Recurrent infections in homozygous sickle cell disease

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Abstract

The characteristics of 214 episodes of invasive bacterial infection among 176 patients with homozygous sickle cell (SS) disease were examined. *Streptococcus pneumoniae* occurred in 81 episodes, *Salmonella* spp in 70, *Haemophilus influenzae* type b in 30, *Escherichia coli* in 24, and *Klebsiella* spp in nine. The cumulative incidence showed that *S pneumoniae* and *H influenzae* occurred predominantly before 5 years of age and were uncommon thereafter, *Salmonella* spp increased almost linearly with age, and *Klebsiella* spp and *E coli* predominated in patients over 10 years of age. *Escherichia coli* had a different epidemiology—it was found in older children, almost entirely girls. Excluding this organism from an analysis of recurrent bacterial infections, the standardised incidence rates for second and third infections were 4.8 and 15.8 times greater, respectively, than the SS population average. This implies that the susceptibility to infection is characteristic of a subgroup of patients with SS disease and that sick patients with previous bacteraemia should be investigated early and aggressively for further infection.

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Patients with homozygous sickle cell (SS) disease are at increased risk of infection with *Streptococcus pneumoniae*, *Haemophilus influenzae* type b, *Salmonella* spp, *Escherichia coli* and *Klebsiella* spp.[1–3] Several mechanisms are believed to contribute to this susceptibility, a major factor being the early loss of splenic function, which may be abnormal as early as the 1st year of life.[4] Development of clinical splenomegaly in the first 6 months of life has been shown to be significantly associated with greater risk of subsequent pneumococcal septicaemia.[5] This susceptibility is assumed to be characteristic of the SS genotype as a whole but because splenic function is lost at different rates in different patients, it might be expected that a subgroup of patients would be particularly susceptible to infection and would perhaps develop recurrent infections. We tested this hypothesis in a retrospective study of Jamaican patients with SS disease.

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Patients and methods

PATIENTS

The patients attended the sickle cell clinic of the University Hospital of the West Indies, Kingston, Jamaica. All had SS disease diagnosed by standard criteria[6] and came from two clinic populations. The cohort group included all patients with SS disease detected during the screening of 100 000 consecutive, non-operative deliveries at the main Government Maternity Hospital (Victoria Jubilee) between June 1973 and December 1981, and these were clinically followed from birth. The main group included all other patients, most of whom had been symptomatically referred, although this symptomatic bias has been reduced by long term follow up of the steady state. To reduce the symptomatic bias in this second group, patients were required to have had at least two clinic visits and not to have been referred initially to the clinic with bacterial infection. Our study was confined to infections caused by *S pneumoniae*, *H influenzae* type b, *Salmonella* spp, *E coli*, or *Klebsiella* spp between 1 January 1974 and 31 December 1997.

There were 3820 patients (including 311 cohort patients) with 218 episodes of infection among 180 patients (90 episodes among 64 cohort patients). Four episodes identified on initial clinic referral in main group patients were excluded, leaving 214 eligible episodes among 176 patients. Differences in recruitment of the cohort and main groups resulted in significantly different age structures. The median age at last clinic visit was 17.8 years (interquartile range, 11.2–21.2; total range, 0.1–24.5) for the cohort and 20.7 years (10.7–31.4; 0.1–80.6) for the main group (Mann-Whitney U test, $z = 7.5$; $p < 0.001$).

METHODS

In the sickle cell clinic, infections receive specific computer codings prospectively and all dockets with such codings were reviewed and cross checked by examination of the records in the department of microbiology laboratory. In the cohort study, complete data were available from birth.

DEFINITIONS

We defined invasive bacterial infections as the isolation of one of the five organisms from cultures of blood or cerebral spinal fluid and, in the case of *Salmonella* spp, from sinuses or aspiration from bone sites. Patients with recurrent isolations of *S pneumoniae* were assumed to have separate infections if the serotype differed, or if the same serotype was isolated after an arbitrary intervals of 14 days.

