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A REVIEW ON TARGETTING WISKOTT ALDRICH SYNDROME (WAS)- INNOVATIONS IN TREATMENT AND CARE

[1]Ramsharan, [2*]Ashok Kumar, [3]Nidhi Chaudhary, [3]Abhishek Bhardwaj, [4]Dr. Amandeep Singh

[1]Student, School of Pharmaceutical Sciences, Jigyasa University (Formerly Himgiri Zee University), Dehradun.
[2]Associate Professor, School of Pharmaceutical Sciences, Jigyasa University (Formerly Himgiri Zee University), Dehradun.
[3]Assistant Professor, School of Pharmaceutical Sciences, Jigyasa University (Formerly Himgiri Zee University), Dehradun.
[4]Principal & Professor, School of Pharmaceutical Sciences, Jigyasa University (Formerly Himgiri Zee University), Dehradun.

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***Corresponding Author: Ashok Kumar**
Associate Professor, School of Pharmaceutical Sciences, Jigyasa University (Formerly Himgiri Zee University), Dehradun.
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ABSTRACT

Wiskott-Aldrich Syndrome (WAS) is a rare X-linked primary immunodeficiency disorder characterized by the classic triad of microthrombocytopenia, eczema, and recurrent infections. Caused by mutations in the WAS gene, which encodes the Wiskott-Aldrich Syndrome protein (WASp), this condition disrupts actin cytoskeleton organization, impairing the function of hematopoietic cells and leading to immune dysregulation. Clinical manifestations range from classic WAS to milder forms such as X-linked thrombocytopenia (XLT) and X-linked neutropenia (XLN). Patients often face severe infections, autoimmune complications, and malignancies, contributing to high morbidity and mortality. Diagnosis relies on clinical evaluation, laboratory findings, and genetic confirmation. Despite advancements in molecular diagnostics and a clinical scoring system that guides management, delayed diagnosis remains a challenge, particularly in low-resource settings. Hematopoietic stem cell transplantation (HSCT) remains the only curative treatment, though accessibility is limited in developing countries. Emerging therapies, such as autologous gene-modified HSCT using lentiviral vectors, offer promising alternatives with improved safety profiles, but require further validation for long-term efficacy. Management of WAS includes infection prevention with intravenous immunoglobulin (IVIG) and prophylactic antibiotics, immunosuppressive therapies for autoimmune manifestations, and supportive care for thrombocytopenia. Splenectomy, while effective for platelet count improvement, poses risks of infection, especially post-HSCT. This study provides a comprehensive overview of the pathophysiology, clinical spectrum, diagnosis, and current and emerging treatment strategies for WAS, with a special focus on challenges in resource-limited regions like India. It underscores the critical need for increased awareness, early diagnosis, infrastructure development, and equitable access to advanced therapies. Future directions include improved gene therapy modalities, immune modulation strategies, and global collaboration to enhance outcomes for affected individuals.

KEYWORDS: Wiskott-Aldrich Syndrome (WAS), Primary Immunodeficiency, Hematopoietic Stem Cell Transplantation (HSCT), Gene Therapy, Autoimmunity, Thrombocytopenia.

INTRODUCTION

Wiskott-Aldrich syndrome (WAS) is a rare X-linked immunodeficiency illness characterised by severe immunodeficiency, microthrombocytopenia, and eczema, affecting less than one in every 100,000 live births.[1] Wiskott-Aldrich syndrome (WAS) is caused by mutations in the WAS gene on the X chromosome that disrupt the WAS protein (WASp), which governs actin polymerisation and cytoskeletal organisation in haematopoietic cells.[2] WAS comprises both severe and lesser variants, such as X-linked thrombocytopenia (XLT) and X-linked neutropenia (XLN). Classic WAS leads to severe immunodeficiency, which raises the risk of autoimmune disorders, cancer, and infections. XLT is characterised primarily by thrombocytopenia and moderate immunodeficiency, whereas XLN is characterised by myelodysplasia and neutropenia in the absence of platelet deficiencies.[1]

