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Polysaccharide Encapsulated Bacterial Infection in Sickle Cell Anemia: A Thirty Year Epidemiologic Experience

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Annual age-specific incidence rates of *Streptococcus pneumoniae* or *Haemophilus influenzae* bacterial septicemia in sickle cell anemia (SS) were determined for the years of 1957 through 1989. Forty-nine patients had 64 episodes of septicemia among a population of 786 SS patients observed for 8,138 person-years. Peak frequency of infection occurred between 1968–1971 and 1975–1981 with a conspicuous absence of episodes in 1972, 1973, 1982–1984, and 1986–1987, thus demonstrating cycles of high and low attack rates. The annual age-specific incidence rate of septicemia varied from 64.5 (1965) to 421.1 (1980) per 1,000 person-years for those under 2 years of age and never exceeded 10.2 per 1,000 in those over 4 years of age. Following the introduction of pneumococcal polyvalent vaccine in 1978, incidence of infection decreased in SS children greater than 2 years of age. No modification of the risk of infection was observed in immunized children less than 2 years of age.

During these three decades, there has been a ten-fold increase in the number of SS adults over 20 years of age. The relative risk of chronic sickle complications comparing the survivors of septicemia to the non-infected patients was: subsequent death 1.76, retinopathy 4.06, avascular necrosis 1.95, symptomatic cholelithiasis 1.33, stroke 1.30, and priapsim 1.26. These data suggest that prognosis for lifetime severe SS is initially manifested as an increased risk of septicemia during childhood.

Key words: bacteremia, epidemiology haplotypes, pneumococcal vaccine

INTRODUCTION

An increased susceptibility to polysaccharide encapsulated organisms such as *Haemophilus influenzae* and *streptococcus pneumoniae* in sickle cell anemia (SS) was first suspected in 1966 [1] and subsequently documented by numerous other reports [2–7]. We have reported epidemiologic data documenting the improved survival of children with SS since 1972 [8]. We observe a concomitant ten-fold increase in the number of surviving SS adults. Multi-institutional prospective studies during the last decade showed a decreased death rate. This was probably the result of early recognition of high risk children in concert with preventative immunization programs and the use of prophylactic penicillin [9,10]. The possible relationship of early childhood bacterial infection to the subsequent clinical course of the surviving SS adult is not known.

We report our 33 year experience with 786 SS patients including 49 with culture-proven *S. pneumoniae* or *H. influenzae* septicemia and/or meningitis. The cyclic nature of the attack rate of these two pathogens is evident during this time period.

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METHODS

Data Collection

The diagnosis of SS was based on the separation and quantification of hemoglobin fractions using standard techniques in conjunction with the usual hematologic criteria and the presence of morphologic sickling. Polymorphisms of DNA of the β^S-gene-cluster and -gene deletions were performed using restriction endonuclease Southern blotting techniques as detailed elsewhere [11]. The β^S-gene-cluster haplotypes are designated according to their African geographic region of predominance: i.e., Benin (Ben), Central African Republic (CAR), and Senegal (Sen). Alpha gene status is designated according to heterozygosity of α-thalassemia-2 (*rightward* deletion of African type). The diagnosis of *S. pneumoniae* or *H. influenzae* septicemia was made in all cases by cultures obtained from the blood and/or cerebrospinal fluid (CSF). Other known polysaccharide organisms including one case of *N. meningitides* were excluded in our analysis.

Polyvalent pneumococcal vaccine (14 valent 1979 through 1984 and then 23 valent) was administered to all children who were at least 1 year of age after 1978. A single booster immunization was given 2 years after the first inoculation.

All patients with a sickling disorder have been entered into our longitudinal demographic study of the natural history of sickle cell disease from birth or the first encounter. Clinical, laboratory, and genetic information is retrieved. Each patient who did not have an encounter within 18 months and who could not be located was censored as of their last date observed.

