Splenectomy and/or Bone Marrow Transplantation in the Management of the Wiskott-Aldrich Syndrome: Long-Term Follow-Up of 62 Cases

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This study describes the effects of two major treatment options, splenectomy and/or bone marrow transplantation, on the natural history of the Wiskott-Aldrich (WAS) syndrome. The records of 62 patients with the WAS evaluated at the National Institutes of Health Clinical Center from 1966 to 1992 were reviewed. Nineteen patients were treated with bone marrow transplantation (BMT) and the results were largely dependent on the source of the graft. Twelve of 12 patients receiving HLA-matched sibling marrow achieved satisfactory immunologic and hematologic reconstitution. By contrast, only 2 of 7 patients receiving haploidentical, parental, or matched unrelated marrow survived more than 1 year after BMT. Thirty-nine patients who lacked suitable bone marrow donors early in their course underwent splenectomy for management of their thrombocytopenia; most received prophylactic antibiotics to minimize the risk of sepsis. Nearly all these patients achieved normal platelet counts and the rate of serious bleeding was reduced nearly sevenfold. Median survival in the untransplanted splenectomy group was 25 years, compared with less than 5 years in unsplenectomized patients. We conclude that HLA-matched sibling donor BMT is the treatment of choice for patients with WAS and that splenectomy and daily prophylactic antibiotics provide a significant survival advantage to those boys without a matched sibling donor. Splenectomy should probably be used in preference to unmatched BMT until results with alternative donor BMT significantly improve or gene therapy becomes available.

THE WISKOTT-ALDRICH syndrome (WAS) is an X-linked syndrome of thrombocytopenia, combined B- and T-cell immunodeficiency, and eczema.[1-3] Without successful bone marrow transplantation (BMT) or splenectomy, these boys usually die in early childhood of infection, hemorrhage, or malignancy. In this syndrome, the spleen sequesters and destroys platelets, releasing into the circulation abnormally small "microplatelets" producing one of the unique characteristics of WAS.[4] After splenectomy, both the platelet count and size become normal and the risk of serious or fatal hemorrhage is significantly reduced. However, splenectomy removes an important host defense against infection and many physicians are reluctant to further weaken the meager immune defenses of these already immunodeficient children, fearing that splenectomy will result in an even earlier death caused by infection.[5-8]

In 1980, we proposed that splenectomy should play an important role in the treatment of patients with WAS who cannot undergo BMT.[9] We report here our extended experience at the National Institutes of Health (NIH) over 26 years with 62 Wiskott-Aldrich patients, 39 of whom underwent splenectomy for treatment of their thrombocytopenia and 19 of whom underwent BMT. The results show that HLA-matched sibling BMT provides excellent outcomes and that splenectomy effectively normalizes platelet counts and reduces serious bleeding. Antibiotic prophylaxis minimizes the risk of postsplenectomy sepsis, transforming splenectomy into a treatment option superior to BMT for those patients who cannot undergo matched sibling BMT.

MATERIALS AND METHODS

The medical records of 69 patients observed for WAS in the Metabolism Branch of the NIH Clinical Center during the years 1966 to 1992 were reviewed. The records of 62 patients were complete enough to include in the analysis. Telephone follow-up interviews were conducted with living patients or their families if they had not visited the NIH Clinical Center in the preceding 18 months. In general, the patients received their primary medical care near their homes and were seen annually at the NIH. The criteria for the diagnosis of WAS (and the number of patients with documented fulfillment of them) included male sex (62 of 62), and the classic triad of thrombocytopenia (62 of 62), eczema (57 of 62), and recurrent infections (59 of 62). Features corroborating the diagnosis included a family history compatible with X-linked transmission (documented in 38 of 62 cases), small platelets (<3 standard deviations [SD] below the mean normal platelet volume; normal range, 6.6 ± 0.8 μm^3 SD) (present in 30 of 31 evaluated),[4] subnormal IgM levels, low isohemagglutinins,[1] impaired antibody production to polysaccharide antigens,[10] impaired in vitro proliferation to allogeneic cells and soluble antigens,[11] skin test anergy,[12] impaired monocyte-mediated antibody-dependent cytotoxicity,[13] and increased rates of catabolism of serum proteins.[14] Fifty-five of 62 fulfilled the classic diagnostic triad. Of the remaining 7, all had evidence of immune dysfunction, and 5 had a positive family history. The 2 patients lacking a family history had small platelets, which, in our experience, has been a nearly invariant feature of the disorder.

