



## PERSPECTIVES IN PEDIATRIC PATHOLOGY

# Asplenic-hyposplenic Overwhelming Sepsis: Postsplenectomy Sepsis Revisited

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### ABSTRACT

Absence of the spleen or splenic function predisposes individuals to risk of overwhelming infection. These infections are most often due to encapsulated organisms, especially pneumococcus, *Haemophilus influenzae* type b, and meningococcus, but any bacterial agent may cause the rapid onset of septicemia, meningitis, pneumonia, and shock characteristic of the asplenic-hyposplenic condition. The risk is greatest in infants and young children, but asplenic-hyposplenic adults also have an increased risk of infection. Prophylactic antibiotics and immunization with polyvalent pneumococcal, *H. influenzae* type b, and meningococcal vaccines have reduced the incidence of infections in asplenic-hyposplenic individuals, but even these measures have not eliminated the risk. Surgeons have adopted techniques to save as much splenic tissue as possible and some splenic functions, such as pitting red cells, have been preserved, but conservative surgery has not provided total protection against overwhelming infection. Therapies designed to interrupt the cascade of overwhelming sepsis have not yet been successful.

In those cases in which the spleen is surgically removed, the underlying disease or condition leading to splenectomy influences the risk of sepsis. Splenectomy incidental to other operations, such as gastrectomy, results in the lowest risk for overwhelming infection, but this is still some 35-fold greater than the risk for overwhelming infections in the general population. In in-

creasing order of risk, the other main indications for surgical removal of the spleen are idiopathic thrombocytopenia purpura, trauma, transplantation procedures, hereditary spherocytosis, staging Hodgkin's disease, portal hypertension with hypersplenism, and thalassemia. Pathologists should comment on the risk of overwhelming sepsis when spleens are processed as surgical specimens, and should carefully weigh all splenic tissue, including accessory spleens and splenic implants (splenosis), in autopsy cases with and without overwhelming sepsis.

**Key words:** asplenia, hyposplenia, splenectomy, sepsis

*Beside your stomach may be seen  
A pulpy organ called the spleen.  
The body seems to perk without it  
But, since its role is still in doubt, it  
Is prudent on the part of man  
To keep it in him if he can.  
There once existed foolish notions  
About the spleen and man's emotions  
But these have now gone out of fashion  
You cannot blame the spleen for passion.*

Irene Warsaw

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### HISTORY

Throughout history philosophers, historians, physicians, and poets have commented on the spleen

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and its role in the body. One proposed function was to provide mirth and laughter, in contrast to the dark and depressing effects of the liver and gall (melancholy) [1]. As poet Warsaw stated, the “body seems to perk without it,” and its loss through accident or design can, for most purposes, be without serious consequence.

Surgery on the spleen has been practiced since ancient times. Pliny the Elder claimed that splenectomy rendered runners more efficient [2]. In his day, removal was accomplished with sharp instruments or by cautery with a hot iron [3]. The French have an expression, “to run as one with his spleen out,” and the Germans have similar expressions [2]. Since Pliny lived in the Mediterranean region where a large part of the population was infected with malaria, and since malaria can cause massive enlargement of the spleen to 10 or more kg, it is no wonder that removal of such a huge organ would enhance athletic performance. Splenectomized rats, previously conditioned to quickly cross a length of thick rope, ran faster times to completion of the course than did their sham-operated littermates [2]. In a real and human experience, Jeff Blatnick, an asplenic, super-heavyweight Greco-Roman wrestler, represented the United States in the 1984 Olympic games. This was 2 years after his splenectomy and radiation therapy for Hodgkin’s disease. He won the gold medal.

From the 16th to 19th centuries, splenectomies and partial splenectomies were performed for a variety of reasons, but most often for splenic trauma [3,4]. In the first decades of the 20th century, surgeons at the Mayo Clinic reported successful treatment of splenic trauma with partial splenectomy [5]. From about 1910 until 1975, because the spleen was considered expendable, total splenectomy became the treatment of choice, not only for splenic trauma but for storage diseases, certain hematologic and malignant diseases, and when the spleen was simply in the way, as in gastrectomy. Most of the diseases were poorly understood. In 1935, an article on splenectomy in childhood listed the indications for splenectomy: “to stop the perverted, pernicious activity of the spleen . . . to rid the body of lurking infections such as malaria, lues, undulant fever, tuberculosis [6].” Dr. William Mayo wrote in 1919 that splenectomy was a reasonable treatment for three diseases of unknown

etiology: pernicious anemia, splenic anemia, and hemolytic icterus. These conditions had in common splenomegaly, severe anemia, jaundice, bile-colored stools, and absence of bile in the urine [7]. We now know the etiology and pathogenesis of pernicious anemia and splenectomy is no longer warranted. As for hemolytic icterus, this had two forms—congenital and acquired. The congenital disease is now called “hereditary spherocytosis.” The diagnosis was reasonably accurate in Mayo’s day, since his colleagues in Rochester had developed a method for measuring the increased fragility of red blood cells in this disease. “The triumph of splenectomy is the cure of haemolytic icterus,” said Mayo. The third condition, splenic anemia, remained a mystery. Mayo offered a comment in which he referred to “hibernianism”; “Incomplete knowledge is essential to the diagnosis. If we know the cause, it is not splenic anemia.” [7]. In retrospect, many of these cases were probably Banti’s syndrome or other causes of hypersplenism with resultant anemia.

Few voices were raised regarding the dangers of sepsis in asplenic patients [8]. Perhaps because infections in general were then more common and antibiotics were not available, severe and fatal sepsis was expected in the natural course of matters in any group of postoperative patients. Then in 1952, King and Schumacker reported fulminant sepsis in five young children whose spleens were removed to abate the effects of hereditary spherocytosis. Two of their patients died from the overwhelming infection. These authors collected additional cases from several centers; 6 of 15 developed severe sepsis and 3 patients succumbed [9].

Between 1952 and 1973, more such cases were reported in the pediatric literature [10–12]. Diamond coined the term “overwhelming postsplenectomy infection” (OPSI) to indicate the rapid and severe nature of the infection and stated that the risks for OPSI were highest in children with portal hypertension, thalassemia major, Wiskott-Aldrich syndrome, histiocytosis, and hepatitis. He failed to recognize the hazard for OPSI in children whose spleens were removed for trauma and he thought splenectomy for spherocytosis or idiopathic thrombocytopenic purpura posed only slight risks. In any case, he advised rapid treatment with antibiotics at the first sign of infection [11].

