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ORIGINAL ARTICLE

Outcomes after splenectomy in children: a 48-year population-based study

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Abstract

Purpose In children who have undergone splenectomy, there may be impaired immunologic function and an increased risk of infection. We aimed to define the long-term rate of and risk factors for post-splenectomy infection using a population-based cohort study.

Methods All children (< 18 years) who underwent splenectomy from 1966 to 2011 in Olmsted County, MN were identified using the Rochester Epidemiology Project (REP). Descriptive statistics, Kaplan–Meier estimates, and Cox Proportional hazard ratios were performed to evaluate for risk factors associated with developing infection.

Results Ninety patients underwent splenectomy and 46% were female. Indications included trauma (42%), benign hematologic disease (33%), malignancy (13%), and other (11%). Most were performed open. Vaccination was completed in (72%) for pneumococcal, *H. influenza*, and meningococcal vectors. Nineteen patients developed infection, and associated factors included non-traumatic, non-malignant disease [HR 4.83 (1.18–19.85)], and performance of multiple surgical procedures [HR 2.80 (1.09–7.21)]. Estimated survival free of infection rates at 15 and 20 years following surgery was both 97%.

Conclusions After splenectomy in children, most patients do not develop infection. Nearly three-quarters of patients were vaccinated with the lowest rates in patients that underwent a splenectomy for trauma. In patients who received multiple procedures during a splenectomy, the infection risk was higher.

Keywords Post-splenectomy · Sepsis · Splenectomy · Population · Outcomes

Introduction

As the largest lymphoid tissue in the human body, the spleen maintains immunologic defense mechanisms against virulent pathogens [1]. Splenectomy can result in loss of adaptive immunity as well as a decrease in several serum immunologic factors [2–4]. This can lead to a well described susceptibility to certain types of infections [5, 6]. Annually, nearly 27,000 splenectomies are performed in the United States and these patients are perceived to be at increased risk for infectious complications, [7], the most serious being overwhelming post-splenectomy infection (OPSI) which is a rare but often fatal condition [8]. Multiple preventive measures are taken to protect against OPSI and these include vaccination as well as early empiric antimicrobial treatment in patients that are febrile [9, 10].

In 1952, King and Shumaker first described the susceptibility of asplenic infants to bacterial infections [11]. Since then, multiple reports have estimated the incidence and risk

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factors associated with infection after splenectomy, but these reports do not assess population-based data and most are comprised of single-center cohorts or were limited to specific disease states such as idiopathic thrombocytopenic purpura [12, 13]. Therefore, it is important to evaluate a population-based pediatric patient cohort that underwent splenectomy so as to better understand the risk of infection after splenectomy during the long term. In this study, we utilized the Rochester Epidemiology Project to describe the long-term incidence and patterns of infection after splenectomy in children within Olmsted County, Minnesota. To improve post-operative management and better understand of the impact of asplenia over time, we hypothesized that indication for splenectomy, vaccination receipt, or multiple procedures in addition to splenectomy would be associated with infection after splenectomy.

Patients and methods

Database and patient cohort

Institutional review board approval was obtained from Mayo Clinic and Olmsted Medical Center; the only two operative institutions seated within Olmsted County which is relatively isolated from other metropolitan areas. It is a unique setting wherein the natural history after splenectomy can be evaluated. The Rochester Epidemiology Project (REP) is a collaboration that maintains patient-specific data for consented community members to pool medical records for epidemiologic and historical cohort research. The REP is a continuously updated, population-based project that uses data specialists to classify historical patient data according to the International Classification of Diseases (ICD) and Current Procedural Terminology (CPT) codes and collate medical treatment of nearly all Olmsted County citizens since 1965 [14]. The REP is able to link at an individual level unique patient identifiers, diagnoses, and medical records of all local residents receiving medical care at both institutions as well as few private practitioners. Diagnoses, surgical procedures, and outcomes in an individual's medical record are listed on a face sheet, which, in turn, is coded and indexed. This is updated and maintained for all inpatient and outpatient encounters including office visits, clinic consultations, emergency department visits, hospital admissions, autopsy examinations, and death certification. Subsequently, the REP covers and provides access to more than 97% of the population in Olmsted County (124,177 in the year 2000) [15]. Attrition from the REP occurs when individuals either die or move out of the county and health care is no longer provided by a participating REP provider. Migration out of Olmsted Country is tracked via patient address data at the time of contact with a health care provider, despite this, if a REP participant were to move away and continue to receive medical care at an REP participating center, this information remains within the REP database. Attrition rates have been described being highest in patients aged 15–25 but as of 2011 in recent data integrity project, only 18% of Olmsted Count residents have been lost to follow-up [15]. Using the detailed resources of the REP, we performed a cohort study of all children (< 18 years) who underwent splenectomy from 1966 to 2011, in Olmsted County, MN were identified using the resources of the Rochester Epidemiology Project (REP).