STATISTICAL METHODS

Age distributions at last visit for cohort and main patients exhibited non-normality and so were summarised by median, interquartile

Table 1 Distribution of infections by age, sex, patient group, and organism

	Main group (age (years))						*Cohort group (age (years))*						
	0–2	*3–5*	*6–9*	*10–19*	*20+*	*Total*	*0–2*	*3–5*	*6–9*	*10–19*	*20+*	*Total*	*Grand total*
Bacterial isolate													
Streptococcus pneumoniae	7/4	5/10	2/6	2/2	1/3	17/25	6/9	8/7	5/0	1/1	1/1	20/18	81 (38%)
Salmonella spp	6/1	1/2	10/2	1/7	10/3	28/15	3/3	4/1	7/5	2/2	0/0	16/11	70 (33%)
Haemophilus influenzae	3/2	7/1	1/0	1/0	1/1	13/4	8/2	1/1	0/1	0/0	0/0	9/4	30 (14%)
Escherichia coli	0/0	0/1	0/0	0/0	0/17	0/18	1/0	0/0	0/0	0/3	0/2	1/5	24 (11%)
Klebsiella spp	1/0	0/0	0/0	1/0	2/0	4/0	0/0	0/0	1/0	2/1	0/1	3/2	9 (4%)
Total (%)	24 (11)	27 (13)	21 (10)	14 (7)	38 (18)	124	32 (15)	22 (10)	19 (9)	12 (6)	5 (2)	90	214

Results are number of male patients/female patients.

range, and total range and differences compared by the Mann-Whitney U test. Sex composition was assessed using the χ^2 test.

Incidence rates for cohort and main groups by organism, age, and sex were estimated as the ratio of the number of events divided by the number of person-years of exposure. Confidence intervals (95% CI) for the incidence rates were calculated using jackknife methodology[7] to compensate for multiple events within patients. Incidence rates were compared using rate ratios, controlling for confounding factors by stratification and subsequent pooling to give the Mantel-Haenszel estimate of the rate ratio. Standardised infection rates were calculated by comparing the infection rate of any subgroup (age, sex, organism) with the appropriate complete sample (cohort, main, or both) reference rate, a technique known as indirect standardisation. Potential disadvantages of age stratified rates are the need for arbitrary breakpoints and the use of narrow bands, which may cause unstable estimates. An alternative procedure plotted the cumulative rate[8] against time divided into short bands. This cumulative rate was compared informally across infection groups.

The risk of recurrent infections was assessed by assuming the hypothesis that episodes of infection were independent events within individuals. Disproving this hypothesis would imply that individual patients were more or less prone to recurrent infection. Incidence rates, standardised infection rates, and risk ratios for first, second, and third episodes were calculated and compared as described. Significance was assumed at the 5% level. All analyses were performed using Stata statistical software (Release 5.0; Stata Corporation, College Station, Texas, USA).

Results

There were 214 bacteraemias, *S pneumoniae* occurring in 81 (37.9%), *Salmonella* spp in 70 (32.7%), *H influenzae* in 30 (14.0%), *E coli* in 24 (11.2%), and *Klebsiella* spp in nine (4.2%). Of the 3820 patients (311 cohort), 3644 (247 cohort) had no bacteraemias, 151 patients (48 cohort) had one episode, 15 (nine cohort) had two, eight (five cohort) had three, and single cohort children had four and five episodes.

AGE AND SEX

The age at infection (table 1) indicates that 68% of infections occurred before the age of 10 years and 80% before 20 years. There was no sex difference overall (53% boys/men; $\chi^2 = 3.2$; $p = 0.07$), although boys/men predominated among infections with haemophilus (risk ratio, 3.1; 95% CI, 1.4 to 7.0; $\chi^2 = 8.4$; $p < 0.01$) and salmonella (risk ratio, 1.9; 95% CI, 1.2 to 3.1; $\chi^2 = 7.2$; $p = 0.01$), but not with *S pneumoniae* (risk ratio, 1.0; 95% CI, 0.6 to 1.5; $\chi^2 = 0$; $p = 0.99$) or klebsiella (risk ratio, 4.0; 95% CI, 0.8 to 19.1; $\chi^2 = 3.5$; $p = 0.06$). Infections with *E coli* predominated among girls/women (risk ratio, 20.3; 95% CI, 2.7 to 150.3; $\chi^2 = 17.6$; $p < 0.001$).