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Bisno was among the first to warn that asplenic adults may also be at risk and he recognized that the disease leading to splenectomy influenced the incidence of infection [13,14]. A large Scandinavian study more or less concurrent with the report of King and Shumacker had the following results: of 460 children with total splenectomies, 56 (12%) had infections postoperatively and 43 (9%) of these were severe. Two of the 43 severe infections were in patients who had abdominal trauma, 11 had spherocytosis, 14 had thalassemia major, and 13 had idiopathic thrombocytopenic purpura [15]. At the Ohio State University Medical Center in Columbus, 2,417 splenectomies had been performed, nearly half of them for hematologic derangements. The risk for postsplenectomy sepsis was about 5% in patients of all ages and whose spleens were removed for all reasons. The septic episodes were fatal in almost half the children and in about one-third of the adults [16].

As only the British can do, a regional study of all of the 1,167 patients who had splenectomy were followed for 2 years. Sepsis occurred in 93 patients (8%) and in 23 patients (2%), the infection was lethal. Most of these patients were adults [17]. In Hodam's review of 310 cases of all ages, 5 patients (1.6%) developed severe postsplenectomy sepsis and 2 (0.6%) died [18].

A review of 2,795 cases of splenectomy was published in *Perspectives in Pediatric Pathology* in 1973 [19]. In this article, there were sufficient outcome data from children and adults to confirm that the reason for splenectomy influences the chance for postsplenectomy sepsis regardless of age. The overall rate of overwhelming sepsis was 4.25%; lethal sepsis developed in 2.52% of cases. As Broberger had shown [15], patients with thalassemia carried the greatest risk of overwhelming sepsis after their spleens were removed [19].

Investigators began to drive home the point that asplenia or hyposplenia conveys a significant risk of developing overwhelming sepsis, no matter what the condition or the reason for surgical removal, the age of the patient, or the duration of time elapsed since removal of the spleen. Surgeons responded with alternate methods of treatment. Partial splenectomy and avoiding surgery, whenever possible, have again come into vogue. Pediatricians and hematologists have developed pro-

grams of prophylaxis with antibiotics and vaccines against pneumococcus, *Haemophilus influenzae* type B, and meningococcus.

Overwhelming sepsis occurs in patients who have congenital absence of the spleen and in patients whose splenic function is impaired, as well as in those whose spleens are surgically removed. Rather than perpetuate the term "postsplenectomy sepsis," we have elected to adopt and discuss asplenic-hyposplenic overwhelming sepsis, a more inclusive and accurate term.

## THE NORMAL SPLEEN AND ITS FUNCTIONS

The spleen's functions include hematopoiesis, phagocytosis, erythrocyte destruction, reservoir for blood (in animals, especially dogs), being a source of factor VIII, culling and pitting erythrocytes, platelet and leukocyte destruction, and immunologic and phagocytic host defense mechanisms [20].

The neonatal spleen in mice has a suppressor function on certain immunologically active cells. This suppressor function resides in natural T cells as well as non-T suppressor cells, and it inhibits T helper cells and immunoglobulin-producing B cells. This inhibitory activity is presumably important in fetal-maternal interactions by preventing the mother's lymphocytes from rejecting the half-foreign placenta and fetus or from entering the fetal circulation and setting up a graft-versus-host reaction [21].

The spleen produces antibodies, although ample lymphoid tissue exists in other parts of the body to provide this form of protection. B cells home to their location in the splenic follicles as long as their surface complement receptors, especially those for C3, are available. If the receptors are blocked, the B cells do not interact properly with the splenic reticular cells and endothelial cells, resulting in faulty B-cell homing. T cells are not adversely affected and migrate properly within the spleen [22].

Studies demonstrated long ago that adequate antibody responses required time, even years, to become effective in protecting the body against pneumococcus and encapsulated *H. influenzae* [23,24]. In asplenic humans, the rise in titer of antibodies in response to certain antigens is one-

tenth that of intact individuals, indicating that the spleen is an important reservoir of immunocompetent lymphocytes [25]. The CD4<sup>+</sup> population in the circulation depends on the presence of the spleen. In asplenia or hyposplenia, antibody responses to newly encountered antigens, in part a CD4<sup>+</sup> function, are impaired [26].

Efficient phagocytosis depends on splenic macrophages and on other splenic products such as opsonins, properdin, and the tetrapeptide known as tuftsin [27]. Fibrinectin, a large glycoprotein that enhances phagocytosis by macrophages and neutrophils, is reduced in the plasma of asplenic animals [28]. In asplenic patients, chemotaxis is reduced in macrophages and neutrophils and phagocytic inactivation of bacteria is reduced in neutrophils [29]. In dogs given billions of organisms intravenously, the bacteria are cleared from the blood in three passes through the spleen [30]. While small numbers of bacteria such as pneumococci and *H. influenzae* can be cleared from the circulation in infants even before they develop specific immunity, larger bacterial loads may be quickly fatal. The spleen is also important in removing other organisms, including parasites such as *Babesia*, *Bartonella*, and *Plasmodium* [20].

Splenomegaly and increased phagocytosis is considered a response to work load. Patients with hereditary spherocytosis or idiopathic thrombocytopenic purpura develop splenomegaly, due in part to proliferation of splenic macrophages [31]. In Sprague-Dawley rats, subcutaneous splenic implants grow much larger in totally splenectomized animals than in those with hemisplenectomy, and suckling rats have a greater response than adult rats [32,33]. In immunized rabbits challenged with I<sup>125</sup>-tagged pneumococci, the spleen has up to 10 times the uptake (phagocytosis of organisms), gram for gram, as that of the liver. The blood stream in such experiments can be cleared of 98% of the injected organisms within 15 min and of 100% of as many as one billion organisms within 1 h [34].

## MECHANISMS OF SEPSIS WITH OR WITHOUT SPLENIC FUNCTION

Septic shock occurs when endotoxins from the lipopolysaccharide (LPS) in cell walls of bacteria break down and are released. Some gram-positive

bacteria and fungi also elicit sepsis. Teichoic acid antigens, toxic shock syndrome antigen, and toxin-A from *Pseudomonas aeruginosa* are some of the other exogenous substances that are produced by microorganisms and that initiate septic shock. The host's macrophages, plasma cells, endothelial cells, and neutrophils produce reactive products such as tumor necrosis factor (TNF), interleukins (IL) 1, 2, 6, and 8, platelet-activating factor (PAF), endorphins, and endothelial-derived relaxin factor. Further reactants in the cascade include arachidonic acid metabolites, prostaglandins, cyclooxygenase, lipooxygenase, complement C5a, leukotrienes, kinins, and bradykinins. Briefly, the bacterial products bind to CD14 molecules on leukocytes, endothelial cells, and other cells. The cascade of cytokine mediators forms LPS → TNF → IL-1 → IL-6, and IL-8 → NO (nitric oxide) and PAF, which, in moderate or high quantities, produce fever and acute phase reactants. Later, blood vessel dilatation and injury develop with thrombosis. The end results, if the cascade is not interrupted, are disseminated intravascular coagulation (DIC), decreased myocardial function, adult respiratory distress syndrome, acute renal failure, hepatic failure, and, finally, shock with leaking plasma fluid from capillaries, multiple organ failure, and death [35,36].