Statistical Methods

The life-table method was used to derive the age-specific incidence rate of septicemia and meningitis episodes. Four age-specific groups were analyzed: 0–23 months, 24–59 months, 5–19 years, and 20 years and older. To derive the incidence rate for each specific age group, patients were entered and exited from the life-table for each specific age group by calendar year. The number of persons at risk and the corresponding incidence rates were calculated using the cohort life-table method [12]. The age-adjusted incidence rate for each calendar year was derived using the indirect method of adjustment.

Survival was calculated using the Kaplan-Meier method and significance was determined with the log-rank test [13]. The frequency of long-term complications (major organ failure) in those who survived septicemia and in those who did not have an episode of septicemia was enumerated and the relative risk of their age-adjusted incidence rates was calculated.

RESULTS

From January 1957 through December 1989 (33 years), we observed 786 SS patients for a total of 8,138 person-years. The recruitment of infants into the study remained relatively constant throughout the observation period. Forty-nine patients had one or more episodes (a total of 64 septic events) of polysaccharide encapsulated bacterial infection. Forty patients had *S. pneumoniae* septicemia and/or meningitis and six had *H. influenzae*. Three patients had *S. pneumoniae* and *H. influenzae* infections on separate occasions. Data on specific serotype reinfection rates were incomplete. Recurrent episodes of *S. pneumoniae* infections were observed in nine patients; one individual had five distinct episodes.

Infection was found in 22 children under 2 years of age (44.9%). Twenty-one patients (42.8%) were between the age of 2 through 4 years. The age-specific incidence rate varied from 64.5 (1965) to 421.1 (1980) for those under 2 years of age (Table I). There were several conspicuous intervals with no infections in this infant group: 1971 through 1974, 1982 through 1983, and 1985 through 1989. Among the 2 through 4 year old children, the age-specific incidence rate varied from 32.8 (1964) to 242.4 (1977). There were time periods with no infection among the older children (2 through 4 years): 1958 and 1959, 1967 and 1968, and 1971 through 1973. After 1978, there was an extended 10 year interval with no infection documented (Table I). Among those children over 4 years of age, no cases were observed during 27 of the 33 calendar years and the age-specific incidence rate never exceeded 10.2 per 1,000. The risk of infection was not always confined to children. In 1971 and 1975, the age-specific incidence rates of infection for those over 20 years of age were 9.4 and 4.1, respectively.

Overall age-adjusted attack rates oscillated between peaks in 1968–1971 and 1975–1981 to an absence of episodes in 1972, 1973, 1982–1984, and 1986–1987 (Fig. 1). Marked annual differences in the attack rate were observed in those younger than 2 years of age. This year-to-year variation did not correlate with the attack rates in the 2 through 4 age group for the same calendar era. It should be noted that no attempt was made to correlate the peak incidence of infection with concomitant viral respiratory illness in the community at large as had been done in other studies [14,15]. Data on community prevalence of *S. pneumoniae* serotypes for the period of observation were not available.

There were 12 deaths causally related to infection (i.e., death occurring within 2 months of bacteremia); 88% were in children under 10 years of age. Prior to 1979 and the availability of pneumococcal vaccines, there were 11 deaths in 41 episodes (26.8%) of septicemia, whereas after 1978, there was only one death in eight episodes (12.5%). Figure 2 compares the cumulative probability

TABLE I. Age-Specific Incidence Rate of Polysaccharide Encapsulated Bacterial* Septicemia/Meningitis In SS Patients 1957-1989

	Age-specific incidence rate per 1,000			
Year	Ages 0-<2	Ages 2-<5	Ages 5-19	Ages 20+
1957		66.7		
1958	76.9			
1959	89.0			
1960		51.3		
1961	76.9	41.7		
1962	66.7	35.7		
1963	66.7	33.9		
1964	66.7	32.8		
1965	64.5	64.5		
1966	71.4	67.8		
1967	100.0			
1968	210.5			
1969	90.9	139.5	6.1	
1970	227.3	227.3[a]		
1971			6.0	9.4
1972				
1973				
1974		125.0		
1975	117.6		5.7	4.1
1976	142.9	66.7	5.9	
1977		242.4[a]		
1978	272.7			
1979	190.5		7.4	
1980	421.1[a]			
1981	266.7			
1982				
1983				
1984	166.7			
1985				
1986				
1987			10.2	
1988				
1989		66.7		
All years	96.8	41.0	1.4	0.4
95% CI	(61.6,132.0)	(25.3,56.8)	(0.3,2.5)	(−0.1,0.9)

