CLINICAL OUTCOME OF AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANTATION IN STIFF PERSON SYNDROME: A LITERATURE REVIEW

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Abstract: Clinical Outcome of Autologous Hematopoietic Stem Cell Transplantation in Stiff Person Syndrome: A Literature Review. *Stiff person syndrome (SPS) is a rare immune-mediated neurological disorder characterized by progressive muscle stiffness and painful spasms that significantly impair functional ability. Although symptomatic and immunomodulatory therapies are commonly used, some patients remain refractory to standard treatments. Autologous hematopoietic stem cell transplantation (aHSCT) has been proposed as a potential therapeutic option for severe or treatment-resistant cases. This literature review aims to evaluate the clinical outcomes and safety of aHSCT in patients with SPS. A narrative literature review was conducted using published studies reporting the use of aHSCT in SPS, including clinical trials, cohort, case series, and case reports. Relevant articles were identified through PubMed and Google Scholar, limited to studies published within the last ten years. A total of 134 articles were initially identified, followed by a selection process, and five eligible articles were included in this review. The reviewed studies demonstrated that aHSCT may lead to clinical improvement in selected patients with refractory SPS. Autologous HSCT reduced muscle stiffness and improved functional status. Treatment responses varied, and some non-responders were reported; however, overall clinical outcomes were favorable with acceptable safety profiles. In conclusion, aHSCT may be considered a potential therapeutic option for severe or treatment-resistant SPS, although further prospective studies are needed to confirm its efficacy and safety.*
Keywords: *Stiff Person Syndrome, Hematopoietic Stem Cell Transplantation*

Abstrak: Luaran Klinis Terapi Sel Punca Hematopoietik Dalam Penatalaksanaan Sindroma Stiff Person: Tinjauan Pustaka. *Sindroma Stiff Person* (SPS) merupakan kelainan neurol-imunologi yang ditandai dengan kekakuan otot yang progresif dan nyeri, sehingga mengganggu aktivitas fungsional pasien. Penatalaksanaan SPS terdiri dari terapi simtomatik dan imunomodulator, namun sebagian pasien ternyata refrakter terhadap terapi standar. Untuk penatalaksanaan kasus SPS refrakter, terdapat pilihan terapi potensial berupa terapi sel punca hematopoietik autolog (*autologous hematopoietic stem cell transplantation* atau disingkat *aHSCT*). Perlu dilakukan reviu literatur untuk mengevaluasi luaran klinis dan tingkat keamanan *aHSCT* pada pasien SPS. Metode yang dilakukan adalah reviu literatur naratif terhadap artikel ilmiah yang telah dipublikasikan, terkait penggunaan *aHSCT* pada SPS. Pencarian dilakukan melalui *PubMed* dan *Google Scholar.* Kriteria inklusi meliputi artikel yang dipublikasikan dalam sepuluh tahun terakhir, berupa uji klinis, kohor, laporan kasus, dan serial kasus. Sebanyak 134 artikel awalnya diidentifikasi, diikuti dengan proses seleksi, dan terdapat lima artikel penelitian yang memenuhi kriteria. Kelimanya menunjukkan bahwa *aHSCT* dapat memperbaiki kondisi klinis pasien SPS refrakter. Spasme otot berkurang dan terdapat perbaikan

fungsional. Memang terdapat beberapa kasus non-responder, namun secara umum perbaikan klinisnya signifikan, dengan sisi keamanan terjamin. Dengan demikian, *aHSCT* merupakan salah satu opsi untuk penatalaksanaan pasien SPS yang resisten terhadap terapi lain. Perlu dilakukan studi lanjut secara prospektif untuk mengevaluasi efikasi dan keamanannya dalam jangka panjang.
Kata Kunci: Stiff Person Syndrome, Transplantasi Sel Punca Hematopoietik

INTRODUCTION

Stiff person syndrome (SPS) is a rare and progressive immune-mediated neurological disorder. There are some hypothesis of the SPS' etiopathogenesis. First, SPS is considered an autoimmune condition associated with high titers of anti-GAD65 antibodies (autoantibodies to the components of inhibitory synapses, which leads to a low level of gamma-aminobutyric acid (GABA)). Second, 5-10% of SPS are paraneoplastic variant related to breast adenocarcinoma, adenocarcinoma of the colon, small-cell pulmonary carcinoma, malignancies of thyroid and thymus and Hodgkin's lymphoma. Genetic predisposition is played some role in the development of SPS (Alexandra Muranova & Shanina Affiliations, n.d.; Dalakas, 2022, 2024; Lenglet et al., 2025; Perera et al., 2024; Vlad et al., 2023).