## PATHOLOGY OF ASPLENIC-HYPOSPLENIC OVERWHELMING SEPSIS

The pathology of the spleen itself is of little consequence in this report. Descriptions of traumatized spleen [37] and those in spherocytosis, idiopathic thrombocytopenic purpura, Gaucher disease and other storage diseases, malaria, babesiosis, and Hodgkin's disease may be found in standard reference works.

Sepsis in asplenic or hyposplenic patients can occur with any organism, be it bacteria, virus, fungus, or protozoan. The most dramatic disease occurs when infections are due to an encapsulated organism. Pneumococcus is the single most common offender; *H. influenzae* type b, *Escherichia coli*, and meningococcus are the next most common ones. The other bacterial organisms, in more or less in decreasing order of frequency, are staphylococci, streptococci, and *Pseudomonas* species [19]. An occasional case report mentions the dog-

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bite bacillus *Capnocytophaga canimorsus* as the cause of severe infection in asplenic humans [38]. *Enterococcus* species, *Salmonella* species, *Bartonella* species, *Plesiomonas shigelloides*, *Eubacterium plautii*, *Pseudomonas pseudomallei*, and many other organisms have been isolated from patients with asplenic-hyposplenic overwhelming sepsis [19,39]. Absence of the spleen allows these organisms to multiply enormously and to spread rapidly throughout the body. Diffuse pneumonia is a frequent finding at autopsy; meningitis is less common. While meningitis or pneumonia accompany sepsis in these patients, about half have a generalized septicemic infection without these localizing signs. DIC is another characteristic feature of asplenic-hyposplenic overwhelming sepsis, as is adrenal hemorrhage and necrosis (Waterhouse-Friderichsen syndrome). Shock intervenes in most cases with renal cortical necrosis or acute tubular necrosis, patchy hepatic necrosis, and fluid accumulations in serosa-lined cavities and in soft tissues. The process may progress in mere hours from the first sign of fever, headache, or vomiting to rapidly evolving generalized sepsis and death. In most cases, particularly in adults, the process evolves over a period of 2 to 5 days. Asplenic-hyposplenic overwhelming sepsis can be successfully treated in most cases, but survivors may have severe thrombotic lesions with intestinal infarcts or gangrene of extremities. The remaining patients succumb to the disease. In those patients who had blunt abdominal trauma, the pathologist may find splenosis. These nodules should be excised and weighed to provide further information regarding the amount of splenic nodules necessary to avoid sepsis. The best estimates are that at least half of the original splenic mass is required for protection against bacterial infection.

Malaria and babesiosis have a special niche in a discussion of asplenic-hyposplenic overwhelming sepsis. The importance of the spleen in malaria is reflected in the splenomegaly that develops with repeated infections. Massive spleens have been described and rupture is common with minimal trauma. Removal of such spleens results in exacerbation of disease with increased numbers of parasitized erythrocytes in the circulation [40]. The phagocytic function of the spleen is paramount in malaria and also in the less common parasitic dis-

ease of erythrocytes, babesiosis [41–43]. The American organism, *Babesia microti*, is less potent than the European variety, *Babesia divergens*, which has produced several deaths in Scotland, France, and the former Soviet Union [44]. While asplenic individuals are at particular risk for acquiring babesiosis, Ruebush and colleagues described five patients with the disease, none of whom had asplenia or hyposplenia [45]. Another erythrocyte-associated organism caused a stubborn, indolent infection in an asplenic man. In this case, the bone marrow provided the reservoir for this still unidentified gram-positive rod. The bacterium seemed to adhere preferentially to erythrocyte membranes but did not invade the cell [46].

Curiously, HIV-infected individuals tend to improve when their spleens are removed, probably because the large viral load carried in splenic lymphocytes is eliminated. Delayed onset of AIDS and increased CD4<sup>+</sup> counts are noted after splenectomy [47].

## HYPOSPLENISM

Hyposplenism occurs when splenic functions are reduced by disease or are absent congenitally or after splenectomy. Laboratory indicators are increased numbers of Howell-Jolly bodies, the nuclear fragments that persist in the red cell's cytoplasm. For unexplained reasons, the surface area of the red blood cells is increased, causing buckling of the cell and target-cell formation. Pits or pocks, the vacuoles in the submembranous cytoplasm of red blood cells, are visible in wet preparations using interference-contrast microscopy. Hyposplenism exists when more than 12% of the red blood cells have pocks [48]. The white blood cell count and platelet count increase moderately. Heinz bodies can be detected in red blood cells by means of supravital stains. Reticulocyte counts and nucleated red blood cells tend to remain unchanged unless they are related to the primary disease. The life span of red blood cells is normal since other organs, such as the liver, remove senescent cells [49].

Patients with sickle cell anemia can develop hyposplenism in the first few months of life. In a multicenter study [50], 4 infants with sickle cell disease developed pneumococcal sepsis at ages less than 12 months and 11 others before 36 months of

age. The problem is not limited to children; teenagers and adults with sickle cell disease are also at risk. The bacterial load in the blood of such septic patients can be enormous, on the order of a millions of organisms per milliliter, and pneumococci are easily found in ordinary peripheral smears [51].

While hyposplenism is especially prevalent among individuals with sickle hemoglobin, S-thalassemia hemoglobin, or S-C hemoglobin, several other diseases are liable to be complicated by hyposplenism. Dermatitis herpetiformis, celiac sprue, and ulcerative colitis are three such diseases. Among 24 patients with ulcerative colitis, 7 (29%) developed hyposplenism. Crohn's disease does not predispose to hyposplenism [52]. Less common conditions associated with hyposplenism are liver disease, systemic lupus erythematosus, rheumatoid arthritis, polyarteritis nodosa with splenic infarct, amyloidosis or sarcoidosis with splenic involvement, splenic radiation for cancer, and high-dose corticosteroid therapy [39]. Bone marrow transplantation may result in functional hyposplenism due to chronic graft-versus-host disease [53].

Congenital absence of the spleen predisposes to overwhelming sepsis. Asplenia may be associated with heterotaxy and failed asymmetry of the body axis or it may be an isolated anomaly and familial [48,54]. The *HOX* family of genes may be involved in such cases. At least in asplenic mice, an orphan homeobox gene designated *HOX11* is mutated [55].