S. pneumoniae and *H. influenzae.*

[a]Ninety-five percent confidence intervals (CI) did not cover 0.

of survival between those SS patients born before to those born after 1972 demonstrating the marked improvement in survival during recent decades. This was observed even in the face of the high *S. pneumoniae* incidence years of 1977 and 1979 (Fig. 1; Table I).

Examination of the number of patients with SS exposed to risk of infection documented an increasing number of patients living into adulthood over time (Fig. 3). There has been a ten-fold increase in the number of surviving adults after 1974 as compared to 1958 and 1959. This occurred in the face of a relatively constant mean annual enrollment rate of 15 (range 3–30) young children per year.

The age-adjusted incidence rate of nine major SS complications among the survivors of pneumococcal or haemophilus infection was compared to those SS persons who never had similar infections (Table II). This comparative analysis was performed on 1) all patients regardless of the age first seen; and 2) those who entered the study before they were 10 years old. The results obtained from the two populations were equivalent. The relative risk of subsequent death was 1.76 in patients with prior infection as compared to uninfected individuals. Patients with prior infection consistently had a higher risk of retinopathy with visual loss, avascular necrosis, stroke and priapism, and a lower risk of leg ulcer and chronic lung disease. Hypersplenism was defined as an enlarged spleen with an anemic crisis marked by a rapid decrease of hemoglobin concentration of more than 2 g/dl and/or an acute splenic sequestration crisis. Hypersplenism was not associated with a differential relative risk comparing infected to non-infected individuals. Using a composite measure of morbidity defined as major organ failure (eye, brain, lung, kidney, leg ulcers, and avascular necrosis), the relative risk was 1.42.

The polymorphisms of DNA of the β^S-gene-cluster (haplotypes) were determined in 20 of the SS patients who survived infection. Ten (50%) had at least one CAR chromosome (three were homozygous CAR) (Table III). This is slightly higher than the observed 37% (82 of total of 221) with at least one CAR chromosome in our SS patient population in Los Angeles [11]. Furthermore, 10 of the 20 infection survivors (50%) had an α-gene deletion (α-thalassemia-2) whereas 37% of the total SS population co-inherited α-thalassemia-2 ($P = 0.37$).

DISCUSSION

The cyclic nature of *S. pneumoniae* infection in SS is demonstrated in this 33 year longitudinal study. A variable incidence of infection occurred in the face of a constant annual recruitment of children under 2 years of age, the age group at high risk for polysaccharide encapsulated bacteria infections (Figs. 1, 3).

Analogous cyclic attack rates and geographic variation in frequency for other infectious agents have been reported [16,17]. Thus, for long-term clinical trials, the evaluation of the effectiveness of preventive therapy should take into consideration the cyclic nature of infection. The degree of effectiveness may be modified by the timing of the clinical trial and the background geographic variations of attack rates. As an example, a recent study from Texas suggested that outpatient management of febrile illnesses in SS patients was now safe [18]. However, their results might have been influenced by a decreased incidence of pneumococcal bacteremia during the study.

