King's College Hospital NHS
NHS Foundation Trust

Renal disease in adults with sickle cell disease

South Thames Sickle Cell and Thalassaemia Network Meeting
27th January 2012

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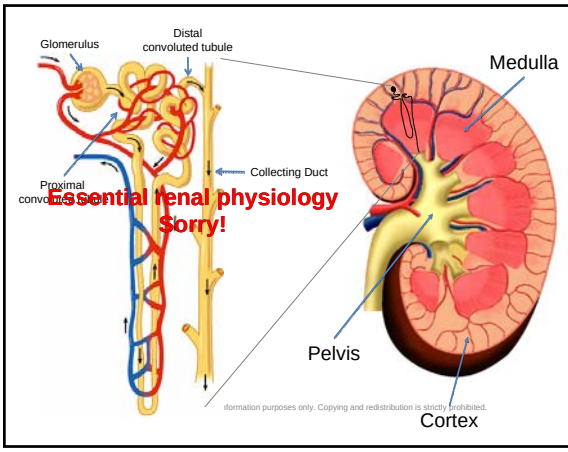
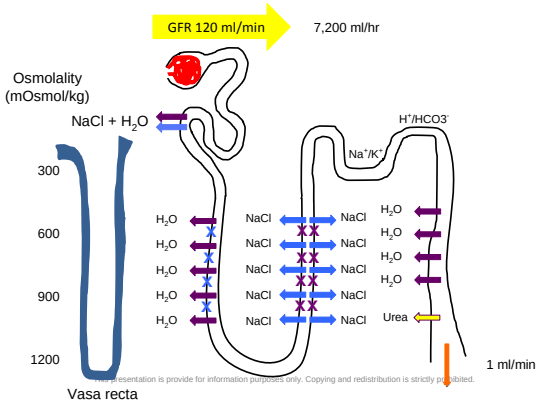
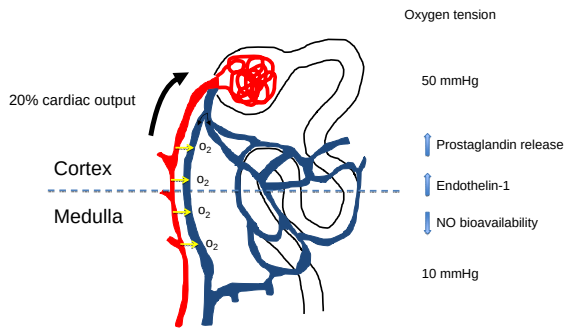


Essential renal physiology
Sorry!



Renal Blood flow



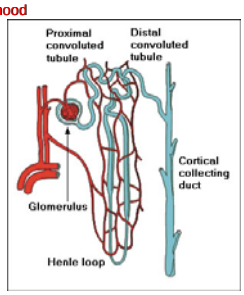
Vasa recta

normal kidney sickle cell trait sickle cell disease

L. W. Statius Van Eps et al, Nature, February 28, 1970.

Clinical manifestations

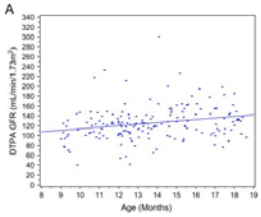
Increased GFR from early childhood to young adulthood



Renal Function in Infants with Sickle Cell Anemia: Baseline Data from the BABY HUG Trial

NHLBI/NICHD-sponsored Phase III double-blinded, placebo-controlled randomized clinical trial testing the hypothesis that hydroxyurea can prevent chronic organ damage in very young children with SCA

176 infants successfully underwent DTPA GFR measurement.
The average age was 13.7 ± 2.6 months (range 9-19 months),



Average baseline quantitative GFR measurement determined by DTPA clearance was 125.2 ± 34.4 mL/min/1.73m²

Compared with the published normal value of 91.5 ± 17.8 mL/min/1.73m²

Ware, RE et al Journal of Pediatrics 2010 Jan;156(1):66-70

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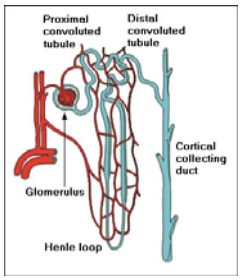
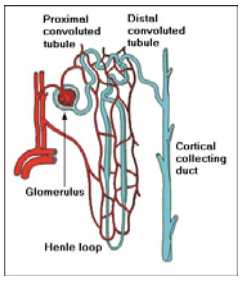