## SEPSIS FOLLOWING SPLENECTOMY

### Spherocytosis

King and Shumacker, working in Indianapolis, deserve credit for finally placing postsplenectomy sepsis on the table for discussion and consideration. With their own cases of hereditary spherocytosis (HS) and those collected from other centers, they exposed the risk attendant to loss of the spleen [9]. In a report 17 years earlier, Penberthy and Cooley described a family with three children suffering from HS. Splenectomies were performed in all three. Two of their patients died 17 and 18 years after surgery with overwhelming infections. The third child had mastoiditis 9 months postoperatively but survived [6]. In a series of 56 patients

with HS, two (3.6%) developed postsplenectomy sepsis, with one death (1.8%) [18]. In still a larger series, 226 patients with HS were followed for up to 45 years following splenectomy. Six (2.7%) had overwhelming sepsis and in four (1.8%), the sepsis was lethal. One of the patients had her spleen removed 30 years earlier [56]. In 1973, from a total of 850 HS postsplenectomy patients, we found 30 HS patients with sepsis, 19 of whom died [19].

Spherocytosis is the only hematologic condition for which splenectomy is absolutely indicated [57]. Even then, the surgery should be delayed, if at all possible, until the patient is 5 years of age or older. Use of combined laboratory and clinical criteria may assist the hematologist and the surgeon in deciding when to operate. One indication is the half-life of tagged red cells less than 10 days, together with a climbing splenic uptake curve; another is splenic uptake at least twice that of the liver; a third indicator is the presence of anemia and an enlarged spleen more than 4 cm below the costal margin, coupled with a plasma volume 50% greater than normal [57].

### Trauma

Particularly long intervals between splenectomy and the onset of sepsis have been noted in patients with splenic trauma [18,58,59]. Military veterans who had their spleens removed during the Second World War have fivefold greater risk of overwhelming fatal sepsis than their comrades whose spleens were preserved. The infections occurred as late as three or more decades after surgery [60].

In 1973, we estimated that postsplenectomy sepsis was 58 times more likely to occur in patients whose spleens are removed for traumatic injury than in the normal population [19]. This estimate has been criticized, mainly because it was based on retrospective and varying data from the literature [61]. If anything, the estimate is low. With the addition of several thousand more cases, the patients with splenectomy for trauma have a still higher rate of asplenic-hyposplenic overwhelming sepsis (see Tables 1 and 2 and the section below regarding estimations of risk of asplenic-hyposplenic overwhelming sepsis).

**Table 1. Asplenic-hyposplenic overwhelming sepsis among individuals, mostly children**

Specific condition	Current series <sup>a</sup>			1973 Series [19]		
	Total cases	With sepsis <i>n</i> (%)	Fatal sepsis <i>n</i> (%)	Total cases	With sepsis <i>n</i> (%)	Fatal sepsis <i>n</i> (%)
Incidental splenectomy	1768	17 (1.0)	11 (0.6)	233	5 (2.1)	2 (0.9)
Idiopathic thrombocytopenic purpura	1271	20 (1.5)	17 (1.3)	489	10 (2.1)	7 (1.4)
Sickle cell disease	105	2 (1.9)	0 (0.0)	NA	NA	NA
Trauma	1444	36 (2.4)	29 (2.0)	688	10 (1.5)	4 (0.6)
Transplantation	120	4 (3.3)	1 (0.8)	NA	NA	NA
Hereditary spherocytosis	1376	49 (3.6)	31 (2.3)	850	30 (3.5)	19 (2.2)
Hodgkin's disease	1256	84 (6.7)	51 (4.1)	69	8 (11.5)	7 (10.1)
Portal hypertension	267	23 (8.6)	14 (5.2)	221	18 (8.2)	13 (5.9)
Thalassemia	265	35 (13.2)	15 (5.6)	109	27 (24.8)	12 (11.0)
Primary anemia	NA	NA	NA	70	6 (8.5)	5 (7.0)
Acquired hemolytic anemia	NA	NA	NA	67	5 (7.5)	2 (2.9)
Total	7872	270 (3.5)	169 (2.1)	2796	119 (4.3)	71 (2.5)

NA, no data available in this series.

<sup>a</sup>The current series includes most of the cases in the 1973 series. It was not possible to tease out the older cases from the more current reports in most instances, but duplication of cases from one report to another was avoided [16,17,19,56,67,68].

### Idiopathic thrombocytopenic purpura

One of the oldest patients recorded with fatal postsplenectomy sepsis is a man, 66 years of age, who died 23 months after his spleen had been removed for steroid-resistant idiopathic thrombocytopenic purpura (ITP) [62]. In younger patients, this hematologic condition is associated with a measurable but relatively low risk for postsplenectomy sepsis. In the current series, episodes of sepsis and septic deaths are less common among asplenic patients with ITP than among those whose spleens were removed for trauma (Fig. 1, Table 1).

### Autoimmune lymphoproliferative syndrome

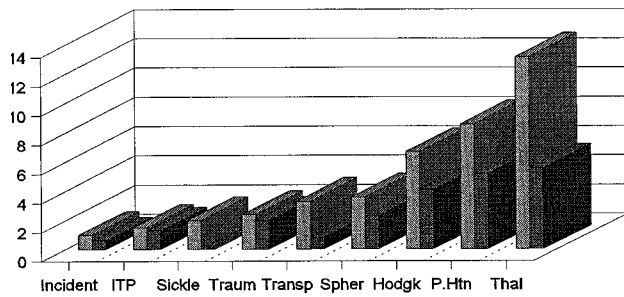
The autoimmune lymphoproliferative syndrome (ALPS), also known as the Smith-Canale syndrome, arises in early childhood and is characterized by lymphadenopathy, splenomegaly that is sometimes massive, and autoimmunity. It is an inherited disorder of lymphocyte apoptosis, and lymphocyte studies in these patients reveal an increased proportion of T lymphocytes with neither CD4 nor CD8 surface markers. ALPS arises as a result of mutations in the *APT1* gene encoding FAS. The most common form of ALPS is associated with heterozygous FAS mutations. In a review

**Table 2. Percent reduction or increase of overwhelming sepsis in all asplenic or hyposplenic cases from 1973 series to current series<sup>a</sup>**

Condition	Sepsis (%)	Death (%)
Incidental splenectomy	-50	-33
Idiopathic thrombocytopenic purpura	-29	-7
Sickle cell disease	NA	NA
Trauma	+60	+230
Transplantation	NA	NA
Hereditary spherocytosis	+3	+5
Hodgkin's disease	-42	-60
Portal hypertension	+5	-12
Thalassemia	-47	-49
Primary anemia	NA	NA
Acquired hemolytic anemia	NA	NA
Total	-18	-16

NA, not applicable; data lacking in one series or the other.