The practice at our center since 1976 has been to recommend BMT for those patients who have had matched sibling donors. Splenectomy has been recommended for those patients without suitable donors who have had platelet counts of less than 50,000/mm.[3] Splenectomies were performed at the Children's National Medical Center or by surgeons in the patients' home communities. After 1978, daily postsplenectomy prophylactic antibiotics were routinely prescribed. The antibiotic regimens were trimethoprim/sulfamethoxazole (SMX) (6 mg/kg/day of SMX in two divided doses) or amoxicillin (40 mg/kg/day in three divided doses). Intravenous Ig (IVIg) was not routinely administered. Fourteen of the 62 did receive IVIg, usually episodically when infected. Four patients

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Table 1. Description of the Patient Population

No. of patients	62
No. alive	33
No. dead	29
Average age (yr) at diagnosis ± SD (range)	2.3 ± 4.0 (0 to 24)
Splenectomy and BMT history	
No. undergoing splenectomy	39
Splenectomy, no BMT	31
BMT, postsplenectomy*	8
No. not undergoing splenectomy	23
BMT, no splenectomy	11
No BMT, no splenectomy	12
Splenectomized patients	
No. alive	22
No. dead	17
Age (yr) at diagnosis ± SD (range)	2.8 ± 5.0 (0.0 to 24)
Age (yr) at splenectomy ± SD (range)	5.2 ± 6.3 (0.4 to 29)

* BMT followed splenectomy by 3.5 ± 2.6 yr (range, 0.5 to 11.2 yr). Splenectomy always preceded BMT in these patients.

received 500 mg/kg every 3 to 4 weeks on a long-term basis. Patients developing fevers over 102°F were advised to immediately seek medical attention including blood cultures and modification of their antibiotic regimen to broaden antimicrobial coverage. For this study sepsis was conventionally defined as an episode of severe illness associated with hemodynamic instability in a bacteremic patient; we have excluded 3 cases of transient bacteremias in 3 febrile patients who were otherwise well. Patients were referred to outside centers for BMT. The 19 transplants were performed at 7 different centers.

Descriptive statistics were calculated by standard methods. Rates for bleeding, sepsis, and death were calculated by dividing the total number of events by the total number of person years at risk. Comparisons were performed by *t*-tests unless otherwise specified. Other tests included χ^2 and Kaplan-Meier life table analyses.[15] The life tables plot the proportion of the evaluable study population alive in a given time interval. In calculating this proportion, members of the study population who are alive but have not reached the interval age are censored. Tick marks on the curves represent the last recorded age of the living subjects.

RESULTS

Patient population and changing natural history of WAS. During the period under study, several advances in the treatment of WAS occurred. Table 1 describes our 62 patients and categorizes the group on the basis of BMT and splenectomy. Eleven males underwent BMT as the initial treatment of their WAS and did not undergo splenectomy. Twelve patients underwent neither BMT nor splenectomy. Nine patients were observed during the period before 1978 when we did not recommend splenectomy for WAS patients. Two boys had platelet counts less than 50,000/μL but splenectomy was refused by their parents despite its recommendation. Life table survival analysis for the entire group of 62 patients projected a median survival of 18 years (Fig 1), a significant improvement compared with historical results.[16]

Effect of splenectomy on platelet count and bleeding. Thirty-nine patients underwent splenectomy and most were less than 4 years of age. No serious perioperative infections occurred, nor did serious surgical complications; approximately half the patients required no platelet transfusions in the perioperative period. The median age at splenectomy was 3.5 years; 16 patients were 2 years old or younger at the time. Those patients undergoing a splenectomy before 5 years of age did not suffer more serious infections or earlier mortality than those whose spleen was removed at a later age. Twenty-two of the splenectomized patients are alive and are an average of 7.3 years from their splenectomy. Four of these 22 underwent successful BMT some time after removal of their spleen. Seventeen of the patients who underwent splenectomy have died; their average survival after splenectomy was 7.2 years. Four of these patients had received BMT after splenectomy; 3 of them died of transplant-related complications and the other of lymphoma shortly after the BMT.

Among patients not receiving transplants, a median survival of 4 years in the group not splenectomized was found, whereas the splenectomy group had a median survival of 25 years (Fig 2).