Based on the clinical classification, stiff person syndrome (SPS) is divided into 3, namely classic SPS, partial SPS variant, and progressive encephalomyelitis with rigidity and myoclonus (PERM). Classic stiff person syndrome (SPS) is the most commonly occurring clinical form that starts with the stiffness of the trunk muscles, especially in the thoracolumbar region, difficulty in turning and bending then the stiffness will spread to the upper extremities and proximal lower parts. Powerful emotions, exaggerated reactions to touch, visual or auditory stimuli, and agonizing spasms are also present. The partial SPS variant is SPS with milder symptoms than classic SPS, where there is stiffness in one limb and spasms of only the axial muscles do not affect the extremities. PERM is a more severe variant of SPS, which characterizes the relapsing-remitting course of the disease and involves parts of the central nervous system, including the brain stem. This condition can lead to a loss of consciousness, eye muscle dysfunction, ataxia, and autonomic disorders (Alexandra Muranova & Shanina Affiliations, n.d.; Vlad et al., 2023).

Classic SPS has a prevalence of 1-2 cases per million in the general population and is twice as common in women. Most patients develop symptoms between the ages of 20 and 60 years, with the most common occurrence between the ages of 30 and 40 years. Whereas PERM generally occurs in adults between 50 and 60 years of age. Also, only 5% of reported SPS cases occur in children (Alexandra Muranova & Shanina Affiliations, n.d.; Dalakas, 2024).

Treatment options for SPS are divided into symptomatic therapy and disease-modifying or immunotherapy. In more severe cases, a combination of both approaches is often used. Symptomatic management includes medications that enhance GABAergic activity, such as benzodiazepines, baclofen, gabapentin, and vigabatrin. Disease-modifying therapies include intravenous immunoglobulin (IVIG), plasma exchange, and monoclonal antibodies such as rituximab. Other immunomodulatory agents, including mycophenolate mofetil, azathioprine, cyclophosphamide, cyclosporine, tacrolimus, and sirolimus, have been reported with variable efficacy and side effects. However, these treatments often provide only transient relief in refractory SPS (Alexandra Muranova & Shanina Affiliations, n.d.; Dalakas, 2022, 2024; Lenglet et al., 2025; Perera et al., 2024; Vlad et al., 2023).

For treatment-resistant SPS, autologous hematopoietic stem cell transplantation (aHSCT) may be considered a therapeutic option (Burt et al., 2021; Dalakas, 2021; Kass-Iliyya et al., 2021; Perera et al., 2024; Yasiry et al., 2021). Although HSCT has shown

promising results in other autoimmune disorders, studies on its clinical effects in SPS patients remain limited, necessitating a literature review. The aim of this literature review is to evaluate the clinical outcomes and safety of autologous HSCT in patients with Stiff-Person Syndrome.

METHODS

This study was conducted as a narrative literature review with a systematic search strategy to summarize and analyze published evidence regarding the clinical outcomes of aHSCT in patients with stiff person syndrome (SPS).

Search Strategy

A comprehensive literature search was performed using PubMed and Google Scholar databases. The search terms were combined using Boolean operators as follows: "stiff person syndrome" AND "stem cell" AND "hematopoietic stem cell transplantation."

The search was limited to articles published in English between 2014 and 2024 to ensure the inclusion of recent and relevant studies.

Eligibility Criteria

Studies were included if they met the following criteria: (1) Original research articles, clinical trials, cohort studies, case series, or case reports; (2) Studies involving patients diagnosed with stiff person syndrome or stiff-person spectrum disorders; (3) Studies reporting clinical outcomes following autologous hematopoietic stem cell transplantation (HSCT).

Exclusion criteria included: (1) Review articles, editorials, commentaries, or expert opinions; (2) Animal or in vitro studies; (3) Studies without clear clinical outcome data related to HSCT (4) Articles not published in English; (5) Review articles without clinical data and duplicate studies.

Study Selection and Data Extraction

All retrieved articles were screened by title and abstract to assess relevance. Potentially eligible articles were further evaluated through full-text review. The selection process was guided by the PICO framework (Population/Patient, Intervention, Comparison, and Outcome), where the population consisted of SPS patients, the intervention was autologous HSCT, the comparison was conventional or previous immunotherapies, and the outcomes were clinical improvement, relapse rate, need for further immunotherapy, and adverse events.

Relevant data from the included studies were extracted and summarized in a matrix table, including author and year of publication, study design, study population, number of subjects, HSCT protocol, and reported clinical outcomes.