Supranormal Proximal tubular function leading to hyperphosphataemia and increased creatinine secretion

Clinical manifestations

Increased GFR from early childhood to young adulthood



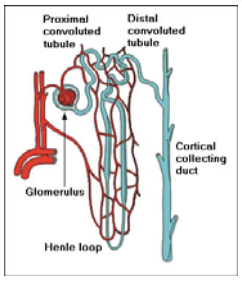
Diminished concentrating ability (hyposthenuria)

Supranormal Proximal tubular function leading to hyperphosphataemia and increased creatinine secretion

Clinical manifestations

Increased GFR from early childhood to young adulthood

Impairment of distal hydrogen ion and potassium secretion



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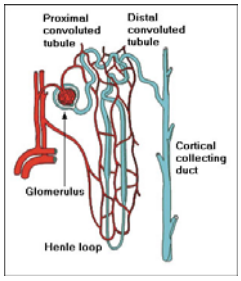

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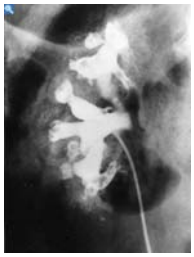
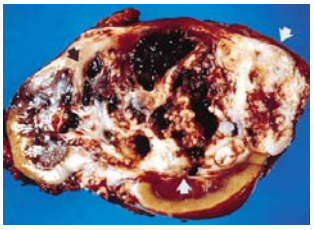
Haematuria



Papillary necrosis

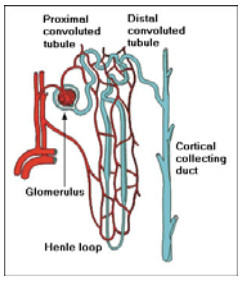


Medullary carcinoma

Clinical manifestations

Increased GFR from early childhood to young adulthood

Impairment of distal hydrogen ion and potassium secretion



Microalbuminuria leading to proteinuria

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Haematuria

Clinical manifestations

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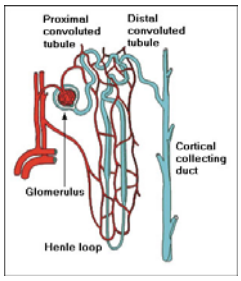

Microalbuminuria leading to proteinuria

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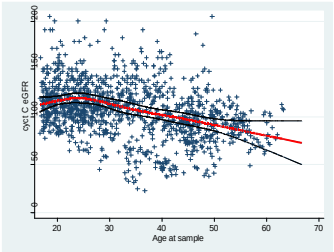
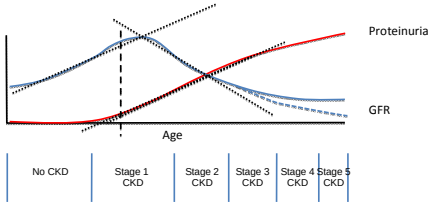
Decreasing GFR from the fourth decade onwards

Haematuria



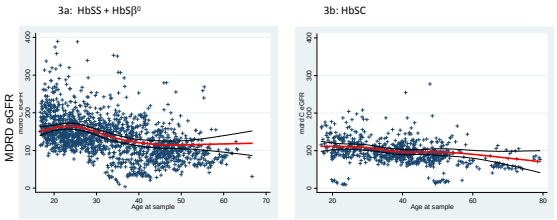


Which patients are most at risk of developing SCN?

Distribution of eGFR with increasing age according to genotype

3a: HbSS + HbSβ⁰

3b: HbSC

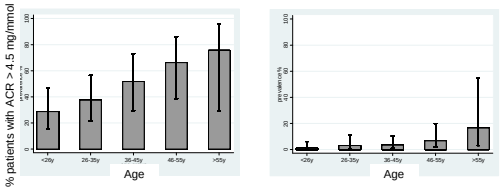


HbSS + HbSβ⁰

HbSC

Day TG, Drasar ER et al, Haematologica, Oct 2011 [Epub ahead of print]

Prevalence of microalbuminuria with increasing age according to genotype



HbSS + HbSβ⁰ HbSC

Day TG, Drasar ER et al, Haematologica, Oct 2011 [Epub ahead of print]

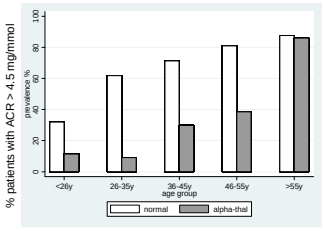
Table 1A. Relationship of hemolytic parameters to ACR in HbSS + HbSβ⁰ group.