Splenectomy clearly improved the patients' thrombocytopenia (Table 2). The average presplenectomy platelet count was 27,878/μL and after the procedure the platelet count averaged 262,805/μL. In general, the platelet counts became normal within a few days of the splenectomy.

Many of the patients had experienced clinically significant episodes of bleeding before splenectomy, commonly, gastrointestinal bleeding and intracranial hemorrhage (Table 2). Most had more than two significant hemorrhagic episodes before splenectomy, with an average of 0.45 episodes per person per year. Eight episodes of intracranial hemorrhage resulted in 3 deaths in patients never splenectomized or before their splenectomy. After splenectomy,

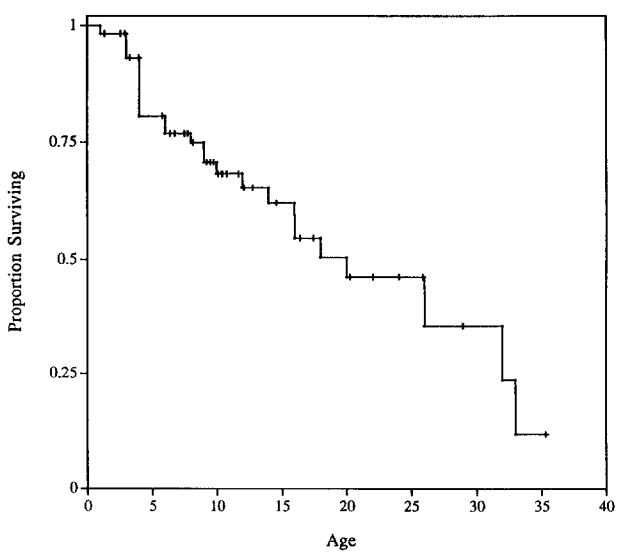

Fig 1. Survival of patients with WAS. Kaplan-Meier plot of proportion of the entire patient population surviving to a given age in years. Tick marks represent the age of patients still alive.

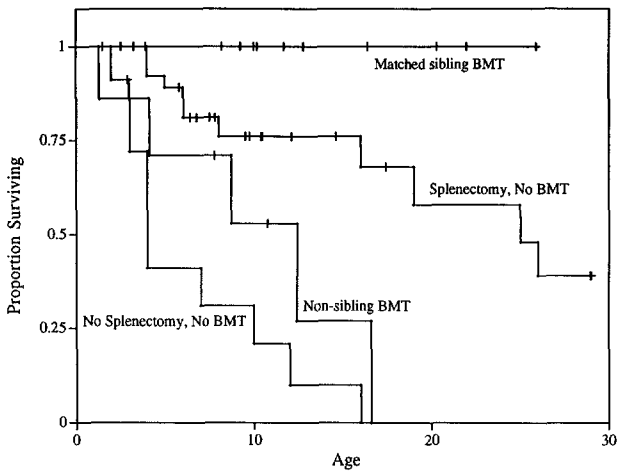

Fig 2. Survival of patients stratified by splenectomy and BMT status in a Kaplan-Meier plot of proportion of patient population surviving to a given age in years. Tick marks represent the age of patients still alive. The "no splenectomy, no BMT" group represents 12 patients. The "splenectomy, no BMT" group represents the 31 patients who underwent only splenectomy and excludes the 8 who later underwent BMT. Eleven of the 12 "matched sibling BMT" recipients for whom accurate dates are known are described in the "matched sibling BMT" group, while 7 are in the "nonsibling BMT" group. Survival of the "splenectomy, no BMT" group is significantly greater than that of the "no splenectomy, no BMT" group ($P < .0001$), and of the "nonsibling BMT" group ($P = .0111$). Survival of the "matched sibling BMT" group is significantly greater than that of the "nonsibling BMT" group ($P = .0005$) and of the "splenectomy, no BMT" group ($P = .0268$).

thrombocytopenic bleeding was reduced to 0.07 episodes per person per year.

However, bleeding was not completely eliminated by splenectomy because patients with WAS are also prone to idiopathic thrombocytopenic purpura (ITP); 14 of our 62 patients developed ITP. Postsplenectomy bleeding was always associated with ITP. In these cases, platelet size remained normal and high levels of platelet-associated IgG were usually present. Seven patients had developed ITP before splenectomy; of these, 6 also had episodes of ITP after splenectomy. Seven patients had episodes of ITP occurring for the first time after splenectomy. Intracranial hemorrhage occurred in 2 patients after splenectomy and 2 patients died of bleeding despite splenectomy.