The natural periodicity of infection may have been affected by the introduction of pneumococcal vaccine after 1978 in those over 2 years of age. In the 2 through 4 year age group, the incidence of polysaccharide septice-

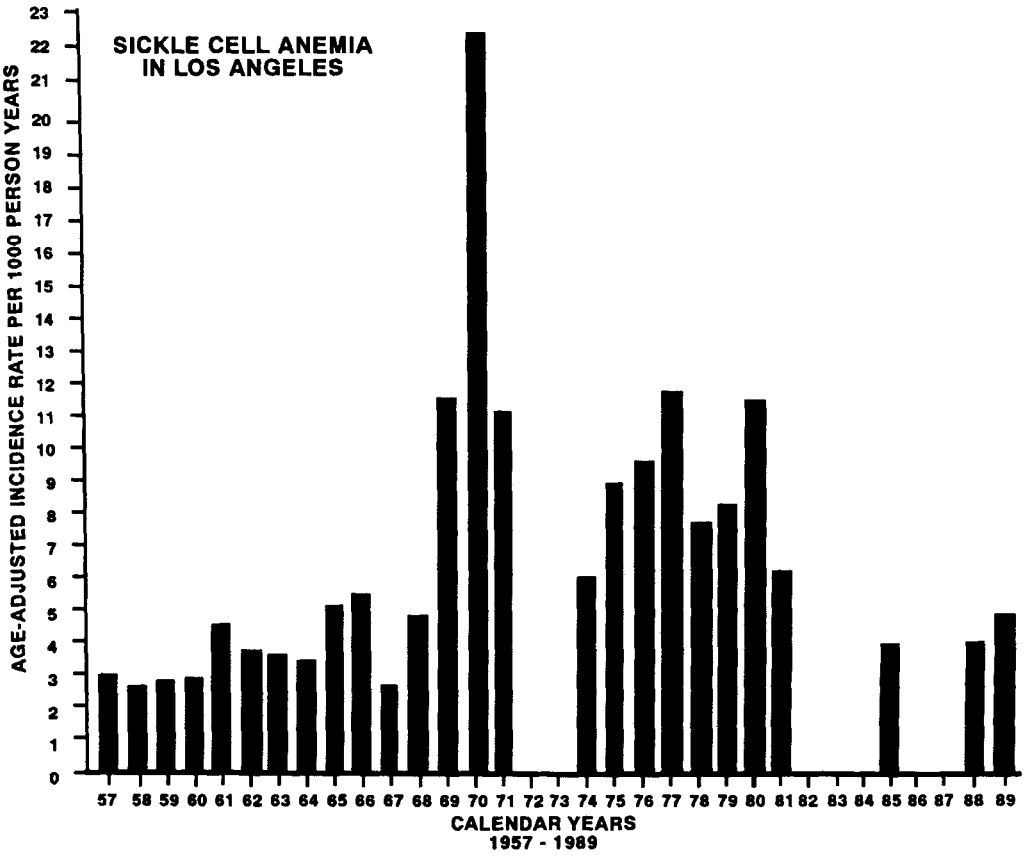

Fig. 1. The incidence of polysaccharide encapsulated bacterial infection (*S. pneumoniae* and *H. influenzae*) septicemia/meningitis in patients with SS for three decades.

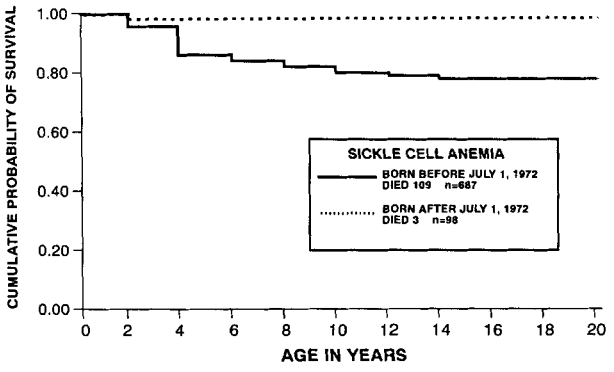

Fig. 2. Cumulative probability of survival in patients with SS comparing the survival of those born before 1972 to those born after 1972. This shows a significant decrease in childhood mortality during the recent era.