<sup>a</sup>The current series is diluted with most of the cases from the 1973 series. Had it been possible to completely tease out the cases since 1973, the results might be different. The totals on the bottom line suggest an overall trend in the favorable direction with reduced incidences of sepsis and death [16,17,19,56,67,68].



**Figure 1.** Percentages of septic cases (light bars) and percentages of septic deaths (dark bars) are shown for nine conditions associated with all cases of asplenia or hyposplenia. Incident, incidental splenectomy; ITP, idiopathic thrombocytopenic purpura; Sickle, sickle hemoglobin disease; Traum, trauma; Transp, transplantation patients; Spher, hereditary spherocytosis; Hodgk, Hodgkin's disease; P.Htn, portal hypertension; Thal, thalassemia.

of a Clinical Staff Conference at the National Institutes of Health (NIH), 26 patients were evaluated and diagnosed with ALPS. The patients initially presented because of lymphadenopathy or pronounced splenomegaly. Sixteen patients underwent splenectomy and five patients developed pneumococcal septicemia despite appropriate antibiotic and vaccine prophylaxis [63]. In a study of an ALPS kindred, Infante and colleagues reported 11 patients with confirmed FAS mutations. Splenectomy was performed in three. One child died of pneumococcal sepsis and meningitis after appropriate vaccination and penicillin prophylaxis [64]. The risk of postsplenectomy sepsis in ALPS is very high. At the NIH clinical staff conference the comment was made that "the major determinants of illness [in ALPS] seem to be the severity of autoimmune disease and the occurrence of sepsis after splenectomy" [63].

### Wiskott-Aldrich syndrome

About 20% of Wiskott-Aldrich patients who have splenectomy will suffer a bout of overwhelming sepsis [10–14]. Lum and colleagues reported the results of splenectomy in 47 patients with Wiskott-Aldrich syndrome. The operations were performed to abate the thrombocytopenia that occurs in these boys and men. In 16 cases, the platelet counts improved. However, during the course of the study, five of the patients died of sepsis despite prophylactic antibiotics. Another patient died 2

weeks after discontinuing antibiotics. Since the basic immunologic defect prevents adequate responses to pneumococcal vaccines, these investigators insist that antibiotics be taken daily if splenectomy is performed [65].

### Hodgkin's disease

Among 115 patients with Hodgkin's disease who had staging splenectomies, 145 episodes of sepsis developed within a postoperative interval ranging from 2 months to 10 years. Not all of these were serious infections and only a small number could be categorized as asplenic-hyposplenic overwhelming sepsis. Deaths due to overwhelming sepsis with DIC occurred in 20 (17.3%) patients. While infections and septic death may be a great risk in Hodgkin's disease with or without a spleen, judging from the descriptions, these latter patients would most likely qualify for sepsis due to asplenia [66].

In another report of 200 children with splenectomy for staging Hodgkin's disease, septicemia or meningitis developed in 18. Two of the 18 had two such episodes. Symptoms were fulminant and eight children died. Leukopenia was not a factor since the average white blood cell count was 12,000/ml<sup>3</sup> in survivors and in children who died. The interval between splenectomy and infection ranged from 1 week to 3 years [67].

In the past several years, staging splenectomies have been virtually eliminated for children with Hodgkin's disease and markedly reduced among adults with this condition. The remaining asplenic patients require continued observation.

### Thalassemia

In our 1973 series, thalassemia stood out as the hematologic disease with the greatest risk for postsplenectomy infection, with almost one of every four patients developing overwhelming sepsis [19]. Broberger and colleagues had similar results [15]. In this updated series, we have collected double the number of patients with thalassemia and splenectomy and note that the risk of infection is decreased by half, but thalassemia is still the condition with the highest risk [16,68] (Table 1).

## CALCULATING RISK OF ASPLENIC-HYOSPLENIC OVERWHELMING SEPSIS

The cumulative risk of a serious but not necessarily overwhelming infection is almost 33% during the first 10 years following splenectomy for a variety of indications [69]. Using a slightly different approach, Schwartz and colleagues found a risk of infection of 1.8 per 1000 patient years and a risk of 0.9 fatal infections per 1000 patient years in patients whose spleens were removed for a variety of reasons [69]. This was considered a small risk by these authors and by another commentator [61], but this is at least 10 times the risk of overwhelming infection in the general population.

In Norway, the population of 4.3 million has a risk of invasive pneumococcal disease of 0.11 per 1000 patient years [70]. If splenectomy is performed to stage Hodgkin's disease in that country, the risk is 2.26 per 1000 patient years, more than 20 times the risk in the general population [70]. In a large cohort of HS patients with splenectomy, Schilling calculated that the risk of sepsis was 0.73 episodes per 1000 patient years [56]. If one extrapolates these risks to the general population in a city the size of New York City, with a population of 9 million, episodes of fulminant sepsis would occur at the rate of at least 18,000 each year and 9000 people would die. Carrying the argument further to include the population of the United States, more than 500,000 Americans would suffer a bout of fulminant sepsis each year and more than 250,000 would die from the disease. The risk may be low by some standards, but it is not trivial for the asplenic patient population.

In our earlier report, we used data regarding septicemia and meningitis occurring during 1 year in the children of Newcastle upon Tyne. The statistics thus obtained were multiplied by 5 to account for a reasonable number of years of follow-up in the various reports on splenectomy and then multiplied again by 2 (for a total factor of 10) to provide a cushion factor. Admittedly, the method is not particularly scientific, but lacking prospective studies in most postsplenectomy patients, this still seems a fair way to arrive at the background estimates and a basis for which to compare the incidence of postsplenectomy sepsis in various categories of patients. In 1973, the rate

stated for patients with splenectomy for abdominal trauma was 58 times that of the children in Newcastle upon Tyne [19]. Today, with more than 800 additional cases, the rate is about 35 times the background rate in the English children (Table 1, Fig. 1).

In our current review of 7872 patients, we have few exact data on total years of follow-up, so we cannot make estimates of risk per 1000 patient years. Table 1 and the chart in Figure 1 show the percentage of overwhelming infections and septic deaths among all patients who have sickle hemoglobin disease or who undergo splenectomy for eight common indications. In Table 2, the more current data suggest an overall reduction in percentages of sepsis (18% less) and septic death (16% less) compared with the 1973 data.

