



Published in final edited form as:

*J Pediatr.* 2010 January ; 156(1): 66–70.e1. doi:10.1016/j.jpeds.2009.06.060.

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

Russell E. Ware, MD, PhD<sup>1</sup>, Renee C. Rees, PhD<sup>2</sup>, Sharada A. Sarnaik, MD<sup>3</sup>, Rathi V. Iyer, MD<sup>4</sup>, Ofelia A. Alvarez, MD<sup>5</sup>, James F. Casella, MD<sup>6</sup>, Barry L. Shulkin, MD<sup>1</sup>, Eglal Shalaby-Rana, MD<sup>7</sup>, C. Frederic Strife, MD<sup>8</sup>, John H. Miller, MD<sup>9</sup>, Peter A. Lane, MD<sup>10</sup>, Winfred C. Wang<sup>1</sup>, Scott T. Miller, MD<sup>11</sup>, and The BABY HUG Investigators\*

<sup>1</sup>St. Jude Children's Research Hospital, Memphis, TN

<sup>2</sup>Clinical Trials & Surveys, Corp., Baltimore, MD

<sup>3</sup>Children's Hospital of Michigan, Detroit, MI

<sup>4</sup>University of Mississippi Medical Center, Jackson, MS

<sup>5</sup>University of Miami School of Medicine, Miami, FL

<sup>6</sup>Johns Hopkins University School of Medicine, Baltimore, MD

<sup>7</sup>Radiology, Children's National Medical Center, Washington DC

<sup>8</sup>Cincinnati Children's Hospital Medical Center, Cincinnati, OH

<sup>9</sup>Radiology, Harbor - UCLA Medical Center, Torrance, CA

<sup>10</sup>School of Medicine, Emory University, Atlanta, GA

<sup>11</sup>SUNY – Downstate Medical Center, Brooklyn, NY

### Abstract

**Objectives**—To examine the feasibility and accuracy of GFR measurements in infants with sickle cell anemia (SCA).

**Study design**—The NHLBI/NICHHD-sponsored Phase III randomized double-blinded placebo-controlled trial (BABY HUG) tests the hypothesis that hydroxyurea can prevent chronic organ damage in SCA. Glomerular filtration rate (GFR) elevation is a co-primary endpoint, measured quantitatively by <sup>99m</sup>Tc-DTPA plasma clearance and estimated by the Schwartz equation using height and creatinine.

Corresponding author: Russell E. Ware MD PhD, St. Jude Children's Research Hospital, Memphis, TN 38105, 901-595-4238 (phone), 901-595-4723 (fax), russell.ware@stjude.org.

\*List of BABY HUG Investigators available at [www.jpeds.com](http://www.jpeds.com) (Appendix 1)

**Publisher's Disclaimer:** This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

The authors declare no conflicts of interest.

**Results**—DTPA GFR measurement was attempted in 191 infants; 176 of 184 completed studies (96%) were interpretable. Average age (mean  $\pm$  1SD) was 13.7 $\pm$ 2.6 months. Average DTPA GFR was 125.2 $\pm$ 34.4 (range 40.2–300.9, normal 91.5 $\pm$ 17.8 mL/min/1.73m<sup>2</sup>), and Schwartz estimates were higher at 184.4 $\pm$ 55.5 mL/min/1.73m<sup>2</sup>. DTPA GFR was correlated with Schwartz GFR ( $r^2=0.0658$ ,  $p=0.0012$ ); also with age, weight, height, and kidney volume (all  $p<0.002$ ); but not with hemoglobin, HbF, WBC, reticulocytes, medical events, or splenic function.

**Conclusions**—Quantitative GFR measurement is feasible but variable among infants with SCA. Schwartz GFR estimates are not highly correlated with quantitative DTPA GFR values. Baseline GFR measurements suggest that renal dysfunction in SCA, evidenced by glomerular hyperfiltration, begins during infancy.

