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CLINICAL RESEARCH STUDY

Evaluation of Severe Infection and Survival After Splenectomy

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ABSTRACT

PURPOSE: Splenectomized patients are known to be at risk of severe infection, but the extent of risk is unclear. We evaluated the incidence of severe infection and survival in 1648 splenectomized patients.

METHODS: Patients who underwent splenectomy between 1988 and 1999 in Scotland were identified through the Scottish hospital discharge records (SMR01) and then linked to the death certificate data recorded by the General Register Office in Scotland to obtain clinical and demographical information.

RESULTS: The overall rate of first severe infection was 7.0 per 100 person-years (95% confidence interval, 6.30-7.78). The overall rate for a second infection per 100 person-years was 44.9 and 109.3 for a third infection after the first episode of infection. Among the repeated episodes of severe infection, 42% to 76% and 61% to 84% of total episodes of second and third severe infection, respectively, occurred within 6 months after the first severe infection. The susceptibility to severe infection was greatest in older age groups (5.5 per 100 person-years in those aged > 50 years) and in patients splenectomized for hematologic malignancy (9.2), and iatrogenic splenectomy for malignancy disease (7.4). Between 50% and 80% of all severe infections or deaths occurred within 1 to 3 years after splenectomy.

CONCLUSIONS: The risk of severe infection is an important health problem in splenectomized patients, especially in those who underwent surgery for malignancies. Antibiotic prophylaxis could offer the most benefits in the first 3 years postsplenectomy or the first 6 months after the occurrence of a first severe infection. © 2006 Elsevier Inc. All rights reserved.

KEYWORDS: Splenectomy; Survival; Severe infection

The removal of the spleen is associated with an increased susceptibility to infection and mortality¹ that has been reported to be lifelong.^{2,3} Although the risk of infection after splenectomy varies by age, reason for surgery, and length of time since surgery,⁴ the extent and magnitude of risk in these patients are not well defined. Thus, we conducted this study to determine the incidence of severe infection, duration of risk of severe infection, and survival after splenec-

tomy by sex, age, and reason for surgery in Scotland during an 11-year period from 1988 to 1998. These data should inform targeting of vaccines and antibiotics.

METHODS

Data Collection and Definitions

Scotland has an estimated population of 5.1 million, divided into 15 Health Boards for health administration purposes. The study was approved by the ethics committees of 10 Health Boards, comprising a total population of 2 900 000. Patients who underwent splenectomy while residing in these Health Board areas between January 1, 1988, and December

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31, 1998 were identified from the Scottish discharge records (SMR01), which are collected on discharge from hospital for all episodes of inpatient or day-case care. SMR01 collects information on demography and the clinical details of patients receiving hospital care. These SMR01 records were linked to the General Register Office (Scotland) death registrations using probability matching⁵ to identify the patients who had died. The extracted information from the SMR01 and General Register Office in Scotland included date of birth, sex, reason for splenectomy, hospitalization with serious infections before and after surgery, and date of death (where appropriate). Information on multiple infections was available for patients who had more than one episode of infection.

Severe infection was defined as an episode of infection that required hospitalization. Overwhelming infection was regarded as septicemia or meningitis. Any infections occurring in the first 28 days after splenectomy were excluded in the analysis to avoid infection related to operation. The SMR01 hospital discharge records provided data on severe respiratory infections or septicemia and reasons for surgery. They were based on the International Disease Classifications codes 9 and 10. Five diagnostic codes were available to identify the reason for splenectomy in each patient. These codes were reviewed and categorized by one of us (F.T.) who has extensive clinical experience in the management of splenectomized patients.

We identified three main reasons why patients underwent splenectomy. First, there was therapeutic splenectomy, generally a planned procedure undertaken expressly to treat a hematologic disease (eg, hereditary spherocytosis, idiopathic thrombocytopenic purpura). Within this group of patients may have been a small number of individuals in whom splenectomy was undertaken for diagnostic rather than therapeutic reasons (eg, Hodgkin's disease undergoing staging), but the data did not allow confident discrimination. Therapeutic splenectomy was further divided into 143 patients (8.7% of total) with malignancy (invariably hematologic malignancy in this group: Th^m) and 447 patients (27.1%) with nonmalignant causes of splenectomy (Thⁿ).

