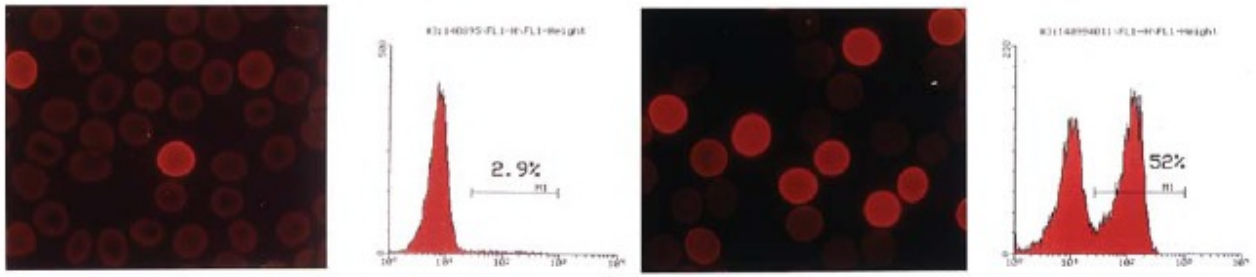
Kulozik et al. Blood 69: 1742 (1987)

Control of fetal hemoglobin: new insights emerging from genomics and clinical implications

Swee Lay Thein[1,2,*], Stephan Menzel[1], Mark Lathrop[3] and Chad Garner[4]