Using diagnostic and procedural index for individual historical patient medical data, patients who were Olmsted County residents at the time of splenectomy were included using the following procedural codes: ICD-9 code 41.5 (total splenectomy) or CPT codes (38,100 excision procedures on the spleen, 38,102 total excision of the spleen, in conjunction with another procedure, and 38,120 laparoscopic procedures on the spleen). Vaccination status was obtained for all included patients for three common encapsulated organisms (*S. pneumonia, H. influenza*, and *N. meningitides*). This was obtained from the patients' medical records. All patients were followed until death, emigration from the county or last follow-up if still alive. Study data were collected and managed using REDCap electronic data capture tools hosted at Mayo Clinic [16].

Definitions

Overwhelming post-splenectomy sepsis (OPSI) was defined as a fulminant and rapidly progressive infection caused by encapsulated bacteria that may occur in asplenic patients. The diagnostic index was evaluated for infections including pneumonia, urinary tract infection, acute otitis media, meningitis, non-surgical abscess, blood stream infection, or peritonitis. The diagnosis index was utilized to determine patients that developed sepsis from the aforementioned infection subtypes. Culture data were evaluated and queried to determine the infectious vector. OPSI-related death occurred when a patient expired after developing a fulminant infection during hospitalization. Severity of the infections were graded based on the SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference [17]. Patient charts were evaluated by the authors and REP data specialists to standardize the definitions of infection throughout the study period.

Data analysis

Continuous variables were summarized with medians, interquartile ranges (IQRs), and ranges; categorical variables were summarized with frequency counts and percentages. Survival free of any type of infection and OPSI were estimated using the Kaplan–Meier method and a competing risks approach to account for the competing risk of death without infection. The duration of follow-up was defined from the date of splenectomy to the date of infection or last follow-up. Associations with time to infection were evaluated using Cox proportional hazard regression models and summarized with hazard ratios and 95% confidence intervals (CIs). The Cox models were stratified by year of surgery to account for changes in clinical features and outcome over time. Associations with the cumulative incidence of infection after accounting for the competing risk of death without infection were evaluated using the proportional sub-distribution model [18]. Incidence rates per 100,000 person-years were calculated using incident cases as the numerator and age- and sex-specific counts of the population of Olmsted County as the denominator. The denominators were obtained from a complete enumeration of the Olmsted County population provided by the Rochester Epidemiology Project [19]. Because the population of Olmsted County is predominantly white, incidence rates were directly age and sex-adjusted to the structure of the 2010 US white population. The relationships of age, sex, and year of splenectomy with incidence rates were assessed by fitting Poisson regression models using the SAS procedure GENMOD. Statistical analyses were performed using version 9.3 of the SAS software package (SAS Institute, Cary, NC, USA). All tests were two-sided and p values < 0.05 were considered statistically significant.