## Keywords

glomerular filtration rate; hydroxyurea; sickle cell anemia

Impaired urine concentrating ability, defects in urine acidification and electrolyte regulation, and supra-normal proximal tubular function are commonly recognized in young patients with SCA [1–4]. Glomerular enlargement with an increased glomerular filtration rate (GFR) is perhaps the earliest renal abnormality in sickle cell anemia (SCA). The elevated GFR is secondary to a potentially reversible increase in renal plasma flow [5, 6]. Proteinuria occurs later, often in the second decade of life [7]. Proteinuria is usually asymptomatic with microalbuminuria, but 10–20% of young adults can develop macroalbuminuria with nephrotic range protein loss [6–8]. Patients with SCA and proteinuria frequently have glomerulomegaly and focal glomerular sclerosis on renal biopsy [9]. In adulthood, about one-third of patients with SCA will develop chronic renal failure, a major cause of mortality in this population [10]. Despite these well-established consequences of sickle nephropathy, there have been no large longitudinal studies to characterize its natural progression. Furthermore, questions remain about: (1) the age of onset of glomerular hyperfiltration; (2) the degree of elevated GFR, especially using estimates based on creatinine; and (3) the feasibility of quantitative GFR assessment in young patients.

BABY HUG is the NHLBI/NICHD-sponsored Phase III double-blinded, placebo-controlled randomized clinical trial ([ClinicalTrials.gov # NCT00006400](https://clinicaltrials.gov/ct2/show/study/NCT00006400)) testing the hypothesis that hydroxyurea can prevent chronic organ damage in very young children with SCA [11]. In BABY HUG, the co-primary endpoints are renal function (GFR) and splenic function (radionuclide uptake). One of the major challenges in the development of the renal endpoint for the BABY HUG trial was determining a feasible method of measuring GFR quantitatively and accurately in this very young patient population. The technique often considered to be the “gold standard” for GFR measurement is inulin clearance, which is quantitative and accurate, but requires bladder catheterization and a 24-hour urine collection [6, 12]. GFR calculations based on creatinine clearance also use timed urine collections, so are technically difficult at any age and not generally considered to be accurate [13]. In contrast, plasma clearance of an injected radionuclide is generally considered to be accurate and technically simpler [14], and has minimal within-day and between-day variation [15]. Among the various radiopharmaceutical compounds that have been used for GFR determination, iothexol clearance may be the most accurate [16], but <sup>99m</sup>Tc-DTPA is readily

available at most medical centers, is relatively safe with a very short half-life (~6 hours), and has been used extensively in children [17]. However, the feasibility of this technique requiring peripheral IV access in infancy was not known and several BABY HUG centers did not have previous or ongoing experience with DTPA procedures.

In BABY HUG, the GFR is measured quantitatively by plasma clearance of injected  $^{99m}\text{Tc}$ -DTPA; GFR is also estimated by the Schwartz equation using creatinine and an age-dependent constant. In this report, we present baseline data from BABY HUG regarding the feasibility of quantitative GFR assessment; comparison of DTPA clearance to Schwartz GFR estimates; and clinical, laboratory, and radiographic associations with GFR elevation in very young patients with SCA.

## METHODS

Infants with known SCA but without regard to clinical severity were enrolled at 9 through 17 months of age as previously described [11]. Subjects were randomized to receive either hydroxyurea or placebo. The primary study outcomes are preservation of renal and splenic function, which are measured at baseline and after 24 months of treatment. Study enrollment and randomization were completed in September 2007.

### GFR measurements

After all screening tests were completed and randomization to study treatment had occurred, a quantitative  $^{99m}\text{Tc}$ -DTPA clearance study was performed on each subject at study initiation, specifically on the first day of study treatment. Briefly, intravenous access was established and a baseline serum creatinine was collected for central measurement by HPLC to 0.01 mg/dL precision. Next, 500 microCuries of  $^{99m}\text{Tc}$ -DTPA were administered intravenously and plasma samples were collected at 1, 2, and 4 hours after injection. After these specimens were analyzed in duplicate, a plasma DTPA clearance curve was calculated and the quantitative GFR value was derived as previously described [12, 17]. (A detailed description of the DTPA clearance method is included as an on-line supplement.) GFR was also estimated using the Schwartz formula, which is based on the height of the patient (cm) and creatinine (mg/dL) as follows:  $\text{GFR} = (\text{height} \times k) / (\text{serum creatinine})$ , where  $k=0.45$  for infants less than 12 months of age and  $k=0.55$  over 12 months of age [18, 19].

### Statistical analyses

Past medical history was collected on all enrolled infants, including previous dactylitis and other acute painful events, acute chest syndrome, splenic sequestration, and bacteremia/sepsis. Laboratory values were collected during screening and analyzed as baseline values, including complete blood counts and reticulocyte counts measured locally, as well as fetal hemoglobin levels and serum chemistries measured centrally.

