Survival in β-thalassaemia major in the UK: data from the UK Thalassaemia Register

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About 50% of UK patients with β-thalassaemia major die before the age of 35 years, mainly because conventional iron-chelation therapy is too burdensome for full adherence. Patients require an idividually-tailored treatment plan incorporating new, more tolerable approaches.

β-thalassaemia major first appeared as a significant problem in the UK in the mid-1950s.[1] Initially, affected children were "low-transfused" for fear of iron overload, but in the late 1960s the mean haemoglobin maintained by transfusion was raised to the normal range. This greatly improves quality of life but leads to transfusional iron overload which, if untreated, causes death from cardiac complications between 12 and 24 years of age. About half of UK patients were started on iron-chelation therapy by daily intramuscular injection of desferrioxamine in the late 1960s. The mode of administration was changed to subcutaneous infusion over 8–12 h per night, at least 5 nights per week in 1977. This became standard management after 1982, when it was shown to improve survival.[1,2] Patients who adhere fully to treatment usually complete their education, work, and find a partner, and are expected to live at least until their mid-forties.

Adherence to treatment, however, is extremely difficult, and many adolescents and young adults allow their iron load to rise. This can lead to complications even after iron load is brought back under control. In recent years there has been a steady increase in the number of deaths reported to the UK Thalassaemia Register, suggesting that at a national level treatment is less successful than had been hoped. The UK Thalassaemia Register includes over 95% of patients ever born or resident in the country. At the end of 1998 it included 820 patients with a diagnosis of β-thalassaemia major (ie, transfusion-dependent from early childhood). 24 have been lost to follow-up. The table shows the status of the remaining 796 patients by 10-year birth cohort. Deaths fall into three broad groups. Death before 12 years of age was common before the mid-1960s caused by anaemia complicated by infection and/or hypersplenism; recent early deaths are related to bone-marrow transplantation. Most deaths between 12 and 24 years of age are due to untreated or minimally-treated iron overload. Survival past 24 years of age is a result of iron-chelation therapy.

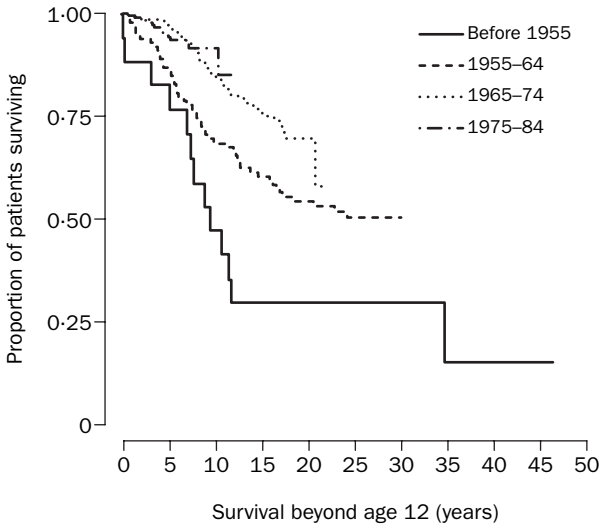
The figure shows Kaplan-Meier survival curves for 736 patients who survived beyond 12 years of age, by 10-year birth cohort. A progressive change in the curve is expected, reflecting the evolution of treatment and extent of patient adherence.

1945–54 birth cohort—Members of this cohort should now be more than 45 years of age. 75% of survivors to age 12 years died of iron overload, mostly before iron chelation was standard treatment. A handful of patients who were "de-ironed" vigorously in their teens are still alive.

1955–64 birth cohort—Members of this cohort should now be over 35 years of age. Some were started on desferrioxamine

Cohort	Patients	Deaths (%)	Age at death		
			<12 y	12–24 y	>25 y
1945–54	25	21 (84)	8	12	1
1955–64	119	67 (56)	19	32	16
1965–74	188	63 (34)	14	37	12
1975–84	237	33 (14)	13	20	0
1985–94	179	5 (3)	5	0	0
1995 onwards	48	1 (2)	1	0	0
Total	796	190 (24)	60	101	29

Present status of 796 UK patients with β-thalassaemia major



Survival beyond 12 years of age by 10-year birth cohort

in early childhood, others only in their teens or not at all. About 30% died before 24 years of age and 20% died between 24 and 35 years of age, indicating inadequate chelation. A plateau at 50% survival to 40 years of age suggests successful control of iron overload in about half the patients, and confirms that long-term survival is possible even with organ damage due to prior iron overload, hepatitis C infection, or both.

1965–74 birth cohort—Members of this cohort should now be between 25 and 35 years of age. Most started iron-chelation therapy when still young so this cohort should show the full benefit of treatment. However, over 30% have died and the survival curve resembles that for the previous cohort, displaced 8 years to the right. There is no sign of a plateau. It seems likely that the curve will converge with that of the previous cohort at about 50% survival.

1975–84 birth cohort—These patients should now be between 15 and 25 years. To date, their survival resembles that of the previous two cohorts.