Quality Consideration

Given the heterogeneity of study designs and the limited number of available studies, a formal meta-analysis was not performed. The methodological quality of the included studies was assessed descriptively using critical appraisal principles adapted from the Joanna Briggs Institute (JBI) guidelines, focusing on study design, clarity of outcome reporting, and risk of bias.

Data Synthesis

The findings were synthesized narratively to identify common clinical outcomes and safety patterns reported across studies.

The steps of study selection are systematically described in the PRISMA Flow Diagram (Figure 1).

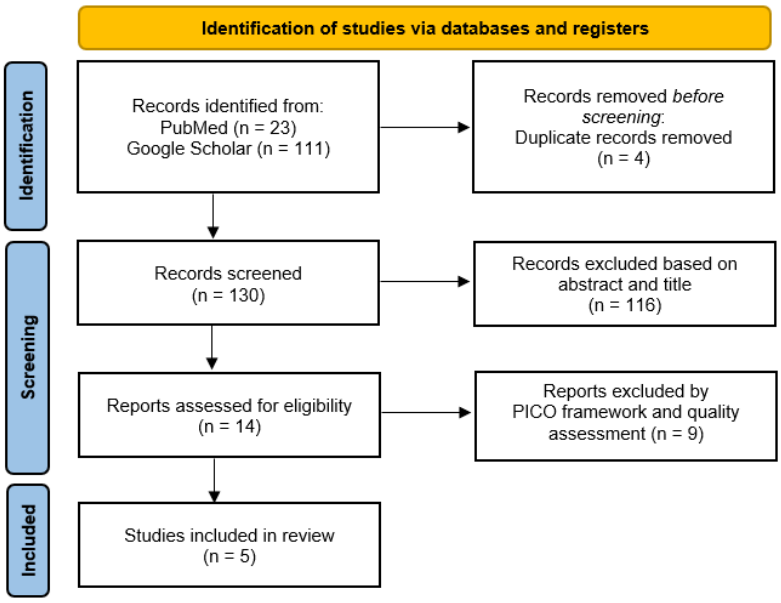

Figure 1. Prisma Flow Diagram

RESULT

A total of 134 articles were identified through database searching, including 23 articles from PubMed and 111 articles from Google Scholar. After the removal of duplicate records (n = 4), 130 articles remained for screening. Title and abstract screening excluded 116 articles due to irrelevance to the research question. The remaining 14 articles were assessed for eligibility.

Following application of the inclusion and exclusion criteria and evaluation using the PICO framework, five articles met the eligibility criteria and included in final analysis. The study flow and selection process is illustrated in Figure 1.

Characteristics of Included Studies

The five included studies were published between 2014 and 2024 and consisted of one prospective open-label clinical trial, and four case reports or case series. Overall, these studies involved approximately 38 patients with stiff person syndrome or stiff-person spectrum disorders who underwent aHSCT.

The majority of patients had severe or treatment-resistant SPS. They failed conventional immunotherapies such as intravenous immunoglobulin (IVIG),

Case reports and case series generally described sustained symptom plasma exchange, and rituximab prior to aHSCT.

HSCT Protocols

The HSCT protocols varied among studies, but we could identify common elements. Stem cell mobilization was generally performed using cyclophosphamide combined with granulocyte colony-stimulating factor (G-CSF). Conditioning regimens frequently used were cyclophosphamide with anti-thymocyte globulin (ATG) or BEAM-based protocols, followed by reinfusion of autologous CD34+ hematopoietic stem cells.

Clinical Outcomes

Across the reviewed studies, most patients showed significant clinical improvement following aHSCT. They experienced positive clinical outcome including reduced muscle stiffness and spasms, improved mobility, and improved quality of life. Several studies revealed that patients were able to reduce or discontinue immunomodulatory and symptomatic therapies after aHSCT.

In the largest prospective study, approximately 48% of patients were classified as responders. Some patients showed partial clinical improvement.
improvement over several months to multiple years.

Safety and Adverse Events

Autologous HSCT was generally well tolerated in the included studies. There were no report of treatment-related mortality. Most adverse events were transient and related to conditioning regimens, including cytopenia and infection risk. Long-term or severe complications were uncommon.