		Uncorrected for covariates				Corrected for covariates	
		Degree of albuminuria		Microalbuminuria		Degree of albuminuria	
Hemolytic parameters	SD	% change per SD (95%CI)	*P* value	OR (95%CI)	*P* value	% change per SD (95%CI)	*P* value
Retics (×10⁹/L)	131.7	11.0 (3.8, 21.0)	0.02	0.57 (0.49, 0.64)	0.06	6.6 (-3.3, 17.4)	0.2
Hb (g/dL)	1.4	-17.8 (-26.9, -7.6)	0.0005	0.32 (0.24, 0.41)	0.00002	-20.0 (-29.7, -8.9)	0.001
LDH (IU/L)	161.6	45.5 (30.8, 61.8)	<0.00001	0.72 (0.64, 0.78)	<0.00001	40.8 (25.5, 58.0)	<0.00001
Bilirubin (μmol/L)	0.6	57.7 (32.5, 87.3)	<0.00001	0.67 (0.53, 0.78)	0.007	51.6 (26.3, 82.1)	<0.00001
RBC Hb/RET Hb	0.5	-26.3 (-42.0, -6.3)	0.01	0.21 (0.07, 0.48)	<0.00001	-25.2 (-44.0, -0.2)	0.05
RBC Hb	0.2	-41.1 (-54.0, -24.7)	<0.00001	0.05 (0.01, 0.20)	0.00003	-48.2(-60.6, -31.7)	<0.00001

Table 1B. Relationship of hemolytic parameters to eGFR in HbSS + HbSβ⁰ group.

		Uncorrected for covariates		Corrected for covariates	
Hemolytic parameters	SD	Absolute change per SD (95%CI)	*P* value	Absolute change per SD (95%CI)	*P* value
Retics (×10⁹/L)	131.7	5.1 (2.69, 7.55)	<0.00001	7.7 (5.13, 10.2)	<0.00001
Hb (g/dL)	1.4	1.1 (-2.23, -4.38)	0.3	0.2 (-3.22, 3.52)	0.5
LDH (IU/L)	161.6	-2.7 (-5.72, 0.25)	0.2	-2.2, (-5.25, 0.82)	0.1
Bilirubin (μmol/L)	0.6	2.3 (-2.44, 7.04)	0.2	5.1 (0.28, 9.92)	0.01
RBC Hb/RET Hb	0.5	-11.0 (-19.29, -2.65)	0.005	-8.6 (-18.08, 1.55)	0.1
RBC Hb	0.2	-2.2 (-11.86, 7.37)	0.8	-2.9 (-14.2, 8.33)	0.7

Day TG, Drasar ER et al, Haematologica, Oct 2011 [Epub ahead of print]



HbSS + HbSβ⁰

How should we monitor patients for SCN in the outpatient clinic?

Recommended investigations for patients with proteinuria

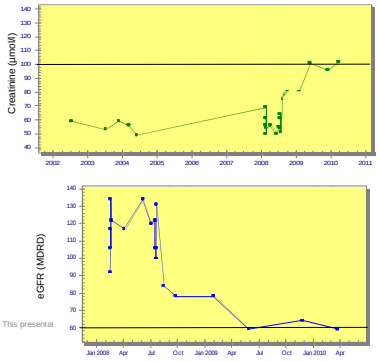
1. Immunology for lupus nephritis
   - Autoantibodies
   - Double-stranded DNA anatibodies
   - Complement levels
2. Virus serology
   - HIV
   - Hepatitis B
   - Hepatitis C
   - HPV B19 (if new-onset nephrotic syndrome or recent transient pure red cell aplasia
3. Myeloma screen (if > 40 years old)
4. Renal tract ultrasound scan
5. Consider renal biopsy if any of 1-3 is positive or acute onset nephrotic syndrome.

