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LETTER TO THE EDITOR

Splenectomised Hodgkin lymphoma patients: does severe pneumococcal disease pose a problem today and what is the best long-term strategy?

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Introduction

Diagnostic laparotomy and splenectomy were introduced for patients with Hodgkin lymphoma (HL) in Sweden in the late 1960s/early –70s. Several benefits were claimed for splenectomy in HL patients, the most important being improved accuracy of staging [1]. It was soon established that HL patients who were splenectomised carried a significantly increased risk of overwhelming post-splenectomy infections, Streptococcus pneumoniae being the major causative agent [2–4]. Despite this, diagnostic laparotomy and splenectomy remained as a staging procedure for more than two decades, typically performed on patients aged below 65–70 years at diagnosis where the clinical stage could be upgraded/downgraded leading to an altered treatment strategy. This most often included patients in stages of IB-IIIA. During the 1970 and 80s, approximately 20% of patients diagnosed with HL in Sweden underwent a splenectomy [5]. Improvements in imaging and treatment led to the cessation of diagnostic laparotomies and splenectomies in early/mid-1990s in most Swedish centres. Several authors have reported that compliance with local as well as international recommendations for the mainly long-term management of splenectomised patients is insufficient [6]. A similar experience was recently reported also for the United States [7].

Notably, prophylactic measures addressing the increased risk for severe pneumococcal disease in splenectomised HL subjects are not harmonised among EU countries. For example, the British Committee for Standards in Haematology [8], states that: *'Lifelong prophylactic antibiotics should be offered to patients considered at continued high risk (including splenectomy for underlying haematological malignancy) of pneumococcal infection'*. In Sweden, prophylactic antibiotic treatment after HL-related splenectomy is recommended in children for 2 years after the surgery and always until the age of 5 years. Adult patients (≥18 years) have not been recommended short- nor long-term penicillin prophylaxis according to national treatment guidelines, although Pneumococcal vaccination was increasingly offered from 1980. With repeated (every one to five years) pneumococcal vaccination the antibody response in these patients did not differ from patients splenectomised for trauma [9,10].

This motivated us to identify all diagnostic laparotomies splenectomies, and severe pneumococcal infections in Swedish HL patients who were diagnosed 1973–1995, when regional treatment guidelines for HL had been introduced and splenectomies were still performed.

Material and methods

This was an observational retrospective cohort study. We identified all patients diagnosed with HL at age 18 and older during 1973–1995 through the nationwide Swedish Cancer Register, which has had national coverage and mandatory reporting since 1958. Splenectomies and the occurrence of septicaemia and other infections caused by pneumococci (see Table 1 for list of ICD codes) were ascertained from the National Inpatient Register, initiated in 1964 and with national coverage from 1987 [11]. The study was approved by the Regional Ethical Review Board in Stockholm (No. 2017/641-31/1). A diagnostic laparotomy and splenectomy was defined as undergoing a splenectomy within 14 days prior to, or at any time after, diagnosis. Follow-up began on the date of diagnosis and ended on the date of first severe pneumococcal infection, death, emigration, or 31 December 2010, whichever came first. Recurrent infections were not considered. We used Cox proportional hazards regression to estimate a hazard ratio (HR) with a 95% confidence interval (CI) comparing the incidence rate of pneumococcal infection after splenectomy to the rate before and/or among those without splenectomy, i.e., modelling diagnostic laparotomy and splenectomy as a time-varying exposure. The estimated HR was adjusted for the year of diagnosis (categorised as 1973–1978/1979–1984/1985–1990/1991–1995), age at diagnosis (categorised as 19-–29/30–39/40–49/50–59/60–69/70–79/80), and sex (male/female).

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Table 1. Included pneumococcal infections and corresponding ICD codes by which they were defined (versions 8, 9, and 10).

Severe pneumococcal infection	ICD-8 (1973–1986)	ICD-9 (1987–1996)	ICD-10 (1997–2010)
Pneumococcal septicaemia	038.20	038C	A40.3
Pneumococcal pneumonia	481.99	481X	J13
Pneumococcal meningitis	320.10	320B	G00.1
Pneumococcal infection	Not applicable	041C	Not applicable
Pneumococci causing diseases classified elsewhere	Not applicable	Not applicable	B95.3