## ANTIBIOTIC PROPHYLAXIS FOR ASPLENIC-HYOSPLENIC PATIENTS

Patients and their parents or caregivers are advised that no infection is trivial and should be treated with penicillin without delay, with or without culture confirmation. Similarly, dental procedures should be covered with penicillin therapy. In a multicenter study of infants and toddlers with sickle cell disease, daily prophylaxis with penicillin V potassium, 125 mg twice daily, provided excellent protection [50]. Among 105 children who received such prophylaxis, only two episodes of pneumococcal sepsis developed and neither child died. Of the 110 children who received placebos, 13 had pneumococcal sepsis and 3 died. Another two infants developed *H. influenzae* sepsis and one of these children died. This study showed an 84% reduction of life-threatening infection using twice-daily penicillin prophylaxis when such therapy is started at 4 months of age [50].

The more recent evaluation of prophylactic penicillin in patients with sickle cell disease produced the slightly relaxed recommendation that daily antibiotics may reasonably be discontinued after 5 years of infection-free life [71].

Empiric use of penicillin has been superseded by other more potent antibiotics in patients who have early signs of postsplenectomy infection. Cefotaxime and Ceftriaxone are now given along with Gentamycin, Ciprofloxacin, or Vancomycin, the latter if resistant strains of pneumococcus are

suspected. The antibiotics may be switched to penicillin or other less expensive products when bacteriologic studies are completed and the sensitivity of the organism is known [39].

Another strategy is the "standby" antipneumococcal antibiotic. The patient keeps a personal supply to be taken at the first sign of respiratory illness, fever, or rigors, especially if there is to be a delay in medical evaluation [39].

In a study at the Hospital for Sick Children in Toronto, children who had splenectomy between 1958 and 1970 were compared with children who had splenectomy between 1971 and 1975. In the earlier study, 6% of the children were infected and 3.9% succumbed. In the latter group, all the children received prophylactic antibiotics and more than two-thirds of them were given polyvalent pneumococcal vaccine. Ten (4%) children had postsplenectomy sepsis and only one child died (0.4%). Of the infections, 77% occurred within 5 years of splenectomy. The advent of prophylactic antibiotics (and vaccination, see below) reduced the infection rate by 47% and the mortality by 88%, as shown by these two studies at this particular hospital [72].

Compliance in taking daily antibiotics is a genuine concern. Half or more asplenic patients fail to maintain their daily antibiotic regimen. A further hazard is the chance of acquiring an antibiotic-resistant species [73,74].

## VACCINATION

Immunization with polyvalent pneumococcal vaccine should be carried out in all patients with asplenia or hyposplenia; in those with splenectomy, the vaccine should be administered before surgery if at all possible. In the Toronto Hospital for Sick Children study, those patients who were vaccinated several months prior to splenectomy had no infections. Infections developed only in children who were vaccinated 2 weeks or less before surgery or as long as 24 months postoperatively [72].

The timing of the vaccination may present a problem in patients who are less than 2 years of age, the earliest age when optimal antibody response is expected. Antibodies decline significantly within 24 months in children who are vaccinated after their spleens are removed. This is especially

true for anti-serotypes 1, 4, 6A, 7F, 8, 19F, and 23F. Revaccination in these patients may be beneficial [75]. In children a vaccine against *H. influenzae* should also be administered and this can be done at 16–18 months of age. At least one study showed that meningococcal vaccines produced good anti-meningococcal antibody responses of all immunoglobulin classes in asplenic adults. Only those patients whose spleens were removed during surgery for abdominal malignant tumors had a poor antibody rise, probably because chemotherapy and radiation treatments blunted the response [76].

In adults who had splenectomy, mostly for trauma, the ratios of postvaccination pneumococcal-specific IgG and IgM to prevaccination IgG and IgM were less than half the ratios in adults who had normal spleens. The absolute titers and the rate of rise were also significantly less in the asplenic patients [77].

In the multicenter study of infants and children with sickle cell disease, vaccination as early as 7 months failed to prevent serious infection. Eleven of 110 subjects were vaccinated but developed serious pneumococcal sepsis and 3 of the 11 died [50].

No data are yet available on the efficacy of new and more potent conjugated vaccines that may be used in younger patients.

## NEW NONSURGICAL THERAPIES FOR ASPLENIC-HYOSPLENIC SEPSIS

Studies of the molecular mechanisms of sepsis and septic shock have led to innovations in treatment, but these approaches are in their infancy and have to date been ineffective [78]. Using antagonists to IL-1 receptor antigen has failed. Steroidal anti-inflammatory treatment results in increased mortality in patients with septic shock. Nonsteroidal anti-inflammatory agents, bradykinin antagonists, PAF antagonists, monoclonal antibody against TNF and against TNF receptors, and prostaglandin antagonists have been studied in literally thousands of patients and have produced little or no benefit. Of these agents, antagonists to PAF have shown the most favorable results. Not yet tried in sufficient numbers of patients are such agents as anti-CD-14 antibodies or antibodies against receptors for endotoxins, etc. It is hoped that persistent

attempts to find molecular therapies will reverse the devastating effects of septic shock [78].

Until the newer molecular-based therapies are proven, recommendations call for vaccination against pneumococcus, *H. influenzae* type B, and meningococcus, along with daily prophylactic penicillin or immediate use of multiple antibiotics at the first sign of infection [79]. Pediatric and adult hematologists seem to be more concerned about the problem than pediatric infectious disease experts. One authority of pediatric infectious diseases is disinclined to recommend such treatment in patients beyond 2 years of age [80].

### **EDUCATION OF THE PATIENT, FAMILY, AND PHYSICIAN**

In 1981, the Lane County Medical Society (Eugene, Oregon) notified 240 splenectomy patients of their need for pneumococcal vaccine as part of a project funded by the National Foundation for Infectious Diseases. In the responses from 135 of the patients, half were not aware of their risk of infection, nor had they received pneumococcal vaccine [81]. This and other notices and letters in the medical literature emphasize the need for patients' and physicians' awareness of the issues [82,83].

Physicians may not be aware that their patients are hyposplenic. In one laboratory's survey of blood smears, Howell-Jolly bodies were found in approximately 1 of every 200 patients who had complete blood counts, for reasons unrelated to asplenia or hyposplenia. Some of these patients may have had Howell-Jolly bodies on some other basis and had normal splenic function, but many were probably hyposplenic. Even when the physician knows of the condition, these patients are not always warned of the dangers implicated by Howell-Jolly bodies [39].

The early signs and symptoms of overwhelming sepsis may be subtle. The prodrome may be mild and nonspecific with muscle aches, stiffness, and low-grade fever. Headache, vomiting, diarrhea, and abdominal pain are other signs and symptoms that should alert the patient to seek attention and to take antibiotics [39,84].