Postsplenectomy sepsis. Twenty-seven of the 39 patients in the splenectomy group have never experienced an episode of sepsis (Table 3). Twelve have been septic and 5 have died as a result. However, the introduction of routine daily prophylactic antibiotics dramatically reduced the incidence of sepsis. All of the 27 patients not experiencing sepsis received prophylactic antibiotics. Seven of the 12 having postsplenectomy sepsis either never had antibiotics prescribed or discontinued them against medical advice; 3 patients experienced fatal episodes. Every patient who did not receive antibiotics or discontinued antibiotic treatment against medical advice experienced at least one episode of sepsis. Antibiotics did not eliminate the risk of postsplenectomy sepsis; 5 patients experienced sepsis despite taking the drugs, and 2 died as a result. For patients taking prophylactic antibiotics, the annual risk of fatal sepsis was 0.012 per person per year. Table 4 details the causes of death among the 17 patients who died after splenectomy. Sepsis played a role in only 5 of these deaths.

BMT. Nineteen patients underwent BMT (Table 5). Eleven patients received BMT without prior splenectomy. Ten of these received HLA-matched sibling grafts and did well. One received a maternal graft and died of severe graft-versus-host disease (GVHD). Eight patients underwent BMT after splenectomy and, as a group, were older than those who received transplants immediately (Table 5). Only

Table 2. Hematologic Effect of Splenectomy

	Average ± SD
Presentation platelet count, all patients (n = 57)	28,000 ± 22,918
Presentation platelet count, splenectomy (n = 33)*	27,878 ± 22,498
Postsplenectomy platelet count† (n = 36)	262,805 ± 135,445§
Major bleeding episodes,‡ presplenectomy (n = 33)	2.3 ± 2.2
Major bleeding rate, presplenectomy	0.45 episodes/yr
Major bleeding episodes, postsplenectomy (n = 34)	0.5 ± 1.1‖
Major bleeding rate, postsplenectomy	0.07 episodes/yr

* Number was sometimes less than the total number of patients undergoing splenectomy (39) because only data known with confidence was used in the calculation of the statistics.

† Four patients had postsplenectomy platelet counts less than 100,000/μL: 25,000, 50,000, 88,000, and 99,000. The 3 with the lowest counts had recurrent ITP and had experienced more bleeding before and after splenectomy than most patients.

‡ Major bleeding episode was one that required medical intervention, such as intracranial hemorrhage, gastrointestinal bleeding, or intractable epistaxis. Rate is average number of episodes per patient year at risk.

§ Significantly greater than presplenectomy count ($P < .001$).

‖ Number of major bleeding episodes and bleeding rate postsplenectomy significantly less than presplenectomy ($P < .001$).

Table 3. Postsplenectomy Sepsis

	Sepsis		Fatal Sepsis		
	No	Yes	No	Yes	Total
Antibiotics	27	5	30	2	32
No antibiotics*	0	7	4	3	7
Total	27	12	34	5	39

Sepsis is conventionally defined as an episode of severe illness associated with hemodynamic instability in a bacteremic patient; we have excluded 3 cases of transient bacteremia in 3 febrile patients who were otherwise well. Differences between groups are statistically significant. For no sepsis versus sepsis comparison, $\chi^2 = 19.2$, df = 1, $P < .001$; for no fatal sepsis versus fatal sepsis comparison, $\chi^2 = 6.89$, df = 1, $P < .009$.

* Five patients never had antibiotics prescribed; 2 patients discontinued antibiotics against medical advice. All experienced episodes of sepsis.

Table 4. Cause of Death in Splenectomy Patients

Contributing Factor	No. of Patients	Age at Death*
Postsplenectomy sepsis	5†	6.0 (3.3 to 25.2)
Cancer	5	8.5 (4.1 to 18.1)
BMT	3	8.7, 12.4, 16.6
Hemorrhage/ITP	2	3.1, 4.2
Secondary infection‡	2	8.7, 32.9
Autoimmune renal insufficiency	1	32.9
Unknown	1	—

* Age at death in years. Median and range presented when more than 3 cases.