Results

During the study period, there were a total of 90 patients who underwent splenectomy within Olmsted County. The median [IQR] age at the time of splenectomy was 14 [7–16] years and the cohort comprised of 41 females (46%). No patients were lost to follow-up. The indications for splenectomy included trauma ($n=38$, 42%), benign hematologic disease ($n=30$, 33%), malignancy ($n=12$, 13%), and other ($n=10$, 11%). Patient diagnoses with benign hematologic diseases included idiopathic thrombocytopenia purpura (ITP) ($n=12$, 40%), spherocytosis ($n=10$, 33.3%), hemolytic anemia ($n=4$, 13.3%), and other ($n=4$, 13.3%). The malignant hematologic conditions included Hodgkin's lymphoma ($n=8$, 66.7%), non-Hodgkin's lymphoma ($n=1$, 8.3%), and other ($n=3$, 25%). Most patients underwent an elective splenectomy ($n=51$, 57%) compared to an emergency procedure ($n=39$, 43%).

Comparisons of patient characteristics based on the timing for splenectomy (emergency versus elective) are presented in Table 1. Those receiving elective splenectomy were younger, more frequently female, and received laparoscopy compared to patients undergoing emergency splenectomy. Vaccinations for three common encapsulated organisms (*S. pneumonia, H. influenza*, and *N. meningitides*) were more frequently administered to patients undergoing elective compared to emergency splenectomy. Despite this, there was an increased rate of any hospital admission due to infection in patients that underwent elective rather than emergency splenectomy. The severity of infection was not considerably different between groups.

Most patients received at least a single vaccination ($n=65$, 72%) against *S. pneumonia* ($n=65$), *H. influenza*

Table 1 Patient characteristics in those underdoing elective and emergency splenectomy

Characteristic	Elective ($n=51$)	Emergency ($n=39$)	p
Age (years)	11 [6–15]	16 [8–16]	0.02
Female sex	30, 59	11, 28	0.005
Laparoscopy	12, 24	0, 0	0.0004
Pneumococcal vaccine receipt	45, 88	19, 48.7	0.0001
H. influenza vaccine receipt	29, 56	8, 21	0.0003
Meningococcal vaccine receipt	34, 67	12, 31	0.0005
Any booster vaccine receipt	29, 56	10, 26	0.004
Infection requiring admission?	15, 29	4, 10	0.03
Patients who developed SIRS	4, 26	1, 25	0.70
Patients who developed sepsis	8, 53	2, 50	
Patients who developed severe sepsis	1, 7	0,0	
Patients who developed septic shock	2, 14	1, 25	

Values are reported using medians with interquartile ranges and categorical variables are summarized as counts with percentages

SIRS systemic inflammatory response syndrome

($n=37$), or *N. meningitides* ($n=46$). There were 25 patients who did not receive a vaccine, 19 who received a single vaccine, 10 who were doubly vaccinated, and 36 patients who received all three aforementioned vaccinations. During the study period, the rates of vaccination increased after splenectomy in children from 1960 to the present. Table 2 stratifies patient characteristics and outcomes based on vaccination receipt (yes versus no). There was no difference in patient age. In patients who were and were not vaccinated, there were considerable differences in the indication for splenectomy, but a few differences in readmission rates due to infection and infection severity. Thirty-nine patients received a booster vaccine later in life. The most common booster vaccine administered was pneumococcal ($n=33$, 36%), followed by *H. influenza* ($n=11$, 12.2%), and meningococcal ($n=7$, 8%). Receipt of booster was not associated with a reduction in infectious-related post-splenectomy complications or infection severity.

There were 19 patients who developed infection of any type at a median of 3.4 years following surgery (IQR 1.5–5.0 years; range 0.1–15.1). The three most common infected sites were the lungs (37%), blood stream (32%), or other (21%). The infection severity was most frequently categorized as sepsis ($n=11$, 58%). Culture data were available for 11 patients and the following microorganisms were demonstrated: *E. coli, S. aureus, S. epidermidis, C. glabrata, K. pneumonia, S. typhi, S. pneumonia*, and *S. viridans* (see Table 3). Three of the eleven infected patients were found to have a polymicrobial infection. Most infected patients required hospital readmission for treatment $n=11$ (58%). Of the nineteen patients that became infected, eight developed OPSI. Of the eight patients with OPSI, only four received the entire set of three post-splenectomy vaccinations. This severe infection was commonly due to encapsulated organisms like *S. pneumonia* and *K. pneumonia*. OPSI-related death occurred in four patients. In the 71 patients who did not develop infection, the median follow-up was 11.8 years (IQR 3.9–24.9 years; range 0 days–45.4 years).

