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Advanced Approaches in the Treatment of Autoimmune Thrombocytopenic Purpura: A Comparative Analysis of Conservative and Surgical Methods

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Abstract: Autoimmune thrombocytopenic purpura (ATP), alternatively designated as primary immune thrombocytopenia (ITP) or Werlhof's disease, is an immune-mediated hematological disorder characterized by accelerated antibody-coated platelet destruction and severely impaired megakaryocyte maturation. While conventional therapeutic strategies heavily rely on systemic oral/parenteral glucocorticosteroids and standard open splenectomy, both arms carry high risks of severe treatment-induced morbidity, including gastrointestinal mucosal degradation and mechanical collateral tissue trauma.

To evaluate the clinical efficacy and safety profile of cold-metered nebulized inhalation glucocorticosteroid delivery against traditional systemic therapy, and to perform a comparative assessment of an anatomically protective, modified splenectomy technique versus conventional open splenectomy.

Nebulized targeted glucocorticoid inhalation and isolated hilar splenectomy constitute major therapeutic advancements, dramatically improving the safety margins, resource utilization, and speed of remission in both adult and pediatric ATP populations.

Keywords: Autoimmune thrombocytopenic purpura, Immune thrombocytopenia, Glucocorticosteroids, Nebulizer therapy, Splenectomy, Hematology, Microvascular hemostasis.

Introduction

Autoimmune thrombocytopenic purpura (ATP) stands as a classic paradigm of acquired autoimmune hematological diseases. The primary driving pathophysiology involves a profound breakdown in immune tolerance, culminating in the synthesis of pathological IgG autoantibodies directed specifically against vital platelet surface glycoprotein complexes, most notably GPIb/IX/V and GPIIb/IIIa.

These autoantibody-coated platelets undergo accelerated clearance via Fcγ receptor-mediated phagocytosis executed by the mononuclear phagocyte system, predominantly within the splenic red pulp and hepatic sinusoids. Compounding this peripheral destruction, these same autoantibodies target bone marrow megakaryocytes, suppressing their maturation, inducing intramedullary apoptosis, and severely inhibiting effective platelet budding (shedding).

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The epidemiological distribution of ATP spans all age groups, presenting an annual global incidence ranging between 1 and 13 cases per 100,000 population. Clinically, the disease presents a highly volatile spectrum. Mild variants present with restricted cutaneous bleeding, such as petechiae, purpura, and ecchymoses. Severer phenotypes manifest as unremitting, profuse mucous membrane hemorrhages, including severe epistaxis, gingival bleeding, intractable menorrhagia, and life-threatening gastrointestinal or intracranial hemorrhages.

For decades, the frontline management of ATP has relied on high-dose systemic glucocorticosteroids (GCS) to suppress macrophage phagocytosis and downregulate autoantibody production. While effective in inducing initial remission, prolonged peroral or parenteral GCS administration routinely induces severe systemic metabolic toxicity, including:

- Gastroduodenal mucosal erosions and ulcerations
- Cushingoid syndrome and systemic hypertension
- Severe psychiatric disturbances and steroid-induced diabetes

For patients who develop refractory or relapsing disease, splenectomy represents the secondary definitive curative option by eliminating the primary site of both platelet destruction and anti-platelet antibody synthesis. However, conventional open splenectomy carries intrinsic surgical risks, including massive intraoperative hemorrhage due to the fragile vascular nature of the splenic pedicle, accidental mechanical trauma to the closely adjacent tail of the pancreas, and postoperative subphrenic abscess formation.

Given these substantial therapeutic hurdles, optimizing both conservative and surgical methodologies is paramount. This paper details a comprehensive 5-year clinical trial evaluating two major therapeutic modifications: the utilization of targeted, cold-metered nebulized GCS inhalation to bypass systemic gastrointestinal toxicity, and a highly refined, structurally protective microvascular splenectomy technique designed to isolate and preserve adjacent visceral structures.

Materials and Methods

Study Design and Ethical Compliance

This research was structured as a combined retrospective and prospective clinical trial over a continuous 5-year period. Institutional review board approval was secured at the Research Institute of Hematology and Blood Transfusion of the Ministry of Health of the Republic of Uzbekistan. All prospective participants or their legal guardians provided written informed consent.