Recommended investigations for patients with haematuria

1. Renal tract ultrasound scan
2. Urine cytology
3. CT urogram
4. Immunology for lupus nephritis
   - Autoantibodies
   - Double-stranded DNA antibodies
   - Complement levels
5. Consider cystoscopy
6. Consider renal biopsy if haematuria is present in combination with proteinuria and the above investigations are negative or if 4 is positive

Renal function

Creatinine based estimations of GFR are consistently higher than isotopic GFR in patients with HbSS disease.



Who should be referred to a nephrologist?

All patients with proteinuria and a positive nephritic screen including:

- Autoantibodies
- Complement levels
- Double-stranded DNA levels
- HIV screen

Anyone with rapid onset nephrotic syndrome (consider parvovirus B19 infection)

Anyone with declining renal function (eGFR<60 ml/min)

Management of sickle cell nephropathy

Treatments for SCD

- Hydroxyurea
- Transfusion Therapy (intermittent or regular)
- Haemopoietic cell transplantation in childhood

Specific treatments for sickle cell nephropathy

- Adequate hydration
- Control of blood pressure if hypertensive
- ACE inhibitors/ARB
- Erythropoietin therapy (±hydroxyurea)
- Dialysis
- Transplantation

Evidence for the use of ACEI and ARB in sickle cell nephropathy

2 studies:

Faulk *et al*, 1992

10 patients with SCD and proteinuria were treated with enalapril.

The proteinuria reduced by 57% below the base line on average but returned to 25% below the base line 2 to 3 weeks following discontinuation of treatment.

GFR was not affected.

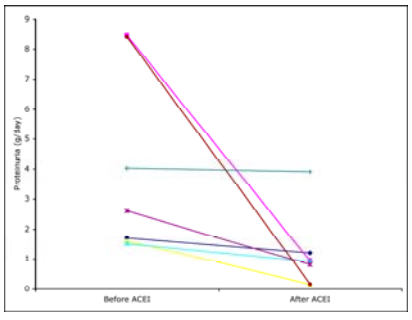
Aoki *et al*, 1995

8 patients with SCD and albuminuria (>30 mg/l) received enalapril for 6 months.

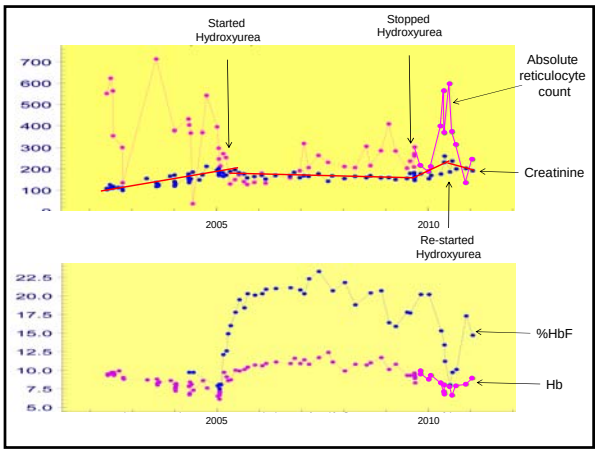
In 7 patients the hyperalbuminuria returned to normal and in 1 patient it was reduced by 70%.

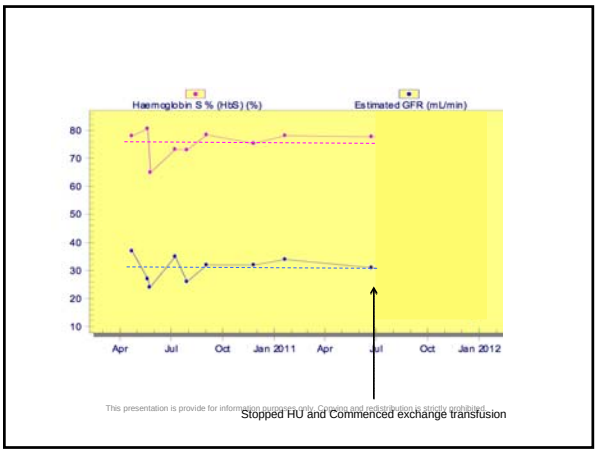
After discontinuation of enalapril the albuminuria returned.

