Background: Splenectomy has been associated with increased risk for infection.

Objective: To assess the magnitude and duration of risk for hospital contact with infection associated with splenectomy.


Setting: Denmark.

Patients: All 3812 persons in Denmark who underwent splenectomy from 1996 to 2005. Splenectomized patients were matched to 3 comparison cohorts: the general population, appendectomized patients, and unsplenectomized patients with indications for splenectomy.

Measurements: Relative risks were assessed for hospital contact involving any infection, pneumonia, and microbiologically confirmed bacteremia among 3812 splenectomized patients and their matched comparisons, during different follow-up periods and after regression analysis for confounder adjustment.

Results: The adjusted relative risk for any hospital contact with infection was highest within 90 days of splenectomy: 10.2% vs. 0.6% among general population comparisons (adjusted odds ratio, 18.1 [95% CI, 14.8 to 22.1]) and 10.2% vs. 4.2% among appendectomized patients (adjusted odds ratio, 2.4 [CI, 2.1 to 2.8]). The hazard of infection was 4.6-fold (CI, 3.8 to 5.5) higher in splenectomized patients than in general population comparisons from 91 to 365 days after splenectomy and 2.5 times (CI, 2.2 to 2.8) higher more than 365 days after splenectomy. The risks were similar for pneumonia and were higher for bacteremia. Markedly increased risks were also found when compared with those of appendectomized patients. Modest increases in infection risk were seen with splenectomy matched-indication comparisons (adjusted 90-day odds ratio, 1.7 [CI, 1.5 to 2.1]; hazard ratios, 1.5 [CI, 1.2 to 1.8]) from 91 to 365 days after splenectomy and 1.2 [CI, 1.1 to 1.4] beyond 365 days after splenectomy. Relative risks for infection were highest in patients who had splenectomy because of hematologic disorders.

Limitation: Increased surveillance among splenectomized patients may have affected the findings.

Conclusion: Splenectomy is associated with increased long-term risk for infections involving hospital contact.

Primary Funding Source: Amgen, Clinical Epidemiological Research Foundation at Aarhus University, and Karen Elise Jensen Foundation.


For author affiliations, see end of text.
From the NRP, we identified all surgical splenectomy procedures from 1 January 1996 to 31 December 2005. We also searched the NRP for patients with any previous medical indication for splenectomy, including diagnoses made during the hospitalization with splenectomy. We classified splenectomized patients into 8 groups according to indication. In cases of multiple indications, the category was determined by using the following hierarchy, regardless of other indications (13): traumatic rupture of spleen, immune thrombocytopenic purpura (ITP), other or unspecified thrombocytopenia, hematopoietic cancer, hereditary hemolytic anemia, abdominal cancer, splenomegaly or other splenic diseases only, and no diagnosis recorded (Appendix, available at www.annals.org).

General Population Comparison Cohort

From the CRS, we randomly chose 10 members of the general population, matched by age and sex, for each splenectomized patient. The general population members had to be alive without history of splenectomy as of the splenectomy date of their matched patient (the index date). For the subset of splenectomized patients living in former North Jutland County (about 500,000 inhabitants), for whom detailed data on bacteremia episodes were available (14, 15), we randomly chose 10 age- and sex-matched population comparisons living in the same county.

Patient Comparison Cohorts

Patients undergoing splenectomy are exposed to surgery and may have other diseases that increase the risk for infection or that involve immunosuppressive therapies. To separate potential effects of those conditions from effects of splenectomy on the risk for infection, we assembled 2 additional comparison groups: patients who had appendectomy (the appendectomized comparison cohort, for whom the index date was the date of appendectomy) and, for splenectomized patients with a recorded indication for splenectomy, patients who had the same condition diagnosed (for instance, myeloid leukemia) but without splenectomy (the matched-indication comparison cohort). For these comparisons, up to 5 matched patients without splenectomy on the index date were identified by using the CRS and NRP. In the matched-indication-cohort, we also matched on year of diagnosis of the medical condition. We then calculated the index date in each matched-indication patient by adding the time between diagnosis of the medical condition and splenectomy in the splenectomized patient to the date of the diagnosis. For patients who had splenectomy because of trauma, we selected trauma patient comparisons who underwent surgery for acute injury of the spleen, liver, or gallbladder but not splenectomy (the Appendix, available at www.annals.org, provides the codes used).

Hospital Contacts Involving Infection

All participants’ records were linked to the CRS and the NRP to identify all hospital contacts involving bacterial and viral infections, pneumonia, and infections other than pneumonia after the index date. We analyzed for bacteremia episodes by using the subset of persons from North Jutland County, whose population-based bacteremia research registry enables identification of all clinically significant bacteremia episodes and all available blood culture samples (14, 15).

Other Covariates

To control for confounding by conditions associated with both splenectomy and risk for infection, we retrieved data on several comorbid conditions, identified as conditions recorded in the NRP before each patient’s index date (Appendix, available at www.annals.org).

Statistical Analysis

We assessed the association between splenectomy for any indication and subsequent infection and for each splenectomy indication versus matched comparisons in the general population, appendectomy, and matched-indication comparison cohorts.

