Acute splenic sequestration in HbSS: observations from the Jamaican birth cohort

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ABSTRACT

Objective To document the prevalence, clinical features, haematology and outcome of acute splenic sequestration (ASS) in homozygous sickle cell disease (HbSS).

Study design A cohort study from birth.

Setting The Medical Research Council Laboratories at the University of the West Indies, Kingston, Jamaica.

Patients 311 cases of HbSS detected during the screening of 100 000 deliveries at the main government maternity hospital between 1973 and 1981.

Interventions Long-term follow-up and free patient care focusing on ASS.

Main outcome measure Acute splenic sequestration.

Results There were 183 episodes of ASS in 105 patients representing 35% of the cohort. The median age for first event was 1.07 years. During ASS, median values for haemoglobin fell by 32 g/dL, reticulocytes increased by 8% and total nucleated cells increased by 10.5%. ASS recurred in 47 (45%) patients. Conservative therapy in 133 episodes of 85 patients was associated with five deaths and splenectomy in 20 patients with 50 episodes had no deaths. Symptoms were generally non-specific but acute chest syndrome occurred in 17, and blood cultures revealed coagulase negative staphylococci in 5. The ASS case fatality rate was 3.6% and may be higher if autopsy evidence of ASS is included. There was no seasonal pattern but higher levels of fetal haemoglobin predicted patients less prone to ASS and its later occurrence.

Conclusions ASS remains an important cause of morbidity and mortality in HbSS in developing societies. ASS appears to be a non-specific response to many possible risk factors including coagulase negative staphylococci.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Acute splenic sequestration (ASS) is a major and serious complication of childhood homozygous sickle cell disease (HbSS) but most observations are based on clinical presentation and the prevalence and features of an unbiased group followed from birth are unknown.

WHAT THIS STUDY ADDS

⇒ The cohort study provides a true population sample for assessing prevalence, haematology and outcome.

⇒ Risk factors have been assessed and show that higher levels of fetal haemoglobin (HbF) protect against ASS and delays its onset.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Patients should be monitored from birth focusing on those with low HbF levels.

⇒ Splenectomy may be the treatment of choice in recurrent attacks.

INTRODUCTION

The post-natal decline of fetal haemoglobin (HbF) in homozygous sickle cell disease (HbSS) is associated with increasing levels of sickle haemoglobin (HbS) and consequently less deformable red cells. Following reports of early splenomegaly,[1] autopsies revealed a progressive splenic fibrosis,[2 3] but even enlarged spleens might lose function as shown by technetium-labelled sulfur colloid or pitted red blood cells in functional asplenia.[4 5] Early loss of splenic function renders patients prone to overwhelming blood infections with *Streptococcus pneumoniae*.[6–8] Genetic factors inhibiting sickling such as alpha thalassaemia[9] and persistence of high levels of HbF may allow splenic function to persist.[10–12]

Superimposed on this general pattern in HbSS, acute or chronic splenic enlargement may trap red cells, exacerbating the anaemia. Acute splenic sequestration (ASS) was first reported by Tomlinson[13] and later characterised by Seeler and Shwiaki[14] with 20 episodes in 14 children, 4 of whom died before transfusion could be given. There followed small series largely confined to symptomatically presenting cases, although a population-based study of 180 children with HbSS was reported from France.[15] In the Jamaican cohort, ASS was an early determinant of morbidity,[16 17] and the last review published in 1985 described 132 episodes of ASS in 89 patients.[18] All patients have now traversed the high-risk period and the current review describes 183 episodes in 105 patients, uses a more rigorous differentiation of ASS in the first 6 months, determines prevalence by auditing haematology from birth, and assesses risk factors and mortality from ASS.