Patient Stratification and Demographics

A total cohort of **224 patients** with verified ATP were enrolled. The cohort was strictly characterized by demographic, gender, and clinical stage distinctions:

Total ATP Cohort: n=224	
Clinical Form	**Gender Distribution**
- Chronic ATP: n=187 (83.5%)	- Females: n=136 (60.7%)
- Acute ATP: n=37 (16.5%)	- Males: n=88 (39.3%)

Anamnesis data indicated a highly protracted disease course among chronic patients, with histories ranging from 8 months to 18 years. Throughout these historical windows, patients reported relying on repetitive courses of oral tablet-form corticosteroids, cycling through them between 3 and 12 separate times, often leading to drug tolerance and cumulative mucosal damage.

Baseline Diagnostic and Laboratory Evaluation

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To establish a definitive diagnosis of primary ATP and exclude secondary thrombocytopenic states, all subjects underwent a rigid diagnostic workup:

Complete Blood Count (CBC): Demonstrated profound isolated thrombocytopenia, with critical hemorrhagic risks multiplying when absolute platelet counts dropped below structural limits of <20.0×109/l to 32.0×109/l.

Hemostatic and Endothelial Testing: * Duke's capillary bleeding time was profoundly prolonged, ranging from **5 to 28 minutes** (normal baseline <4 minutes).

Conversely, the intrinsic coagulation pathway monitored via the Lee-White whole blood clotting time remained within normal parameters, highlighting that the defect was purely platelet-mediated rather than a plasma coagulopathy.

Coagulograms revealed a severe drop in blood clot (thromb) retraction and a parallel rise in systemic fibrinolytic activity (exceeding the standard baseline norm of 2%).

Microvascular endothelial fragility was universally confirmed via highly positive capillary stress tests, including the Rumpel-Leede (tourniquet) test, pinch test, cupping test, and local intradermal injection marks.

Bone Marrow Aspirate Morphology: Microscopic evaluation of bone marrow punctate specimens confirmed a state of hypercellular or normocellular megakaryocytopoiesis. An abundance of young, immature megakaryocytic forms characterized by large, round unsegmented nuclei and deeply basophilic, blue cytoplasm was evident. Crucially, the vast majority of these cells exhibited a complete absence of peripheral platelet budding or platelet marginal zones.

Immunological Profiling: Serological assays confirmed highly elevated titers of circulating immune complexes (CICs), directly correlating with the systemic autoantibody burden.

Visceral Screening: Patients underwent complementary diagnostic profiling based on clinical indications, including abdominal ultrasonography (US), electrocardiography (ECG), and upper gastrointestinal endoscopy (esophagogastroduodenoscopy) to map out pre-existing steroid-induced mucosal lesions.

Detailed Treatment Protocols

Patients were allocated into two primary therapeutic arms based on clinical staging, response to prior medical therapies, and the structural threat of life-threatening bleeding.

1. Conservative (Hormonal) Therapy Protocols (n=102)

Glucocorticosteroid dosages were tailored to the clinical phase. In acute ATP presentations, initial loading doses were set at 2.0–2.5 mg/kg/day, whereas chronic forms received 1.0–1.5 mg/kg/day.

Traditional Systemic Subgroup (n=52): GCS (prednisolone or dexamethasone) was administered via conventional peroral tablet forms or systemic intravenous infusions. This cohort comprised 31 adults (35.5% male, 64.5% female) and 21 pediatric patients (19.0% boys, 57.1% girls).

Nebulized Inhalation Subgroup (n=50): GCS was delivered via a specialized **"Boreal" (Italy) nebulizer system**, producing a targeted, cold-metered aerosol cloud at a calculated dosage of 1.0–2.0 mg/kg/day. This cohort contained 29 adults (55.2% male, 44.8% female) and 21 pediatric patients (19.0% boys, 23.8% girls).

Pharmacokinetic and Physiological Rationale for Inhalation GCS

The clinical deployment of nebulized GCS relies on specialized mucosal absorption pharmacokinetics. When administered via the "Boreal" system, approximately 40–50% of the ultra-fine aerosolized

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steroid particles cross the respiratory tract mucosal linings, entering the pulmonary capillary system to achieve rapid systemic bioavailability without entering the portal vein circuit.

Approximately 40% of the remaining aerosolized volume is naturally swallowed into the upper gastrointestinal tract. However, as this swallowed fraction passes through the intestinal wall, it enters the portal circulation and undergoes nearly complete first-pass hepatic inactivation (metabolic clearance) by liver enzymes. This structurally prevents the active hormone from exerting local or systemic gastroduodenal mucosal toxicity. External environmental dissipation accounts for the remaining 20% of the dose.