WASP gene mutations interfere with WASp protein function, compromising signal transduction, cell motility, and immunological response. WASp is essential for both innate and adaptive immunity, notably immunological synapse development.[2] WAS severity varies, with individual gene mutations influencing clinical outcomes, although genotype-phenotype relationships are unknown. Recent investigations have found mutant hotspots associated with disease severity. Patients with the same mutation, however, may exhibit a variety of symptoms.[1] Antibiotics, immunoglobulin treatment, and symptom control have all contributed to increased survival. Despite these developments, therapies remain palliative, with haematopoietic stem cell transplantation (HSCT) being the only curative option. However, HSCT presents difficulties, including post-transplant autoimmune problems. More research is needed to enhance treatment techniques and outcomes for patients with WAS.[1]

This study seeks to offer a complete overview of WAS, including its pathogenesis, symptoms, and treatments, with a particular emphasis on new therapeutics such as autologous gene-modified HSCT.[3]

HISTORICAL BACKGROUND: Wiskott-Aldrich Syndrome (WAS) is a rare hereditary condition that affects blood coagulation and the immune system, caused by mutations in the WASP gene on the X chromosome. This causes aberrant protein action in haematopoietic cells, resulting in dermatitis, recurrent infections, and low platelet counts with abnormally tiny platelets.[4]

Table No. 1: Timeline, Clinical Findings, and Challenges Associated with Wiskott-Aldrich Syndrome (WAS)."

Year/Event	Description[4,5,6,7,8,9]
1937	Dr. Alfred Wiskott first recognised WAS as an eczema-thrombocytopenia syndrome.
1954	Dr. Robert Aldrich verified its X-linked inheritance.
1994	Genetic research connected WAS to mutations in the WASP gene, revolutionising diagnosis and treatment.
Incidence	1-10 individuals per million. Milder forms include X-linked neutropenia and X-linked thrombocytopenia (XLT).
2006-2010 (Chandigarh Study)	Study at Advanced Paediatrics Centre, Chandigarh, India on 8 children. Symptom onset ranged from 13 weeks to 9 years (average diagnostic age: 117 days). Common symptoms included eczema and recurring respiratory and diarrhoeal infections. Autoimmune symptoms observed in two cases. Genetic testing revealed WASP gene mutations, including two novel variations. One child successfully treated with HSCT. Two responded to cotrimoxazole and immunoglobulin therapy. Four children died due to severe disease and lack of access to HSCT.
Findings & Challenges (India)	Early diagnosis crucial; HSCT effective but limited by fewer than 12 specialised transplant centres in India. Diagnosis prior to 2006 was difficult due to lack of genetic testing facilities, improved through international collaborations. Need for enhanced infrastructure and awareness.

Global Studies (1964-1977)	Early research in the US and Canada identified cases using medical records, literature, and national surveys. Survival studies (birth cohorts 1892-1974) showed high cancer risk, especially lymphoma, and survival issues. Established clinical and laboratory criteria for early diagnosis significantly improving detection.
Current Challenges & Recommendations	Challenges persist in resource-limited settings due to limited awareness, diagnostic infrastructure, and HSCT access. Establishing national primary immunodeficiency registries and international collaboration recommended. Early detection, genetic testing, HSCT, and improved healthcare infrastructure essential.

PATHOPHYSIOLOGY OF WAS: Wiskott-Aldrich syndrome (WAS) is an X-linked genetic illness caused by mutations in the WAS gene on the X chromosome, which encodes the Wiskott-Aldrich protein (WASp) present in non-erythroid haematopoietic cells. Over 300 mutations, including missense, nonsense, splice site, and short deletions, cause protein problems. This genetic variation causes varied disease severity, ranging from typical WAS to milder versions such as X-linked thrombocytopenia (XLT) and X-linked neutropenia (XLN).[10]

WASp relates cell signalling to actin cytoskeleton dynamics, which are essential for cell shape, intracellular transport, and immune cell communication. It is essential for the formation of the immunologic synapse, which is where T cells interact with antigen-presenting cells such as dendritic cells. This mechanism is dependent on lipid raft formation, which recruits signalling molecules required for immune response stability.[11,12,13]