We observed the patients from the index date until a hospital contact involving an outcome of interest (any infection, pneumonia, or nonpneumonia infection), death, emigration, or 31 December 2006, whichever came first. Referent patients who underwent splenectomy during the follow-up were censored at the time of splenectomy. We first compared overall rates of infectious events in the cohorts during total follow-up.

We then compared occurrence of infection requiring hospitalization in patients with and without splenectomy within 90 days, from 91 to 365 days, and more than 365 days after the index date. Because the NRP does not list the exact date of the infectious event during the hospitalization in which the splenectomy was performed (4, 6), we estimated odds ratios with 95% CIs, by using logistic regression.
sion as the measure of relative risk for infections within 90 days of the index date. We counted all discharge diagnoses of infection documented either for ongoing hospitalizations ending within 90 days or for new hospital contacts occurring within 90 days after the surgery date.

For infections more than 90 days after splenectomy, we used Cox proportional hazards regression to compute hazard ratios as measures of relative risk separately for the intermediate (91 to 365 days) and long-term (>365 days) follow-up. Thus, for each period we computed the time to the first infectious event among all patients alive and at risk at days 91 and 366, respectively, also including participants who had a hospital contact with infection during a previous period. We conducted similar analyses for bacteremia in the North Jutland County subcohort (6, 16).

We adjusted for age (0 to 39, 40 to 59, 60 to 69, and ≥70 years), sex, and comorbid conditions (Appendix, available at www.annals.org) as a priori confounders. In the matched-indication cohort analysis, presence of comorbid conditions was dichotomized (yes or no) because the sample was small. We used stratified regression models to account for matching. The traumatic rupture comparisons were unmatched because of sparse data; therefore, the overall estimates of splenectomy versus indication comparisons were calculated as an inverse variance weighted average of the individual indication estimates. We analyzed data by using SAS software, version 9.2 (SAS Institute, Cary, North Carolina). The Danish Data Protection Agency and Aarhus University Hospital Registry Board approved the study.

Role of the Funding Source
This study was supported in part by a grant from Amgen to Aarhus University, by the Clinical Epidemiological Research Foundation at Aarhus University, and by the Karen Elise Jensen Foundation. In collaboration with the investigators, Amgen designed the study. Amgen representatives participated in the interpretation of the data, which Aarhus University holds, and in the writing of this report.

RESULTS
Descriptive Data
We identified 3812 splenectomized persons, 38,120 general population members, 16,962 appendectomized cohort members, and 8,310 matched-indication patients for the 2,394 splenectomized patients with recorded indication. The median patient age was 60 years (interquartile range, 41 to 72 years). Splenectomized patients and matched-indication comparisons had a higher burden of comorbid conditions than the general population or appendectomized comparison group (Table 1).

The most common medical indications for splenectomy were traumatic rupture of the spleen (20.1%) and abdominal cancer (19.3%). Other indications were spleno-