The second major reason for splenectomy was trauma. This group comprised 271 patients (16.4%) who had undergone severe trauma before surgery (eg, road traffic accident), resulting in splenic rupture requiring splenectomy. Intraoperative trauma requiring splenectomy was excluded

from this group and categorized as iatrogenic, the third major reason for splenectomy. Iatrogenic splenectomy typically occurred as a presumably unintended accompaniment to surgery to other abdominal organs (eg, resection of gastric carcinoma). Within this iatrogenic group, we identified 530 patients (32.2%) with malignant disease (Ia^m) and 246 patients (14.9%) with nonmalignancy (Iaⁿ). A small group of 11 patients (0.7%) could not have a cause for splenectomy identified from the available data (U).

The ages of patients were expressed as their ages at splenectomy, which was categorized into 6 groups: 0 to 16 years, 17 to 29 years, 30 to 49 years, 50 to 59 years, 60 to 69 years, and 70 years and above.

Statistical Analysis

Age at splenectomy and survival were calculated from date of splenectomy, date of birth, and date of death. Person-years at risk of infection after splenectomy were calculated from the date of splenectomy until the first episode of serious infection or the date of

death. Survival time and time to infection were censored at December 28, 1998.

Incidence rates of first, second, and third severe infection per 100 person-years and 95% confidence intervals (CIs) were calculated for sex, age group, and indication for splenectomy. All infection times were included in a proportional hazards model. A Weibull hazard function was found to be appropriate and showed that the rate of infection decreased over time. Differences between groups were examined by hazard ratios; these may be interpreted as relative risks. This modeling was performed in Stata (Stata Corporation, version 8.0, College Station, Tex). Survival curves were calculated in Stata version 8 for both time to death and time to first infection for sex, age group, and indication for splenectomy. The curves were summarized by the cumulative death and mean survival times. The dependent (outcomes) variables were severe infection and death, and the independent variables (predictors) were age, sex, and indications for splenectomy.

RESULTS

A total of 1648 patients underwent splenectomy in the 10 Health Boards over the study period, consisting of 939 males (56.9%) and 912 (55.2%) alive. The age of the patients at splenectomy ranged from 1.4 to 94.5 years, with a mean age at splenectomy of 53.2 years. There were 7337 person-years follow-up with a mean of 4.45 years.

CLINICAL SIGNIFICANCE

- The risk of severe infections or deaths is highest in the first 3 years after splenectomy.
- The risk of the second or third infection is particularly high among those have a first severe infection and most episodes of repeated post-splenectomy infection occurred within 6 months after the first episode.
- The greatest risk of severe infections was observed in patients splenectomized for hematological malignancy.
- Severe post-splenectomy infection is not confined to children and is also an important health problem in adults.