MATERIAL AND METHODS

Ascertainment of cohort patients

The Jamaica cohort recruited 311 patients with HbSS during the screening of 100 000 consecutive, non-operative deliveries at the Victoria Jubilee Hospital, Kingston, Jamaica, between 1973 and 1981.[19] The diagnostic criteria of HbSS have been described.[20] All children were followed up in a dedicated Sickle Cell Unit at the University of the West Indies in Kingston which provided monthly assessments to 6 months, every 2 months to 1 year, 3

monthly to 5 years, and six monthly thereafter, although patients were encouraged to attend at any time, if sick. Admissions to other hospitals were traced for clinical details. All services and therapy were provided free and, if necessary, reimbursement of bus fares and occasionally transport was provided. These mechanisms restricted default for more than 1 year to less than 2%.

Methods of assessment

Capillary blood samples were taken at monthly intervals to 1 year and venous samples taken at 6-monthly intervals starting at 6 months, unless clinically indicated earlier. Splenomegaly was measured by centimetre tape in the splenic axis from the left costal margin to the splenic tip. On each visit, a clinical code of a letter and number was assigned including I7 (clinical ASS), I8 (subclinical ASS), I9 (hypersplenism) and I0 (splenic pain presumed to represent splenic infarction). An initial survey extracted events with these clinical codes up to the current age. A second survey identified all falls in haemoglobin level ≥2.0 g/dL associated with increased spleen size over the same period to detect cases not identified by appropriate splenic clinical codes.

Haematological indices were assessed in electronic haematology analysers. Reticulocyte counts were performed after staining with 2% brilliant cresyl blue, HbF by alkali denaturation,[21] and alpha globin gene status and the beta haplotype were determined by collaborating laboratories.[9 22] Of the 105 patients with ASS, the number of alpha globin genes was available in 97 and the beta globin haplotype in 80.

Clinical definitions

ASS was defined by a haemoglobin fall ≥2 g/dL, an enlarging spleen and evidence of increased bone marrow activity which was usually an increase in reticulocytes or nucleated cell count. In patients followed up from birth, the early postnatal fall in haemoglobin, occasionally associated with early splenomegaly, also fulfils this definition of ASS. To avoid confusion with normal haematological changes in HbSS before 0.5 year, the diagnosis of ASS was confined to those with a doubling of reticulocytes[23] or of nucleated red cells relative to immediately preceding values. This procedure found that 11 of the 20 events in this age group were not consistent with true ASS (figure 1). Mortality was described using ASS case-fatality, defined as the number of deaths divided by the number of patients with one or more ASS events.

Statistical methods

Selected haematology (total haemoglobin, reticulocyte count, total nucleated cell count) were compared before and during the ASS event. HbF levels at age 5 years were compared by gender using median regression. The potential role of HbF in delaying ASS onset was explored by regressing HbF on age at first ASS event using a Weibull regression model, unadjusted and adjusted for the potential effects of alpha globin genes and beta haplotype. For analysis, the latter were divided into three groups (Group 1 Benin/Benin in 45 patients, Group 2 Benin/CAR or CAR/CAR in 21 patients and Group 3 Benin/Senegal or Senegal/Senegal in 12 patients). The monthly or seasonal distribution of ASS was assessed using Poisson regression. Risk factors for ASS were assessed by logistic regression for HbF, alpha globin gene number and beta globin haplotype. Concordance of ASS in sibling-pairs was compared with that generated by 10 000 random-pairings.

RESULTS

Of the 311 patients, 15 could not be assigned to splenic groups because of early losses (9 died from other causes, 1 emigrated, 4 defaulted for periods and 1 was on chronic transfusion). Of the remaining 296 patients, 105 (35%) met the criteria for ASS (figure 2).

