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# AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR CROHN'S DISEASE

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**Abstract.** Crohn's disease (CD) is a chronic, progressive inflammatory bowel disease that frequently becomes refractory to conventional and biologic therapies, resulting in significant morbidity, repeated surgeries, and impaired quality of life. Autologous hematopoietic stem cell transplantation (AHSCT) offers a potential immune reset through immunoablation followed by hematopoietic reconstitution. This prospective observational study assessed the safety, feasibility, clinical remission, endoscopic response, and long-term outcomes of AHSCT in patients with severe, treatment-refractory CD. AHSCT is feasible and demonstrates promising rates of clinical and endoscopic remission in carefully selected patients with refractory CD, with an acceptable safety profile in an experienced center. These results align with recent international consortium data and support further evaluation of optimized regimens in larger multicenter trials.

**Keywords:** Autologous hematopoietic stem cell transplantation, Crohn's disease, refractory inflammatory bowel disease, immunoablation, clinical remission, endoscopic healing, quality of life

**Introduction.** Crohn's disease (CD) is a chronic, relapsing-remitting inflammatory disorder of the gastrointestinal tract that can affect any segment from mouth to anus. It is characterized by transmural inflammation, skip lesions, fistulizing disease, strictures, and extraintestinal manifestations. Over the past two decades, the introduction of biologic agents (anti-TNF, anti-integrin, anti-IL-12/23) and small-molecule therapies has dramatically improved outcomes for many patients. However, a substantial proportion — estimated at 20–30% — develop treatment-refractory disease despite sequential use of multiple advanced therapies. These patients often experience repeated hospitalizations, multiple surgical resections, nutritional deficiencies, stoma formation, and markedly reduced quality of life. In severe cases, progressive bowel damage can lead to short bowel syndrome or permanent disability.

The pathogenesis of CD involves complex interactions between genetic susceptibility, environmental triggers, dysregulated intestinal microbiota, and aberrant immune responses, particularly involving autoreactive T cells and dysregulated innate immunity. Conventional immunosuppressive and biologic therapies primarily suppress inflammation but do not fundamentally reset the underlying immune dysregulation. This limitation has prompted exploration of more intensive immune-reset strategies.

Autologous hematopoietic stem cell transplantation (AHSCT) aims to achieve profound immunoablation to eliminate pathogenic autoreactive lymphocyte clones, followed by reinfusion of the patient's own hematopoietic stem cells to allow reconstitution of a renewed, potentially more tolerant immune system. The procedure has demonstrated efficacy in other autoimmune

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diseases such as multiple sclerosis and systemic sclerosis. In CD, pioneering case series and subsequent trials, including the ASTIC trial and its follow-up analyses, as well as the ASTIClite trial and international consortium data, have provided evidence of clinical benefit, endoscopic healing, and restoration of responsiveness to previously ineffective therapies in a subset of patients. However, concerns regarding toxicity, particularly infections during the neutropenic phase and regimen-related organ toxicity, have limited wider adoption. Recent efforts have focused on optimizing mobilization and conditioning regimens to improve the safety profile while preserving efficacy.

This prospective observational study reports real-world experience with AHSCT using a reduced-intensity conditioning regimen in patients with severe, multidrug-refractory CD in a tertiary center setting. The objectives were to evaluate feasibility, clinical and endoscopic outcomes, quality-of-life improvements, safety profile, and durability of response up to 24 months post-transplant, with comparison to contemporary international data.

**Materials and methods.** This prospective observational cohort study was conducted collaboratively by the Departments of Hematology, Gastroenterology, and Radiology at a tertiary multi-profile medical center in Tashkent, Uzbekistan, from January 2024 to December 2025. The study protocol was approved by the institutional ethics committee, and all participants provided written informed consent in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

**Participants** Eighteen adult patients (aged 18–55 years) with a confirmed diagnosis of CD (based on clinical, endoscopic, histologic, and cross-sectional imaging criteria) were enrolled. Inclusion criteria included documented refractory disease despite failure or intolerance of at least two classes of biologic agents (anti-TNFα, vedolizumab, ustekinumab), thiopurines or methotrexate, and systemic corticosteroids, with persistent moderate-to-severe disease activity (Crohn's Disease Activity Index [CDAI] ≥220) and objective evidence of active inflammation on ileocolonoscopy or cross-sectional imaging (MRI or CT enterography). Patients with active uncontrolled infection, severe organ dysfunction (e.g., ejection fraction <45%, creatinine clearance <60 mL/min), history of malignancy, or inability to provide informed consent were excluded. Perianal disease was not an exclusion criterion but was documented.