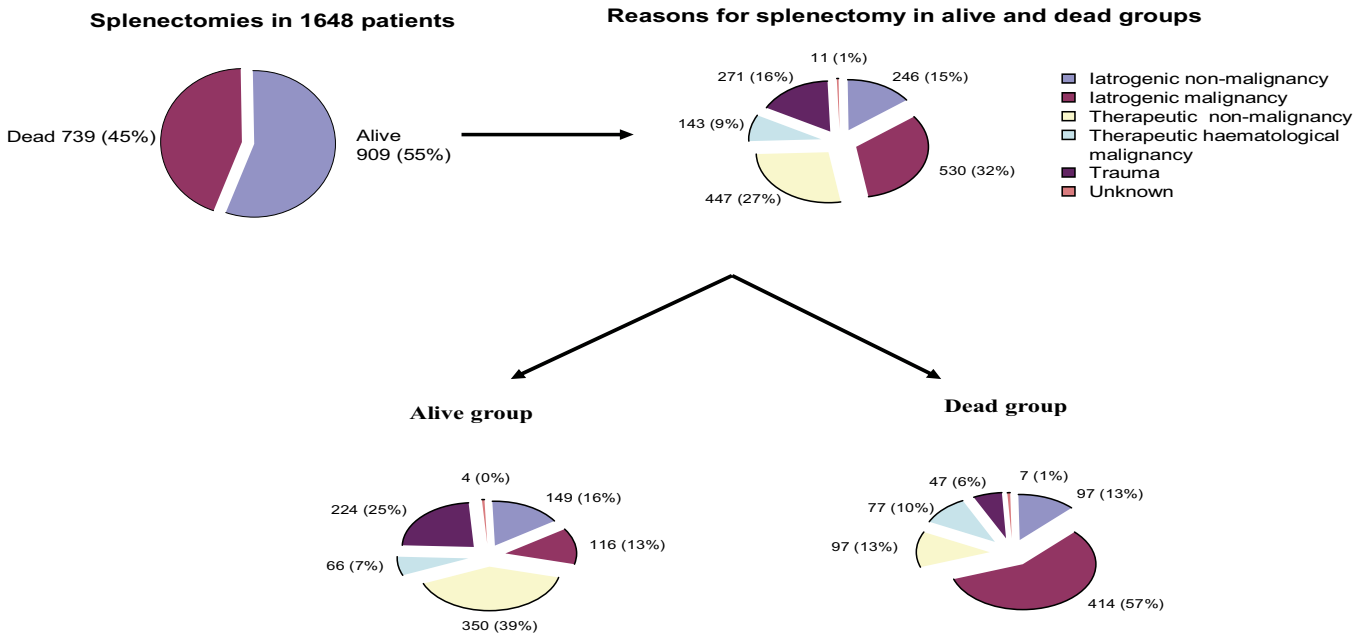


Figure 1 Cohort of 1648 splenectomized patients by vital status and reason for surgery.

Reasons for Splenectomy

Reasons for splenectomy are shown in Figure 1. The most common reasons for splenectomy were Ia^m (530, 32.1%) and Thⁿ (447, 27.1%). The lower mean age at splenectomy was observed in patients who were splenectomized for trauma (35.1 years) and Thⁿ (43.3 years) compared with Th^m (57.7 years), Iaⁿ (59.8 years), and Ia^m (66.5 years). Most cases of splenectomy were caused by Th^m (350, 38.5%) and trauma (224, 24.6%) in living patients. The

highest proportion of splenectomies in the deceased patients were performed for Ia^m (414, 56%) (Figure 1).

First Severe Infection

A total of 350 patients (21.2%) were reported to have severe infection requiring hospitalization after splenectomy. The overall incidence of first severe infection was 7.0 per 100 person-years (95% CI, 6.3-7.8). There were significant dif-

Table 1 Incidence of First, Second, and Third Severe Infection by Sex, Age, and Reasons for Splenectomy*