Guidelines for prophylaxis and vaccination have been published in the National Health Service in Great Britain, but adherence to the recommendations is poor [85]. In Newcastle upon Tyne, the

Northern Health Region set up an asplenia register. In the 2 years from 1995 to 1997, 1111 cases had been registered from the region with a population of approximately 3.1 million. Continuous prophylactic antibiotic use was claimed by 498 (45%) patients and another 166 (15%) were aware of and had used antibiotic prophylaxis from time to time. Only 18 (1.6%) wore any type of warning bracelet. Antipneumococcal antibodies were adequate in 405 (36%) registrants but 43 others (4%) failed to produce satisfactory antibody levels despite repeated vaccinations. In the 2 years of study, two patients succumbed to overwhelming sepsis. Long-term compliance with prophylaxis was an acknowledged problem, even in this highly organized setting; so was achieving protective levels of antibodies in patients who had lost their spleens before receiving vaccines [83].

Each registrant received a personalized laminated warning card to carry at all times. The following advice was inscribed: "As you do not have a spleen, it is important that you remember to: 1 Take your antibiotic tablets regularly as instructed by your doctor; 2 Ensure that you get regular immunisations (sic) as recommended by your doctor; 3 Discuss any foreign travel in advance with your doctor. Special precautions may be required and your doctor may advise a change of antibiotic tablets." And further: "If you become suddenly unwell with a high temperature, shivering or shaking, and feel dizzy or faint, you should: 1 Immediately take a double dose of your normal antibiotic; 2 Contact your own doctor at once; 3 If your own doctor is not available or there is any delay, go at once to the nearest hospital. Show the hospital doctors this card and your normal antibiotic tablets." The authors of this article felt that the registry was helping save lives, but they noted with dismay that the funding for the registry was discontinued [83].

### **SURGICAL CONSERVATION OF SPLENIC TISSUE**

The historical background for favoring complete splenectomy following trauma dates from the mid-19th century when a mortality of about 90% attended the attempts to repair a ruptured spleen [5]. A few partial splenectomies were the subjects of case reports and these procedures have persisted throughout the 20th century, but the main thrust

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of surgical treatment for ruptured spleens was total splenectomy. The reasons stated included the poor tensile strength of the splenic capsule and the difficulty in handling and containing the softened traumatized pulp. The main reason, though, was the persisting notion that the spleen was essentially and totally expendable. In addition, a total splenectomy could be performed in half the time, or less, than could a spleen-conserving surgical procedure. In the past 10 or 15 years, textbooks of surgery have included detailed sections on preservation of splenic tissue in cases of trauma [86], but even then, one text published as recently as 1989 has comments expressing skepticism about partial splenectomies [87].

Morgenstern and Shapiro are credited with changing this trend when they reported their results in surgical repair of the traumatized spleen [5]. They perfected their techniques in 200 experimental animals including dogs, rabbits, monkeys, and baboons, and stressed the importance of exposing the vasculature of the spleen, which is most often bipolar but which may be tripolar or occasionally even quadripolar. When the vasculature is visible, an intelligent choice can be made as to which pole to remove and which to preserve. The senior author is quoted as saying "the salvaged spleen or splenic remnant in the left upper quadrant is a far greater trophy for the surgeon than the spleen in the pathologist's hands" [88]. Pachter and colleagues conducted successful splenorraphies with a variety of suture materials and microcolloidal collagen [88]. Metal clips, ligation, and topical agents for surface bleeding are employed. Injection of latex or silicon particles may slow or halt bleeding in a portion of the spleen's bipolar, tripolar, or infrequent quadripolar arterial supply [5]. Mattress sutures are used to try to seal off large, denuded areas and microfibrillar collagen is spread over the raw surfaces. Splenic nubbins can be sewed into the omentum, although this procedure, even if the implants "take" and grow, does not often produce phagocytic protection against overwhelming infection. According to Witte and colleagues, at least one-third of the original spleen must be preserved to avoid postsplenectomy sepsis, but this may be an underestimate [89].

Buntain and Lynn claim that repairs are possible in most cases, particularly in children, be-

cause their splenic capsules are thick relative to the splenic pulp. They described several suturing techniques and wrapping the spleen in the omentum. Past reluctance to repair the spleen was in part due to the time-consuming nature of the task and "a natural aversion to suturing the spleen." [4]. From the older surgical literature, preoperative treatment with adrenalin to shrink a spleen is described, thus making surgical manipulations easier [6].

In the past two decades, surgeons have adopted a much less aggressive approach to splenectomy. Watchful waiting after abdominal trauma is now practiced in the majority of cases. Measuring the patient's hematocrit, blood pressure, and abdominal signs can often obviate laparotomy. In fact, the bleeding from a ruptured spleen has frequently stopped by the time a laparotomy is performed [90].

Several studies indicate that the trend to splenic conservation is preventing overwhelming sepsis, but exact figures have not yet been calculated [82,91,92]. Partial splenectomy for nontraumatic benign conditions, such as cysts, is now the rule. When hypersplenism intervenes in Gaucher disease, partial splenectomy is indicated. The disadvantages of total splenectomy are the risk of overwhelming sepsis and the more rapid accumulation of storage material in the bone marrow, liver, and other tissues rich in reticuloendothelial cells. With partial splenectomy, the protective action against sepsis is preserved and the accumulation of the glucocerbroside in other tissues is slowed [93,94].

## **SPLENOSIS AND ACCESSORY SPLEENS**

Accessory spleens are usually located in the hilum of the main spleen. Wadham and colleagues examined 250 consecutive autopsies prospectively to determine the incidence and found 46 cases (18.4%) with accessory spleens. A single accessory spleen was present in 39 (85%), 2 accessory spleens in 5 (11%), and 3 accessory spleens in 2 (4%) cases. The sizes of the accessory spleens ranged from 2 mm to 3.5 cm and the largest weighed 6.6 g. The hilum of the main spleen was the site of 41% of the accessory spleens; other sites and percentages were the lienorenal ligament (23%), gastrosplenic ligament (13%), tail of the pancreas (11%), greater omentum

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(7%), and in the connective tissue beneath the left diaphragm (4%) [95].

Splenuis occurs in patients who suffer rupture of the spleen with bits of tissue scattered in the abdomen. These small fragments literally implant on the peritoneal surfaces of the omentum, liver, stomach, and other structures. Solid, fleshy, purple masses from 2 mm to several cm dapple the surfaces of the stomach and liver; many implants coalesce to form a plaque or layer of splenic tissue. Microscopically, they appear similar to the normal spleen, but the capsules are fibrotic and the vessels feeding the splenic nodules are small and multiple, unlike the main arteries in the hilus of the normal spleen. Trabeculae may be absent [96]. While almost all splenuis is localized to the abdomen, rare cases have been described in the thorax when the diaphragm has been penetrated at the time of abdominal trauma [97]. Still more rare are examples of splenuis in the liver, kidney, pericardium, and even the brain [98].