A summary of the key characteristics and clinical outcomes of the included studies is presented in Table

Table 1. Results of literature review

Title (Author, year)	Study Design	Study Population	Number of Research Subject	HSCT Protocol	Clinical Outcomes
Autologous haematopoietic stem cell transplantation for refractory stiff-person syndrome: the UK experience (Kass-Iliyya et al., 2021)	Case reports	Patients with stiff person syndrome (SPS) who have failed immunotherapy.	4 (3 SPS, 1 PERM)	Mobilization: Cyclophosphamide 2g/m^2 + G-CSF Conditioning: Cyclophosphamide 200 mg/kg + ATG	All patients experienced significant improvement in clinical symptoms, did not require further immunotherapy, and in the next studies there were no complications or unexpected things.
Successful Autologous Hematopoietic Stem Cell Transplant In Glycine Receptor Antibody-Positive Stiff Person Syndrome: A Case Report (Celli et al., 2024)	Case report	A single 55 year old man with glycine receptor (GlyR) antibody positive stiff person syndrome (SPS) refractory to multiple immunomodulatory therapies, including plasma exchange (PLEX), intravenous immunoglobulin (IVIg), rituximab, and mycophenolate mofetil.	1	Mobilization: - Cyclophosphamide 3.000 mg/m^2 (day 1) - G-CSF 16 mcg/kg/d (day 2 until completion of apheresis) Conditioning: - Melphalan 140 mg/m^2 (day 1) - Etoposide 100 mg/m^2 + Cytarabine 100 mg/m^2 (day 2 to 5) - Carmustine (BCNU) 300 mg/m^2 (day 6)	The patient showed a sustained significant subjective and objective clinical response over an 18 month follow up period, with improvements in mRS (4 to 3), stiffness index (4/6 to 3/6), and ambulation, as reflected by a reduced 25-foot walk time (28.4 to 13.5 seconds). Cognitive function returned to baseline despite an initial decline, while the hypersensitivity score remained relatively stable.

				- Rabbit antithymocyte globulim (rATG) 2.5 mg/kg/d	
Autologous stem cell transplantation for stiff person syndrome: two cases from the Ottawa blood and marrow transplant program (Sanders et al., 2014)	Case reports	Two female patients with anti-GAD antibody positive SPS who had a progressive disease course and were refractory to multiple immunomodulatory therapies (IVIg, plasma exchange, and immunosuppressive agents).	2	Mobilization: Cyclophosphamide 2.5 g/m^2 + G-CSF 10 µg/kg/d Conditioning: Busulfan 2.4 mg/kg/d+ Cyclophosphamide 50-60 mg/kg/d + rATG 1.25 mg/kg/d	Resolution in case 1, improvement in case 2. The first patient achieved complete remission with resolution of spasms, discontinuation of symptomatic therapy, and return to premorbid functional status. In contrast, the second patient demonstrated a marked reduction in the frequency and severity of spasms, with residual episodes that were infrequent, milder, and self-limiting, alongside recovery of functional capacity.
Autologous Hematopoietic Stem Cell Transplantation for Stiff-Person Spectrum Disorder: A Clinical Trial (Burt et al., 2021)	Clinical Trial, prospective open-label cohort study of safety and efficacy.	Patients with stiff person spectrum disorder (SPSD)	23	Mobilization: Cyclophosphamide 2g/m^2 + Filgrastim 5-10 µg/kg/d Conditioning: Cyclophosphamide 200 mg/kg + rATG + Rituximab	HSCT was well tolerated with no treatment related mortality, with 74% of participants demonstrating a clinical response, including 47% achieving sustained remission (mean 3.5 years), while 26% showed no response.
Case report: Approaches to treatment-	Case reports	Among eight patients with SPS, one refractory case	8 (6 SPS and 2	Mobilization: Cyclophosphamide + G-CSF	Significant improvement on day 14 of aHSCT and achieved complete spasm resolution by day 27, remaining spasm

refractory and super-refractory glutamic acid decarboxylase antibody-spectrum disorders (Rajmohan et al., 2023)	who underwent autologous HSCT. She was a 47 year old woman with anti-GAD antibody positive SPS and multiple autoimmune comorbidities	cerebellar ataxia).	Conditioning : Cyclophosphamide + ATG	free at 2 month follow up, with residual weakness, hyperreflexia, and stable clinical status.

DISCUSSION

Stiff person syndrome (SPS) is a rare neuroimmunological disorder characterized by progressive muscle stiffness and painful spasms resulting from impaired inhibitory neurotransmission within the central nervous system. The main pathogenesis of SPS is the presence of autoantibodies targeting components of inhibitory synapses, particularly glutamic acid decarboxylase (GAD), which contribute to reduced gamma-aminobutyric acid (GABA)–mediated inhibition and neuronal hyperexcitability (Dalakas, 2022, 2024; Kass-Iliyya et al., 2021; Lenglet et al., 2025; Perera et al., 2024; Yahyaoui et al., 2024). The standard treatment for SPS included symptomatic and immunomodulatory therapies: benzodiazepines, baclofen, intravenous immunoglobulin (IVIG), plasma exchange, and monoclonal antibodies. But despite the available standard therapy, a subset of patients develops severe, treatment-refractory disease (Dalakas, 2022, 2024; Kass-Iliyya et al., 2021; Yahyaoui et al., 2024).