Some laboratory values were  $\log_{10}$  transformed to stabilize the variance before data analysis. All descriptive statistics and analyses used SAS Version 8.2 (SAS Institute, Cary NC). Univariate regression was performed to determine correlations of DTPA and Schwartz GFR with each other, as well as to patient characteristics and laboratory values. The Student t-test was used to assess associations with sex and previous medical events. The Fisher exact

test and the Cochran-Armitage chi-square exact test for trend compared categorical age with DTPA GFR values and Schwartz GFR estimates.

## RESULTS

The total number of infants who enrolled in the BABY HUG trial and underwent screening tests, as well as the number who underwent DTPA GFR assessment at the time of study initiation, are shown in Figure 1. All enrolled subjects had either HbSS or HbS/ $\beta^0$ -thalassemia. The average age at GFR measurement was  $13.7 \pm 2.6$  months (range 9–19 months) and 59% of subjects were female. A total of 157 subjects had simultaneous baseline DTPA and Schwartz GFR values available for analysis.

Baseline (mean $\pm$ 1SD) hematological results for this cohort included hemoglobin concentration =  $9.0 \pm 1.4$  gm/dL, absolute reticulocytes =  $296 \pm 137 \times 10^9$ /L, white blood cell (WBC) count =  $14.3 \pm 5.7 \times 10^9$ /L, and fetal hemoglobin (HbF) =  $25.6 \pm 8.8\%$ . Baseline past medical history included at least one episode of dactylitis (34% of subjects), splenic sequestration (7%), and acute chest syndrome (5%). There were no cases of previous invasive bacteremia, sepsis, or meningitis.

### GFR values and age

For the entire infant cohort, the average baseline quantitative GFR measurement determined by DTPA clearance was  $125.2 \pm 34.4$  mL/min/1.73m<sup>2</sup> (range 40.2 – 300.9 mL/min/1.73m<sup>2</sup>). These baseline DTPA GFR values are elevated, compared with the published normal value of  $91.5 \pm 17.8$  mL/min/1.73m<sup>2</sup> (10%–90% range of 60–120 mL/min/1.73m<sup>2</sup>) for this age group [20]. On average, the baseline DTPA GFR values significantly increased by 3.1 mL/min/1.73m<sup>2</sup> for every one month increase in age ( $p=0.0013$ , Figure 2, A); however, this correlation was low ( $r^2=0.058$ ). Using a quantitative GFR threshold of 110 mL/min/1.73m<sup>2</sup> (the normal GFR value for age plus 1 SD) and age thresholds of 12 and 15 months, higher DTPA GFR values were observed in older infants,  $p=0.032$  (Table). In comparison to DTPA GFR values, the average baseline GFR values by Schwartz estimate were substantially higher at  $184.4 \pm 55.5$  mL/min/1.73m<sup>2</sup>, range 65.8–355.4 mL/min/1.73m<sup>2</sup>, which also correlated with age.

### GFR correlations

In univariate analysis, the DTPA GFR value was positively correlated with the Schwartz GFR estimate ( $r^2=0.0658$ ,  $p=0.0012$ , slope=0.169), although this correlation was weak and showed considerable variation (Figure 2, B). The DTPA GFR was also positively correlated with weight, height and kidney volume (all  $p<0.002$ ), but not with sex, baseline hemoglobin concentration, %HbF, WBC count, platelets, or reticulocytes; there was a negative correlation with serum creatinine ( $p=0.0299$ ). Similarly, the DTPA GFR was not correlated with previous sickle cell-related events either measured individually or as a composite of clinical severity, and also was not correlated with measures of splenic function including qualitative radionuclide uptake on liver-spleen scan and quantitative measures of pitted erythrocytes [21] and micronuclei [22].

## DISCUSSION

Infants 9 through 17 months of age were enrolled in one BABY HUG trial at 14 centers across the United States, underwent baseline screening studies, then were randomized to a single daily oral 20 mg/kg dose of liquid hydroxyurea formulation or placebo for 24 months of treatment. The co-primary endpoints are splenic and renal function, assessed by qualitative  $^{99m}\text{Tc}$ - sulfur colloid uptake in the spleen and quantitative GFR measurement, respectively. The renal endpoint of GFR was selected because glomerular hyperfiltration is known to be an early marker of renal dysfunction in SCA [4, 6, 8] and likely contributes to the development of glomerulosclerosis, the predominant lesion observed as renal insufficiency develops in older patients with SCA [9].