Table 3 Culture data and infection outcomes

Type of culture available ($N=11$)[a]	*N* (%)
Blood	9 (81)
Secretion	3 (27)
Tissue	2 (18)
Other	2 (18)
Monoculture species ($N=8$)[a]	
E. coli	2 (25)
Staphylococcus aureus	2 (25)
Staphylococcus epidermidis	2 (25)
Candida glabrata	1 (13)
Klebsiella pneumonia	1 (13)
Salmonella typhi	1 (13)
Streptococcus pneumonia	1 (13)
Streptococcus viridans	1 (13)

[a]Patients can be listed in more than one group

Overall, this cohort represents a total of 1342 person-years of follow-up. Among the 74 patients alive at last follow-up, the median duration of follow-up was 12.2 years (IQR 6.0–24.9; range 7 days to 45.4 years). Within this cohort, the estimated rates of not developing OPSI following surgery at 1, 2, 3, 4, 5, and 10 years were 99% (95% CI 96–100) with 65, 60, 59, 55, 52, and 44 patients left at risk respectively. Furthermore, the estimated rates of not developing OPSI at 15 and 20 years following surgery were both

Table 2 Patient characteristics and outcomes based on vaccination receipt

Characteristic	No vaccination ($n=25$)	Any vaccination ($n=65$)	*p*
Vaccination receipt during 1960–1969	4, 16	3, 4.6	0.01
Vaccination receipt during 1970–1979	9, 36	9, 13.9	
Vaccination receipt during 1980–1989	8, 32	19, 29.2	
Vaccination receipt during 1990–1999	2, 8	16, 24.6	
Vaccination receipt during 2000-present	2, 8	18, 27.6	
Female sex	7, 28	34, 52	0.03
Readmitted for infection?	2, 8	17, 26.1	0.08
Number of readmissions for infection	1 [0–2]	1 [0–2]	0.70
Splenectomy indication benign	2, 8	28, 43	0.0001
Splenectomy indication malignant	1, 4	11, 16.9	
Splenectomy indication trauma	20, 80	18, 27.7	
Splenectomy indication other	2, 8	8, 12.3	

Values are reported using medians with interquartile ranges and categorical variables are summarized as counts with percentages

SIRS systemic inflammatory response syndrome

97% (91–100) with 32 and 21 patients left at risk. The risk of developing any infection within this cohort at 1, 2, 3, 4, 5, 10, 15, and 20 years following surgery after accounting for the competing risk of death without infection was 97%, 92%, 90%, 85%, 83%, 80%, 76%, and 74%, respectively. Univariable associations with time to infection are summarized in Table 4. The features of pancreatectomy and gastrectomy were not evaluated, since only 1 patient underwent pancreatectomy and only 1 patient under gastrectomy. Covariates associated with an increased risk for infection included performing an additional procedure and the indication for splenectomy defined as "other." Multivariable modeling was not performed since at least 20 outcomes were needed to support two features in a multivariable model and only 19 were observed.

Since only one patient underwent splenectomy in 2011, all trend analyses were evaluated for the cohort using patients that underwent splenectomy between 1966 and 2010. Overall, the age- and sex-adjusted incidence of splenectomy was 6.3 per 100,000 person-years. Incidence rates by year of splenectomy are illustrated in Fig. 1. Incidence rates were significantly higher for males compared with females for the 1966–1969 time period ($p = 0.003$). However, incidence rates did not differ significantly by sex for the remaining time periods ($p = 0.76$). When females and males were combined, there was evidence that incidence rates increased between 1966 and 1984 ($p = 0.017$), with a peak incidence of 11.0 per 100,000 person-years for the 1980–1984 time period. Starting at this peak, incidence rates significantly declined until the end of the study period ($p = 0.008$).