### Table 1. Characteristics of Study Sample at Baseline

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Splenectomized Cohort (n = 3812), n (%)</th>
<th>General Population Comparison Cohort (n = 38,120), n (%)</th>
<th>Appendectomy Patient Comparison Cohort (n = 16,962), n (%)</th>
<th>Patients With Splenectomy Indication (n = 8,310), n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–39 y</td>
<td>916 (24.0)</td>
<td>9176 (24.1)</td>
<td>4580 (27.0)</td>
<td>2008 (24.2)</td>
</tr>
<tr>
<td>40–59 y</td>
<td>1015 (26.6)</td>
<td>10,112 (26.5)</td>
<td>5058 (29.8)</td>
<td>1774 (21.4)</td>
</tr>
<tr>
<td>60–69 y</td>
<td>751 (19.7)</td>
<td>7543 (19.8)</td>
<td>3245 (19.1)</td>
<td>1379 (16.6)</td>
</tr>
<tr>
<td>≥70 y</td>
<td>1130 (29.6)</td>
<td>11,289 (29.6)</td>
<td>4079 (24.1)</td>
<td>3149 (37.9)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1641 (43.1)</td>
<td>16,410 (43.1)</td>
<td>7973 (47.0)</td>
<td>3968 (47.8)</td>
</tr>
<tr>
<td>Male</td>
<td>2171 (57.0)</td>
<td>21,710 (57.0)</td>
<td>8989 (53.0)</td>
<td>4342 (52.3)</td>
</tr>
<tr>
<td>Comorbid condition</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>167 (4.4)</td>
<td>1300 (3.4)</td>
<td>645 (3.8)</td>
<td>378 (4.6)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>120 (3.2)</td>
<td>880 (2.3)</td>
<td>438 (2.6)</td>
<td>391 (4.7)</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>229 (6.0)</td>
<td>863 (2.3)</td>
<td>417 (2.5)</td>
<td>321 (3.9)</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>198 (5.2)</td>
<td>1762 (4.6)</td>
<td>800 (4.7)</td>
<td>508 (6.1)</td>
</tr>
<tr>
<td>Chronic pulmonary disease</td>
<td>266 (7.0)</td>
<td>1744 (4.6)</td>
<td>859 (5.1)</td>
<td>587 (7.1)</td>
</tr>
<tr>
<td>Connective tissue disease</td>
<td>117 (3.1)</td>
<td>652 (1.7)</td>
<td>331 (2.0)</td>
<td>298 (3.6)</td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
<td>101 (2.7)</td>
<td>338 (0.9)</td>
<td>202 (1.2)</td>
<td>151 (1.8)</td>
</tr>
<tr>
<td>Peptic ulcer disease</td>
<td>293 (7.7)</td>
<td>1060 (2.8)</td>
<td>593 (3.5)</td>
<td>642 (7.7)</td>
</tr>
<tr>
<td>Liver disease</td>
<td>93 (2.4)</td>
<td>244 (0.6)</td>
<td>121 (0.7)</td>
<td>223 (2.7)</td>
</tr>
<tr>
<td>Renal disease</td>
<td>100 (2.6)</td>
<td>286 (0.8)</td>
<td>157 (0.9)</td>
<td>158 (1.9)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>140 (3.7)</td>
<td>1090 (2.9)</td>
<td>479 (2.8)</td>
<td>406 (4.9)</td>
</tr>
<tr>
<td>Hemiplegy</td>
<td>5 (0.1)</td>
<td>50 (0.1)</td>
<td>27 (0.2)</td>
<td>20 (0.2)</td>
</tr>
<tr>
<td>Obesity</td>
<td>62 (1.6)</td>
<td>449 (1.2)</td>
<td>256 (1.5)</td>
<td>153 (1.8)</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>157 (4.1)</td>
<td>220 (0.6)</td>
<td>134 (0.8)</td>
<td>128 (1.5)</td>
</tr>
<tr>
<td>Alcoholism and alcoholism-related conditions</td>
<td>190 (5.0)</td>
<td>882 (2.3)</td>
<td>442 (2.6)</td>
<td>311 (3.7)</td>
</tr>
<tr>
<td>Malignant conditions</td>
<td>1065 (28.0)</td>
<td>2227 (5.8)</td>
<td>1722 (10.2)</td>
<td>3327 (40.0)</td>
</tr>
<tr>
<td>AIDS</td>
<td>6 (0.2)</td>
<td>8 (0.0)</td>
<td>5 (0.0)</td>
<td>11 (0.1)</td>
</tr>
<tr>
<td>Dementia</td>
<td>20 (0.5)</td>
<td>206 (0.5)</td>
<td>81 (0.5)</td>
<td>59 (0.7)</td>
</tr>
</tbody>
</table>
megaly (11.9%; often combined with other indications, such as hematopoietic cancer), hematopoietic cancer (7.6%), and ITP (7.1%; often combined with nonspecific thrombocytopenia codes) (Table 2).

**Risk for Hospital Contacts With Infection**

Among the 3812 splenectomized patients, 955 (25.1%) had at least 1 hospital contact involving infection during a median follow-up of 2.2 years. The respective summary measures were 10.8% and 5.1 years in the general population comparison cohort, 14.9% and 4.7 years in the appendectomized comparison cohort, and 20.2% and 2.1 years in the matched-indication comparison cohort. The corresponding overall incidence rates of infection were 7.7 per 100 person-years in splenectomized patients, 2.0 per 100 person-years in the general population cohort, 3.0 per 100 person-years in the appendectomized cohort, and 6.4 per 100 person-years in the matched-indication comparison cohort.

The highest increase in the risk for infection was seen within the first 90 days, with 10.2% prevalence among splenectomized patients versus 0.6% among the general population cohort (adjusted odds ratio, 18.1 [95% CI, 14.8 to 22.1]); the increase in risk was similar for pneumonia and nonpneumonia infections (Table 3). The 90-day estimates were lower but still increased compared with those in appendectomized patients (adjusted odds ratio, 2.4 [CI, 2.1 to 2.8]) and matched-indication comparisons (adjusted odds ratio, 1.7 [CI, 1.5 to 2.1]). The estimates changed little after we excluded 1086 patients with splechnectomy more than 2 days after the initial hospitalization; in these patients, infection could in theory have preceded splenectomy (data not shown).

Compared with the general population, the hazard ratio of infection among the splenectomized patients was 4.6 (CI, 3.8 to 5.5) from 91 to 365 days after splenectomy and 2.5 (CI, 2.2 to 2.8) more than 365 days after splenectomy. We observed a similar pattern and magnitude of effect with the appendectomized comparison cohort and lower, although still increased, estimates with the matched-indication comparison cohort (Table 3 and Figure). The risk estimates were similarly increased for pneumonia and nonpneumonia infections. The distribution of nonpneumonia infection types was similar between cohorts, with septicemia, gastrointestinal infections, respiratory tract infections, and miscellaneous or unspecified bacterial infections representing the most frequent infections (data not shown). Analyses restricted to hospital contacts after 90 days with infection as the first-listed diagnosis (>75% of all contacts) did not substantially affect the relative risk estimates (data not shown).