Human Molecular Genetics, 2009, Vol. 18, Review Issue 2
doi:10.1093/hmg/ddp401

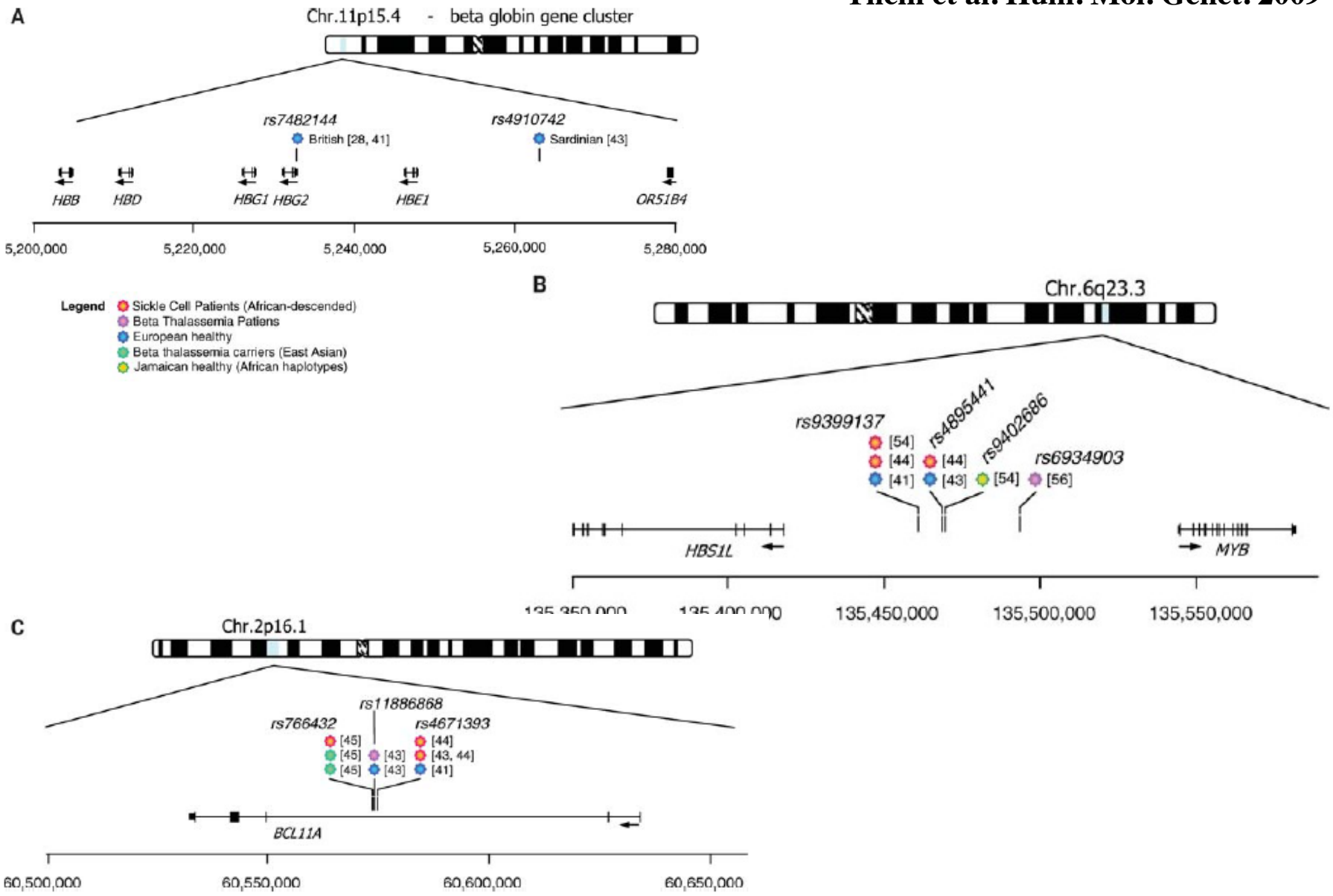




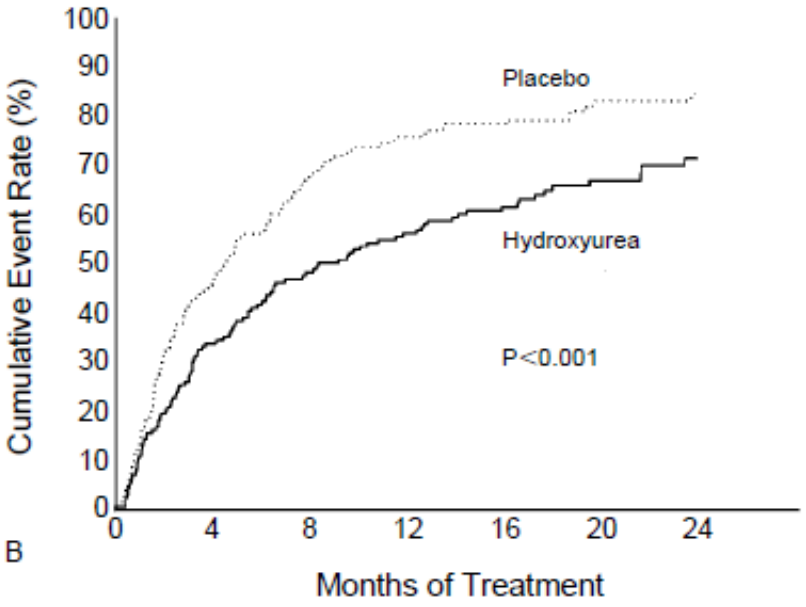
Hb F 0.4%, F cells 2.9%

Hb F 4.8%, F cells 52%

Thein et al. Hum. Mol. Genet. 2009



Hydroxycarbamid vermindert Komplikationen von Kindern und Erwachsenen mit Sichelzellkrankheit