Splenectomy rates by indication are illustrated in Fig. 1. Incidence rates of splenectomy for trauma increased between 1970 and 1979 ($p = 0.014$), and then declined until the end of the study period ($p = 0.003$). Incidence rates of splenectomy for malignancy did not change significantly over time ($p = 0.60$), although there were only 11 patients with this indication during the study period. Incidence rates of splenectomy for benign hematologic diseases increased between 1970 and 1989 ($p = 0.008$), and then remained fairly constant ($p = 0.50$). Incidence rates for other indications did not change significantly over time ($p = 0.15$), although there were only ten patients with other indications during the study period.

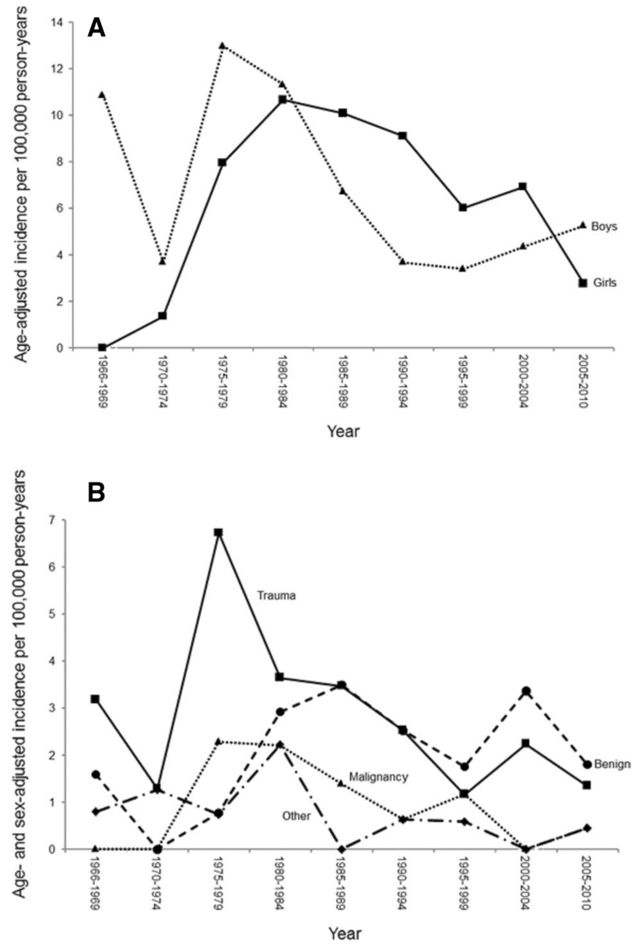

Fig. 1 Incidence rates of splenectomy by indication and sex during the study period for pediatric patients. *Incidence per 100,000 person-years age-adjusted to 2010 US white population. †Incidence per 100,000 person-years age- and sex-adjusted to 2010 US white population

Table 4 Univariable associations with time to infection for pediatric patients

Feature	Hazard ratio (95% CI)	*p* value
Age at surgery in years	0.94 (0.86–1.02)	0.13
Sex		
Female	1.0 (reference)	
Male	0.44 (0.17–1.16)	0.099
Indication for splenectomy		
Trauma	1.0 (reference)	
Malignancy	2.14 (0.50–9.16)	0.30
Benign hematologic disease	1.31 (0.36–4.75)	0.68
Other	4.83 (1.18–19.85)	0.029
Type of splenectomy		
Elective	1.0 (reference)	
Emergent	0.49 (0.16–1.52)	0.22
Technical approach		
Open	1.0 (reference)	
Laparoscopic	0.84 (0.15–4.83)	0.84
Other procedure performed	2.80 (1.09–7.21)	0.033