Our data indicate that DTPA GFR measurement using a standardized protocol is feasible in this very young age group across multiple centers because the quantitative DTPA technique was successful in 92% of attempts (Figure 1). Almost all completed DTPA studies were interpretable ( $176/184 = 96\%$ ), thereby providing baseline GFR values that will be used in this prospective trial. The baseline GFR results indicate that glomerular hyperfiltration appears to begin very early in life for infants with SCA and rises with increasing age (Table and Figure 2, A). The average GFR value of  $125 \text{ mL/min/1.73m}^2$  measured in our patient cohort is almost two standard deviations higher than reported for normal infants [16, 20], but with a larger standard deviation than these reports. Although these references for normal GFR values used iothexol clearance [16] or  $^{51}\text{Cr-EDTA}$  plasma clearance [20], the renal clearance of  $^{99m}\text{Tc-DTPA}$  is very similar [23]. Although the exact progression of renal disease in SCA is not completely understood, it seems ominous that glomerular hyperfiltration should appear so early in life. These results suggest that therapeutic intervention for preservation of renal function in SCA would need to begin early in life, in order to prevent glomerular hyperfiltration and other early manifestations of sickle nephropathy.

DTPA GFR elevation was not correlated with other laboratory abnormalities or previous acute medical events. This observation highlights the difficulty in defining clinical severity in SCA: acute vaso-occlusive events, laboratory abnormalities, and chronic organ damage do not always develop simultaneously in individual patients. Furthermore, the pathophysiology of SCA may selectively affect different organs, or even different anatomic and functional portions of organs such as the kidney. Recent attempts to classify SCA into two exclusive phenotypes [24], one related to sickling and vaso-occlusion and the other related to hemolysis and endothelial dysfunction, is problematic for the kidney; early sickle nephropathy has not been clearly associated with a single phenotype and may involve both processes.

GFR estimation using serum creatinine has long been considered an attractive alternative to DTPA GFR measurement, due to its comparative simplicity. For over 30 years, estimation of GFR has been possible using the Schwartz equation, in which GFR is calculated from the patient's height and creatinine level [18, 19]. The Schwartz formula, widely used in the general clinical pediatric setting, was developed in children with renal disease (i.e., low GFR) by adjusting serum creatinine for height and age, and developing constants to best fit

data obtained by inulin clearance. However, data specific to the second year of life, which is most appropriate for baseline GFR estimates in the BABY HUG trial, are relatively sparse. To determine whether or not the Schwartz GFR estimate is accurate in infants with SCA, serum creatinine was collected on the same day as the DTPA determination, and was measured centrally to 0.01 mg/dL precision. In our cohort, the Schwartz GFR estimates were much higher than the DTPA GFR values (Figure 2B), with a statistically significant but weak positive correlation and best-fit slope that is far from unity. The reasons for this weak correlation are not entirely clear, but likely relate to the fact that the Schwartz equation (and almost all published methods for estimating GFR) were designed and validated in patients with renal dysfunction and low GFR values. Because children with SCA have normal to elevated GFR values, these estimates are likely to be less accurate in the BABY HUG patient population. In addition, the Schwartz equation has creatinine in the denominator of the formula. Serum creatinine is very low in patients with SCA due to glomerular hyperfiltration and tubular secretion of creatinine [4, 25], so small changes in creatinine can make a large difference in the calculated value. Alternative measures such as cystatin C can be used to estimate GFR [26–28], but the newly revised Schwartz formula that includes cystatin C and creatinine has not yet been validated in SCA [29].

Taken together, these baseline data from the BABY HUG trial confirm age- and disease-related glomerular hyperfiltration in SCA. The data indicate that renal dysfunction in SCA as measured by GFR elevation may begin very early in life. Quantitative GFR measurement is feasible but highly variable in this very young patient population. The Schwartz estimates and DTPA GFR values are only weakly correlated. Specific data regarding the impact of hydroxyurea on the kidney in SCA are limited to small series, but short-term therapy in children with proteinuria has documented benefit [30–32]. Perhaps by improving anemia, hydroxyurea therapy may reduce glomerular hyperfiltration and slow the progression of renal dysfunction in SCA.

BABY HUG should yield important information regarding the ability of hydroxyurea to prevent glomerular hyperfiltration among infants with SCA. Longer follow-up will be required to determine if hydroxyurea reduces the incidence of proteinuria, which begins later in childhood; such a reduction would be a further indication that hydroxyurea prevents renal damage in children with SCA.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

We thank the BABY HUG personnel at the participating Clinical Centers (Appendix 1), and the efforts of the BABY HUG subjects and their families.

