

Bleeding and splenectomy in Wiskott-Aldrich syndrome: A single-centre experience

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Clinical Implications

- This single-center retrospective review shows that splenectomy is an effective option for the management of thrombocytopenia in X-linked thrombocytopenia. In contrast, more than half the patients with classical Wiskott-Aldrich syndrome experienced postsplenectomy thrombocytopenia relapse.

TO THE EDITOR:

Wiskott-Aldrich syndrome (WAS), caused by loss-of-function mutations in the *WAS* gene, results in a classical triad of combined immunodeficiency, eczema, and microthrombocytopenia, associated with an increased risk of autoimmunity and malignancy.¹ Attenuated WAS, also known as X-linked thrombocytopenia (XLT), represents a milder form of the disease mainly limited to thrombocytopenia^{2,3} (see Table E1 in this article's Online Repository at www.jaci-inpractice.org). Despite differences in other disease features, patients with XLT and WAS demonstrate similarly low levels of platelets.^{4,5} In both groups, the severity of thrombocytopenia is categorized by platelet count as mild ($50\text{--}150 \times 10^9/\text{L}$), moderate ($20\text{--}50 \times 10^9/\text{L}$), or severe ($<20 \times 10^9/\text{L}$). Serious bleeding has been reported to occur in up to 30% of patients, including a 10% to 20% risk of intracranial hemorrhage (ICH).^{1,4,6} Surprisingly, no clear correlation between degree of thrombocytopenia and serious bleeding episodes has been identified.⁶

Although there is broad consensus that thrombocytopenia in classical WAS should be treated by early allogeneic hematopoietic stem cell transplantation (HSCT) or experimental gene therapy, management in XLT continues to be the subject of debate, as the risks and complications of definitive treatments are still widely considered to be unacceptable in this milder disease. The role of splenectomy in WAS and XLT is contentious mainly due to concerns about severe infection and reliability to reduce serious episodes of bleeding.⁶ In the absence of other effective therapies, our center offers splenectomy to patients with XLT where severe thrombocytopenia significantly limits normal activity and quality of life. To assess the efficacy and safety of this practice, we reviewed our outcomes for splenectomy in patients with XLT and classical WAS.

A retrospective study was conducted of patients with a confirmed molecular diagnosis of WAS from 1992 to 2017 (all clinical severities). Information on platelet counts, serious bleeding, and treatment was recorded. For patients who underwent splenectomy, vaccine responses, infections, and prophylactic antibiotics were documented.

Of 102 patients, 68 had a diagnosis of classical WAS and 34 of XLT. Nineteen children have undergone splenectomy (19%), 10 of whom had XLT (Table 1). Median follow-up is 8 years (range, 1–24.6 years), with 187 total years of patient follow-up. Shorter follow-up for patients with XLT compared with classical WAS (4.93 and 16.45 years, respectively) reflects our recent trends in favor of splenectomy for XLT to allow engagement in normal physical activity and decline in use of splenectomy in WAS as a standard of care.

We observed only 6 episodes of serious bleeding (defined as requiring medical intervention) in our whole WAS cohort of 102 patients (overall incidence 6%), none of whom had at the time undergone splenectomy. Of these, 5 occurred in patients with classical WAS, 3 of whom had an ICH (1 fatal) and 2 had serious gastrointestinal bleeds. Serious bleeding episodes in classical WAS were associated with documented immune-mediated thrombocytopenia (ITP) in 2 out of 5 patients and suspected, on the basis of worsening thrombocytopenia and presence of other autoimmune cytopenias, in another 2 patients. One patient with XLT required surgery for an ICH following significant blunt trauma and fully recovered.

Six patients with classical WAS underwent splenectomy before definitive stem cell therapy: 2 following episodes of serious bleeding, 1 to prevent serious bleeding in a patient with gastrointestinal angiodysplasia, and 3 to manage thrombocytopenia in patients in whom corrective stem cell therapy was delayed. Three patients with classical WAS underwent splenectomy after corrective stem cell therapy (2 HSCT, 1 gene therapy) for persistent thrombocytopenia. All 10 patients with XLT underwent elective splenectomy for quality-of-life reasons to allow engagement in normal physical activities including contact sports.