	Total No. of Patients	First Infection		Second Infection		Third Infection		Relative Risk	(95% CI)	P Value
		No. (%)	Rate (95% CI) of Severe Infection per 100 Person-Years	No. (%)	Rate	No. (%)	Rate			
Overall	1651	349 (21.2)	7.00 (6.30-7.78)	165 (47.3)	44.9	95 (57.6)	109.3	—	—	—
Males	939	184 (19.6)	6.48 (5.61-7.48)	91 (49.5)	45.9	58 (63.7)	170.5	1		.860
Females	709	165 (23.3)	7.72 (6.63-8.99)	74 (44.8)	43.8	37 (50.0)	70.0	0.97	(0.78-1.21)	
Age group										
0-16 y	85	14 (16.5)	2.94 (1.74-4.96)	7 (50.0)	19.5	3 (42.9)	24.9	1		
17-29 y	209	27 (12.9)	2.66 (1.82-3.88)	7 (25.9)	12.9	4 (57.1)	64.1	0.72	(0.35-1.51)	
30-49 y	265	55 (20.7)	5.35 (4.11-6.97)	24 (43.6)	34.5	12 (50.0)	79.1	1.43	(0.75-2.73)	<.001
50-59 y	282	65 (23.1)	7.46 (5.84-9.49)	29 (44.6)	58.8	19 (65.5)	112.5	1.98	(1.05-3.73)	
60-69 y	334	80 (24.0)	11.07 (8.89-13.80)	39 (50.0)	60.3	27 (67.5)	223.0	2.44	(1.31-4.52)	
70+ y	388	88 (22.7)	13.85 (11.24-17.07)	50 (56.8)	75.5	22 (44.0)	107.2	2.60	(1.41-4.80)	
Reasons for splenectomy										
Trauma (Tr)	271	36 (13.3)	3.12 (2.25-4.32)	15 (41.7)	23.7	6 (40.0)	56.5	1		
Iatrogenic nonmalignant (Ia ⁿ)	246	71 (28.9)	10.16 (8.05-12.82)	36 (50.7)	42.0	22 (61.1)	104.2	2.76	(1.80-4.23)	
Iatrogenic malignancy (Ia ^m)	530	94 (17.7)	12.08 (9.87-14.79)	43 (45.7)	82.8	18 (41.9)	88.2	2.18	(1.43-3.34)	<.001
Therapeutic nonmalignancy (Th ⁿ)	447	91 (20.4)	4.81 (3.91-5.90)	37 (40.7)	28.3	27 (73.0)	96.2	1.62	(1.05-2.50)	
Therapeutic hematological malignancy (Th ^m)	143	55 (38.5)	13.26 (10.18-17.27)	32 (58.2)	96.9	20 (62.5)	302.7	4.07	(2.61-6.34)	

Did not account for infection that occurred <28 days after splenectomy to avoid infection related with operation.
CI = confidence interval.