Clinical ASS

Twenty episodes occurring before 0.5 year were edited as described, leaving nine consistent with clinical ASS. There were

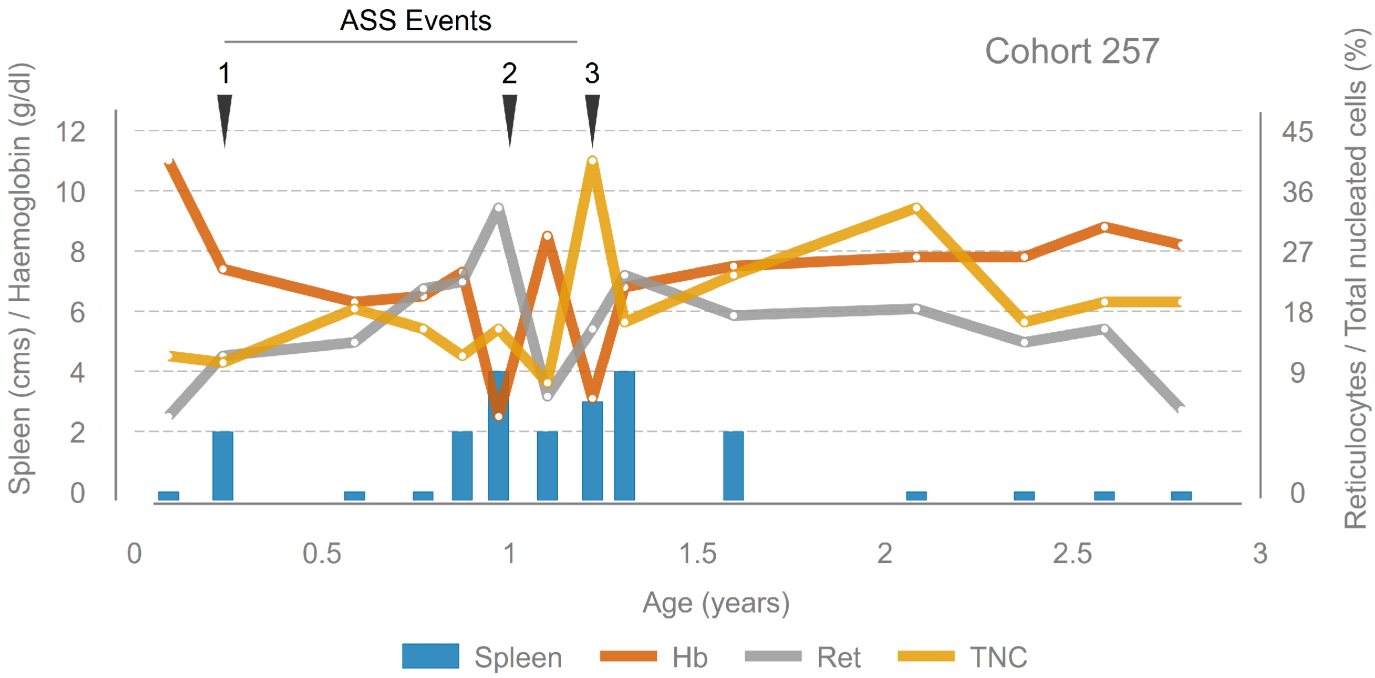

Figure 1 Serial observations of three events potentially qualifying for acute splenic sequestration (ASS). Event 1 had minimal increase in reticulocytes and no change in total nucleated cell count so was discounted, events 2 and 3 qualified for the definition. The sharp rise in haemoglobin (Hb) followed blood transfusion for events 2 and 3. TNC, total nucleated cell count.

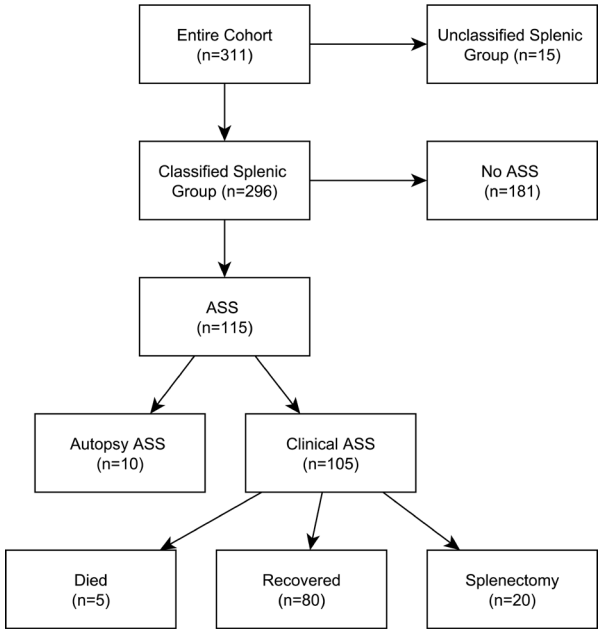

Figure 2 Flow chart of patients recruited to the Jamaican cohort identifying individuals with acute splenic sequestration (ASS). Numbers refer to patients.