Table 2 Age related incidence of infections among 311 patients in the cohort group and 3509 patients in the main study patients given as standardised infections rates (SIR)

	Age group (years)				
	0–2	*3–5*	*6–9*	*10–19*	*20+*
Cohort group					
Events	30	26	17	13	4
Patient-years × 1000	0.87	0.81	1.01	1.94	0.24
Rate	34.5	32.1	16.9	6.7	17.0
95% CI	(23.1 to 53.9)	(20.9 to 51.8)	(10.5 to 29.0)	(3.7 to 13.5)	(6.6 to 57.8)
SIR	1.9	1.7	0.9	0.4	0.9
95% CI	(1.3 to 2.9)	(1.1 to 2.8)	(0.6 to 1.6)	(0.2 to 0.7)	(0.4 to 3.1)
Main group					
Events	21	30	21	13	39
Patient-years × 1000	1.07	2.31	3.53	9.69	16.62
Rate	19.6	13.0	6.0	1.3	2.4
95% CI	(11.9 to 34.7)	(8.8 to 20.0)	(3.9 to 9.6)	(0.8 to 2.5)	(1.7 to 3.3)
SIR	5.3	3.5	1.6	0.4	0.6
95% CI	(3.2 to 9.4)	(2.4 to 5.4)	(1.1 to 2.6)	(0.02 to 0.7)	(0.5 to 0.9)
Both patient groups					
Events	51	56	38	26	43
Patient-years × 1000	1.94	3.12	4.54	11.63	16.85
Rate	26.3	17.9	8.4	2.2	2.6
95% CI	(19.2 to 36.9)	(13.4 to 24.5)	(6.1 to 11.9)	(1.5 to 3.5)	(1.9 to 3.5)
SIR	4.7	3.2	1.5	0.4	0.5
95% CI	(3.4 to 6.6)	(2.4 to 5.4)	(1.1 to 2.1)	(0.3 to 0.6)	(0.3 to 0.6)

CI, confidence intervals.

Table 3 Secular pattern showing incidence rates for the two most common bacteraemias

	1974–79	*1980–85*	*1986–91*	*1992–97*
Streptococcus pneumoniae				
Main group				
Events	5	13	8	16
Patient-years × 1000	5.2	7.8	10.0	10.3
Incidence	1.0	1.7	0.8	1.6
95% CI	(0.4 to 2.9)	(0.8 to 4.2)	(0.4 to 1.8)	(1.0 to 2.7)
Cohort group				
Events	14	17	4	4
Patient-years × 1000	0.7	1.5	1.4	1.2
Incidence	19.9	11.5	2.9	3.5
95% CI	(9.5 to 48.8)	(6.9 to 20.4)	(1.1 to 10.2)	(1.3 to 12.3)
Salmonella spp				
Main group				
Events	0	3	13	27
Patient-years × 1000	5.2	7.8	10.0	10.3
Incidence	0.0	0.4	1.3	2.6
95% CI	—	(0.1 to 1.9)	(0.8 to 2.4)	(1.8 to 3.9)
Cohort group				
Events	6	11	8	2
Patient-years × 1000	0.7	1.5	1.4	1.2
Incidence	8.5	7.4	5.7	1.7
95% CI	(3.9 to 22.2)	(4.2 to 14.3)	(3.0 to 12.7)	(0.4 to 17.2)

CI, confidence intervals.