Hazard ratio and 95% CI represent a 1-year increase in age

Discussion

Utilizing a robust population-based tool, the Rochester Epidemiology Project, we were able to evaluate and provide long-term follow-up in 90 patients who underwent splenectomy during childhood. We demonstrate that, after splenectomy in pediatric patients, the incidence of infection is rare. On univariable analysis, the greatest risks were associated with needing additional procedures and a non-malignant or non-traumatic indication. Finally, we estimated the survival free duration from OPSI and determined that (1) the rate of OPSI was low and that (2) the overall OPSI free survival of patients post-splenectomy was high with 97% of patients still without infection at 20 years. Despite a low OPSI rate, among those who did develop OPSI, there was 50% mortality rate which underscores the severity of developing this fatal complication. Mortality after OPSI should not be under recognized and this study's findings suggest a need for further research to augment this outcome. Moreover, these data demonstrate changes in the incidence of pediatric splenectomy within the REP; specifically, a few pediatric patients receive splenectomy with the greatest reduction in indication for trauma consistent with management changes proposed over time.

Despite the commonality of the procedure, there remains a perceived risk for increased rates of infection and life-threatening overwhelming post-splenectomy infection (OPSI) in pediatric patients that undergo splenectomy. Several population-based cohort studies have evaluated the long-term risk of infection post-splenectomy. Meekes et al. determined that, in 91 children that underwent splenectomy for various indications, very few patients developed infections ($n=3$, 3.8%) [20]. Similarly, Ein et al. demonstrated a serious infection rate of 6% in 182 infants or children who underwent splenectomy with a 2–15-year follow-up [12] and Elsenberg et al. demonstrated a 6% post-splenectomy sepsis rate [21]. More recently, the post-splenectomy infection rate in children with idiopathic thrombocytopenic purpura was 5.2% during 18-year follow-up [22]. In the present study, we demonstrated a low long-term risk for infection. Nineteen patients experienced an infection during follow-up; however, only 2.2% of patients developed OPSI which is similar to previously reported and more current reports. Despite a low rate of OPSI, four patients (50%) expired. While OPSI was infrequent, the severity of this infection should not be underestimated and healthcare providers should remain vigilant to prevent this complication. The current analysis provides similar follow-up and highlights the appreciable risk to develop a spectrum of infections well-past post-operative convalescence. The present analysis provided granular long-term follow-up and that neither indication nor technique (open/laparoscopic) was associated with an increased risk for developing any PSS; however, performance of an additional procedure was associated with increased infection risk.

The incidence of infection in patients post-splenectomy within a defined United States population has been previously reported in 1982 by Schwartz et al. [23]. More contemporary publications regarding incidence and patterns of infection have been reported from Europe [24–26]. These studies demonstrated that, in patients that underwent splenectomy, the risk for infection was increased compared to the general population and that vaccination protocols appeared to be most beneficial in patients with malignant diseases. In the present study, in patients that underwent elective procedures, vaccine receipt was increased compared to patients underwent emergency splenectomy. This is most evident in that 82% of traumatically injured patients did not receive a vaccination. The present study also demonstrates that vaccination utilization increased with time, with highest rates from 1980 onwards. In general, we favor routine vaccination, ideally in the preoperative setting during elective cases. In the case of trauma, pediatric splenectomy has fallen out of favor and our data reflect an increasing utilization of non-operative management as in traumatic indication has diminished considerably.

Mortality after splenectomy in children is often associated with concomitant severe primary diseases or in patients who required urgent or emergent care. In a large multi-institutional analysis, Eraklis and Filler evaluated 1413 patients and determined that 112 (8.2%) of children died during the follow-up period (4–10-year post-splenectomy), and in that, 34 patients expired (30.3%) due to infection [27]. Within the cohort that expired due to infectious causes, the mortality was associated with diagnosis type with higher rates in patients with malignancies or portal hypertension for example. Furthermore, Aronis et al. determined that the mortality rate due to severe sepsis was 3% [28]. In the present study, nearly one quarter of patients expired in-hospital, and of these, 100% were associated with sepsis. Comparing this study with others, it appears that overall and infectious-related mortality remains low; however, in patients who do develop infection, mortality can be early.