183 events in 105 patients (1 event in 58 subjects, 2 events in 27 subjects, 3 events in 12 subjects, 4 events in 7 subjects and 7 events in 1 subject). Recurrence occurred in 47 out of 105 (45%). In 71 events in 20 patients with three or more episodes, the median interval between first and second event was 137 days, between second and third event was 110 days, between third and fourth events 56 days, a trend not reaching statistical significance (median regression, p=0.27).

Age/gender

There were two outliers, a female with three events at ages 6, 8 and 10 years was the only patient homozygous for alpha thalassaemia and another female with events at 10, 11, 15 and 16 years (figure 3) was the only patient homozygous for the Senegal haplotype. The median age at first episode was 1.07 years, the second at 1.58 years, the third at 1.94 years and the fourth at 2.03 years. The first episode of ASS occurred at 0–0.9 years (44 patients), 1–1.9 years (40 patients), 2–2.9 years (9 patients), 3–3.9 years (4 patients), 4–4.9 (4 patients), 5–10.9 (4 patients). Although marginally earlier in males, the difference was not significant (log-rank test, p=0.12).

Haematology

Compared with immediately preceding values in 105 first episodes, the mean haemoglobin fell by 35.4 g/L (SD 15.3, median 32.0, range 20–125), mean reticulocyte counts increased by 8.96% (median 8.0%, range −18% to +28%) and mean total nucleated red cells increased by 15.17×10^9/L (median, 10.5×10^9/L, range −9 to $+71\times10^9$/L). Reticulocytes fell in 15 subjects, but in these, total nucleated cell counts largely represented by nucleated red blood cells, increased by a mean of 8.1×10^9/L consistent with an urgent bone marrow response. Of the six patients with neither an increase in reticulocytes or total nucleated red cells, four had the acute chest syndrome which could have suppressed bone marrow response. Mean HbF at age 5 years was lower in males, 5.3% vs 6.7% (median regression, p=0.02).

Spleen

In 105 first episodes, the spleen was not palpable before ASS in 70 patients, measured 1–3 cm in 29 and 4–7 cm in 6. At ASS, the spleen measured 1–3 cm in 60, 4–6 cm in 38 and 7–10 cm in six episodes (one value was missing). Assessed 2 weeks to 2 months