In the North Jutland County subcohort, 62 of 416 (14.9%) splenectomized patients had bacteremia (5.5 episodes per 100 person-years) (Table 4). The adjusted 90-day odds ratios for bacteremia were 138.2 (CI, 41.5 to 461.0) versus the general population, 3.6 (CI, 2.1 to 6.0) versus the appendectomized comparison cohort, and 3.2 (CI, 1.7 to 6.1) versus the matched-indication comparisons. Adjusted hazard ratios were 13.5 (CI, 4.4 to 41.4) and 1.9 (CI, 1.1 to 3.6) for bacteremia occurring from 91 to 365 days after splenectomy and after 365 days, respectively, compared with the general population, and these hazard ratios were lower than those in the appendectomized comparison cohort (Table 3). Too few episodes of bacteremia existed within splenectomy indication subcohorts to calculate weighted overall longer-term hazard ratios. The abdomen was a much more frequent focus of bacteremia among splenectomized and appendectomized patients than among the other cohorts, whereas a urinary tract focus was relatively rarer in the splenectomized and splenectomy indication cohorts (Table 4). The distribution of microbial agents was similar between groups. Of note, encapsulated bacteria, such as pneumococci, meningococci, and Haemophilus influenzae, were rarely encountered in the splenectomized cohort.

Laparoscopic splenectomy was performed in 33 patients, 2 of whom had an infection involving hospital contact within 90 days; another 5 had an infection more than 365 days after the procedure. This corresponds to overall infection incidence rates per 100 person-years of 5.5 among those undergoing laparoscopic splenectomy and 7.6 among those undergoing a nonlaparoscopic procedure. For the period of more than 365 days after splenectomy, the risk for infections involving hospital contact among patients who underwent laparoscopic splenectomy was 4.2 times (CI, 1.3 to 14.0) higher than the corresponding risk for the general population.

**Risk for Hospital Contact With Infection, by Splenectomy Indication**

The adjusted odds of hospital contact with infection 90 days after splenectomy were 14- to 46-fold higher in all indication groups than in the general population comparisons, whereas odds ratios ranged from 1.0 to 12.7 with appendectomized patients. This pattern differed during
later follow-up periods (Table 5). Compared with the general population and appendectomized comparison cohorts, the increase in the infection hazard among patients with underlying hematopoietic cancer was 13.2 and 8.6 during the 91- to 365-day period and 5.8 and 5.2 after more than 365 days of follow-up. By comparison, elderly patients who had splenectomy after abdominal cancer (80% were aged ≥60 years) had only a 1.3- to 1.4-fold increased hazard after 365 days of follow-up. Among relatively young and previously healthy persons who had splenic trauma (82% aged <60 years), the hazard of infection remained 1.8- to 2.5-fold higher than in the appendectomized or general population comparison cohorts more than 365 days after splenectomy. For patients with ITP, the corresponding hazard ratios were 2.6 to 4.0 (Table 5).

We generally found that the odds of 90-day infection were increased 2- to 3-fold when comparing splenectomized patients with unsplenectomized patients matched on the same nontraumatic indication for splenectomy. In the long term, hazard ratios approached 1.0, except in patients with ITP (hazard ratio, 1.4 [CI, 1.0 to 2.0]) and hematopoietic cancer (hazard ratio, 1.6 [CI, 1.2 to 2.2]). Among patients splenectomized because of trauma, the 90-day risk for infection was not increased (odds ratio, 0.8 [CI, 0.5 to 1.2]) compared with matched trauma patients with abdominal surgery; however, the corresponding hazard ratio after 1 year was 1.3 (CI, 0.9 to 1.9).

**DISCUSSION**

Our large nationwide, population-based study provides strong evidence of an increased risk for pneumonia...
and other infections, in particular early bacteremia, among patients undergoing splenectomy. This excess risk was most pronounced during the first 90 days after splenectomy, persisted for more than 365 days, and was seen regardless of the medical indication for splenectomy.

Our data are largely consistent with previous observations of a high incidence of infections after splenectomy. We observed an incidence similar to the estimate of 7.2 serious infections per 100 person-years reported by Schwarz and colleagues (9) more than 30 years ago. In a recent Scottish cohort study of 1648 splenectomized patients, the risk for hospitalizations for infections was 21% with a mean follow-up of 4.5 years (excluding the first 28 days). As in our study, patients splenectomized because of hematologic malignant conditions had the highest rates of infection, and patients with splenic trauma had the lowest

| Table 3—Continued |

| Infections Among Splenectomized Patients vs. Appendectomized Comparisons | Infections Among Splenectomized Patients With Recorded Indication vs. Matched-Indication Comparisons |