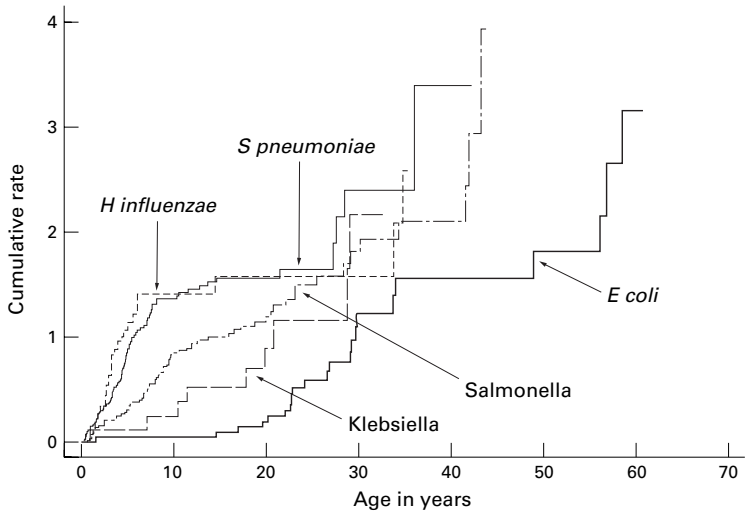

Figure 1 Cumulative incidence rate of five bacteraemias in relation to age among 214 bacteraemic episodes.

Table 4 Standardised infection rates (95% CI) for the three most common infections relative to the whole sickle cell population

	Age group (years)		
Organism	*0–2*	*3–5*	*6–9*
Haemophilus influenzae type b	9.2 (5.3 to 17.1)	4.5 (2.5 to 8.7)	0.6 (0.1 to 5.6)
Streptococcus pneumoniae	5.3 (3.4 to 8.9)	5.1 (3.4 to 17.9)	1.3 (0.8 to 2.5)
Salmonella spp	3.6 (2.2 to 6.6)	1.7 (0.9 to 3.8)	2.6 (1.8 to 4.1)

CI, confidence intervals.

INCIDENCE

Crude incidence for all bacteraemias was 5.6/1000 patient-years (95% CI, 4.8 to 6.6), with cohort patients showing a fivefold greater frequency than patients in the main group (18.5/1000 patient-years (95% CI, 15.1 to 22.8) *v* 3.7/1000 patient-years (95% CI, 3.1 to 4.5)). This difference will have been exaggerated by the predominance of older subjects, less prone to bacteraemia, in the main group of patients. When this difference was allowed for by comparing relative incidence within age bands (table 2), the risk ratio for bacteraemia among cohort relative to main group patients fell to 2.6 (95% CI, 1.9 to 3.5). In individual age bands, the risk ratios for the cohort group relative to the main group were as follows: ages 0–2 years, 1.8 (95% CI, 1.0 to 3.1); ages 3–5 years, 2.5 (95% CI, 1.5, 4.2); ages, 6–9 years, 2.8 (95% CI, 1.5 to 5.4); ages 10–19 years, 5.0 (95% CI, 2.3 to 10.8); and age 20 years and above, 7.2 (95% CI, 2.6 to 20.3). Incidence decreased linearly with age both in patients in the cohort group ($\chi^2 = 21.6$; $p < 0.001$) and the main study group ($\chi^2 = 61.6$; $p < 0.001$). Incidence rates for the five bacteraemias were consistently higher in the cohort group than the main study group: pneumococcus, 8.0 *v* 1.3; salmonella, 5.6 *v* 1.3; haemophilus, 2.7 *v* 0.5; *E coli*, 1.2 *v* 0.5; and klebsiella, 1.0 *v* 0.1, respectively.

SECULAR TRENDS

The introduction of penicillin prophylaxis in the middle of the 1980s might have been expected to modify incidence rates; therefore, a secular analysis was performed for the two most common bacteraemias (table 3). The incidence of pneumococcal infection declined significantly among patients in the cohort group ($\chi^2 = 19.1$; $p < 0.001$), and this trend was most marked between 1980 and 1985 and 1986 and 1991. However, this apparent secular change could be an artefact from the age structure of the cohort group, which meant that by 1986 few subjects remained in the high risk age group. Adjusting for age by stratifying into two age groups (0–5 years, ⩾ 6 years) showed a smaller, non-significant decline ($\chi^2 = 0.8$; $p = 0.38$). No secular change occurred within patients from the main clinic, either before or after stratification. For *Salmonella* spp, the incidence did not change over time for patients in the cohort group, either before ($\chi^2 = 2.8$; $p = 0.10$) or after controlling for age ($\chi^2 = 1.3$; $p = 0.25$), but among patients in the main group, the incidence of infection increased significantly with time ($\chi^2 = 16.8$; $p < 0.001$), and this persisted after controlling for age ($\chi^2 = 17.0$; $p < 0.001$).