Supported by Contracts N01-HB-07150 to N01-HB-07160 from the National Heart, Lung, and Blood Institute (NHLBI), with partial support of the Best Pharmaceuticals for Children Act and the National Institute of Child Health and Human Development (NICHD).

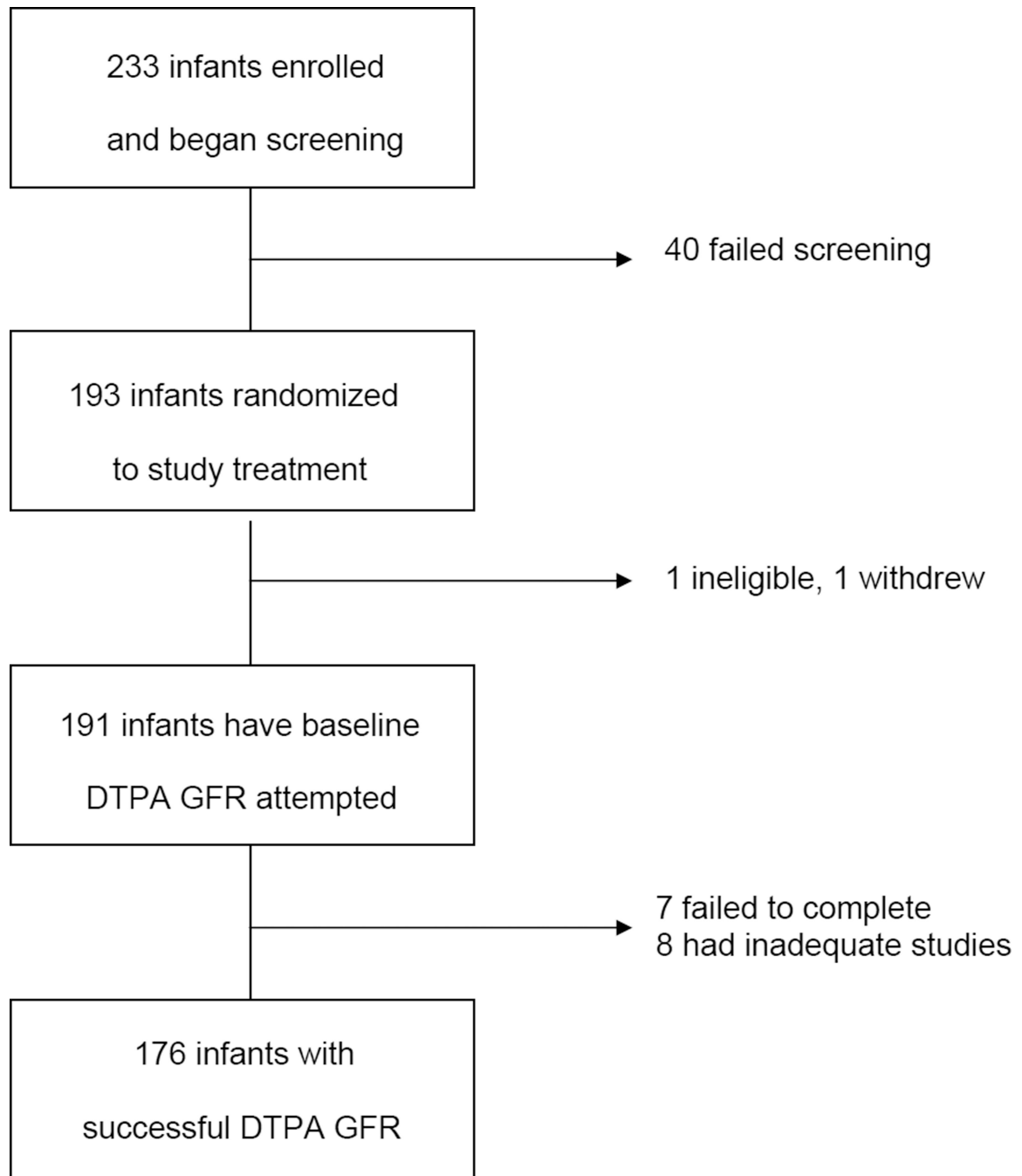


## REFERENCES

1. Etteldorf JN, Smith JD, Tuttle AH, Diggs LW. Renal hemodynamic studies in adults with sickle cell anemia. *Am J Med.* 1955; 18:243–248. [PubMed: 13228447]
2. Whitten CF, Younes AA. A comparative study of renal concentrating ability in children with sickle cell anemia and in normal children. *J Lab Clin Med.* 1960; 55:400–415. [PubMed: 13844489]
3. Oster JR, Lespier LE, Lee SM, Pellegrini EL, Vaamonde CA. Renal acidification in sickle-cell disease. *J Lab Clin Med.* 1976; 88:389–401. [PubMed: 8574]
4. Allon M. Renal abnormalities in sickle cell disease. *Arch Intern Med.* 1990; 150:501–504. [PubMed: 2178577]
5. Anderson S, Meyer TW, Rennke HG, Brenner BM. Control of glomerular hypertension limits glomerular injury in rats with reduced renal mass. *J Clin Invest.* 1985; 76:612–619. [PubMed: 2993362]
6. Allon M, Lawson L, Eckman JR, Delaney V, Bourke E. Effects of nonsteroidal anti-inflammatory drugs on renal function in sickle cell anemia. *Kidney Int.* 1988; 34:500–506. [PubMed: 3199668]
7. Wigfall DR, Ware RE, Burchinal MR, Kinney TR, Foreman JW. Prevalence and clinical correlates of glomerulopathy in children with sickle cell disease. *J Pediatr.* 2000; 136:749–753. [PubMed: 10839871]
8. Ataga KI, Orringer EP. Renal abnormalities in sickle cell disease. *Am J Hematol.* 2000; 63:205–211. [PubMed: 10706765]
9. Tejani A, Phadke K, Adamson O, Nicastrì A, Chen CK, Sen D. Renal lesions in sickle cell nephropathy in children. *Nephron.* 1985; 39:352–355. [PubMed: 3982580]
10. Platt OS, Brambilla DJ, Rosse WF, Milner PF, Castro O, Steinberg MH, et al. Mortality in sickle cell disease. Life expectancy and risk factors for early death. *N Engl J Med.* 1994; 330:1639–1644. [PubMed: 7993409]
11. Thompson BW, Rogers ZR, Miller ST, Rees RC, Ware RE, Waclawiw MA, et al. The pediatric hydroxyurea Phase III clinical trial (BABY HUG) design. submitted.