The data indicate that only about 50% of UK patients are able to adhere fully to current iron-chelation therapy, and that less adherent patients gain on average only 10 years of life in exchange for a lengthy struggle with burdensome and often painful treatment. Similar observations have been reported from specialist treatment centres in other countries. For example, survival to age 30 among 257 patients attending the centre in Torino is 55%. The aggregate figure represents 88% survival among 60% of patients able to adhere fully (60%), and only 10% survival among 40% not able to adhere fully.[3] The UK data are rather more pessimistic, as is to be expected in a national study including patients attending non-specialist as well as specialist centres. Fortunately, the existence of several new approaches for increasing the tolerability of treatment now makes it possible to negotiate tailor-made chelation schemes with individual patients.[4] These approaches include: intensive "de-ironing" by 24 h intravenous infusion of desferrioxamine using an implantable device (eg, a Portacath) that can reverse established disease in severely iron-loaded patients; weekly home delivery of disposable infusors with a desferrioxamine dose tailored to individual patients (eg, Baxter balloon pumps) that greatly improves adherence; the oral iron-chelating agent deferiprone (L1), which although is less safe than desferrioxamine, is acceptable and effective for many patents who cannot tolerate conventional treatment;[4] and combined regimens including less frequent desferrioxamine infusion with oral iron chelation.[5] About 50% of adolescents and young adults need to be offered one or more of these options (personal communication). Monitoring and patient-

specific adjustment of the chelation scheme is best done through a specialist centre with a doctor/nurse specialist team. Several such centres exist in major conurbations, but many patients live far away. The Register includes 70 consultants with one patient and 57 with one to five patients. Many of these consultants refer their patients to an expert centre annually for review. The data presented here show that this should become standard practice nationally.

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Meningococcal disease among children of Indian subcontinent ethnic origin

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The rate of meningococcal septicaemia and meningitis was significantly lower in children of Indian subcontinent ethnic origin than in children of other origins over 12 years in the Blackburn area of the UK.

16% of children aged under 5 years in the Blackburn, Hyndburn, and Ribble Valley (BHRV) area of East Lancashire Health Authority, UK, are of Indian subcontinent ethnic origin.[1] However, doctors have noted that few such children are admitted with invasive meningococcal disease. This finding led to the hypothesis that the disease is less common in children of Indian subcontinent ethnic origin.

Case notifications for meningococcal meningitis or septicaemia in children aged under 5 years in the BHRV area were obtained for the 12 years 1987–98. These notifications often recorded laboratory evidence of invasive meningococcal disease: blood or cerebrospinal fluid culture, PCR, or serological tests. When this information was unavailable medical notes were reviewed. For an illness that included fever and a petechial rash, and which was treated as invasive, meningococcal disease was accepted as a clinical diagnosis. The child's ethnic origin was determined from the first name and surname.[2] The total number of children living in the region aged under 5 was obtained from the local public-health department (figures based on the 1991 census).

Table 1 shows details of cases of invasive meningococcal disease in children aged under 5 years. Table 2 shows the rate of invasive meningococcal disease and the rate for cases with bacterial confirmation only. These results show that the rate of invasive meningococcal disease in children of Indian subcontinent origin aged under 5 is significantly lower than the rate among children not of this ethnic origin over the 12-year period. We examined birth records, looking at the numbers of births to all mothers, and the records suggested that the actual proportion of children of Indian subcontinent origin may be higher (24%) than the official number (16%) from public health records. Indeed, underestimation of ethnic minority groups in the 1991 census has been discussed.[3] Thus, with the higher number of such children the results might be even more important. The public-health department for East Lancashire Health Authority are not aware of any unexplained deaths occurring in children of Indian subcontinent origin, and thus it is likely that ascertainment of cases is accurate.

	Bacterial confirmation*	Clinical diagnosis	Notes unavailable	Total
ISC	4 (2B + 1C)	1	1	6
Non-ISC	69 (42B + 11C)	38	34	141
Total	73 (44B + 12C)	39	35	147

Type shown in parentheses.

Table 1: **Cases of invasive meningococcal disease in children aged under 5 years, of Indian subcontinent (ISC) or non-ISC origin**

	ISC	Non-ISC	P value
All cases	15·8	68·7	<0·001
Bacterial confirmation only	10·5	33·6	<0·025

Table 2: **Rate of invasive meningococcal disease (per 100 000 population) and rate for bacteriologically confirmed cases**

In England and Wales in 1995 there were 675 culture-confirmed cases of meningococcal disease in a total population aged under 5 of 3 422 888. By extrapolation the national incidence of culture confirmed cases would be 19·7/100 000. The higher incidence among children not of Indian subcontinent origin with bacterial confirmation could represent a local epidemic; but if so why were the children of Indian subcontinent origin not affected?

Some workers have shown varying rates of infection in different ethnic groups, including Russian investigators who linked increased vulnerability in an ethnic group to possession of certain HLA antigens.[4] It is noteworthy that people of Indian subcontinent origin in the Blackburn area are concentrated in underprivileged wards, and household overcrowding is associated with meningococcal disease.[5] Research into ethnic differences in health have often been criticised for failing to adequately allow for confounding factors such as poor socioeconomic status. However, our study shows a significantly lower rate of a disease that might be expected to have a high incidence in a deprived group, such as the population of Indian subcontinent origin in the BHRV area. This difference in disease incidence could be attributable to genetic or cultural factors.

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