CUMULATIVE INCIDENCE

In the whole group, cumulative incidence rose sharply to 10 years of age and then at a lower rate. Different cumulative incidence rates occurred with the different organisms (fig 1), *H influenzae* and *S pneumoniae* occurring predominantly before 5 years of age, although salmonella showed no age predilection and increased linearly with age. Standardised infection rates (table 4) confirm the different age patterns for the three most common organisms. The small numbers of both *E coli* and *Klebsiella* spp occurred predominantly in those aged over 20 years.

RECURRENT INFECTION

The different epidemiology of *E coli* infections (later age, confined mainly to girls/women) implies different risk factors; therefore, this organism was excluded from the analysis of recurrent bacteraemia. The probability of subsequent infection after an initial bacteraemic episode, assessed by standardised infection rates, was 4.8 (95% CI, 3.2 to 7.4) times greater, and among those with two previous

Table 5 Patients with three or more infections

Patient number and organism		Source	Age (years)
Cohort group			
1	*Salmonella schwartzendgrund*	Pus	1.3
	Haemophilus influenzae type b	Blood	3.6
	Salmonella heidelberg	Blood	10.6
	Salmonella montevideo	Blood	17.2 (died)
2	*Streptococcus pneumoniae* type 23	Blood	2.4
	Haemophilus influenzae type b	Blood	2.7
	Streptococcus pneumoniae type ?	Blood	3.6
	Streptococcus pneumoniae type ?	Blood	3.7
	Streptococcus pneumoniae type 23	Blood	4.8
3	*Haemophilus influenzae* type b	Blood	2.0
	Streptococcus pneumoniae type ?	Blood/CSF	4.3
	Streptococcus pneumoniae type ?	Blood/CSF	7.3 (died)
4	*Salmonella montevideo*	Pus	3.8
	Salmonella montevideo	Blood	5.2
	Streptococcus pneumoniae type 6	Blood	7.7
5	*Haemophilus influenzae* type b	Blood	0.8
	Haemophilus influenzae type b	Blood	1.6
	Streptococcus pneumoniae type 23	Blood	1.8 (died)
6	*Streptococcus pneumoniae* type 23	Blood	3.8
	Streptococcus pneumoniae type ?	Blood	5.8
	Streptococcus pneumoniae type 23	Blood	19.7 (died)
Main group			
7	*Streptococcus pneumoniae* type 23	Blood	4.5
	Streptococcus pneumoniae type 23	Blood	4.6
	Streptococcus pneumoniae type 23	Blood	4.8
8	*Streptococcus pneumoniae* type 6	CSF	1.8
	Salmonella enteritidis	Blood	13.7
	Salmonella heidelberg	Blood	23.1
9	*Streptococcus pneumoniae* type ?	CSF	0.5
	Salmonella spp	Blood	1.3
	Streptococcus pneumoniae type ?	Blood	1.8

CSF, cerebrospinal fluid.

infections was 15.8 (95% CI, 8.3 to 30.5) times greater than the average for the SS population. The combinations of organisms in the 14 patients with two infections (excluding *E coli*) were two *S pneumoniae* isolations in six, *S pneumoniae*/salmonella in five, two salmonella isolations in one, salmonella/klebsiella in one, and *H influenzae*/klebsiella in one. Results from the nine patients with three or more infections (table 5) show recurrent *S pneumonia* bacteraemia in two, *S pneumoniae*/salmonella in three, *S pneumoniae*/haemophilus in three, and *S pneumoniae*/salmonella in one.

Discussion

Presentation of infection data is complicated by the need to categorise by more than one criterion, which produces small or unreliable incidence data. A report of bacteraemias from the cooperative study in the USA[9] stratified events into five age groups but not by sex or bacteraemia. The cumulative incidence approach used in our study has enabled further analysis. The organism and isolation rate were influenced by patient age and sex.