Figure 2a: Cumulative incidence of first infection after splenectomy

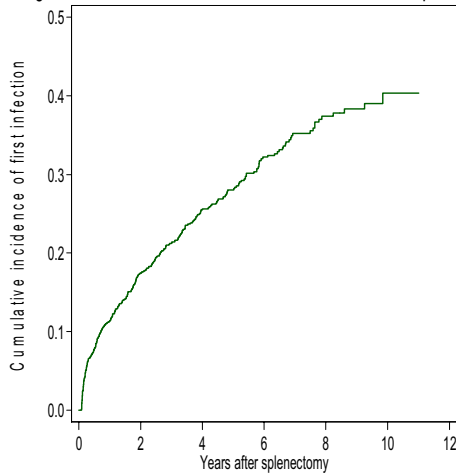


Figure 2b: Cumulative incidence of first infection by sex after splenectomy

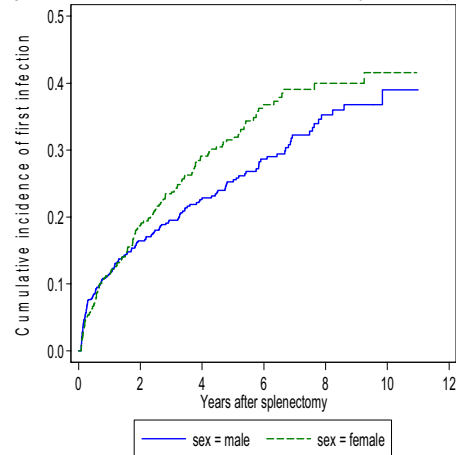


Figure 2c: Cumulative incidence of first infection by age at splenectomy

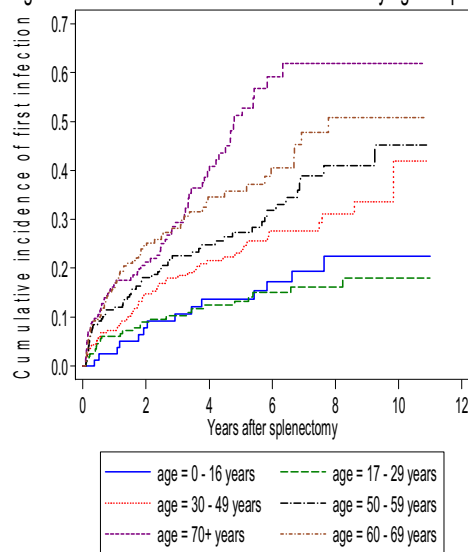


Figure 2d: Cumulative incidence of first infection by reasons for splenectomy

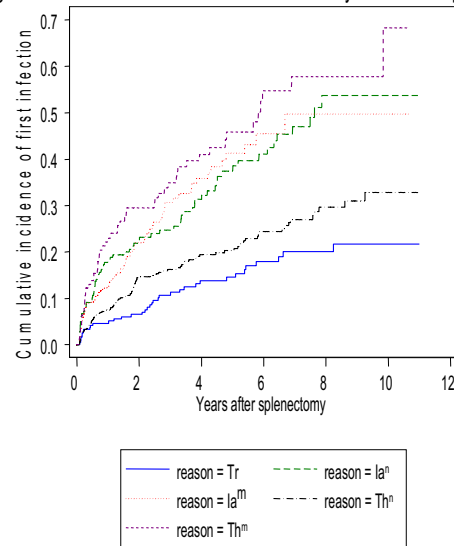


Figure 2 A, Cumulative incidence of first infection after splenectomy. B, Cumulative incidence of first infection by sex after splenectomy. C, Cumulative incidence of first infection by age at splenectomy. D, Cumulative incidence of first infection by reasons for splenectomy.

ferences in rates of first severe infection between age groups and reasons for surgery but not between sexes (Table 1).

The risk of first severe infection was significantly higher in older age groups than the younger age groups, with rates ranging from 9 to 14 per 100 person-years in those aged 50 years and more. The greatest susceptibility to first severe infection was observed in patients splenectomized for Th^m (13.3 per 100 person-years) followed by Ia^m (12.1 per 100 person-years). The incidence of second and third severe infection was highest in patients splenectomized for Th^m.

The risk of infection was higher in the first 3 years after splenectomy (Figure 2) and reduced substantially beyond that period. More than half of all severe infections occurred in the first year after splenectomy, and more than 84% occurred within the first 3 years after splenectomy. The onset of first severe infection was shorter in patients who underwent splenectomy for Th^m (mean = 6.9 years) than

other groups but did not vary significantly between sexes and age groups. The rate of first infection was fairly similar for both males and females in the first 2 years after splenectomy but was observed to be higher in females after that period (Figure 2).

Rates of Multiple Infections

Repeated severe infections were more likely to occur in patients splenectomized for Th^m and Iaⁿ or those who were splenectomized at age 50 years of age and more. The risk of the second and third infections increased after the first episode of severe infection in all variables (Table 1). The overall rate was 44.9 for the second infection per 100 person-years and 109.3 for the third infection. In contrast with the first infection, the incidence of second and third infections was higher in males than females especially for the third infection (170.5 vs 70 per 100 person-years).