In WAS, cytoskeleton abnormalities impede T cell function, limiting their capacity to move, adhere, and interact with immune cells. This disruption also impacts B cell homeostasis, causing the slow loss of mature B cells and splenic marginal zone precursors, as well as increased apoptosis over time.[14]

Natural killer (NK) cells in WAS can be normal or augmented in quantity, but they have lower cytotoxicity due to defective immunologic synapse development. Interleukin-2 (IL-2) promotes compensatory proteins, which can help restore NK cell function. Furthermore, invariant natural killer T (iNKT) cells are lacking in WAS and XLT, increasing the risk of autoimmune diseases and cancer.[15,16] Autoimmunity in Wiskott-Aldrich Syndrome (WAS) arises from multiple mechanisms shown in Table No. 1. [16,17,18,19]

Table No. 2: Mechanisms Underlying Immune Dysregulation in Wiskott-Aldrich Syndrome(WAS).

Mechanism	Description
Defective Regulatory T (Treg) Cell Function	WASp-deficient Treg cells exhibit impaired proliferation, cytokine production, and suppressive capabilities, leading to a breakdown in immune tolerance.
Loss of B Cell Tolerance	Intrinsic defects in WASp-deficient B cells contribute to the survival and activation of autoreactive B cells, disrupting B cell tolerance mechanisms.
Impaired Apoptosis of Self-Reactive Lymphocytes	Defective restimulation-induced cell death (RICD) in WASp-deficient T cells results in the persistence of self-reactive lymphocytes, contributing to autoimmunity.
Defective Phagocytosis	WASp-deficient myeloid cells, such as monocytes and macrophages, exhibit impaired phagocytosis and chemotaxis, leading to inefficient clearance of apoptotic cells and persistent immune activation.

Myeloid cells, such as monocytes, macrophages, and dendritic cells, exhibit poor migration and chemotaxis because they lack the ability to build actin-rich structures required for movement. As a result, their reactivity to certain chemoattractants is greatly diminished.[20,21,22] Wiskott-Aldrich Syndrome (WAS) is characterized by thrombocytopenia due to several factors shown in Table No. 2.[4,23,24]

Table No. 3: Mechanisms Contributing to Thrombocytopenia and Neutropenia in Wiskott-Aldrich Syndrome (WAS).

Mechanism	Description
Increased Platelet Clearance	Mutations in the WAS gene lead to instability of the Wiskott-Aldrich Syndrome protein (WASp) in platelets, resulting in their premature clearance from circulation.
Defective Platelet Production	While the exact mechanism remains unclear, studies suggest that defective proplatelet formation may not be the primary cause of thrombocytopenia in WAS.
Shortened Platelet Lifespan	WASp deficiency affects platelet survival, leading to a reduced lifespan.
Immune-Mediated Destruction	Autoimmune mechanisms contribute to the destruction of platelets in WAS patients.
Gain-of-Function Mutations Leading to Congenital Neutropenia	Specific gain-of-function mutations in the WAS gene result in excessive actin polymerization, leading to congenital neutropenia.

CLINICAL MANIFESTATIONS IN WAS

MICROTHROMBOCYTOPENIA; Haemorrhages occur in more than 80% of WAS and XLT patients, ranging from moderate (epistaxis, petechiae) to severe (intestinal and brain haemorrhage), with bleeding accounting for 21% of WAS mortality. Thrombocytopenia with reduced platelet size is a defining feature of many disorders, occurring regardless of mutation severity. The specific mechanisms of WASP-related thrombocytopenia and haemorrhage are unknown, while most patients have normal megakaryocyte counts. Platelet breakdown in the spleen is hypothesised to contribute to thrombocytopenia since splenectomy increases platelet count and size. This could be the result of an innate deficiency in WASP-deficient platelets or an autoimmune reaction. Furthermore, anomalies in filopodia and podosomes may affect megakaryocyte migration and proplatelet formation. Research with Was−/− mice revealed ectopic platelet release in the bone marrow, emphasising the necessity for additional inquiry into thrombocytopenia mechanisms.[25]