<table>
<thead>
<tr>
<th>Appendectomized Comparisons</th>
<th>Relative Risk (95% CI)*</th>
<th>Matched-Indication Comparisons</th>
<th>Relative Risk (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Crudé</td>
<td>Adjusted</td>
<td>Crudé</td>
</tr>
<tr>
<td>16 962</td>
<td>713 (4.2)</td>
<td>2.5 (2.2–2.9)</td>
<td>2.4 (2.1–2.8)</td>
</tr>
<tr>
<td></td>
<td>346 (2.0)</td>
<td>2.7 (2.3–3.3)</td>
<td>2.7 (2.2–3.3)</td>
</tr>
<tr>
<td></td>
<td>403 (2.4)</td>
<td>2.3 (1.9–2.7)</td>
<td>2.1 (1.8–2.6)</td>
</tr>
<tr>
<td></td>
<td>42 (2.8)</td>
<td>3.7 (2.2–6.2)</td>
<td>3.6 (2.1–6.0)</td>
</tr>
<tr>
<td></td>
<td>7087</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16 469</td>
<td>354 (2.9)</td>
<td>3.4 (2.8–4.1)</td>
<td>2.9 (2.3–3.6)</td>
</tr>
<tr>
<td></td>
<td>159 (1.3)</td>
<td>3.5 (2.6–4.6)</td>
<td>2.9 (2.1–4.1)</td>
</tr>
<tr>
<td></td>
<td>217 (1.8)</td>
<td>3.7 (2.9–4.7)</td>
<td>3.2 (2.5–4.2)</td>
</tr>
<tr>
<td></td>
<td>12 (1.2)</td>
<td>7.2 (2.4–21.6)</td>
<td>5.2 (1.7–16.3)</td>
</tr>
<tr>
<td>15 942</td>
<td>1722 (2.4)</td>
<td>2.2 (2.0–2.5)</td>
<td>2.0 (1.7–2.2)</td>
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<tr>
<td></td>
<td>940 (1.3)</td>
<td>2.4 (2.0–2.8)</td>
<td>2.2 (1.8–2.6)</td>
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<tr>
<td></td>
<td>995 (1.4)</td>
<td>2.4 (2.0–2.7)</td>
<td>2.0 (1.8–2.4)</td>
</tr>
<tr>
<td></td>
<td>34 (0.6)</td>
<td>2.0 (0.9–4.4)</td>
<td>1.2 (0.5–2.8)</td>
</tr>
</tbody>
</table>

| Table 4. Bacteremia-Related Characteristics in Splenectomized Patients and Comparisons |

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Splenectomized Cohort (n = 416)</th>
<th>General Population Comparison Cohort (n = 4160)</th>
<th>Appendectomized Patient Comparison Cohort (n = 1530)</th>
<th>Splenectomy Indication Comparison Cohort (n = 764)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microbiologically confirmed bacteremia during total follow-up, n (n per 100 PYs)</td>
<td>62 (5.5)</td>
<td>97 (0.5)</td>
<td>87 (1.3)</td>
<td>62 (3.3)</td>
</tr>
<tr>
<td>Focus of infection, n (%)*</td>
<td>8 (13)</td>
<td>16 (31)</td>
<td>22 (25)</td>
<td>10 (16)</td>
</tr>
<tr>
<td>Urinary tract</td>
<td>2 (3)</td>
<td>3 (6)</td>
<td>2 (2)</td>
<td>5 (8)</td>
</tr>
<tr>
<td>Abdominal</td>
<td>10 (16)</td>
<td>6 (12)</td>
<td>6 (7)</td>
<td>7 (11)</td>
</tr>
<tr>
<td>Respiratory tract</td>
<td>4 (6)</td>
<td>3 (6)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Skin, central nervous system, or other</td>
<td>13 (20)</td>
<td>15 (29)</td>
<td>20 (22)</td>
<td>15 (24)</td>
</tr>
<tr>
<td>Undetermined focus</td>
<td>13 (21)</td>
<td>14 (27)</td>
<td>17 (20)</td>
<td>16 (26)</td>
</tr>
<tr>
<td>Microbial agent group, n (%)*</td>
<td>2 (3)</td>
<td>3 (6)</td>
<td>2 (2)</td>
<td>5 (8)</td>
</tr>
<tr>
<td>Strepotoccus pneumoniae</td>
<td>10 (16)</td>
<td>6 (12)</td>
<td>6 (7)</td>
<td>7 (11)</td>
</tr>
<tr>
<td>Enterococci</td>
<td>4 (6)</td>
<td>3 (6)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Other gram-positive bacteria</td>
<td>2 (3)</td>
<td>3 (6)</td>
<td>13 (15)</td>
<td>5 (8)</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>14 (23)</td>
<td>15 (29)</td>
<td>31 (36)</td>
<td>21 (34)</td>
</tr>
<tr>
<td>Other enterobacteria</td>
<td>10 (16)</td>
<td>8 (15)</td>
<td>7 (8)</td>
<td>7 (11)</td>
</tr>
<tr>
<td>Other gram-negative rods (including Haemophilus influenzae and meningococci)</td>
<td>0 (0)</td>
<td>3 (6)</td>
<td>2 (2)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>5 (8)</td>
<td>3 (6)</td>
<td>2 (2)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Other microorganisms (anaerobic bacteria, Candida species, polymicrobial growth)</td>
<td>15 (24)</td>
<td>8 (15)</td>
<td>24 (28)</td>
<td>14 (23)</td>
</tr>
</tbody>
</table>