12. Rehling M, Moller ML, Thamdrup B, Lund JO, Trap-Jensen J. Simultaneous measurement of renal clearance and plasma clearance of  $^{99m}\text{Tc}$ -labelled diethylenetriaminepenta-acetate,  $^{51}\text{Cr}$ -labelled ethylenediaminetetra-acetate and inulin in man. *Clin Sci.* 1984; 66:613–619. [PubMed: 6423339]
13. Toto RD, Kirk KA, Coresh J, Jones C, Appel L, Wright J, et al. Evaluation of serum creatinine for estimating glomerular filtration rate in African Americans with hypertensive nephrosclerosis: Results from the African-American Study of Kidney Disease and Hypertension (AASK) Pilot Study. *J Am Soc Nephrol.* 1997; 8:279–287. [PubMed: 9048347]
14. Russell CD, Bischoff PG, Rowell KL, Kontzen F, Lloyd LK, Tauxe WN, et al. Quality control of  $\text{Tc}^{99m}$  DTPA for measurement of glomerular filtration: concise communication. *J Nucl Med.* 1983; 24:722–727. [PubMed: 6348219]
15. Perrone RD, Steinman TI, Beck GJ, Skibinski CI, Royal HD, Lawlor M, et al. Utility of radioisotopic filtration markers in chronic renal insufficiency: Simultaneous comparison of  $^{125}\text{I}$ -Iothalamate,  $^{169}\text{Yb}$ -DTPA,  $^{99m}\text{Tc}$ -DTPA, and inulin. The Modification of Diet in Renal Disease Study. *Am J Kidney Dis.* 1990; 16:224–235. [PubMed: 2205098]
16. Schwartz GJ, Furth SL. Glomerular filtration rate measurement and estimation in chronic kidney disease. *Pediatr Nephrol.* 2007; 22:1839–1848. [PubMed: 17216261]
17. Rodman JH, Maneval DC, Magill HL, Sunderland M. Measurement of  $\text{Tc}^{99m}$  DTPA serum clearance for estimating glomerular filtration rate in children with cancer. *Pharmacotherapy.* 1993; 13:10–16. [PubMed: 8437963]
18. Schwartz GJ, Haycock GB, Edelmann CM Jr, Spitzer A. A simple estimate of glomerular filtration rate in children derived from body length and plasma creatinine. *Pediatrics.* 1976; 58:259–263. [PubMed: 951142]
19. Schwartz GJ, Furth SL. Glomerular filtration rate measurement and estimation in chronic kidney disease. *Pediatr Nephrol.* 2007; 22:1839–1848. [PubMed: 17216261]
20. Piepsz A, Tondeur M, Ham H. Revisiting normal  $^{51}\text{Cr}$ -ethylenediaminetetraacetic acid clearance values in children. *Eur J Nucl Med Mol Imaging.* 2006; 33:1477–1482. [PubMed: 16865393]