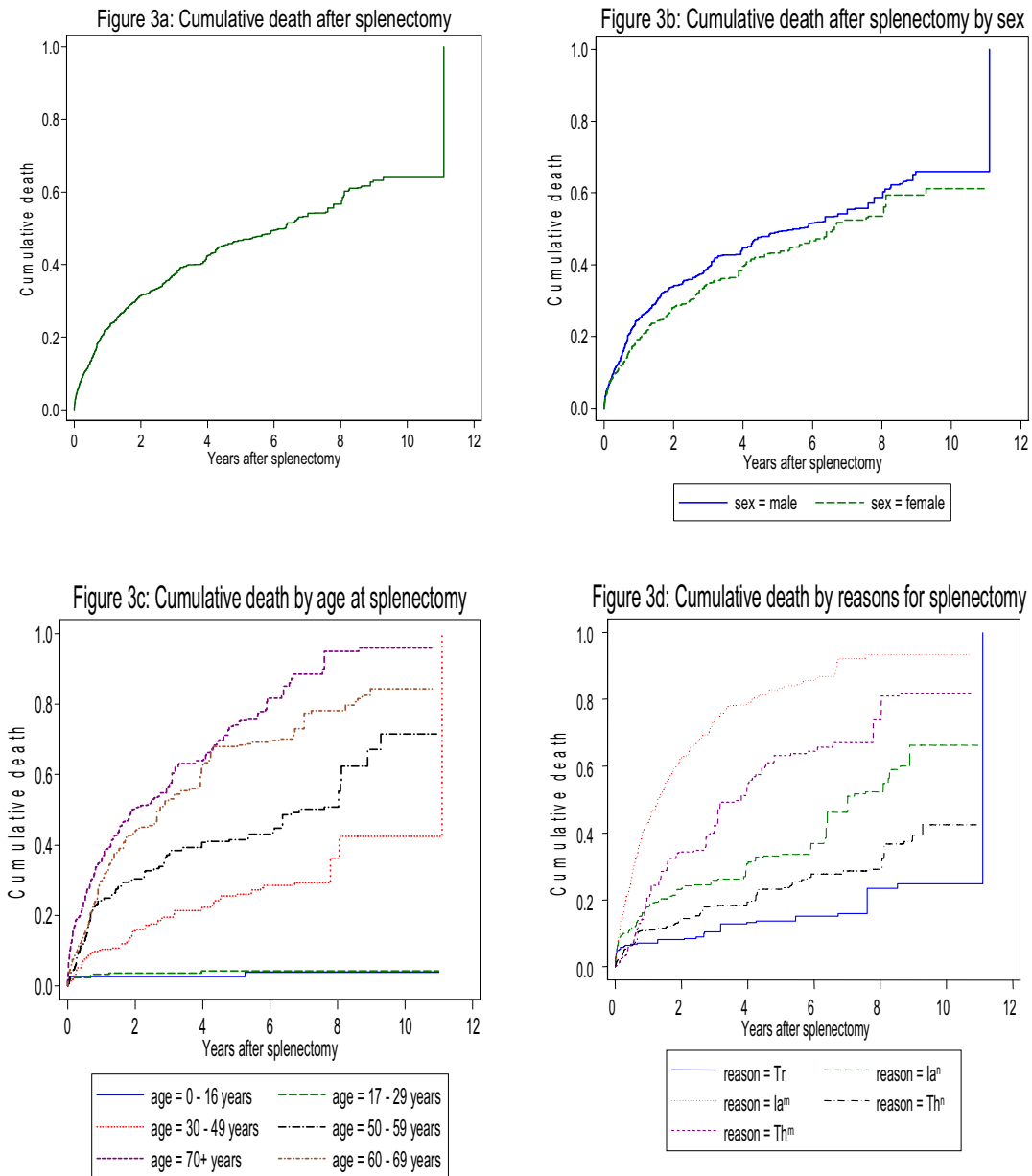


Figure 3 A, Cumulative death after splenectomy. B, Cumulative death after splenectomy by sex. C, Cumulative death by age at splenectomy. D, Cumulative death by reasons for splenectomy.

Although patients with trauma had the lowest incidence of first infection, the incidence of subsequent infection was substantially higher (23.7 per 100 person-years for the second infection and 56.5 per 100 person-years for the third infection) compared to patients with Th^m who had the highest incidence of first infection (13.3 per 100 person-years). Similar findings were also observed for age groups.

The rate of first severe infection was 11.4% at 1 year and 21.4% at 3 years after splenectomy (Figure 2, A). A high proportion of repeated severe infection occurred within 6 months in those who had a first severe infection: 42% in less than 1 month, 65% in less than 3 months, and 76% in less than 6 months after the first infection. The corresponding figures were 61%, 76%, and 84%, respectively, in those with a third severe infection.