In the past 50 years, advances in perioperative management have improved the safety and tolerability of surgery. The rapid expansion of laparoscopy has provided surgeons with the ability to resect patients' spleens in a minimally invasive manner. Rescorla et al. evaluated the efficacy and complication profile of laparoscopic splenectomy in children over more than a decade, concluding that laparoscopy was safe and provided similar outcomes without undue increases in morbidity, duration of stay, and mortality [29]. Our current analysis demonstrated that the majority of splenectomies were performed open; however, this coincided with a majority of the procedures completed prior to the advent of laparoscopy. Nevertheless, on univariable analysis, there was no association with the development of post-splenectomy infection based on operation type.

In a study of 42 episodes of OPSI, 37 cases were due to streptococcal pneumonia infection [30]. The authors found that only 12 patients were vaccinated and of those 4 likely had vaccine failure [30]. In 2015, Nived et al. investigated the extent with which vaccine protocols were adhered toward and the authors suggested that adherence to protocols varied based on vaccine type (highest for streptococcal but lowest for meningococcal) [31]. In our study, only very few patients had culture data available and there was a variety of pathogens with no specific subtype comprising a majority. This suggests that not all causes of infection may be adequately vaccinated against after splenectomy. Furthermore, in a patient the expired from *S. pneumoniae*, this patient was vaccinated, but did not receive a booster shot. This highlights that OPSI remains a risk long-term despite vaccination efforts.

Arnott et al. suggest that, in addition, vaccination, the maintenance of a rigorous and systematic database, can assist providers in post-splenectomy management [32]. Our current study represents the population-based analysis that is broadly inclusive and captures medical data in a relatively unchanging population. Further analysis of this cohort and future patients will continue to provide an in-depth understanding of patients at risk and identify patients who demonstrate poor compliance or adherences to post-splenectomy care. Changes to the REP database might improve infection surveillance. This data point would be important for research both retrospectively and prospectively given the high rates of individual patient data capture for residents of Olmsted County.

This study is limited by its retrospective nature and we were not able to determine any independent predictors of OPSI and post-splenectomy sepsis likely due to a small sample size. This also limited comparisons to determine any associated infection risk in patients vaccinated or not. A future study might focus on post-splenectomy infection and mortality rates in comparison to healthy, age and gender matched controls. This would allow for an analysis comparing the rates of OPSI and highlight the considerable risk of mortality in patients who underwent a splenectomy compared to those who did not. Data regarding antibiotic prophylaxis (long term—weeks–months–years) were not available for this study. This limits the ability to understand the impact on reduction of post-splenectomy infections and the risk of developing OPSI and potentially mortality. Finally, the limitation of follow-up bias is possible due to a reported attrition rate of 18%; however, in this study, no included patients were lost to follow up. Despite these limitations, the granular patient data generated using the REP in addition to generating high quality epidemiologic data permitted this analysis that demonstrates similar findings to prior work. In addition, patients with the longest follow-up (splenectomy for trauma, now a rare occurrence) were at the lowest risk for OPSI. The risk declined as post-splenectomy interval increased and this may have skewed the results.

Conclusion

After splenectomy in children, most patients do no develop OPSI or PSS. Nearly three-quarters of patients were vaccinated with the lowest rates in patients that underwent a splenectomy for trauma. Vaccination increased over time. Booster vaccinations were administered but with less frequency to common encapsulated organisms. In patients who received multiple procedures during a splenectomy, the infection risk was higher. Several microorganisms were responsible for developing post-splenectomy sepsis.

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Author contributions Drs. MAK, NC-P, MCH, DHJ, MDZ, and CL conceptualized and designed the study, designed the data collection instruments, collected data, carried out the initial analyses, drafted the initial manuscript, and reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all the aspects of the work.

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Compliance with ethical standards

Conflict of interest Mohammad A. Khasawneh, MBBS declares that he has no conflict of interest, Nicolas Contreras-Peraza, MD declares that he has no conflict of interest, Matthew C. Hernandez, MD declares that he has no conflict of interest, Christine Lohse, MSc declares that she has no conflict of interest, Donald H. Jenkins, MD declares that he has no conflict of interest, and Martin D. Zielinski, MD declares that he has no conflict of interest.

Animal rights No animals were utilized in this study.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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