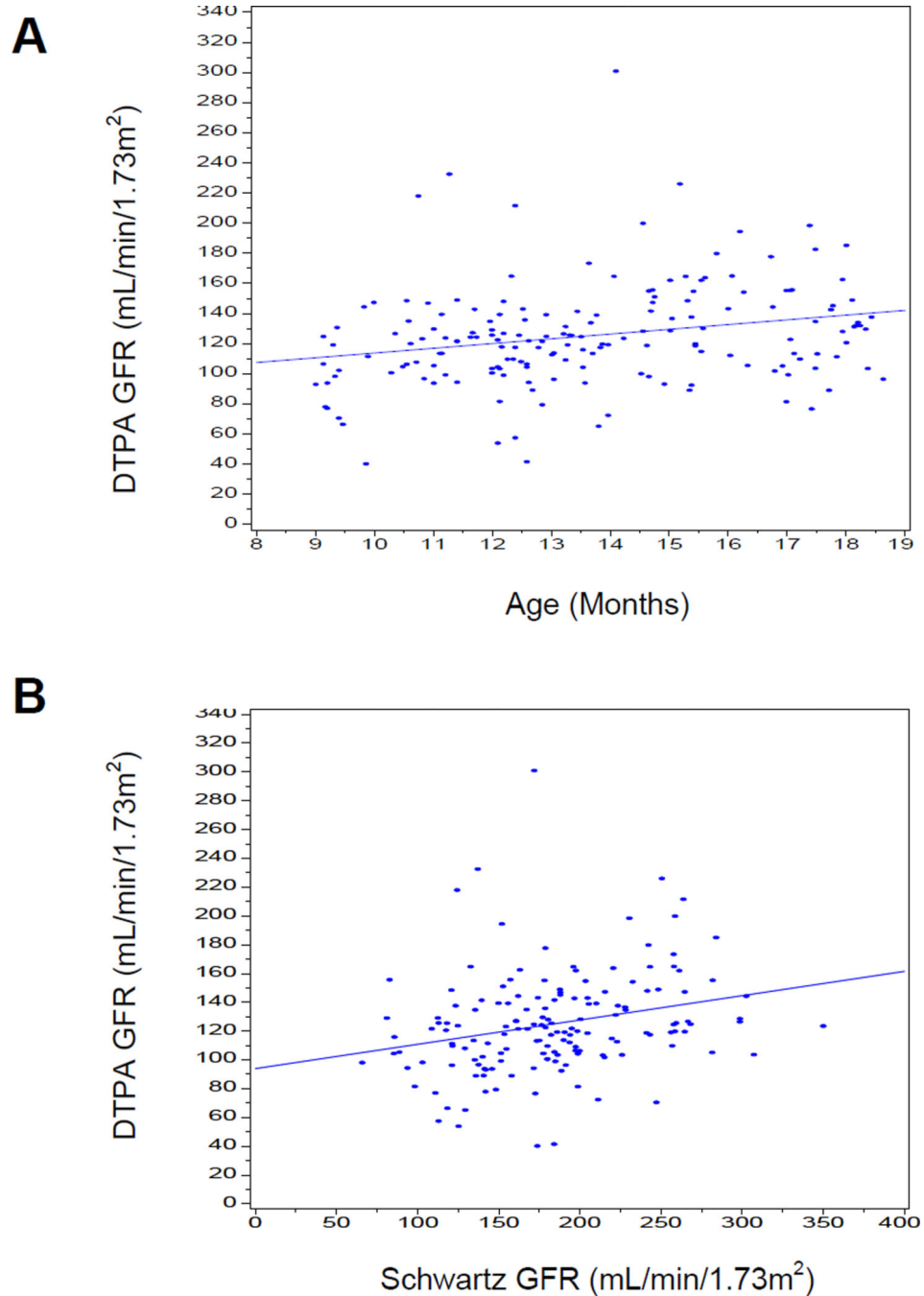
21. Zago MA, Bottura C. Splenic function in sickle-cell disease. *Clin Sci*. 1983; 65:297–302. [PubMed: 6872464]
22. Harrod VL, Howard TA, Zimmerman SA, Dertinger SD, Ware RE. Quantitative analysis of Howell-Jolly bodies in children with sickle cell disease. *Exp Hematol*. 2007; 35:179–183. [PubMed: 17258066]
23. Hilson AJ, Mistry RD, Maisey MN. <sup>99</sup>Tcm-DTPA measurement of glomerular filtration rate. *Br J Radiol*. 1976; 49:794–796. [PubMed: 822911]
24. Kato GJ, Gladwin MT, Steinberg MH. Deconstructing sickle cell disease: reappraisal of the role of hemolysis in the development of clinical subphenotypes. *Blood Reviews*. 2007; 21:37–47. [PubMed: 17084951]
25. Rahn KH, Heidenreich S, Brückner D. How to assess glomerular function and damage in humans. *J Hypertens*. 1999; 17:309–317. [PubMed: 10100067]
26. Coll E, Botey A, Alvarez L, Poch E, Quintó L, Saurina A, et al. Serum cystatin C as a new marker for noninvasive estimation of glomerular filtration rate and as a marker for early renal impairment. *Am J Kidney Dis*. 2000; 36:29–34. [PubMed: 10873868]
27. Voskaridou E, Terpos E, Michail S, Hantzi E, Anagnostopoulos A, Margeli A, et al. Early markers of renal dysfunction in patients with sickle cell/ $\beta$ -thalassemia. *Kidney Int*. 2006; 69:2037–2042. [PubMed: 16501491]
28. Alvarez O, Zilleruelo G, Wright D, Montane B, Lopez-Mitnik G. Serum cystatin C levels in children with sickle cell disease. *Pediatr Nephrol*. 2006; 21:533–537. [PubMed: 16491413]
29. Schwartz GJ, Muñoz A, Schneider MF, Mak RH, Kaskel F, Warady BA, et al. New equations to estimate GFR in children with CKD. *J Am Soc Nephrol*. 2009 in press.
30. Fitzhugh CD, Wigfall DR, Ware RE. Enalapril and hydroxyurea therapy for children with sickle nephropathy. *Pediatr Blood Cancer*. 2005; 45:982–985. [PubMed: 15704213]
31. McKie KT, Hanevold CD, Hernandez C, Waller JL, Ortiz L, McKie KM. Prevalence, prevention, and treatment of microalbuminuria and proteinuria in children with sickle cell disease. *J Pediatr Hematol Oncol*. 2007; 29:140–144. [PubMed: 17356390]
32. Alvarez O, Lopez-Mitnik G, Zilleruelo G. Short-term follow-up of patients with sickle cell disease and albuminuria. *Pediatr Blood Cancer*. 2008; 50:1236–1239. [PubMed: 18293385]