PY = person-year.  
* Percentages are based on total of all infectious foci and microbial agent groups.
<table>
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<th>Indication for Splenectomy</th>
<th>Splenectomized Patients</th>
<th>Infections Among Splenectomized Patients vs. General Population Comparisons</th>
<th>Infections Among Splenectomized Patients vs. Appendectomized Patients</th>
<th>Infections Among Splenectomized Patients vs. Matched-Indication Comparisons</th>
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<td>Appendectomized Comparisons</td>
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<td>44 (0.6)</td>
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<td>127 (3.5)</td>
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<td>91 to 365 d, n (n per 100 PYs)</td>
<td>23 (4.6)</td>
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<td>94.6 (10.0–895.7)</td>
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<td>42 (2.3)</td>
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<td>&gt;365 d, n (n per 100 PYs)</td>
<td>69 (14.1)</td>
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<td>5.8 (3.8–8.8)</td>
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Continued on following page
Table 5—Continued

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<th>Infections Among Splenectomized Patients vs. Appendectomized Comparisons</th>
<th>Infections Among Splenectomized Patients vs. Matched-Indication Comparisons</th>
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<td>Appendectomized Comparisons Adjusted Relative Risk (95% CI)†</td>
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<td>5 (0.4) 31.5 (6.4–153.7)</td>
<td>36 (5.1) 1.0 (0.4–2.5)</td>
<td>11 (1.8) 3.6 (1.1–12.5)</td>
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<td>91 to 365 d, n (n per 100 PYs) 6 (5.8)</td>
<td>13 (1.2) 4.3 (1.4–13.4)</td>
<td>8 (1.5) 7.8 (1.8–34.1)</td>
<td>27 (6.4) 1.0 (0.4–2.6)</td>
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<td>&gt;365 d, n (n per 100 PYs) 18 (3.1)</td>
<td>61 (1.0) 4.0 (2.3–7.2)</td>
<td>45 (1.5) 2.3 (1.2–4.2)</td>
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Abdominal cancer

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<td>53.0</td>
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<td>Persons with comorbid condition, %</td>
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<td>43.9</td>
<td>73.9</td>
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<td>11</td>
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<td>Infection involving hospital contact</td>
<td>0 to 90 d, n (%) 59 (8.3)</td>
<td>60 (0.8) 15.3 (9.2–25.6)</td>
<td>131 (4.6) 1.9 (1.3–2.9)</td>
<td>155 (4.4) 2.0 (1.5–2.8)</td>
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<td></td>
<td>91 to 365 d, n (n per 100 PYs) 33 (9.4)</td>
<td>144 (2.8) 3.6 (2.3–5.7)</td>
<td>77 (3.9) 2.5 (1.4–4.5)</td>
<td>107 (6.3) 1.4 (0.9–2.2)</td>
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<td>&gt;365 d, n (n per 100 PYs) 65 (5.4)</td>
<td>966 (3.4) 1.4 (1.1–2.0)</td>
<td>391 (3.7) 1.3 (0.9–1.9)</td>
<td>308 (5.2) 1.0 (0.7–1.4)</td>
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Splenomegaly or splenic disease

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<td>46 (33–63)</td>
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<td>54.9</td>
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<td>–</td>
<td>3</td>
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<td>Infection involving hospital contact</td>
<td>0 to 90 d, n (%) 36 (17.9)</td>
<td>4 (0.2) 118.2‡ (36.4–384.1)</td>
<td>24 (2.6) 12.7 (6.0–27.1)</td>
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<td>91 to 365 d, n (n per 100 PYs) 11 (8.3)</td>
<td>23 (1.5) 17.0 (4.7–61.4)</td>
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<td>&gt;365 d, n (n per 100 PYs) 34 (5.4)</td>
<td>116 (1.4) 3.6 (2.2–5.9)</td>
<td>76 (2.0) 2.3 (1.3–4.1)</td>
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No specified indication for splenectomy recorded

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<td>54.5</td>
<td>49.4</td>
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<tr>
<td>Persons with comorbid condition, %</td>
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<td>35.7</td>
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<td>Infection involving hospital contact</td>
<td>0 to 90 d, n (%) 158 (11.1)</td>
<td>92 (0.7) 18.3 (13.3–25.1)</td>
<td>290 (4.7) 2.3 (1.8–2.95)</td>
<td>91 to 365 d, n (n per 100 PYs) 62 (8.7)</td>
<td>255 (2.4) 3.7 (2.7–5.2)</td>
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<td>&gt;365 d, n (n per 100 PYs) 181 (5.7)</td>
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<td>696 (2.8) 1.8 (1.4–2.2)</td>
<td>696 (2.8) 1.8 (1.4–2.2)</td>
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NA = not applicable (matched-indication comparisons applicable for only splenectomized patients with a specified splenectomy indication recorded); PY = patient-year.