This review demonstrates that autologous hematopoietic stem cell transplantation (aHSCT) is associated with clinical improvement in patients with refractory SPS. Most included studies reported decreased muscle stiffness and spasms, improvement in mobility and functional status, and no longer need longterm immunotherapy following aHSCT (Boccia et al., 2024; Kass-Iliyya et al., 2021; Ritter et al., 2025; Sanders et al., 2014; Yasiry et al., 2021).

The UK experience reported by Kass-Iliyya et al. showed sustained clinical improvement in patients with refractory SPS following aHSCT, with no treatment-related mortality and limited short-term complications. Similarly, subsequent case series and reports have reinforced these findings, including patients with severe or multi-refractory disease who experienced symptom control after transplantation (Alsuliman et al., 2025; Celli et al., 2024). In the largest prospective open-label clinical trial, Burt et al. reported that approximately half of the treated patients achieved sustained clinical response, while a subset demonstrated partial improvement, highlighting inter-individual variability in treatment response (Burt et al., 2021).

Importantly, several studies observed clinical improvement independent of changes in circulating anti-GAD antibody titers. These observations could be related with the possibility that antibody levels may not directly correlate with disease activity (Kass-Iliyya et al., 2021; Mariottini et al., 2023).

Recent comprehensive reviews emphasize that stiff person syndrome represents a spectrum of related disorders with substantial heterogeneity in clinical presentation, autoantibody profiles, disease severity, and therapeutic response (Vlad et al., 2023). This heterogeneity may partly explain the variable outcomes observed following aHSCT, including partial response or non-response in certain patients.

Furthermore, clinical perspectives highlight that disease chronicity and immunological phenotype are likely correlated with treatment response, underscoring the importance of careful patient selection and individualized therapeutic decision-making when considering aHSCT (Bose & Jacob, 2025; Vlad et al., 2023).

The therapeutic rationale of aHSCT in SPS is immune ablation followed by immune reconstitution, aiming to eliminate autoreactive immune cells. Conditioning regimens most commonly involved cyclophosphamide with anti-thymocyte globulin (ATG) or BEAM-based protocols, reflecting established approaches in other immune-mediated neurological diseases (Burman et al., 2018; Sharrack et al., 2020).

From a safety perspective, autologous AHSCT was generally well tolerated in the reviewed literature. Reported adverse events were primarily related to conditioning regimens and included transient cytopenia and infection risk, while long-term

complications were infrequently documented (Burman et al., 2018; Ritter et al., 2025). In some studies, expert emphasized the need for caution of the adverse reaction of aHSCT, as limited long-term data. There could be the potential for late toxicity. Careful patient selection is essential before considering aHSCT (Dalakas, 2021; Sharrack et al., 2020).

Clinical implications: Autologous hematopoietic stem cell transplantation may be considered in patients with severe or treatment-refractory SPS. Careful risk–benefit assessment, appropriate patient selection, and multidisciplinary management in experienced transplant centers are essential to optimize safety and clinical outcomes.

This study has several limitations. First, the review is limited by the small number of available studies and the small sample size, comprising only 38 patients. In addition, there was considerable heterogeneity in study design, patient characteristics, and outcome measures, with most included studies being case reports or small case series. The predominance of case-based evidence increases the risk of selection bias and limits the generalizability of the findings. These limitations highlight the need for further prospective and controlled studies to better define the role of autologous aHSCT in the management of refractory SPS.

CONCLUSION

Based on the available literature, autologous hematopoietic stem cell transplantation (aHSCT) appears to be a promising therapeutic option for patients with severe and treatment-refractory stiff person syndrome (SPS). Across the reviewed studies, aHSCT was associated with clinical improvement, reduced disease activity, and reduced the need of longterm immunomodulatory or symptomatic therapies, with an acceptable short-term safety profile.

However, the current evidence is limited by small sample sizes, heterogeneous study designs, and outcome measures. Long-term efficacy and safety data remain insufficient. Therefore, autologous aHSCT should be considered on a case-by-case basis, following careful patient selection.

Future prospective and controlled studies with standardized outcome measures and long-term follow-up are necessary to establish the definitive role of aHSCT in SPS management.

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