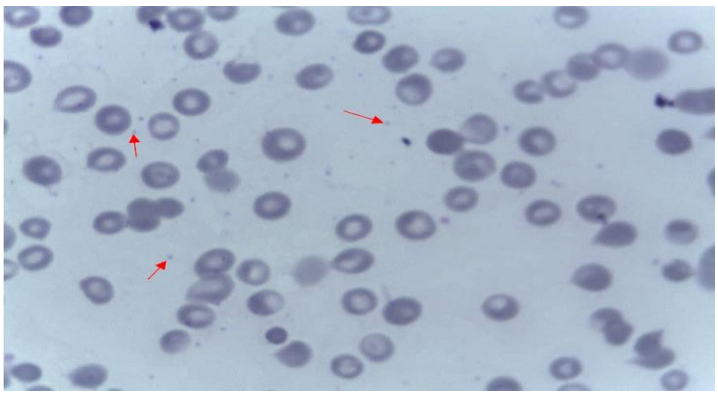

Figure No. 1: Microthrombocytes- A Peripheral blood smear slide; Red arrows showing micro thrombocytes.

ECZEMA IN WAS: Skin lesions in WAS and XLT mirror acute or chronic dermatitis and affect 80% of patients to various degrees of severity. Severe eczema can be treatment-resistant, last into adulthood, and cause skin infections. Eczema is less common and more severe in those with residual WASP expression. The source of eczema in WAS patients is unknown, but they frequently have elevated IgE levels and allergies, indicating an atopic origin. An imbalance in Th2-type cytokine production has been identified in T-cell lines, which may contribute to eczema and allergies. Abnormal T lymphocyte priming and faulty dendritic cell chemotaxis may also be involved.[26]

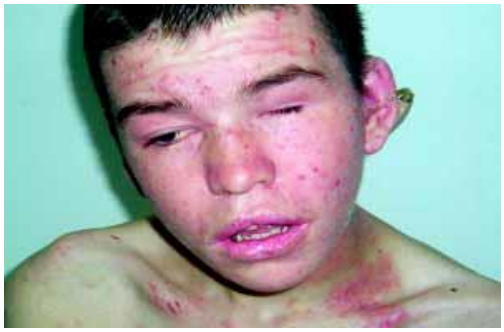

Figure No. 2: Eczema- Clinical Symptoms in WAS.

AUTOIMMUNE MANIFESTATIONS: Autoimmune disorders are frequent in WAS, with rates ranging from 40% to 72% in Western nations but just 22% in Japan. Common symptoms include autoimmune haemolytic anaemia, cutaneous vasculitis, arthritis, and nephropathy. Idiopathic thrombocytopenic purpura, neutropenia, and inflammatory bowel disease are among the less common symptoms. Multiple autoimmune diseases frequently occur simultaneously. Autoimmunity can impair the prognosis, especially if autoimmune haemolytic anaemia or thrombocytopenia develop after splenectomy. It has also been related to increased cancer risk and mortality. The mechanisms are unknown, however they may include tissue damage caused by chronic inflammation or a failure in self-antigen tolerance, as well as decreased regulatory T cell activity due to WASP deficiency.

TUMORS IN WAS: Tumour incidence in WAS patients ranges between 13% and 22%, with myelodysplasia being more common in childhood and lymphoreticular malignancies such as leukaemia, myelodysplasia, and lymphoma (typically Epstein-Barr virus-positive) predominating in teenagers and young adults. The prognosis is terrible, with fewer than 5% survival after two years. However, current treatments, such as anti-CD20 monoclonal antibodies, have improved outcomes. Tumours can develop as a result of immunological inadequacies, such as reduced NK-cell function and other immune surveillance problems. Mutations in the WASP gene, which alter cytokinesis and genomic integrity, may also contribute to tumour formation by disrupting cellular homeostasis.[27] A clinical scoring system has been developed to categorize these phenotypes (XLT,XLN) based on specific clinical features.[28]

Table No. 4: Clinical Scoring System and Associated Syndromes for Wiskott-Aldrich Syndrome (WAS).