* Includes patients within mutually exclusive categories of splenectomy indications; see text for classification.
† Relative risk estimated as the odds ratio of infection within 90 days and the hazard ratio of infection within 91 to 365 days and >365 days after splenectomy. Estimates adjusted by age, sex, and presence of any comorbid condition at the time of splenectomy.
‡ Crude 90-day odds ratio shown; too few events occurred to calculate adjusted 90-day odds ratio.
Risk for Infection After Splenectomy

rates. However, we also found high rates of infection among patients splenectomized because of benign hematologic disorders. A previous cohort study of 98 patients splenectomized for trauma and 98 control participants undergoing laparotomy without splenectomy reported more early postoperative infections in the splenectomized cohort (45% vs. 30%; \( P = 0.040 \)), most of which were pneumonia (30% vs. 14%; \( P = 0.020 \)) (4). Several studies have reported a high risk for bacteremia and severe sepsis very early after the splenectomy procedure (3, 5–7, 9). Ejstrud and colleagues (6) found a risk for bacteremia of 7% during 3.2 years of follow-up, with 45% of episodes occurring within 30 days after splenectomy. The lack of comparison groups or long-term follow-up in many earlier studies limited their potential for clarifying the clinical impact of splenectomy on infections.

The mechanisms underlying the association between splenectomy and infections are not entirely clear. Although splenectomy and infections may share risk factors, such as cancer and chemotherapy, we also found markedly increased long-term rates of infection among patients undergoing splenectomy because of disorders other than cancer. Modest associations persisted for most splenectomy indications even after we used appendectomized or matched-indication comparison groups. In particular, encapsulated bacteria (such as Streptococcus pneumoniae) have been associated with early severe postsplenectomy infections. However, our study corroborates earlier findings (7) in which pneumococci caused only 4% of bacteremia episodes. In contrast to common belief, enteric rods seem to be the predominant cause of early and late postsplenectomy bacteremia.

Abdominal surgery itself may increase infection risk, as also suggested by the less markedly increased early risks we found compared with those in patients who underwent appendectomy. Laparoscopic splenectomy may have lower infection rates than open surgery (17), although in our cohort, we also observed infections requiring hospitalization in the few patients undergoing laparoscopic procedures.

Our study has several strengths, including examination of hospital contacts with important clinical infections, such as pneumonia and bacteremia. In addition, our estimates are derived from a population-based cohort study with negligible referral and diagnostic biases. The large population we studied was well-defined, and follow-up for infections requiring hospitalization and death was complete. We had access to long-term hospital registry data and complete outpatient clinic data.

Despite the advantages of the high-quality data, our database study has limitations. First, we had access to limited clinical information. Second, the validity of our findings depends on the accuracy of coding for splenectomy and infection end points. In this context, the predictive value of hospital registry diagnoses of major infections is reportedly high (18) and, in our research registries, is 90% for pneumonia (19) and close to 100% for bacteremia (20). The surgical procedure data we used are also known to have high validity (21), and any misclassification is likely to attenuate our relative risk estimates.

Another concern is that increased surveillance of splenectomized patients may have led to an overestimation of infection risk. Prophylactic guidelines for splenectomized patients in Denmark include information about the risk for serious infections, and instructions to take a dose of penicillin V at home and to seek medical care in case of pyrexia greater than 38.5 °C (22, 23). However, for such severe infections as bacteremia, which had the highest risk increase associated with splenectomy, the number of undetected cases in all comparison cohorts used is probably low because of severe symptoms and need for hospitalization. Although splenectomized patients may also be more likely to experience nosocomial infections because of more frequent hospital contacts, analyses restricted to hospital contacts in which infection constituted the primary diagnosis yielded virtually unchanged estimates.

In Denmark, pneumococcal vaccination is recommended within 2 weeks before elective splenectomy, or as soon as possible and within less than 2 weeks after emergent splenectomy (22–25). However, previous studies in Denmark and elsewhere found that between 10% and 40% of splenectomized patients received no pneumococcal vaccination, and an even larger percentage was not vaccinated at the recommended time (6, 23, 26–29). Unfortunately, we did not have data on vaccinations, yet higher vaccination rates in patients with splenectomy probably would have caused underestimation of their relative risks for bacteremia and pneumonia. Neither Haemophilus influenzae type B vaccination nor continuous antibiotic prophylaxis is currently recommended in Denmark.

Our findings may have clinical implications. Within 3 months, bacteremia is diagnosed in almost 10% of splenectomized patients, and more than 5% have hospital-diagnosed pneumonia. Thus, preventive measures should be intensified (24). This includes pneumococcal vaccination, which has been associated with decreased bacteremia risk in splenectomized persons (6). Use of continuous antibiotic prophylaxis remains controversial because of concerns regarding patient adherence and bacterial resistance, as well as lack of clear evidence for efficacy (28).

Our study showed that splenectomy is associated with increased short- and long-term risk for infections involving hospital contact. Although relative risks decrease after the initial months, they remain clearly elevated compared with those in the general population or appendectomized patients and modestly elevated compared with those in patients with the same medical indications for splenectomy.

From Aarhus University Hospital, Aalborg, Denmark, and Amgen, Uxbridge, Middlesex, United Kingdom, and Thousand Oaks, California.

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Reproducible Research Statement: Study protocol and statistical code: Available from Dr. Sørensen (e-mail, hts@dce.au.dk). Data set: The Danish Data Protection Agency does not allow transferal of the project data to external research institutions. Most of the source data are stored with Statistics Denmark and can be made available for analysis from www.dst.dk/research.