mia was absent from 1978 through 1988. The single case in 1989 occurred in a child given the 23-valent pneumococcal vaccine at 1 year of age and had culture-proven bacteremia with *S. pneumoniae* type 6B. Contrariwise, in the infant group (immunized at 1 year and given a single booster at 3 years of age), the attack rates after 1978 were virtually the same prior to and after this year. These data support other epidemiologic findings that suggest that the very young (<2 years of age) are not protected by the available pneumococcal vaccines [19]. The conjugate *H. influenzae* type b vaccine (PRP-D) appeared to be partially effective at preventing *H. influenzae* septicemia during infancy (up to 1 year) in Finnish children but not in native Americans [20–22]. No information is available regarding antibody responses to conjugate *H. influenzae* type b vaccine in African children. Hopefully, a pneumococcal vaccine can be developed that is effective in those children under 2 years of age, taking into consideration reports of penicillin resistant *S. pneumoniae* in young children heavily exposed to antibiotics [23].

Prophylactic penicillin has been demonstrated to be efficacious in children with SS less than 36 months of age [9]. The widespread use of prophylactic penicillin and the ready availability of antibiotics in the home may have precluded culture and latex slide agglutination documentation of some incidence of bacterial infection during the last few years. We find little data to support the use of prophylactic penicillin (or other antibiotic) regimens in previously untreated but immunized American SS patients greater than 3 years of age who have developed antibodies to the indigenous flora. At what age should prophylactic antibiotics be discontinued? John et al. re-

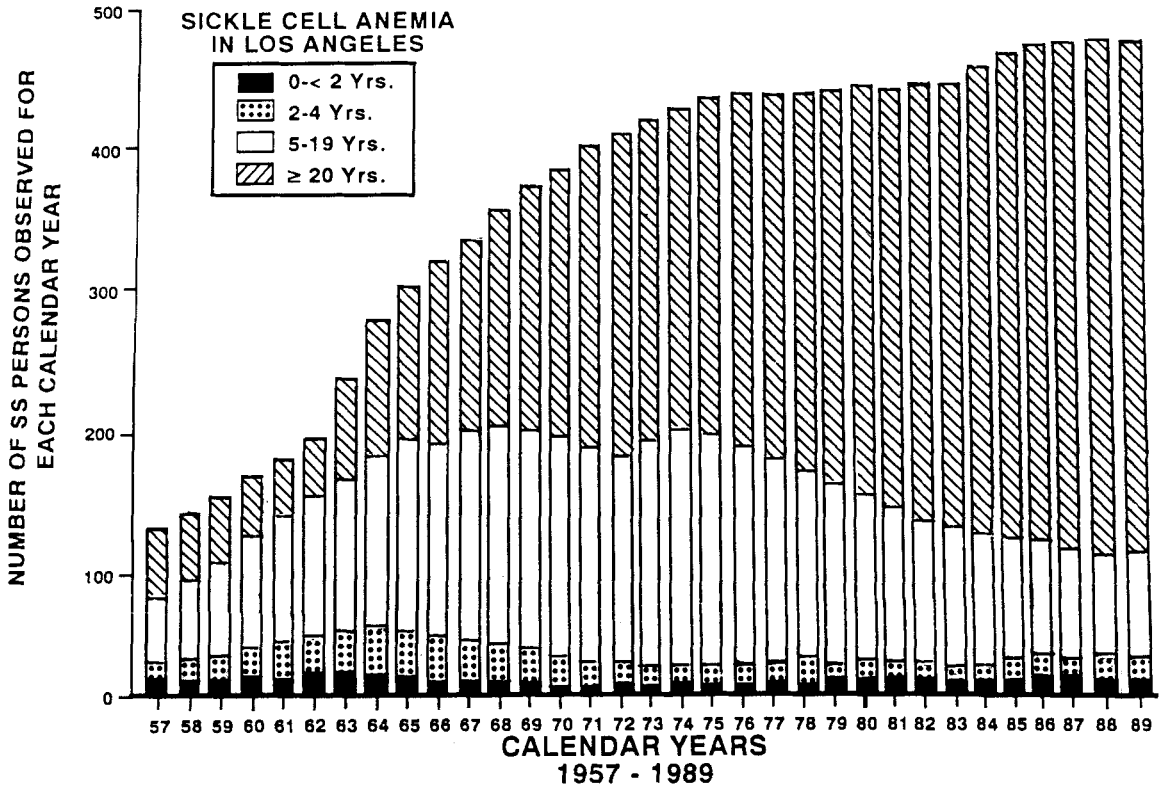

Fig. 3. Stacked bar graph demonstrating the increasing numbers of surviving adults with SS. The change in survival was greatest during the 1960 decade.