Adjuvant Medical Care

All conservative patients received optimized supportive care, including fibrinolysis inhibitors (ϵ-aminocaproic acid), vascular endothelial protectors (etamsylate), biological membrane stabilizers, and aggressive local hemostatic maneuvers (topical thrombin, fibrin sponges) for localized gingival or epistaxis control. Packed red blood cells (PRBCs) were transfused only when profound symptomatic anemia was documented.

2. Surgical Splenectomy Protocols (n=138)

Splenectomy was strictly restricted to chronic ATP cases meeting rigid criteria: complete refractoriness to maximal medical/hormonal regimens, high-frequency clinical relapses, or the persistent manifestation of life-threatening hemorrhagic crises. To protect against acute adrenal crisis secondary to long-term hypothalamic-pituitary-adrenal (HPA) axis suppression, all surgical candidates underwent a mandatory pre-operative GCS dose escalation, where daily systemic dosages were amplified 2- to 3-fold for 2–3 days prior to the incision. Surgical access was achieved using an upper midline laparotomy approach.

Conventional Splenectomy Subgroup (n=70): Underwent traditional open surgical mobilization. This involved mass clamping of the primary splenic vascular pedicle, digital mobilization of the splenic retroperitoneal attachments, and sequential structural ligation. The cohort comprised 30 adults (30.0% male, 70.0% female) and 40 children (35.0% boys, 65.0% girls).

Modified Splenectomy Subgroup (n=68): Underwent an anatomically modified, isolated ligation technique. The group comprised 44 adults and 24 pediatric patients.

Technical Execution of the Modified Splenectomy

The author's modified approach eliminates the use of blind mass-clamping within the splenic hilum. The procedure is executed via a highly disciplined sequence:

1. Access to the lesser sac is achieved with minimal traction, carefully visualizing the splenic hilum.
2. Rather than incising the anterior layer of the gastrosplenic peritoneum near the hilum, the surgeon performs an ultra-isolated dissection.
3. Every individual splenic arterial and venous branch, along with the short gastric vessels within the gastrosplenic ligament, is isolated individually.
4. Each vessel is independently clamped, divided, and doubly ligated with non-absorbable silk sutures close to the splenic capsule. This occurs completely clear of the anatomical boundaries of the pancreatic tail, eliminating any risk of direct or thermal tissue injury.
5. The vascular stump is then cleanly peritonized by closing the peritoneal folds, minimizing raw retroperitoneal surfaces and reducing postoperative oozing.

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Results

1. Analysis of Conservative Therapy Cohorts

The clinical response rates demonstrated a clear therapeutic advantage for nebulized inhalation delivery over traditional oral/parenteral routes, dramatically reducing both length of hospital stay and mucosal toxicity.

Among the 31 chronic ATP patients treated via traditional systemic routes, 22 patients (71.0%) eventually reached a combined clinical-hematological response, requiring an average hospitalization period of 10.2 bed-days. Crucially, 19 of these individuals (61.3%) developed significant, documented gastrointestinal tract complications directly caused by the enteral/parenteral hormone exposure.

In sharp contrast, when the 29 chronic ATP patients in the nebulized inhalation cohort were analyzed, an excellent clinical-hematological response was achieved in 25 patients (86.2%), while simultaneously dropping the average length of stay to just 6.4 bed-days.

A matching trend was observed in the acute ATP presentations. Traditional systemic GCS delivery induced remission in 16 out of 21 patients (76.2%) over a protracted average of 15.0 bed-days, with 9 patients (42.9%) suffering from severe treatment-induced GI side effects.

Conversely, acute ATP patients treated with nebulized inhalation therapy achieved an 81.0% clinical response rate (n=17/21), while accelerating the onset of stable remission to an average of just 5.8 bed-days. At the time of baseline admission, 20 patients in the chronic arm and 6 patients in the acute arm already possessed pre-existing, steroid-induced GI pathologies from historical oral usage, including 4 severe cases of active gastrointestinal hemorrhage. Following initiation of the nebulized regimen, zero (0%) new or aggravated GI complications were recorded.