WAS Clinical Score	Definition	Clinical Syndrome
0	Neutropenia (low white blood cell count) or myelodysplasia only	X-linked neutropenia (XLN)
0.5	Intermittent thrombocytopenia (low platelet counts sometimes but not always)	X-linked thrombocytopenia (XLT)
1	Thrombocytopenia and small platelets (microthrombocytopenia)	XLT
2	Microthrombocytopenia plus normally responsive eczema or occasional upper respiratory tract infections	XLT
2.5	Microthrombocytopenia plus therapy-responsive but severe eczema or airway infections requiring antibiotics	XLT/Wiskott-Aldrich syndrome (WAS)
3	Microthrombocytopenia plus both eczema and airway infections requiring antibiotics	WAS
4	Microthrombocytopenia plus eczema continuously requiring therapy and/or severe or life-threatening infections	WAS
5	Microthrombocytopenia plus autoimmune disease or malignancy	XLT/WAS with autoimmune disease or cancer

DIAGNOSIS: WAS is an X-linked illness that affects males alone; obligate female carriers do not exhibit clinical symptoms. Rare cases of WAS in females have been reported, involving a detrimental mutation of the paternally derived X chromosome and nonrandom inactivation of the maternally derived X chromosome.WAS should be examined in any guy who presents with a clinical history, physical exam findings, and laboratory results indicating the disease. Clinical symptoms consistent with WAS may be present or missing at different stages of the illness's progression. Reassessment is required due to the changing nature of clinical, physical, and laboratory results throughout time. Clues to the diagnosis of wiskott–Aldrich syndrome.[28,29,30]

Table No. 5: Clinical and Laboratory Features for Diagnosis of Wiskott-Aldrich Syndrome (WAS).

Category	Findings
Physical Exam	Rash:Eczema , Bleeding: Petechiae, ecchymoses
Past Medical History	Rash: Eczema, Bleeding: Mucosal bleeding (easy bruising, epistaxis, hematochezia, hematuria) or intracranial hemorrhage Infections: Recurrent or severe sinopulmonary infections, viral infections, fungal infections, or opportunistic infections Autoimmunity: Cytopenias, vasculitis, inflammatory bowel disease, arthritis, renal disease , Malignancy: Lymphoma.
Family History	X-linked disorder, Every generation affected; predominant male susceptibility
Laboratory Exam	Complete blood cell count: Anemia, microcytosis, thrombocytopenia, low mean platelet volume, Peripheral blood smear: Microthrombocytes Serum Immunoglobulins (IgG, IgA, IgM, IgE): Low IgG, IgA, IgM; high IgE , Isohemagglutinin and vaccine titers: Abnormal isohemagglutinin titers and diminished vaccine responses to protein, polysaccharide, and conjugate vaccines, Lymphocyte subsets and mitogen responses: T-cell lymphopenia and abnormal proliferative responses to mitogens.

EMERGING TREATMENTS: Autologous gene-modified HSCT is a developing treatment for primary immunodeficiency, including WAS. Unlike allogeneic HSCT, it prevents graft rejection and GVHD by correcting CD34+ grafts ex vivo with viral vectors for gene integration. Nonmyeloablative conditioning increases gene-modified cell survival, which leads to clinical benefits.

Using γ-retroviral vectors in ten WAS patients resulted in stable gene integration and WASp expression, leading to improved symptoms in nine cases. However, five individuals developed insertional oncogenesis, and some needed allogeneic HSCT. To improve safety, lentiviral vectors were tested in three individuals, resulting in steady gene expression and therapeutic advantages without any documented oncogenesis. New techniques, such as direct gene repair and WASp stabilisation via interacting proteins, are being studied, but their practical applicability is unknown.[28,31,32]

CURRENT MANAGEMENT OF WAS

TREATMENT – INFECTION: Preventing infections is critical. IVIG is advised for patients with recurrent infections or aberrant immunoglobulin levels, with subcutaneous delivery also an option. Prophylactic medicines serve to avoid bacterial infections, and following a splenectomy, penicillin is required for the rest of one's life. Immunisation with conjugated and unconjugated vaccinations is recommended; however, live vaccines should be avoided. Bactrim is required to avoid P. jiroveci pneumonia, and antiviral medication can help with severe viral infections. Suspected infections necessitate immediate assessment, empiric medications, and comprehensive testing. Infection prevention is critical for minimising pretransplant morbidity in patients having HSCT.[28,33]