Lowest presplenectomy platelet counts in the 2 groups were comparable, but response to splenectomy differed (Figure 1). Five of the 9 patients with classical WAS (56%) had recurrence of thrombocytopenia postsplenectomy (defined as 2 consecutive platelet counts of $<100 \times 10^9/\text{L}$), 4 of whom relapsed within a year. Three of these, 2 of whom had splenectomy for ITP, had recurrence of severe thrombocytopenia that corrected post-HSCT. One had recurrence of thrombocytopenia in the context of graft failure post-HSCT, which corrected after a second transplant, and another had undergone splenectomy in the setting of suspected post-HSCT autoimmunity (autoimmune hemolysis and neutropenia with suspected ITP) and has ongoing mild thrombocytopenia. In contrast, all patients with XLT responded well to splenectomy with an immediate and sustained platelet rise to more than $100 \times 10^9/\text{L}$ ($>150 \times 10^9/\text{L}$ in all but 1 patient), and no relapse.

There have been no major infectious complications post-splenectomy in either group. All XLT and post-HSCT WAS patients were vaccinated with Prevnar 13, Hib, and Men B and C conjugate vaccines before splenectomy. Twelve of 12 patients who had specific antibody responses recorded postsplenectomy generated a protective antibody response (11 to tetanus $\pm$ Hib and 8 to at least 9 of 13 pneumococcal serotypes). In addition, all patients are taking antibiotic prophylaxis, which together may account for the lower incidence of serious infection in our cohort compared with others. It is, however, important to note that

TABLE I. Characteristics of patients with WAS and XLT who have undergone splenectomy

Patient no.	XLT/WAS	Mutation	WAS score	Age at splenectomy (y)	Timing of splenectomy (pre/post definitive therapy)	ITP	Platelet response to splenectomy	Bleeds	Follow-up (y)
1	XLT	Gly40A (c.118G>A)	1	5.90	NA	No	Yes	None	1.63
2	XLT	T45M (c.134C>T)	2		NA	No		None	
3	XLT	R86C (c.256C>T)	2	2.50	NA	No	Yes	None	5.90
4	XLT	trp500arg (c.1498T>C)	2	3.45	NA	No	Yes	None	3.98
5	XLT	p.Thr45Met (c.134C>T)	1	7.13	NA	No	Yes	None	1.63
6	XLT	p.Arg86Cys (c.256C>T)	2		NA	No		None	
7	XLT	R86C (c.256C>T)	1	5.12	NA	No	Yes	None	8.31
8	XLT	R86C (c.256C>T)	5	3.74	NA	No	Yes	None	8.24
9	XLT	p.Val75Met (c.223G>A)	1	10.47	NA	No	Yes	None	4.93
10	XLT	p.Gly119arg (c.355G>A)	1	4.88	NA	No	Yes	None	1.04
11	WAS	F84L (c.250T>C)	5	1.52	Pre-HSCT (HSCT 8 y after splenectomy)	No	Severe recurrence after 423 d, corrected post-HSCT	GI (pre)	24.55
12	WAS	Large (350-kb) deletion	3	0.58	Pre-HSCT (HSCT 2 y after splenectomy)	Yes	Severe recurrence after 14 d, corrected post-HSCT	None	11.17
13	WAS	E133K (c.397G>A)	5	1.39	Pre-HSCT (HSCT 4 mo after splenectomy)	Yes	Severe recurrence after 86 d, corrected post-HSCT	ICH (pre)	10.18
14	WAS	IVS6+2 T>C	4	3.87	Post-HSCT	Suspected	Mild recurrence after 224 d, ongoing	None	11.55
15	WAS	DelC1493	3	4.75	Pre-HSCT (HSCT 20 mo after splenectomy)	No	Yes	None	24.43
16	WAS	IVS9+2 T>C	5	8.68	Pre—gene therapy (gene therapy 19 y after splenectomy)	No	Yes	None	23.97
17	WAS	A134V (c.401C>T)	5	14.47	Post—gene therapy	No	Yes	None	2.68
18	WAS	Q20X	5	2.81	Post-HSCT	Suspected	Severe recurrence after 175 d, corrected after second HSCT	GI (pre)	16.45
19	WAS	F84L (c.250T>C)	5	2.22	Pre-HSCT (HSCT 10 y after splenectomy)	No	Yes	None	26.67

GI, Gastrointestinal; NA, not applicable/available.

Patients 2 and 6 live abroad and access to some data was limited. Patients 7 and 8 are brothers with the same mutation, consistent with XLT, but 1 has a more severe phenotype. “Bleeds” refers to significant bleeds requiring medical intervention. Recurrence of thrombocytopenia is defined as 2 consecutive platelet counts of $<100 \times 10^9/L$.