Requests for Single Reprints: Reimar W. Thomsen, MD, PhD, Department of Clinical Epidemiology, Aarhus University Hospital, Aalborg Hospital Science and Innovation Center, Søndre Skovvej 15, DK-9000 Aalborg, Denmark; e-mail, r.thomsen@rn.dk.

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APPENDIX: SURGERY AND DIAGNOSIS CODES

Diagnosis codes were assigned from the International Classification of Diseases (ICD), Eighth Edition or Tenth Edition. Surgical procedure codes were assigned from the Danish National Board of Health Classification of Surgical Procedures until 31 December 1995 and the Nordic Medico-Statistical Committee (NOMESCO) Classification of Surgical Procedures (NCSP) thereafter (30).

Splenectomy
Partial or total (transabdominal, laparoscopic, or transthoracic) splenectomy: 48700–48710, JMA.

Splenectomy Indications
Traumatic rupture of spleen: S36.0 (ICD-10); 865.9 (ICD-8).
Hematopoietic cancer: C81–C96 (ICD-10); 200–207, 275.59 (ICD-8).
Hereditary hemolytic anemias: D55–D58 (ICD-10); 282 (ICD-8).
ITP: D69.3 (ICD-10); 287.10 (ICD-8).
Other or nonspecific thrombocytopenia: D69.4, D69.5, D69.6 (ICD-10); 287.11, 287.18, 287.19, 287.29 (ICD-8).
Splenic diseases and splenomegaly: D73, R16.1, R16.2 (ICD-10); 289.4, 782.89 (ICD-8).
Abdominal cancers: C16, C18 (ICD-10); 151, 153 (ICD-8).
Other or unknown indications: Various codes (ICD-10); various codes (ICD-8).

Matched Indication for Splenectomy Due to Trauma
Any of:
Injury of spleen: S36.0 (ICD-10); 865.9 (ICD-8).

Injury of liver or gallbladder: S36.1 (ICD-10); 864.9 (ICD-8).
Together with any of:
Explorative laparotomy: 40220, JAH00.
Laparoscopy: 40240, JAH01.
Repair (including suture) of spleen: 48930, JMB10.
Operations on liver or biliary tract: 47000–48299, JJ, JK.

Appendectomy
Open appendectomy (excluding laparoscopic or with drainage): 43000, JEA00.

Comorbid Conditions
Myocardial infarction: I21; I22; I23 (ICD-10); 410 (ICD-8).
Congestive heart failure: I50; I11.0; I13.0; I13.2 (ICD-10); 427.09; 427.10; 427.11; 427.19; 428.99; 782.49 (ICD-8).
Vascular disease: I70; I71; I72; I73; I74; I77 (ICD-10); 440; 441; 442; 443; 444; 445 (ICD-8).
Cerebrovascular disease: I60–I69; G45; G46 (ICD-10); 430–438 (ICD-8).
Chronic pulmonary disease: J40–J47; J60–J67; J68.4; J70.1; J70.3; J84.1; J92.0; J96.1; J98.3 (ICD-10); 490–493; 515–518 (ICD-8).
Connective tissue disease: M05; M06; M08; M09; M30–36; D86 (ICD-10); 712; 716; 734; 446; 135.99 (ICD-8).
Inflammatory bowel disease: K50–K52 (ICD-10); 563 (ICD-8).
Pepic ulcer disease: K22.1; K25–K28 (ICD-10); 530.91; 530.98; 531–534 (ICD-8).
Liver disease: B15.0; B16.0; B16.2; B18; B19.0; K70–K74; K76.0; K76.6; I85 (ICD-10); 070.00; 070.02; 070.04; 070.06; 070.08; 571; 573.00; 573.01; 573.04; 456.00–456.09 (ICD-8).
Renal disease: I12; I13; N00–N05; N07; N11; N14; N17–N19; Q61 (ICD-10); 403; 404; 580–583; 584; 590.09; 593.19; 753.10–753.19; 792 (ICD-8).
Diabetes: E10–E11 (ICD-10); 249; 250 (ICD-8).
Hemiplegy: G81; G82 (ICD-10); 344 (ICD-8).
Obesity: E65; E66 (ICD-10); 277.99 (ICD-8).
Pancreatitis: K85; K86.0; K86.1 (ICD-10); 577.00–577.19 (ICD-8).
Alcoholism and alcoholism-related conditions: F10; G31.2; G62.1; G72.1; I 42.6 K29.2; R78.0; T51; Z72.1 (ICD-10); 291; 303; 979; 980 (ICD-8).
Malignant conditions: C00–C96 (ICD-10); 140–207 (ICD-8).
AIDS: B21–B24 (ICD-10); 079.83 (ICD-8).
Dementia: F00–F03; F05.1; G30 (ICD-10); 290.09–290.19; 293.09 (ICD-8).

Infectious Outcomes
Bacterial and viral infections: A00–B99 (ICD-10).
Upper and lower respiratory tract infections: J00–J22 (ICD-10).