TREATMENT – AUTOIMMUNITY: Severe autoimmune symptoms may improve with immunomodulatory medication, such as IVIG. Corticosteroids, cyclosporine, azathioprine, and cyclophosphamide are examples of immunosuppressive drugs that can be used; however, corticosteroids have a high toxicity risk. Monoclonal antibodies, such as anti-CD20, may be useful in Epstein-Barr virus (EBV)-related diseases or suspected autoimmune disorders. Infectious microorganisms can cause certain autoimmune diseases, such as persistent EBV or cytomegalovirus-related arthritis. Autoimmunity management is critical for HSCT candidates to prevent pretransplant morbidity, as it can raise post-HSCT autoimmune hazards.[28,34]

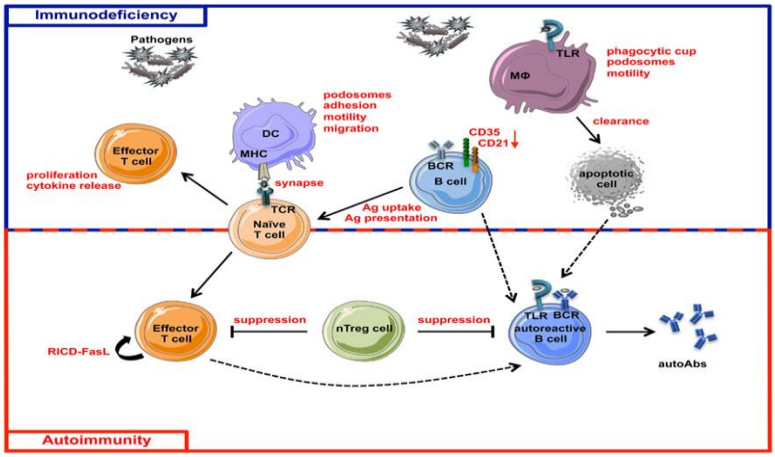

Figure No. 3: Schematic view of immunodeficiency in WAS.

TREATMENT – THROMBOCYTOPENIA: IVIG has no meaningful effect on platelet counts in WAS patients. Splenectomy boosts platelets but carries concerns, including increased post-HSCT morbidity. A study found that splenectomised HSCT recipients had a 21% infection rate, whereas non-splenectomized individuals had no serious infections. Except in genitourinary situations, antifibrinolytics are successful at managing mucosal bleeding. Irradiated, CMV-negative platelet transfusions are required for severe bleeding, such as brain haemorrhage, notwithstanding the hazards of alloimmunisation. Thrombopoietin mimetics have been investigated, but they do not reliably improve thrombocytopenia or bleeding.[28,35,36]

TREATMENT – TRANSPLANTATION: HSCT is the sole curative treatment for WAS. HLA typing should be performed on all potential family donors, with an unrelated donor search if no match is identified. Early donor identification is critical. Patients with HLA-matched donors should receive HSCT, however those with a high WAS score (≥3) may require alternate donor HSCT. Infants under the age of two with severe thrombocytopenia may benefit from an early HSCT. XLT patients without sibling donors may be eligible for supportive treatment. HSCT is not indicated for isolated thrombocytopenia unless there is a matched sibling donor available. WAS care continues to focus on infection prevention, autoimmune treatment, and transplantation.[28,34,35,36]

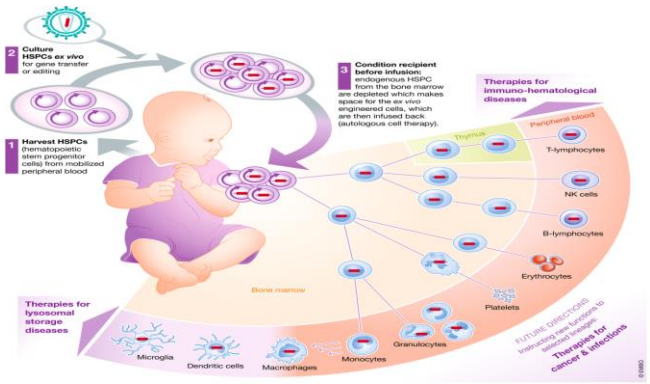

Figure No. 4: Gene Therapy Using Hematopoietic Stem and Progenitor Cells (HSPCs) for Treatment of Genetic and Immune-Hematological Disorders.