Overwhelming Infection (Septicemia and Meningitis)

Of the patients with any type of infection, 49 (3.0%) had at least 1 overwhelming infection. Of these, 30 (61.2%) experienced only 1 overwhelming infection, 9 (18.4%) had 2 infections, and 10 (20.4%) had 3 or more severe infections. The incidence of first overwhelming infection was 0.89 per 100 person-years (95% CI, 0.76-1.17).

Mortality

The overall mean survival was 6.2 years (95% CI, 5.9-6.4) after splenectomy. The cumulative survival was 73%, 65%, 60%, 57%, and 54% by 1, 2, 3, 4, and 5 years of splenectomy, respectively (Figure 3). The risk of death was highest

in the first 2 years after splenectomy. Between 60% and 92% of all deaths occurred within 3 years after splenectomy. There were differences in cumulative survival between sexes, age groups, and reasons for splenectomy (Figure 2). The poorest survival was noted in patients with Ia^m who underwent iatrogenic splenectomy for malignancy (mean = 2.39 years) or aged 70 years and more at splenectomy (mean = 2.86 years). Males had a shorter survival compared with females after splenectomy.

DISCUSSION

The estimated incidence rate for postsplenectomy severe infection was 7.0 per 100 person-years but varied by age and reason for splenectomy. The mean survival time was 6.2 years after splenectomy. A US study that used a similar definition for severe infection reported a comparable result: 7.2 per 100 person-years.⁶ The estimated incidence per 100 person-years varied among studies, from 0.42 to 7.2 for any severe infection.^{6,7} It has been suggested that variations in incidence of postsplenectomy infection may in part be attributable to the differences in the definition of severe infection used in studies.⁸ The inclusion of a small number of patients and relatively short follow-up period may also contribute these variations.⁹ Numerous studies have shown that the risk of postsplenectomy sepsis was low, between 0.18 and 0.42 person-years,^{6,7} but observed substantial case fatality rate was 50% to 90%.^{10,11} We found that the overall incidence of overwhelming infection (including septicemia and meningitis) was 0.89 per 100 person-years. The incidence of overwhelming infection by sex, age groups, and reasons for splenectomy could not be estimated precisely because of the small number of cases in the individual groups.

Our data confirm that age and underlying reason for surgery are clearly important factors influencing infection and mortality after splenectomy. A higher rate of infection and a shorter survival were noted in older age groups than younger age groups at the time of splenectomy. Most reports indicated that the susceptibility to infection was higher^{8,12} and the interval to infection was shorter¹³ in young children, especially aged less than 5 years. In contrast, our data showed that the risk of severe infection after splenectomy increased with advancing age. The cumulative severe infection rate was 21.4% in those aged 17 years or more and 16.5% in those aged 16 years or less. This evidence gives some support to the previous results⁶ that severe infection after splenectomy is not confined to children and is indeed an important problem in adults. However, there were only six patients aged less than 5 years, and only one of them developed severe infection in the present study. This small number did not allow for estimation of severe infection in this vulnerable age group and, thus, should be interpreted with caution.

Studies comparing the risk of severe postsplenectomy infection by reason for splenectomy showed that rates of postsplenectomy infection were lowest in patients splenec-

tomized for trauma and highest for hematologic disorders.^{6,7,14} We also observed that patients splenectomized for Th^m and Iaⁿ were at higher risk of severe infection than other categories. In addition, patients with hematologic malignancy experienced more recurrent infection than other groups, suggesting that they are the most vulnerable subgroups for severe infection.