† Three of these patients were not taking prophylactic antibiotics.

‡ Total number of contributing causes (19) exceeds the number of deaths (17) because in two cases multiple factors contributed to the patient's death. One patient developed infection during BMT, whereas the other had infection complicate end-stage renal insufficiency.

2 received matched sibling grafts and these 2 patients were cured. Of the 6 patients who had had a prior splenectomy and who did not receive matched sibling grafts, 4 died during or shortly after BMT. One patient died from veno-occlusive disease, another of acute GVHD, a third failed to engraft, and the fourth developed chronic GVHD and died with a lymphoproliferative disorder. Figure 2 compares survival after BMT for all patients. All patients with matched sibling donors appear to be long-term survivors, whereas 5 of 7 of those receiving maternal haploidentical or unrelated matched grafts died shortly after transplantation. As a group, patients receiving nonsibling BMT did worse than the splenectomy-only group. However, 3 of the nonsibling BMT patient deaths occurred in patients with serious pretransplant illnesses (liver disease and steroid-dependent ITP for 2 of the unrelated BMT recipients, and Burkitt's lymphoma in remission in the case of 1 patient who had had a haploidentical BMT).

DISCUSSION

This report describes the long-term evaluation of WAS patients who underwent splenectomy and/or BMT. The results corroborate our 1980 report, which proposed that splenectomy could be an effective management tool in these boys.[9] Splenectomy clearly normalized the platelet count in nearly all patients and resulted in a reduced incidence of bleeding episodes. The risk of fatal postsplenectomy sepsis was effectively reduced but not totally eliminated by the use of prophylactic antibiotics.

Although the patients' platelet counts were increased by the procedure, the key question is whether it resulted in improved survival and/or quality of life. In the absence of a prospective controlled trial of splenectomy, one must rely on previously published material on the natural history of the syndrome. A comprehensive review of 301 cases was published in 1980 by investigators at the University of Minnesota.[16] It estimated that for boys born after 1964 (a cohort similar to ours) average survival was 6.5 years and that 23% of all deaths in this group resulted from hemorrhage. As a group, our patients who underwent splenectomy are living longer. Excluding patients receiving BMT, projected median survival is 25 years for those with splenectomy and 4 years for those not undergoing splenectomy. In the splenectomy group, only 5% have died from hemorrhage, less than one quarter of the incidence reported in the Minnesota series. It should be noted that most of the boys not undergoing splenectomy were followed in the 1970s; it is certainly possible that changes in supportive care during the 1980's have contributed to the difference in survival in the splenectomy patients. However, during this decade there were no dramatic improvements in antibiotic efficacy or blood-product support that we believe account for the survival differences observed. It is important to note that no stable survival plateau is achieved, reinforcing the point that, although splenectomy is useful, it is not curative.

The boys' quality of life has improved with splenectomy. Without the specter of dangerous thrombocytopenia, they have had the opportunity to lead normally active lives. None has had to endure restricted play nor wear protective headgear. In addition, those who have suffered the frequent arthralgias and arthritides associated with the syndrome have been able to use anti-inflammatory agents previously contraindicated because of their antiplatelet activity. Splenectomy has also made management of later episodes of ITP easier; ITP-related thrombocytopenia has been briefer and less profound in the splenectomized patients. Finally, normalization of platelet counts by splenectomy has allowed patients who later developed malignancies to receive full therapeutic doses of chemotherapy that would have otherwise been limited by thrombocytopenia.

The principal concern about splenectomy is that it may predispose WAS patients to a significantly higher incidence of fatal sepsis. Five of the 38 patients in our series did die of sepsis. When we initially recommended splenectomy as a treatment for WAS and reviewed the relevant literature,[9] the critical importance of prophylactic antibiotics in preventing this complication was emphasized. The present data confirm the importance of our initial recommendations. Of the 27 patients never experiencing sepsis, all were regularly receiving prophylactic antibiotics and/or IVIg. By striking contrast, all 7 of the 7 patients not taking antibiotics experienced at least one episode of sepsis and 3 of these patients died of this catastrophic complication. However, it

Table 5. Outcome of BMT in WAS Patients

Prior Splenectomy	No. Alive/No. Grafted*				
	Sibling	Parental	Unrelated	Age†	Alive
No	10/10‡	0/1	0/0	3.6 ± 1.1	10/11‡
Yes	2/2	1/3	1/3	6.9 ± 1.6	4/8
Total	12/12	1/4	1/3	5.1 ± 1.2	14/19

* Designates number of patients still alive and whether bone marrow donor was an HLA-matched sibling, a parent, or an HLA-matched unrelated donor.