CHALLENGES IN LOW-RESOURCE SETTINGS

Despite breakthroughs in diagnosis and therapy, WAS is still challenging to control in countries with insufficient healthcare infrastructure. In India, for example, just a few centres do HSCT, and many instances go untreated due to a lack of awareness and genetic testing resources. National registries and increased access to genetic tests can dramatically improve early detection and management.[37]

Prognosis and Future Directions

The median survival time for WAS patients without HSCT is around 20 years, with infections, bleeding problems, and cancer being the primary reasons of death. Survival rates improve considerably following a successful transplantation. Ongoing research into gene therapy and tailored immune regulation provides hope for improved treatments in the future.[38]

DISCUSSION ON WISKOTT-ALDRICH SYNDROME (WAS)

Overview: Wiskott-Aldrich Syndrome (WAS) is a rare X-linked immunodeficiency associated with thrombocytopenia, eczema, and immunological dysfunction. Advances in genetics, diagnostics, and treatment have improved results, but obstacles still exist, particularly in resource-limited situations. **Genetic Basis and Clinical Implications:** Mutations in the WAS gene disrupt the actin cytoskeleton and immune cell signalling, increasing the risk of infections, autoimmunity, and cancer. The disorder's severity ranges from classic WAS to lesser versions such as X-linked diseases such as thrombocytopenia (XLT) and X-linked neutropenia (XLN).

Diagnostic and Clinical Scoring: Clinical symptoms, laboratory findings, and genetic testing all help to make a diagnosis. A rating system is useful for determining severity and guiding treatment. Early genetic testing allows for early discovery and family screening. **Emerging treatments:** Gene therapy is an alternative to haematopoietic stem cell transplantation (HSCT). Autologous gene-modified HSCT has showed promise, although retroviral vectors have oncogenesis hazards. Lentiviral vectors provide increased safety, and research on gene repair and WASp stabilisation is ongoing. **Current Management Strategies:** Infection Control: IVIG, prophylactic antibiotics, and antivirals can help avoid infections. Live vaccinations should not be administered. **Autoimmune Disease Management:** Immunosuppressants, such as corticosteroids and monoclonal antibodies, can help manage autoimmunity, particularly before HSCT**. Thrombocytopenia Treatment:** Splenectomy boosts platelet count but increases infection risk. Antifibrinolytics help to control bleeding, whereas platelet transfusions are reserved for severe instances.

HSCT as a Curative Option: HSCT is still the only definitive cure, with greater results for younger patients and matched donors. When matches are lacking, alternative donors are consider. **Challenges in Low-Resource Settings:** Insufficient genetic testing, delayed diagnosis, and financial constraints impede care. Expanding registries and testing capabilities is critical. **Prognosis and Future Directions:** Without HSCT, median survival is approximately 20 years. Successful HSCT increases survival, with future research focussing on safer gene therapy, immunological regulation, and autoimmune reduction.

CONCLUSION

Wiskott-Aldrich Syndrome (WAS) is a complicated immunodeficiency illness that presents considerable therapeutic problems. Advances in genetic research, early detection, and treatment strategies, such as gene therapy and HSCT, have significantly increased patient survival and quality of life. However, access to specialised care and treatment remains a significant challenge, particularly in resource-constrained countries. Ongoing research into safer and more effective gene therapies, immune modulation, and WASp-targeted medicines shows potential for improved long-term outcomes. Expanding worldwide efforts in early screening, registry development, and treatment accessibility will be critical for reducing inequities and improving patient care.

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