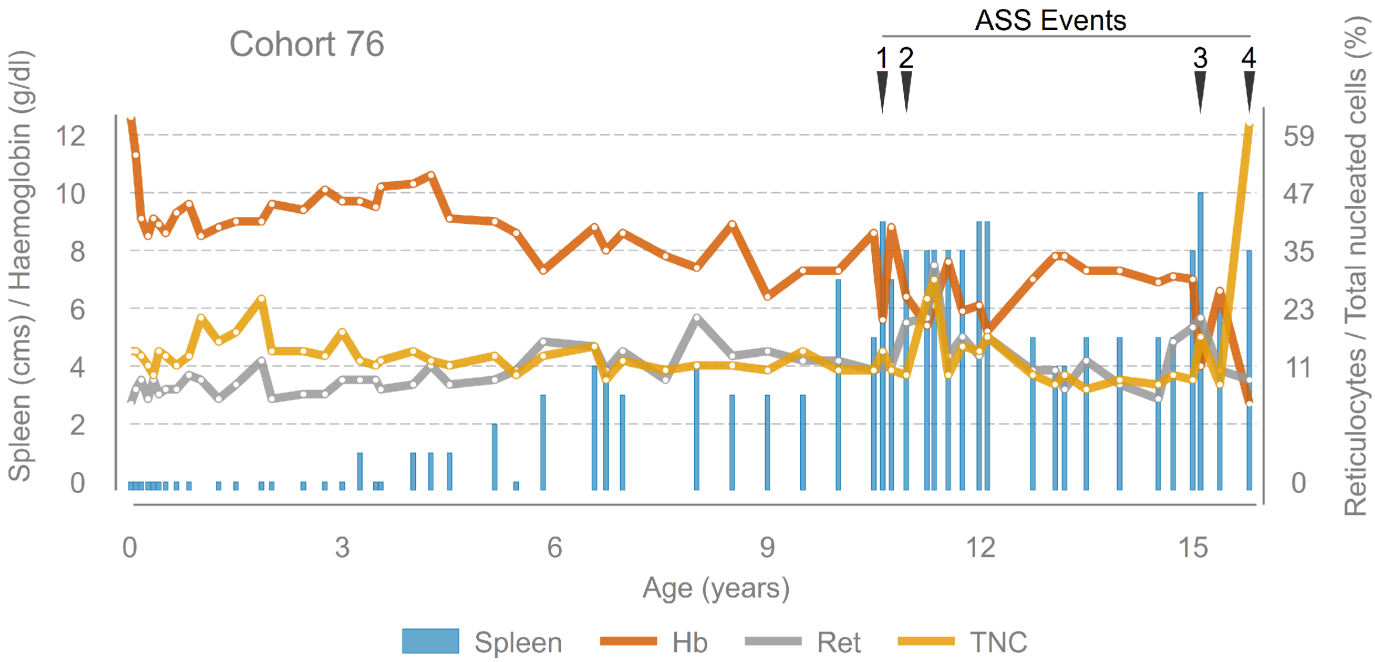

Figure 3 Serial haematological observations in patient who died in her fourth acute splenic sequestration (ASS) event. She was not transfused for the first three events with haemoglobin (Hb) levels of 5.6 g/dL, 6.4 g/dL and 4.0 g/dL and increases in Hb reflect spontaneous recovery. Her fourth event occurring while on holiday on the north coast led to admission to a rural hospital and then transferred to Kingston with a Hb of 2.7 g/dL. TNC, total nucleated cell count.

after ASS, the spleen was impalpable in 20, measured 1–3 cm in 44, 4–6 cm in 16 and 7–12 cm in 4 (post-ASS values were not available in 20 episodes, and in one splenectomy). Mean spleen size at the time of ASS increased by 2.8 cm (SD 1.4, median 3, IQR 2–4, range 1–8 cm).

Coincident pathology

Of the 183 episodes, 43 denied symptoms and were detected by the haematological change during routine appointments. Non-specific symptoms occurred in 98 events (57 fever/cold/upper respiratory tract infection, 16 gastroenteritis, 4 avascular necrosis of bone and 21 pallor). Other pathology included acute chest syndrome in 17 patients, abdominal swelling from the enlarged spleen in 7, and 18 with infections, 11 with positive blood cultures (3 with *Streptococcus pneumoniae*, 1 each of *Haemophilus influenzae*, *Klebsiella*, *Escherichia coli* and 5 with coagulase negative *Staphylococci*), 2 with otitis media, 1 with mumps, 2 simultaneously seroconverted to parvovirus B19 and 2 were of unknown aetiology.

Outcome

Conservative therapy alone in 85 patients (133 episodes) was associated with 5 deaths and 20 patients (50 episodes) were treated by splenectomy without mortality. Splenectomised patients had more frequent admissions (78% vs 41%), transfusion (90% vs 35%) and a higher recurrence rate (90% vs 36%). Splenectomy was performed on recurrent ASS in 15 patients (two or more events often at diminishing intervals), and after a single ASS in 5 patients (three developing hypersplenism and two for social reasons). The latter illustrated by one child with splenectomy at age 0.79 year after a single life-threatening episode, in whom consciousness was restored by transfusion and the mother with HbSS who had lost an earlier child from ASS at age 1.75 years did not appear to realise the gravity of the situation. The most striking difference was the secular increase in splenectomy rising from 4 out of 28 (14%) between 1973 and 1977, to 6 out of 38 (16%) between 1978 and 1981, and to 10 out of 21 (48%) between 1982 and 1986.