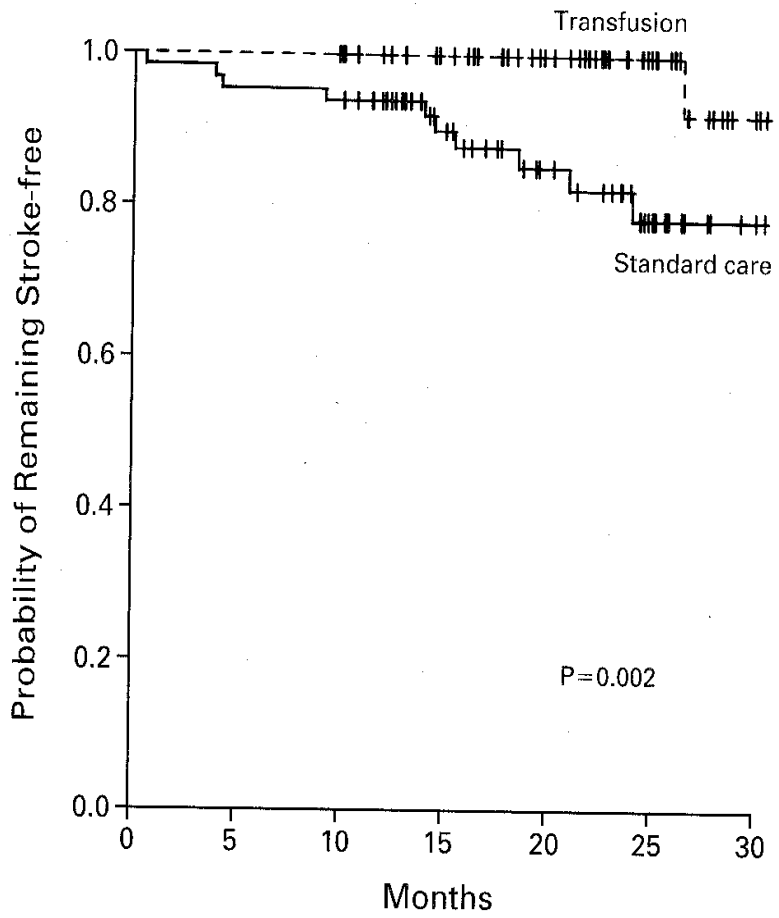
	Before	after	
Hb	8,2 ± 1,0	9,5 ± 1,5	g/dl
HbF	6,9 ± 6,2	15,2 ± 9,8	%
Bili	2,5 ± 0,8	1,6 ± 0,4	mg/dl
Hospital	2,5 ± 0,8	1,1 ± 2,1	Days/mth
	7,0 ± 2,4	1,1 ± 2,1	Adm/year

Charache et al. N. Engl. J. Med. 332: 1317 (1995)

Scott et al. J. Pediatrics, 128:820 (1996)

Prävention eines ersten Schlaganfalls durch Identifikation von Risikopatienten durch transcranielle Doppler Sonographie (TCD)

Variable	Total (N=130)	Transfusion (N=63)	Standard Care (N=67)
Follow-up (mo)			
Total	2550	1321	1229
Median	21.1	22.2	18.3
Mean ±SD	19.6±6.5	21.0±5.7	18.3±7.0
No. of strokes	12	1	11
Cerebral infarction	11	1	10
Intracerebral hematoma	1	0	1



Adams et al., N. Engl. J. Med. 339: 5-11 (1998)

Basisversorgung von Patienten mit einer Sichelzellerkrankung

- **Diagnostik**
  - Neugeborenenscreening
  - Palpation der Milz durch die Eltern
  - Jährliche Fundoscopie ab 10 Jahre
  - 6 monatliche Urinanalyse mit quantitativem Albumin ab 15 Jahre
  - TCD ab 2 Jahre (bis 16 Jahre? oder länger?)

Basisversorgung von Patienten mit einer Sichelzellerkrankung

- **Behandlung**
  - Penicillinprophylaxe mindestens bis 6 Jahre
  - Impfungen gegen Pneumokokken, HIB und Meningokokken
  - Hydroxycarbamid >2 years unabhängig vom Auftreten von Symptomen
  - Regelmäßige Transfusionen von Pat. mit path. TCD
  - ACE Inhibitoren bei Pat. mit Proteinurie
  - SZT bei Verfügbarkeit eines MSD
  - Schulung von Patienten und Eltern

Vielen Dank

Meine Kollegen an der
Kinderklinik in Heidelberg

Insbesondere:
Joachim Kunz
Eva Roth

Kollegen der Leitung
des GPOH Registers
Sichelzellerkrankung

Andrea Jarisch
Regine Grosse
Stepahn Lobitz
Holger Cario
Joachim Kunz