Results

A total of 4,237 HL patients were included, among whom 735 (17.3%) underwent a diagnostic laparotomy and splenectomy (Table 2). The median time between HL diagnosis and splenectomy was 61 days (inter-quartile range, IQR: 35–124 days). Median age at splenectomy was 34.9 years (range 18.1–81.5 years). At the end of the follow-up, 403 splenectomised patients were deceased, 315 alive, and 17 had emigrated. Median potential follow-up time was 28.0 years (IQR: 21.8–33.8 years). Among the 735 patients who had undergone a splenectomy, 39 (5.3%) later experienced a severe pneumococcal infection. The median time between splenectomy and infection was 6.8 years (range 0.1–30.8 years). A total of twenty-four of these patients died during follow-up, nine within 30 days after pneumococcal diagnosis (median 3.5 days; range 0–25 days). Under the assumption that all deaths within 30 days after pneumococcal diagnosis occurred due to the infection, 23% (9/39) died because of the pneumococcal disease. The numbers of deaths and infections broken down by calendar period of infection were 4/9, 5/22, and 0/8 for the periods 1973–85, 1986–1998, and 1999–2010. Patients undergoing a splenectomy had a higher incidence rate of severe pneumococcal infection than non-splenectomised patients (adjusted HR = 2.43, 95% CI: 1.55–3.81).

Table 2. Frequencies and percentages of patient characteristics among 4,237 patients aged 18 years or older diagnosed with Hodgkin lymphoma (HL) in Sweden between 1973 and 1995, by diagnostic laparotomy and splenectomy.

	Patients with a splenectomy	All patients
Total, *n (row %)*	735 (17.3)	4237 (100)
Severe pneumococcal infection	*n (col %)*	*n (col %)*
Yes	39 (5.3)	99 (2.3)
No	696 (94.7)	4,138 (97.7)
HR (95% CI)*	*2.43 (1.55–3.81)*	
Year of HL diagnosis	*n (row %)*	*n (col %)*
1973–1978	253 (18.4)	1377 (32.5)
1979–1984	186 (17.5)	1066 (25.2)
1985–1990	219 (21.8)	1,005 (23.7)
1991–1995	77 (9.8)	789 (18.6)
Age at HL diagnosis	*n (row %)*	*n (col %)*
19–29	283 (32.2)	879 (20.8)
30–39	183 (30.2)	605 (14.3)
40–49	112 (24.8)	452 (10.7)
50–59	80 (16.9)	473 (11.1)
60–69	66 (9.9)	744 (17.6)
70–79	10 (1.3)	763 (18.0)
≥80	1 (0.3)	321 (7.6)
Sex	*n (row %)*	*n (col %)*
Male	442 (17.9)	2471 (58.3)
Female	293 (16.6)	1766 (41.7)

Due to rounding, not all percentages add up to 100.
Abbreviations: n: number; col: column; HR: hazard ratio; CI: confidence interval.
**Comparing the pneumococcal infection rate after DLS to that before and/or among patients with no diagnostic laparotomy and splenectomy. Adjusted for calendar year of diagnosis, age at diagnosis, and sex.*

Conclusion

We conclude that, although severe pneumococcal disease *per se* is a serious event that can appear very late after splenectomy in HL patients, the decreasing proportions of deaths during later decades is reassuring. Since neither short- or long-term antibiotic prophylaxis has been recommended in Sweden, we believe that this favourable development likely is attributable to adequate pneumococcal vaccination in combination with patient and doctor education about the risks of infection. At present, the Swedish HL study group follows the vaccination guidelines as recommended by the Swedish Association of Infectious Disease Physicians [12], which include the combined use of a pneumococcal conjugate and a pneumococcal saccharide vaccine. In addition, labelling of patient records to indicate the increased risk of infection was introduced during the early 1980s, which in turn could have increased awareness.

Laparotomy with splenectomy was performed in defined subgroups for assessing the extent of the disease and the decision to perform it only excluded a few subjects with surgical contraindications for open splenectomy. We see no reason to believe that the baseline characteristics (age was adjusted for) of the patients who underwent a splenectomy during the prevailing time period were otherwise different from those who did not with respect to the risk of future infection. However, the vaccination program of patients in the two groups obviously differed.

In summary, despite the improvements noted in the last decades, severe infections with capsulated bacteria remain a threat in splenectomised HL patients, and knowledge of this risk and the importance of swift measures when suspected are still crucial for both physicians and patients.

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Authors' contributions

CEW, PWD, and MB designed the study, CEW and PWD analysed the data, MB and JS drafted the paper, all authors revised the paper and approved the final version.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Data availability statement

The data underlying this study are available at the National Board of Health and Welfare, Sweden, and Statistics Sweden for investigators with the appropriate approvals, but restrictions apply. However, data can be made available from the authors upon reasonable request for meta-analyses, and with the appropriate approvals of the Swedish Ethical Review Authority (https://etikprovningsmyndigheten.se).

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