TABLE II. Risk of Long-Term Complications in Patients With SS; Comparison of Those Who Did to Those Who Did Not Have Polysaccharide Encapsulated Bacterial Infections: Relative Risk in Patients Followed Since Early Childhood*

Sickle related complication	Number of persons	Those with infection (n = 46) Rate[a]	No Infection (n = 288) Rate[a]	RR[b]	95% CI[c]
Retinopathy with visual loss	10	0.73	0.18	4.06	(1.05 16.46)
Avascular necrosis	37	1.60	0.82	1.95	(0.88 4.68)
Death	58	2.06	1.17	1.76	(0.95 3.46)
Cholelithiasis	39	1.19	0.89	1.33	(0.52 3.42)
CVA	48	1.49	1.15	1.30	(0.60 2.79)
Priapism	11	0.58	0.46	1.26	(0.27 5.86)
Hypersplenism	40	0.97	0.98	0.99	(0.43 2.24)
Leg ulcer	26	0.48	0.62	0.77	(0.18 3.29)
Sickle chronic lung disease	14	0.22	0.33	0.67	(0.09 5.11)

*Age of entry under 10 years of age.
[a]Age adjusted incidence rate per 100 person-years.
[b]The relative risk of those who were infected/those who were not infected.
[c]Confidence interval.

ported that children over 3 years of age had pneumococcal infections upon stopping penicillin prophylaxis [24]. This issue is currently under investigation in Phase II American trials.

As more infected SS children survive to adulthood, they are at higher risk of developing chronic complications post-infection as compared to their uninfected SS peers. During the past 20 years, overall survival in SS has resulted in a ten-fold increase in the adult SS population. The relative risk of long-term complications was increased in the survivors of infection for retinopathy with visual loss and for avascular necrosis, stroke, and priapism.

TABLE III. Comparison of βs Haplotype and α-Gene Deletion Among Survivors of Polysaccharide Encapsulated Infection to the Distribution Found in Random SS Population Studies

β^S-gene-cluster haplotype combinations	Los Angeles[25] SS population		SS infection survivors	
		α-Gene deletion		α-gene deletion
	n (column %)	n (row %)	n (column %)	n (row %)
Ben/Ben	84 (38)	33 (39)	8 (40)	4 (50)
CAR/Ben	55 (25)	20 (36)	4 (20)	2 (50)
Sen/Ben	28 (13)	7 (25)	2 (10)	0 (0)
CAR/CAR	10 (5)	4 (40)	3 (15)	1 (33)
CAR/Sen	7 (3)	4 (57)	2 (10)	2 (100)
Sen/Sen	3 (1)	2 (67)	0 (0)	0 (—)
Others	34[a] (15)	12 (35)	1[b] (5)	1 (100)
Total	221 (100)	82 (37)	20 (100)	10 (50)

[a]Ten had at least one CAR chromosome in *trans* to a rare β^S haplotype.
[b]This case had one CAR chromosome in *trans* to a rare β^S haplotype.

The observation that there may be an increased risk of vital organ damage and failure as a long-term sequela following infection was suggested by Seeler et al. who observed that pneumococcal meningitis appeared to predispose the patient to subsequent cerebral infarction [5]. It can be speculated that early development of a dysfunctional spleen during infancy may be the first evidence that there is a predisposing factor in the patient for the development of subsequent major organ failure.