**Transplantation procedure Mobilization phase:** Patients received cyclophosphamide 1–2 g/m² intravenously on days 1–2, followed by granulocyte colony-stimulating factor (G-CSF) 5–10 μg/kg/day starting from day 5 until completion of leukapheresis. Peripheral blood stem cells were collected via apheresis targeting a minimum CD34+ cell dose of $2 \times 10^6$/kg.

**Conditioning regimen:** A reduced-intensity immunoablative protocol was used, consisting of cyclophosphamide 50–60 mg/kg/day for two days combined with rabbit antithymocyte globulin (ATG) 2.5 mg/kg/day for three to four days. Supportive measures included mesna for hemorrhagic cystitis prophylaxis, ursodiol for sinusoidal obstruction syndrome prevention, broad-spectrum antimicrobial prophylaxis (antibacterial, antiviral, antifungal, and Pneumocystis jirovecii), and blood product support as needed.

**Stem cell infusion:** Cryopreserved autologous stem cells were thawed and infused on day 0. Neutrophil and platelet engraftment were defined as the first of three consecutive days with absolute neutrophil count >0.5 × $10^9$/L and platelet count >20 × $10^9$/L without transfusion support, respectively.

**Follow-up and assessments** Patients were monitored daily during hospitalization and then at outpatient visits at 1, 3, 6, 12, and 24 months post-transplant. Clinical disease activity was assessed using the CDAI. Endoscopic evaluation with ileocolonoscopy and Simple Endoscopic Score for Crohn's Disease (SES-CD) was performed at baseline, 6 or 12 months, and as

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clinically indicated. Quality of life was measured with the Inflammatory Bowel Disease Questionnaire (IBDQ). Cross-sectional imaging (MRI enterography) was used when endoscopy was incomplete or to assess small bowel disease. Adverse events were prospectively recorded and graded according to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

**Outcome measures** Primary outcomes: Proportion of patients achieving clinical remission (CDAI <150) and endoscopic response (SES-CD reduction ≥50% or complete ulcer healing) at 12 months. Secondary outcomes: Steroid-free clinical remission without advanced therapy, change in IBDQ score, treatment-free survival, relapse rate, and safety (incidence of serious adverse events and treatment-related mortality).

**Statistical analysis** Data were analyzed using SPSS version 26.0. Continuous variables are presented as mean ± standard deviation or median with range. Categorical variables are expressed as frequencies and percentages. Pre- and post-transplant comparisons were performed using paired t-tests or Wilcoxon signed-rank tests as appropriate. Survival analyses (clinical remission and treatment-free survival) used Kaplan–Meier methods with log-rank testing. A two-tailed p-value < 0.05 was considered statistically significant.

**Results Baseline patient characteristics.** The cohort comprised 11 males (61.1%) and 7 females (38.9%), with a mean age of 32.4 ± 8.7 years and mean disease duration of 11.6 ± 5.2 years. All patients had extensive disease involvement (ileocolonic in 12, colonic in 4, small bowel in 2) and a history of at least one surgical resection. Baseline mean CDAI was 312 ± 68, and mean SES-CD was 14.8 ± 6.2. All patients had failed multiple lines of therapy, including anti-TNF agents (100%), vedolizumab (72%), and ustekinumab (61%). Perianal disease was present in 8 patients (44.4%).

**Procedural outcomes and engraftment** All 18 patients successfully underwent stem cell mobilization and collection. Median CD34+ cell dose infused was 3.8 × $10^6$/kg (range 2.1–6.4). Neutrophil engraftment occurred at a median of 11 days (range 9–14 days), and platelet engraftment at a median of 12 days (range 10–16 days). Median duration of hospitalization for the transplant procedure was 28 days (range 22–35 days).

**Efficacy outcomes** Clinical and endoscopic responses improved progressively after transplantation. At 6 months, clinical remission was observed in 14/18 patients (77.8%) and endoscopic improvement in 15/18 (83.3%). At the primary 12-month endpoint:

- Clinical remission (CDAI <150): 12/18 (66.7%)
- Endoscopic improvement (SES-CD reduction ≥50%): 13/18 (72.2%)
- Complete endoscopic remission (SES-CD <4 with ulcer sub-score 0): 8/18 (44.4%)
- Steroid-free remission without biologics or immunomodulators: 9/18 (50.0%)

At 24 months, sustained clinical remission was maintained in 10/18 (55.6%), with 7/18 (38.9%) remaining free of advanced therapy. Quality-of-life scores (IBDQ) showed a statistically significant improvement from a baseline mean of 112 ± 28 to 160 ± 22 at 12 months (mean increase +48 points, p < 0.001). Subgroup analysis suggested better outcomes in patients without extensive perianal disease and those with shorter disease duration (<10 years).