Three patients were unconscious from severe anaemia but recovered consciousness, two after urgent transfusion and another after unmatched blood (later shown to be compatible) was injected into a femoral vein at another hospital.

Risk factors for ASS

Frequency did not vary with calendar month analysed by first or all episodes. ASS occurred later in patients with higher HbF at 5 years of age, 4% HbF predicting ASS at 0.92 year (95% CI 0.78 to 1.05), 8% HbF at 1.44 years (95% CI 1.24 to 1.63) and 12% HbF at 2.24 years (95% CI 1.83 to 2.66) (Weibull regression, $p<0.001$). Higher HbF protected against ASS, the odds of ASS declining by 10% for every 1% increase in HbF (OR 0.91, 95% CI 0.86 to 0.96, $p=0.001$), with no demonstrable effect of alpha thalassaemia and beta globin haplotype. Among 20 sibling pairs, concordance occurred in 13 (65% pairs) compared with 56% (IQR 52%–60%) among random pairings, and although 9 percentage points higher, this difference failed to reach significance (one-sided permutation test $p=0.94$).

Mortality

In the 311 patients with HbSS, there have been 138 deaths, 81 emigrations and 92 remain in Jamaica. Five deaths occurred with clinical ASS for a case fatality rate of 3.6%, but a further 10 patients had autopsies consistent with ASS (table 1) which could increase the ASS case fatality rate to 10.9%. The autopsy group had splenic weight five times (range 1.9–11.1) above age-related normal values and cultures at autopsy revealed *Streptococcus pneumoniae* in three, *Klebsiella* in two and Enterobacter in one, but these were from sources not normally clinically available.

Table 1 Features of 15 cases dying in acute episode, ranked by age at death

No.	Coh number	Age	Sex	Clinical features	Spleen at autopsy: Autopsy number	Weight: Obs	Weight: Exp	Ratio: Obs/Exp	Culture
Documented ASS in life									
1	101	0.6	F	Dead on arrival, pallor ++ (2nd event)	9434	122	22	5.5	*Streptococcus pneumoniae**
2	52	0.6	F	Died day after admission (2nd event), Hb 5.3	8977	60	23	2.6	*S. pneumoniae*†
3	75	1.8	M	Died on way to hospital, pallor ++ (2nd event), Hb 2.4	9742	62	33	1.9	*S. pneumoniae*‡
4	12	4.5	M	Died during admission (3rd event), Hb 2.5	10302	445	49	9.1	Nad
5	76	15.5	F	Died during admission (4th event), Hb 2.7	14628	946	100	9.5	Nad
Possible ASS at death									
6	314	0.4	F	Died on way to hospital, fever, pallor	11421	110	16	5.3	Nad
7	285	0.6	M	Died on way to hospital, pallor ++, ACS	11172	90	17	3.8	Nad
8	200	0.6	M	Died on way to hospital, Hb 0.8	10496	115	19	6.1	Nad
9	65	0.8	F	Died on way to hospital, pallor ++	X75/10	92	25	3.7	*S. pneumoniae*§
10	120	0.9	F	Died at home, pallor ++	9705	60	25	2.4	Nad
11	102	1.0	F	Died during admission, ACS, Hb 5.8	9584	45	22	2.0	Nad
12	41	1.5	F	Died at home, pallor ++	9314	172	30	5.7	Nad
13	135	1.5	F	Died during admission, pallor ++	Govt	140	30	5.5	*Enterobacter*†
14	138	1.7	F	Died during admission, pallor ++	10329	160	30	5.3	*Klebsiella*†
15	70	2.7	F	Died during admission, drowsy ++	10134	140	37	3.8	*Klebsiella*†

*Bronchus.
†Cardiac blood.
‡Bronchus, middle ear and lung.
§Middle ear.
ACS, acute chest syndrome; Exp, Expected; Hb, haemoglobin; Nad, no significant growth on culture; Obs, observed.