In common with other studies,^{7,9,13} the susceptibility to infection was greatest in the first 1 to 3 years after splenectomy. Nevertheless, the occurrence of sepsis 30 to 50 years after splenectomy has been documented.^{3,12} We found that the mean time to first infection after splenectomy was considerably shorter in patients with splenectomy for hematologic malignancy (Th^m) and iatrogenic malignancy (Ia^m) than other indications for splenectomy, indicating the immune deficit relation to increased risk of severe infection. The cumulative death after splenectomy was substantially higher in patients who underwent splenectomy for Ia^m than other indications for splenectomy, as similar to a previous study.⁶

We observed a significant increase in the overall incidence of subsequent severe infection after the first episode of infection. Compared with the incidence of the first severe infection, there was a 6-fold increase for the second severe infection and a 14-fold increase for the third severe infection. The incidence of subsequent severe infection was consistently higher than the first severe infection by sex, age groups, and reasons for splenectomy, suggesting that the identification of patients who had the first episode of severe infection might be a useful way for targeting appropriate prophylaxis. This strategy is likely to reduce the risk of subsequent infection in these at-risk patients.

The present study has certain limitations. Our study data presented approximately 60% of the population in Scotland. We were unable to find out whether the characteristics of splenectomized patients (eg, age distribution or indication for splenectomy) in four Health Boards that were not included in the study differed with those in the study. This may bias the estimates of incidence for severe infection and survival time among age groups, sex, and indications for splenectomy. The incidence rates of severe postsplenectomy varied by the definition of severe infection used in various studies.⁷ Thus, careful attention is needed when comparing data from our study with other findings. In addition, the causative organisms of severe infection were not recorded on the SMR01 data. Such information can help in guiding correct use of appropriate vaccines in these at-risk patients. However, current evidence shows that the majority of postsplenectomy infections are caused by pneumococcus, meningococcus, and *Haemophilus influenzae*.^{13,15} Vaccines or antibiotic prophylactic regimens against infection caused by these three bacteria are available. Although no absolute data are available for the protection of vaccines¹⁶ and antibiotics¹⁷ in splenectomized individuals, they are generally recommended for this at-risk group.¹⁸ However, current evidence suggests that guidelines for minimizing the risk of

postsplenectomy infection have not been followed in the United Kingdom.^{15,19} Although bacterial vaccines are recommended 2 weeks before elective splenectomy, a recent survey found that the compliance to these guidelines is low.²⁰ The prevalence of asplenic patients²¹ is estimated to be 1.09 per 1000 registered patients, indicating that there are substantial numbers of at-risk patients. Thus, efforts to increase the use of current preventive measures should be intensified.

Because a higher risk of severe infection occurred in patients who underwent splenectomy for malignancy, whether hematologic or otherwise, the need for recommended vaccines is greater in these groups than others. The first 1 to 3 years after splenectomy is the most important time for the risk of infection and mortality. Therefore, the institution of antibiotic prophylaxis in this period is likely to reduce morbidity and mortality. Because the risk of severe infection declines significantly beyond that time, continuing antibiotic prophylaxis would provide lesser benefits. It is a frequent experience of one of the authors (F.T.) that patients are often unwilling to continue daily antibiotic prophylaxis lifelong, but can usually be persuaded to take prophylaxis for an agreed finite period. Our data indicate this negotiated finite period should be 3 years. It is important to recognize that the risk of the second or third infection is particularly high among those who have a first severe infection. We found that a large proportion of repeated infection occurred within 6 months after a first episode of severe infection. Thus, antibiotic prophylaxis could offer the most benefits in this period for patients who had a first severe infection. These data have important implications for the current lifelong recommendations for prophylactic antibiotics after splenectomy. However, given the increasing prevalence of drug resistance worldwide, especially the pneumococcus,²² the greater use of pneumococcal vaccine, which covers most drug resistant serotypes, should be encouraged.

In addition, patients should be aware that the best preventive measures do not offer complete protection against infection.^{3,23} Thus, patient education is also an important strategy in reducing postsplenectomy infection.^{17,24} Conjugate vaccines for pneumococci and meningococci (non-group B) may offer better protection in splenectomized patients through the induction of good antibody responses and immunologic memory. Pneumococcal conjugate vaccines have been shown to produce high immunogenicity in patients with asplenia²⁵ and sickle cell²⁶ and, thus, may be of value in management of postsplenectomy infection.

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