The hypothesis that there is a genetic determinant in SS persons that modifies the risk of *S. pneumoniae* septicemia is suggested by our documentation of an increased incidence of the CAR haplotype among infected patients (Table III). Previous studies demonstrated a high degree of correlation of vital organ failure of the brain and kidney, and osteonecrosis with the presence of the CAR β^S haplotype [11,25]. The predominance of the β^S CAR haplotype found in our infected SS population suggests that this is a potential genetic predictor of early splenic dysfunction. Although the molecular mechanisms behind this genetic association are obscure they most likely involve loci at or linked to the β^S globin gene-cluster. Patients in Kenya (homozygous CAR β^S haplotype) are known to have the most severe form of SS and one half of reported survivors also co-inherited α-thalassemia-2 [26]. Since the CAR haplotype is associated with low Hb F levels and since the age of loss of splenic function is directly correlated with a rapid postnatal decline of Hb F [27], it is expected that the infant with a CAR β^S cluster polymorphism would have a rapid loss of splenic function and a resultant higher risk of invasive pneumococcus infection. Among our group, 50% of the patients with α-thalassemia-2 had at least one CAR chromosome. Some of our patients who survived septicemia seem analogous to surviving SS homozygous CAR patients in Kenya. Further support comes from data of SS Saudi infants with a decreased risk of infection [28] when compared to Benin (patients found in W. Saudi Arabia or the Bight of Benin) or CAR β^S haplotype patients (homozygous Saudi haplotype reported to have milder disease). The possibility exists that early identification of genetically at-risk individuals will warrant a higher clinical index of suspicion and allow targeted therapeutic intervention.

REFERENCES

1. Robinson MG, Watson RJ: Pneumococcal meningitis in sickle cell anemia. N Engl J Med 7274:1006–1008, 1966.
2. Kabins SA, Lerner C: Fulminant pneumococcemia and sickle cell anemia. JAMA 211:467–471, 1970.
3. Eeckels R, Gatti F, Renoirte AM: Abnormal distribution of haemoglobin genotypes in Negro children with severe bacterial infections. Nature 216:3820, 1967.
4. Barrett-Connor E: Bacterial infection and sickle cell anemia. Medicine 50:97–112, 1971.
5. Seeler RA, Metzger W, Mufson MA: Diplococcus pneumoniae infections in children with sickle cell anemia. Am J Dis Child 123:8–10, 1972.
6. Overturf GD, Powars D, Baraff L: Bacterial meningitis and septicemia in sickle cell disease. Am J Dis Child 131:784–787, 1977.
7. Zarkowsky HS, Gallagher D, Gill FM, Wang W, Faletta JM, Lande WM, Levy PS, Verter JI, Wethers D, the Cooperative Study of Sickle Cell Disease: Bacteremia in sickle hemoglobinopathies. J Pediatr 109:579–585, 1986.
8. Powars D, Overturf G, Weiss J, Lee S, Chan L: Pneumococcal septicemia in children with sickle cell anemia. Changing trend of survival. JAMA 245:1839–1842, 1981.
9. Gaston MH, Verter JI, Woods G, Pegelow C, Kelleher J, Presbury G, Zarkowsky H, Vichinsky E, Iyer R, Lobel JS, Diamond S, Holbrook CT, Gill FM, Ritchey K, Falleta JM: Prophylaxis with oral penicillin in children with sickle cell anemia: A randomized trial. N Engl J Med 314:1593–1599, 1986.
10. Leikin SL, Gallagher D, Kinney TR, Sloane D, Klug P, Rida W, the Cooperative Study of Sickle Cell Disease: Mortality in children and adolescents with sickle cell disease. Pediatrics 84:500–508, 1989.
11. Schroeder WA, Powars DR, Kay LM, Chan LS, Huynh V, Shelton JB Shelton JR: β-cluster haplotypes, α-gene status, and hematological data from SS, SC, and Sβ-thalassemia patients in Southern California. Hemoglobin 13(4):325–353, 1989.