All deaths were associated with precipitate clinical courses with extreme pallor and died either at home, en route to hospital or during admission. The mean age at death in the 15 patients was 2.3 years (SD 3.8, median 1.0) or 1.4 years (SD 1.1, median 1.0) after excluding the outlier who died at the age of 15.5 years. Of the 15 deaths, 9 had no haematology in the terminal episode, and in 6, the mean haemoglobin was 33 g/L (range 8–5.8).

DISCUSSION

The age interval characterised by ASS covered approximately 18 years, during which there have been changes in management such as parental education in diagnosis of ASS,[18] pneumococcal prophylaxis, treatment by splenectomy and the increasing use of hydroxyurea.[24] Following up children from birth created a novel challenge as the early establishment of haemolysis in HbSS, also qualified for the accepted diagnosis of ASS. Potential weaknesses include the diligence of different doctors recording splenomegaly, difficulties of assessment in sometimes sick children and that clinical splenic enlargement imperfectly reflects spleen size on ultrasonography.[25] The prevalence of ASS in the Jamaican cohort at 35% exceeded the 10% reported from the cooperative study in the USA,[26] 7% in western Saudi Arabia[27] and 16% in a French study.[15] All studies used similar definitions for ASS, and the greater frequency in the cohort may reflect clinically mild cases from auditing serial haematology, a hypothesis consistent with the relatively benign clinical course, 90 out of 183 (49%) events resolving without admission and 90 out of 183 (49%) without transfusion.

Recurrence in the cohort was 45%, and 14%–67% elsewhere.[15 26 27] Splenectomy was deemed necessary in 20 patients, mostly for recurrence at shorter intervals or the emergence of hypersplenism. With increasing experience in the cohort, splenectomy rose to 48% in later years, a trend noted elsewhere with splenectomy rates between 37% and 73%,[15 26 28] although a literature review found no evidence of benefit from splenectomy.[29]

The study from Paris describing 180 patients with HbSS based on newborn screening presents a valuable population-based group for comparison.[15] For first event, median age was similar (France 1.4 years, Jamaica 1.1 years), spleen size was 3 cm in both studies, the spleen was not palpable prior to ASS in 68% Jamaican and 79% Parisians, and management was conservative in both (66% vs 54%). Differences occurred in the recurrent rate (Jamaica 45% vs Paris 67%), coincident pathology (27% vs 57%) and the ASS case fatality rate (3.62% vs 0.56%).

Nucleated red cell counts emerged as a valuable indicator of bone marrow activity, and although much of the elevation was due to nucleated red cells, differential counts were only available in a limited number. Another concern relates to the historical nature of the cohort observations since the last recorded event was in August 1990, and relative mortality has declined sharply in the ensuing 30 years with newborn screening, parental education in diagnosis of ASS,[18] the widespread use of hydroxyurea[29] and holistic care.

Nine children within the cohort developed ASS before 6 months and cases have been reported elsewhere as early as 5 weeks[30 31] with a fatal case at 4 months.[32] Coagulase negative staphylococci in five blood cultures raised the possibility that HbSS may be susceptible to this organism as may occur in some other immunocompromised patients.[33] Of the 15 deaths, all had precipitate terminal events, 5 with documented recurrence in which current knowledge would have dictated splenectomy and 10 others with autopsy evidence consistent with ASS. The cohort data appeared to support the increasing use of splenectomy, and until the risk factors are better understood, ASS remains an important determinant of morbidity and mortality in developing societies.

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Contributors GS conceived the cohort study. KM and BES oversaw the laboratory investigations over the last 40+ years. KM and GS maintain contact with the cohort. IRH undertook the statistical analysis. GS is guarantor.

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Data availability statement Data are available upon reasonable request.

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