Pearson et al. have shown that splenic nodules can be "born again" [99]. They demonstrated that pitted erythrocytes were removed and Howell-Jolly bodies were not evident when splenuis was demonstrated by radiotechnicium scans. At least 20–30 g of splenic tissue are necessary to achieve functions of removing pitted erythrocytes and Howell-Jolly bodies [100]. While some splenic functions are restored, protection against bacterial infections is at best questionable. The reason for poor protection against infection may be found in the low amount of splenuis or in the nature of its altered blood supply, in which small vessels feed the sinusoids but not the cords or vice-versa. In autopsies on children and adults, aggregate weights of residual splenuis varying from 4 to 92 g have failed to protect patients from overwhelming sepsis [19,59,100].

## EXPERIMENTAL SPLENECTOMY

In 1919, Morris and Bullock [8] reported their studies in splenuctomized male rats. From each rat in the control group they removed one of the testes, an intraabdominal organ roughly the same size as the spleen. In the first experiment, they left asplenic and orchietomized animals without further treatment. The asplenic rats acquired endemic infections at four times the rate of the castrated rats.

In another experiment, they exposed the rats to the rat plague bacillus. Infectious fatalities occurred in 87.5% of the asplenic rats but in only 22.7% of the castrated rats. They concluded that splenuctomy in otherwise healthy rats predisposed the animals to severe infections and that the conclusions they reached might be translated to humans. They stated "It is an observation of great antiquity that the operation of splenuctomy is not followed by death. Indeed one may live for years without suffering any apparent ill effect from the absence of the organ, but this does not settle the problem as to whether or not a splenuctomized person can weather a critical illness." [8] Leonard and colleagues performed partial and complete splenuctomies in chinchillas. Pneumococci were cleared from the blood stream sluggishly if two-thirds or more of the spleen were removed. When half the spleen was preserved, bacterial clearance was normal [84]. Kovacs and colleagues compared splenic autoimplants in suckling and adult Sprague-Dawley rats. Spleens were excised and diced, and the fragments were reintroduced into the abdomen as loose fragments. All of the sucklings but only 1 of 10 adult rats had visible splenic tissue at exploratory laparotomy 4 months later [33]. Offenbartl and colleagues gave doses of either human gamma globulin or albumin to splenuctomized rats at varying time intervals after challenge with intravenous injections of pneumococcus. The rats protected with gamma globulin had 75% to 83% survival while all those who received albumin died [101]. Splenuctomized rats have depleted levels of fibrinectin, a large glycoprotein (440,000–450,000 Da) that modulates phagocytic functions of both macrophages and neutrophils [28]. Such animals are especially susceptible to experimental peritonitis. Heparin counters the lack of fibrinectin by reducing the fibrinous exudates, allowing the phagocytic cells to move about more freely [102]. Splenic artery ligation in rats preserves protection against pneumococcal challenge compared with total splenuctomy. Apparently, the collateral arterial network keeps the spleen sufficiently viable to function as a filter for bacteria [103].

Splenuctomy improves the outcome in certain granulomatous infections. In mice with amebiasis, listeriosis, or toxoplasmosis, survival was improved by removing the spleen, a large source of

interferon, thereby enhancing the phagocytic function of macrophages [104–106]. In a similar manner, splenectomized mice are tolerant to endotoxin and do not produce the expected early phase of colony-stimulating factor when exposed to lipopolysaccharide. They do, however, respond vigorously with the later macrophage-colony-forming unit, resulting in a release of macrophages from the bone marrow of the animals [107].

## CONCLUSIONS

Asplenic-hyposplenic overwhelming sepsis remains a distinct hazard for children and adults. In the case of splenectomy, the indications for removing the spleen have changed slightly over the past three decades, but marked differences persist in the incidence of sepsis, depending on the underlying condition (Fig. 1, Tables 1 and 2).

Physicians must continue surveillance for patients with staging procedures for Hodgkin's disease and other patients whose immune system is altered by similar diseases or by radiation and chemotherapy. Renal transplant patients whose spleens are removed are at relatively high risk for sepsis since they receive immunosuppressive drugs to prevent rejection. The ALPS poses a newly recognized and special risk, since splenectomy is considered unnecessary in this condition. Thalassemia is still the hematologic disease with the greatest risk (1 in 7) of postsplenectomy sepsis.

Molecular approaches to therapy are not yet successful, but the value of prophylactic antibiotics has been proven, especially in patients with sickle cell disease. Yet adherence to recommendations for many years, if not a lifetime, tends to be poor. Vaccinations with polyvalent antipneumococcal vaccine have also been beneficial, but many failures are reported in the literature. Some of these patients were younger than the recommended age for vaccination when their spleens were removed; in others, vaccines given after splenectomy elicit slow or negligible responses; in still others, sepsis may be due to a pneumococcal type that has a low immunogenic capacity in the vaccine. Then, too, some patients are infected with organisms other than pneumococci.

Surgeons have strived to conserve splenic tissue, especially in patients with trauma, but also in patients with storage diseases and other condi-

tions. Individual studies from several centers show promising results with fewer infections, but a large cohort, perhaps 1000 or more of such patients, needs to be studied prospectively and over many decades to determine the usefulness of splenic conservation.

The overall incidence of asplenic-hyposplenic overwhelming sepsis has been reduced, but the biggest obstacle to approaching the absolute minimum seems to be education of the patients and, in some cases, the physician. Asplenic and hyposplenic patients and their families must be made aware of the hazard of sepsis. Recommendations include medical warning bracelets and home supply of in-date antibiotics. Booster vaccinations may also be in order. While children under 2 or 3 years of age are most susceptible to asplenic-hyposplenic overwhelming sepsis, adults with intervals as long as six decades postoperatively are still at risk.

Progress toward lowering the incidence of this disorder has been made. Table 2 shows an overall reduction of sepsis (18% less) and septic death (16% less) in the current evaluations compared with those made in 1973, but the problem of asplenic-hyposplenic overwhelming sepsis has not yet been solved. Pathologists can continue to contribute to reducing this problem by adding a comment to their reports on resected spleens that the literature indicates an increased risk of postsplenectomy sepsis. We can also record autopsy results, especially sizes, aggregate weights, and microscopic descriptions of splenic implants in cases of splenosis with and without overwhelming sepsis.

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