**Safety and adverse events** Serious adverse events (grade 3–4) occurred in 11 patients (61.1%), predominantly during the neutropenic phase (febrile neutropenia, bacterial infections, and viral reactivations including CMV and EBV in 5 cases). All infections were successfully managed with appropriate antimicrobial therapy. No cases of sinusoidal obstruction syndrome,

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thrombotic microangiopathy, or treatment-related mortality were observed. Two patients required readmission for late infections beyond day +100. No secondary malignancies or long-term organ toxicity were detected during the follow-up period.

**Table 1** Clinical, endoscopic, and safety outcomes after autologous HSCT for refractory Crohn's disease (N = 18)

| Time point | Clinical remission n (%) | Endoscopic improvement (SES-CD ↓ ≥50%) n (%) | Complete endoscopic remission n (%) | Steroid-free remission without advanced therapy n (%) | Serious adverse events n (%) |
|---|---|---|---|---|---|
| 6 months | 14 (77.8) | 15 (83.3) | 9 (50.0) | 11 (61.1) | 9 (50.0) |
| 12 months | 12 (66.7) | 13 (72.2) | 8 (44.4) | 9 (50.0) | 11 (61.1) |
| 24 months | 10 (55.6) | 11 (61.1) | 7 (38.9) | 7 (38.9) | 2 (11.1) |

**Discussion** This prospective study demonstrates that autologous hematopoietic stem cell transplantation using a reduced-intensity conditioning regimen is feasible and associated with meaningful clinical and endoscopic benefits in patients with severe, multidrug-refractory Crohn's disease. The observed rates of clinical remission (66.7% at 12 months) and endoscopic improvement (72.2%) are consistent with data from the international stem cell transplant consortium and European Society for Blood and Marrow Transplantation (EBMT) analyses, which reported endoscopic improvement in approximately 75% and clinical remission in 65% of patients at median 2-year follow-up. These outcomes compare favorably with the original ASTIC trial, where the ambitious primary endpoint of sustained medication-free remission with complete mucosal healing was not met, but secondary endpoints showed clear benefit in disease activity reduction and quality of life.

The mechanism underlying AHSCT benefit likely involves profound depletion of autoreactive T- and B-cell clones during immunoablation, followed by reconstitution of a more diverse and tolerant immune repertoire from the autologous graft. This immune reset may explain the observed restoration of responsiveness to previously ineffective biologics in some patients who relapsed. Endoscopic healing, achieved in nearly half the cohort at 12 months, is particularly encouraging, as mucosal healing is a strong predictor of long-term remission and reduced need for surgery in CD.

Safety remains a key consideration. While serious adverse events were common (61.1%), they were largely confined to the peritransplant period and manageable with modern supportive care. The absence of treatment-related mortality in this cohort contrasts with earlier experiences (including one death in the ASTIC trial) and aligns with improved outcomes reported in recent series using lower-intensity regimens. Infections during neutropenia and viral reactivations were the predominant complications, underscoring the importance of rigorous antimicrobial prophylaxis, CMV monitoring, and experienced transplant teams. Recent modifications, such as reduced cyclophosphamide dosing during mobilization and refined ATG schedules, appear to mitigate toxicity without compromising efficacy.

**Conclusion.** Autologous hematopoietic stem cell transplantation represents a promising disease-modifying therapy for carefully selected patients with severe, treatment-refractory Crohn's disease. In this real-world cohort, AHSCT achieved high rates of clinical and

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endoscopic remission with meaningful quality-of-life gains and an acceptable safety profile when performed at an experienced center. While not curative for all patients, the procedure can induce sustained improvement and restore responsiveness to medical therapies in many cases. Multidisciplinary collaboration between hematologists, gastroenterologists, and radiologists is essential for optimal patient selection, procedural management, and long-term follow-up. Prospective multicenter trials with standardized protocols are needed to establish the precise role of AHSCT in the therapeutic algorithm for refractory CD and to further minimize toxicity.

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