† Age at transplant in years (average ± SEM).

‡ Fraction receiving sibling grafts and the fraction alive significantly greater in the no prior splenectomy group ($P < .05$ by χ^2 analysis).

is also important to note that 2 of 31 splenectomy patients in our series who were taking antibiotics also died of sepsis.

Thus, the use of prophylactic antibiotics after splenectomy substantially reduced, but did not totally eliminate, the risk of sepsis. In our series, the risk of a fatal episode of sepsis in a splenectomized WAS patient taking antibiotics was 0.012 cases per person per year. This compares favorably with the fatal sepsis rate of 0.0025 cases per person per year found in a large series of nonimmunodeficient children after splenectomy.[17] A study of patients who underwent splenectomy for Hodgkin's disease (immunodeficient on the basis of their malignancy and the therapy they received) showed the incidence of sepsis to be 0.0035 cases per person per year.[18] A large study of adults undergoing splenectomy for hematologic disorders (72% of whom had nonmalignant diseases) found a rate of 0.0068 cases of sepsis per person per year or 0.0051 sepsis deaths per person per year.[19] Other large studies of postsplenectomy sepsis in the general population have estimated sepsis rates of 0.0042 per person per year and fatalities at 0.0008 per person per year.[20] WAS patients receiving a splenectomy before the age of 5 years did not suffer more infections than our older patients, unlike the pattern in immunologically normal children. This is likely attributable to the failure of WAS patients as they grow older to normally acquire immunity to organisms with polysaccharide antigens.

However, without prophylaxis, the risk of sepsis is great. All WAS patients failing to receive antibiotics had life threatening infections. Antibiotics must be continued for life; sepsis has been observed in patients in their late 20s, more than 20 years following splenectomy. Fatal infections can occur, even with organisms sensitive in vitro to the antibiotic,[21,22] although it is likely that in many such cases the prophylactic antibiotics may slow the pace or diminish the magnitude of the infection. Therefore, it must be emphasized that vigilance for infection must be maintained even when patients faithfully take prophylactic antibiotics. Education of patients and families to immediately seek medical attention when fever occurs despite antibiotics is very important.

The treatment of choice for patients with WAS is matched sibling BMT. All of our patients who received such grafts have survived the procedure and seem to be cured. Others have made similar observations.[23] However, most WAS patients do not have a matched sibling donor at the time of their diagnosis. For such patients splenectomy is a useful procedure because it reduces the chances of fatal bleeding. Unlike successful BMT, it does not remove the serious problems of immune deficiency, lymphoid malignancies, or severe autoimmune disease (Table 4). Despite this, the poor outcome seen in the patients who did not receive matched sibling grafts suggests that splenectomy may be safer and more effective than a suboptimal graft. Our observation may be somewhat confounded by the fact that several of the patients receiving such grafts were ill at the time of transplant. However, most others have also reported poor success with haploidentical donors,[24,25] although there is one report to the contrary[26]; we strongly discourage these patients receiving transplants with haploidentical or parental grafts. Our experience with unrelated matched grafts is limited. Others have seen fairly good results with such grafts[27] and, in the future as this technology develops, it may be a good alternative for the patient without a matched sibling who is doing poorly with splenectomy alone.

A frequently voiced concern among families is whether splenectomy compromises the success of later BMT, should circumstances change to make a transplant possible. Our splenectomy patients have fared much more poorly in BMT than patients going to BMT without prior splenectomy. However, the nonsplenectomized BMT patients were younger, healthier, and much more likely to receive marrow from a completely matched sibling. We believe that these factors rather than the splenectomy account for the difference between the groups.

In summary, our experience with a large group of WAS patients over more than 25 years suggests that, for those WAS patients without suitable bone marrow donors who have platelet counts less than 50,000/μL, splenectomy is effective in treating their thrombocytopenia. Moreover, as long as antibiotic prophylaxis is faithfully continued, the procedure does not add significantly to the risk of fatal infection in these boys but does add to their longevity and quality of life.

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