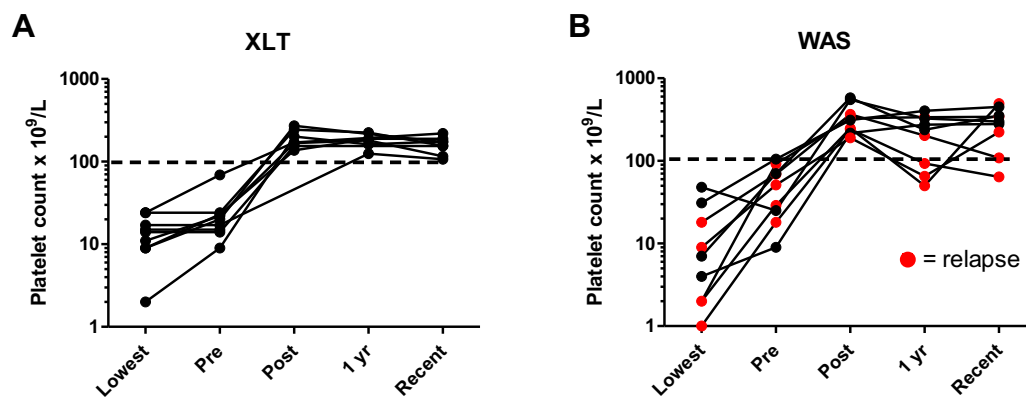


FIGURE 1. Platelet response to splenectomy. Platelet counts for patients with XLT (A) and classical WAS (B) are compared at their lowest, immediately presplenectomy, 2 to 3 days postsplenectomy, 1 year postsplenectomy, and most recently. Red dots represent patients with relapse of thrombocytopenia (2 consecutive counts of $<100 \times 10^9/L$, represented by dotted line) postsplenectomy.

median age of serious infection in splenectomized patients with WAS reported elsewhere is in their 20s,⁶ highlighting the need for not only longer term follow-up but also close engagement with medical care and reinforced compliance.

Here we present a single-center experience of bleeding and splenectomy in classical WAS and XLT. In contrast with previous literature, we observed a surprisingly low incidence of serious bleeding (6%), lower in XLT compared with classical WAS (3% and 7%, respectively). These findings may relate to a number of factors including (1) tight criteria for assigning a diagnosis of XLT, (2) prompt diagnosis and aggressive treatment of ITP, and (3) early definitive therapy for patients with classical WAS. In our experience, splenectomy in classical WAS has variable efficacy, with less than half the patients achieving a significant and sustained rise in platelet count, probably because of the contribution of early onset autoimmunity. In contrast, we found splenectomy to be universally successful in treating thrombocytopenia in patients with XLT, where autoimmune destruction has not been demonstrated in our cohort. This has allowed broad engagement in physical activities and participatory contact sports. We have not formally measured quality-of-life indices in this group, but anecdotally normalization of platelet counts substantially reduces patient and family anxiety over bleeding risk and suspicion of physical abuse.⁷ We have not observed any serious infections postsplenectomy. Limitations of this study include its small sample size and relatively short follow-up time, particularly for patients with XLT, which means that caution should be exercised when interpreting these results. Although a retrospective review is the only feasible study design for this rare disease, we now have an opportunity for prospective evaluation.

In conclusion, we believe that splenectomy for classical WAS is not recommended unless there is likely to be significant delay in definitive therapy, or in emergency situations. In particular, caution should be exercised when considering splenectomy in the context of ITP, where our data suggest that it is less likely to be successful. In contrast, we recommend splenectomy for XLT where the child's quality of life is significantly impaired by bleeding risk, limiting engagement in physical activity or resulting in substantial anxiety.

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TABLE E1. Differences in typical characteristics between XLT and classical WAS

Genotype/phenotype	XLT	Classical WAS
Typical mutations	Missense	Deletions/insertions/early stop
WASp expression	Detectable	Usually absent or truncated
Clinical features		
Thrombocytopenia	Yes	Yes
Infections	None/mild; not on replacement immunoglobulin	Yes
Eczema	None/mild	Moderate/severe
Autoimmunity	No	Yes
Malignancy	No	Yes

Scoring systems can be used to help differentiate diagnosis of XLT or classical WAS by assigning 1 point for each of the clinical features; a diagnosis of classical WAS typically corresponds to a score ≥ 3 . This table indicates how features of XLT and WAS were scored in this cohort.