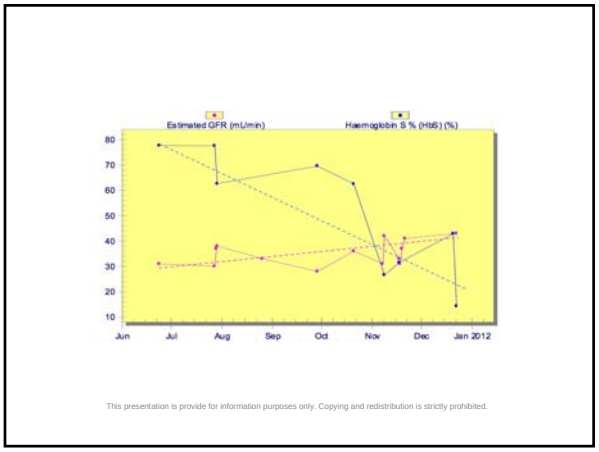
Response to ACE inhibition in 7 patients with SCD at Kings



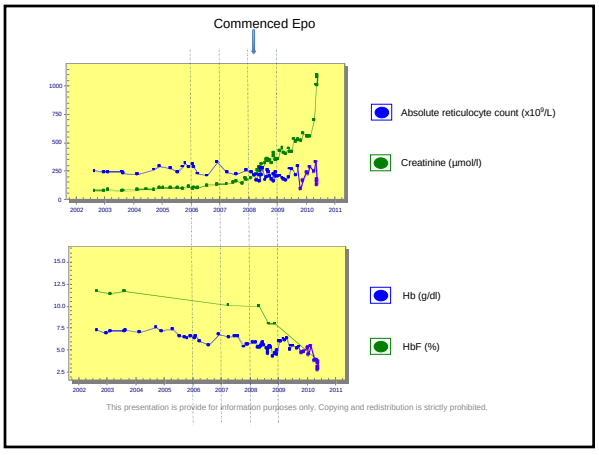
Hydroxyurea and exchange transfusion

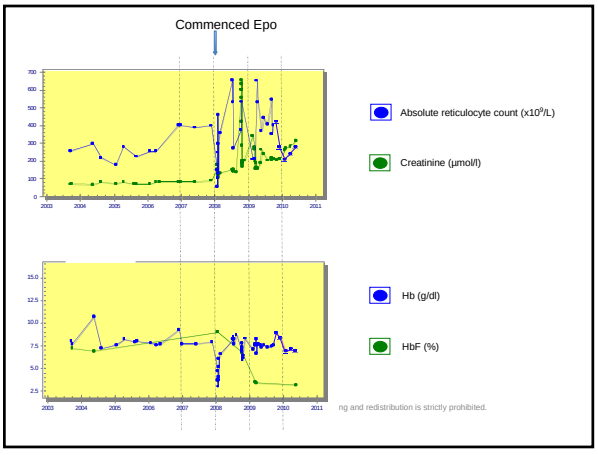






Erythropoietin





End-stage kidney disease

May be as high as 12% and increasing with increasing longevity

Dialysis and Transplantation

Scheinman 2004

Retrospective analysis of patients receiving RRT from the United States Renal data System from 1991-2000,

957 patients with SCD developed ESRD. Only 53 received a transplant.

The projected 7 year survival for transplanted patients was 67% vs 83% for African Americans overall.

However, the 10 year survival of patients with SCD on dialysis was 14%

Conclusion

- Sickle cell nephropathy is a relatively common and significant complication of sickle cell disease. Although most patients don't progress to end-stage renal failure, this complication is becoming more common.
- Moderate to severe renal impairment is associated with a markedly increased risk of mortality
- Patients should be monitored regularly for proteinuria and declining renal function, treated with ACE inhibitors if PCR>50-100 and referred to a nephrologist if necessary.
- HU, exchange transfusion or epo therapy may be beneficial in stabilising deteriorating renal function
- Early transplantation should be considered in patients with severe renal impairment but patient optimization with regular exchange transfusion should be considered both pre and post op.

Thank you