Streptococcus pneumoniae was the most common organism followed by salmonella and *H influenzae*. The last two organisms predominated in boys/men whereas *E coli* infection predominated in girls/women. Boys/men were marginally more prone to haemophilus bacteraemia, and a male preponderance (seven of 10) was also found in a previous study.[2] Isolations of *E coli* showed a different pattern, developing after the age of 15 years and being virtually confined to girls/women. The epidemiology of this infection clearly differs from other infections, possibly reflecting sexual activity, and a greater chance of urinary tract infections and ischaemic renal damage, rather than being consequent on loss of splenic function. Standardised infection rates for *S pneumoniae* and *H influenzae* fell sharply after 5 years of age, whereas that for salmonella remained relatively constant, giving an almost linear cumulative incidence rate. The declining prevalence of bacteraemias after the age of 5 years is consistent with previous reports,[9–11] and implies a role of actively acquired immunity, although pneumococcal prophylaxis may also have contributed.

A secular analysis adjusting for age did not confirm an expected fall in pneumococcal bacteraemias in the middle of the 1980s consistent with effective prophylaxis, which was surprising. The incidence of salmonella, on the other hand, did not change in the cohort group but increased significantly in the main group of patients, indicating a real and not just a relative increase in *Salmonella* spp isolations. This reflects the greater importance of salmonella in Jamaica[3]: this organism was the most common one to be isolated after 6 years of age.

Substantial differences were apparent between the cohort and main patient groups. The age structure of these groups differed, the oldest subjects being 24.5 years in the cohort group compared with 80.6 in the main group. Although the interquartile ranges were less disparate (cohort group, 11.2–21.2; main group, 10.7–31.4), this difference in age distribution affected the pattern of infection, because 19 of 38 bacteraemias in patients in the main group aged 20 years and above were caused by *E coli* compared with two of six in the cohort group. However, although it complicated assessment of the data, the inclusion of patients from the main group contributed most of the events, thereby increasing the sensitivity of analysis. The unadjusted fivefold increase in infections among patients in the cohort group (18.5/1000 patient-years) compared with main clinic patients (3.7/1000 patient-years) was also a concern, raising the possibility of considerable underdiagnosis in patients in the main group, but analysis of incidence within narrower age bands reduced this relative incidence to 2.6-fold. Factors contributing to this difference included the more comprehensive and complete follow up of the cohort group and the fact that patients in the main study group are more likely than those in the cohort group to attend other health care institutions, which might not have the same access to microbiological facilities. Under such circumstances, patients would be treated empirically, without culture confirmation of diagnosis. The cohort group who have been monitored closely in this clinic since birth, would almost certainly attend for illness and be investigated aggressively. Because care of sickle cell patients worldwide more closely resembles that in our main clinic group, the implications are that bacteraemia is underdiagnosed.

The clinical impression that a subgroup of patients with SS may be prone to recurrent infection was supported by our data, which showed that the risks of second and third infections were 4.8 and 15.8 times greater, respectively, than the SS population average. The most common pattern was recurrent

pneumococcal bacteraemia, which occurred in six of 14 patients with two bacteraemias and in five of nine patients with three or more bacteraemias. The next most common was the occurrence of pneumococcal and salmonellae bacteraemias in five and three of the two groups, respectively, and haemophilus bacteraemia, which occurred with other bacteraemias in three and four of the two groups, respectively. This extreme susceptibility is also demonstrated by patient number 1 of the cohort group (table 5), who harboured three different strains of salmonella over 16 years and also had a haemophilus bacteraemia. The importance of these observations are threefold. First, these patients represent a subgroup of patients with SS who are particularly prone to bacteraemia, and in whom the mechanism of such susceptibility should be investigated. The possible importance of the early loss of splenic function is supported by data from eastern Saudi Arabia, in which high concentrations of fetal haemoglobin are associated with persisting splenic function[12 13] and a lower incidence of bacteraemia. Second, there are implications for management because the greater risk of bacteraemia in patients who have already had one or two events should lead to aggressive investigation and management. Third, the greater increase in the bacterial isolation rate in patients monitored closely in the cohort group implies that many bacteraemias may pass undiagnosed in ordinary clinical practice.

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