**Figure 1.**

Quantitative GFR analysis by DTPA clearance in the BABY HUG trial. A total of 233 infants were initially screened for eligibility, 40 of whom failed screening. Reasons for inadequate or uninterpretable DTPA results were variable but included poor venous access, extravasated radionuclide, and difficulties with blood collection. A total of 176/191 DTPA attempts (92%) were successful with interpretable results.



**Figure 2.**

Quantitative baseline DTPA GFR correlations in infants with SCA. A, DTPA GFR compared with age, with GFR increasing in older infants,  $N=176$ ,  $r^2=0.058$ ,  $p=0.0013$ . B, DTPA GFR compared with the estimated Schwartz GFR, showing a positive correlation but wide variation,  $N=157$ ,  $r^2=0.0658$ ,  $p=0.0012$ , slope = 0.169.

**Table**

Baseline DTPA GFR values in the BABY HUG trial, according to age.

Age at Treatment Initiation	DTPA GFR value 110 mL/min/1.73m <sup>2</sup>	DTPA GFR value > 110 mL/min/1.73m <sup>2</sup>	Total
9.0 – 11.9 months	21	29	50
12.0 – 14.9 months	24	44	68
15.0 months	13	45	58

Using the thresholds of 12 and 15 months for age and 110 mL/min/1.73m<sup>2</sup> for GFR, baseline quantitative DTPA GFR values were significantly higher among older infants with SCA,  $p=0.032$ .