12. Chan LS, Powars D, Lee J, Weiss J: A modified life-table method to study congenital genetic disorders: An application in sickle cell anemia. J Chron Dis 35:401–409, 1982.
13. Peto R, Pike MC, Armitage P, Breslow NE, Cox DR, Howard SV, Mantel N, McPherson K, Peto J, Smith PG: Design and analysis of randomized clinical trials requiring prolonged observation of each patient. II. Analysis and examples. Br J Cancer 35:1–39, 1977.
14. Gwaltney JM Jr, Sande MA, Austrian R, Hendley JO: Spread of Streptococcus pneumoniae in families. II. Relation of transfer of S. pneumoniae to incidence of colds and serum antibody. J Infect Dis 132:62–68, 1975.
15. Gray BM, Converse GM II, Dillon Jr HC: Epidemiologic studies of streptococcus pneumoniae in infants: Acquisition, carriage, and infection during the first 24 months of life. J Infect Dis 142:923–933, 1980.
16. Glezen WP, Denny FW: Epidemiology of acute lower respiratory disease in children. N Engl J Med 288:498–505, 1973.
17. Brimblecombe FSW, Cruickshank R, Masters PL, Reid DD: Family studies of respiratory infections. Br Med J 1:119–128, 1958.
18. Rogers ZR, Morrison RA, Vedro DA, Buchanan GR: Outpatient management of febrile illness in infants and young children with sickle cell anemia. J Pediatr 117:736–739, 1990.
19. Broome CV, Facklam RR, Fraser DW: Pneumococcal disease after pneumococcal vaccination: An alternative method to estimate the efficacy of pneumococcal vaccine. N Engl J Med 303:549–552, 1980.
20. Eskola J, Kayhty H, Takala AK, Peltola H, Rönnberg, P-R, Kela E, Pekkanen E, McVerry PH, Mäkelä PH: A randomized, prospective field trial of a conjugate vaccine in the protection of infants and young children against invasive haemophilus influenzae type b disease. N Engl J Med 323:1381–1386, 1990.
21. Siber GR, Santosham M, Reid GR, Thompson C, Almeido-Hill J, Morell A, Delange G, Ketcham JK, Callahan EH: Impaired antibody response to haemophilus influenzae type b polysaccharide and low IgG2 and IgG4 concentrations in Apache children. N Engl J Med 323:1387–1392, 1990.
22. Ward J, Brenneman G, Letson GW, Heyward WL, the Alaska H. Influenzae Vaccine Study Group: Limited efficacy of a Haemophilus Influenzae type b conjugate vaccine in Alaska native infants. N Engl J Med 323:1393–1401, 1990.
23. Rauch AM, O'Ryan M, Van R, Pickering LK: Invasive disease due to multiply resistant Streptococcus pneumoniae in a Houston, Tex, Day-care Center. Am J Dis Child 144:923–927, 1990.
24. John AB, Ramlal A, Jackson H, Maude GH, Sharma AW, Serjeant GR: Prevention of pneumococcal infection in children with homozygous sickle cell disease. Br Med J 288:1567–1570, 1984.
25. Powars D, Chan LS, Schroeder WA: The variable expression of sickle cell disease is genetically determined. Semin Hematol 27:360–376.
26. Ojwang PJ, Ogada T, Beris Y, Lanclos KD, Kutlar A, Kutlar F, Huisman THJ: Haplotypes and globin analyses in sickle cell anaemia patients from Kenya. Br J Haematol 65:211–215, 1987.
27. Pearson HA, Gallagher D, Chilcote R, Sullivan E, Wilimas J, Espeland M, Ritchey AK, the Cooperative Study of Sickle Cell Disease: Developmental pattern of splenic dysfunction in sickle cell disorders. Pediatrics 76:392–397, 1985.
28. El-Mouzan MI, Al-Awamy BH, Al-Torki MT: Clinical features of sickle cell disease in Eastern Saudi Arab children. Am J Pediatr Hematol Oncol 12:51–55, 1990.