The baseline gastrointestinal comorbidities documented at admission across the conservative cohort (n=54 total affected patients) included:

- Gastroduodenitis: n=23
- Gastric Ulceration: n=7
- Duodenal Ulceration: n=5
- Colitis: n=3
- Generalized GI Discomfort/Dyspepsia: n=11
- Acute Gastralgia: n=5

2. Analysis of Surgical Splenectomy Cohorts

Operative Efficiency and Hemostasis Metrics

The modified isolated splenectomy technique significantly optimized all intraoperative safety indicators. The total duration of the operation was consistently reduced by **12 to 15 minutes** compared to the conventional group.

Mean intraoperative blood loss was reduced by 48.5 mL, and postoperative drainage volume dropped 2- to 3-fold. This enhanced hemostasis allowed surgeons to safely remove the subphrenic drainage tubes on Postoperative Day 1 in 92% of the modified cases, whereas over 55% of conventional splenectomy patients required indwelling drains for 2 to 3 days.

Complication Profiles and Visceral Protection

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The incidence of mechanical structural trauma to adjacent organs was drastically reduced. Mechanical laceration or crushing injuries to the fragile tail of the pancreas occurred in 12 patients (17.1%) during conventional mass pedicle clamping.

In the modified group, the incidence of localized pancreatic tail trauma dropped to just 3 cases (4.4%). Consequently, the clinical manifestation of acute postoperative pancreatitis was completely avoided (0%) in the modified group, compared to a 4.3% incidence rate in the conventional group.

Furthermore, the modified technique achieved a 0% relaparotomy rate, while 2.9% of patients in the conventional arm required emergent re-exploration to manage immediate postoperative hemorrhage or structural failure. There were zero mortalities recorded across both operational groups.

Blood Product and Resource Conservation

By mitigating perioperative blood loss, the modified technique substantially reduced the utilization of homallogenic blood components. The detailed fluid and blood mass balance sheets demonstrate clear clinical benefits:

Plasma Conservation

Conventional Group: Required a mean volume of 84.5 mL of fresh frozen plasma per patient.

- Modified Group: Required a mean volume of only 30.5 mL per patient.
- Net Benefit: A savings of 54.0 mL per surgical case, culminating in a cumulative saving of **3,672 mL (3.67 Liters)** of plasma across the modified cohort.

Packed Red Blood Cell (PRBC) Conservation

- **Conventional Group:** Required a mean volume of 152.0 mL of PRBC mass per patient (totaling 10,640 mL).
- **Modified Group:** Required a mean volume of only 44.0 mL per patient (totaling 2,992 mL).
- Net Benefit: A mean savings of 108 mL per patient, resulting in a collective conservation of 7,648 mL (7.65 Liters) of PRBC mass.

Total Combined Transfusion Savings

Summing all components (plasma, PRBCs, and whole blood products), the traditional cohort consumed 16,555 mL (mean: 236.5 mL/patient), whereas the modified cohort required only 5,275 mL (mean: 77.5 mL/patient). The modified technique successfully prevented the exposure of patients to **11,280 mL (11.28 Liters)** of donor blood products.

Comparative Data Summary

The complete comparative datasets for both conservative and surgical interventions are structured below for quick clinical reference.

Table 1

Comparative Efficacy and Safety of GCS Delivery Methods

Clinical Parameter Assessed	Traditional Systemic GCS (n=52)	Nebulized Inhalation GCS (n=50)	Statistical Significance / Impact
Chronic ATP Remission Rate	71.4%	88.0%	Significant increase in response
Chronic Mean Hospitalization	10.2 Days	6.4 Days	Reduced by 3.8 bed-days
Acute ATP Remission Rate	76.2%	81.0%	Improved clinical yield

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Clinical Parameter Assessed	Traditional Systemic GCS (n=52)	Nebulized Inhalation GCS (n=50)	Statistical Significance / Impact
Acute Mean Hospitalization	15.0 Days	5.8 Days	Accelerated by 9.2 bed-days
Therapy-Induced GI Complications	42.9% – 61.3%	0.0%	Complete elimination of GI toxicity

Table 2
Perioperative Metrics and Complication Rates in Splenectomy

Surgical Outcome Metric	Conventional Splenectomy (n=70)	Modified Splenectomy (n=68)	Absolute Clinical Advantage
Reduction in Operative Time	Baseline Reference	12–15 Minutes Faster	Decreased anesthesia exposure
Postoperative Drainage Loss	Baseline Reference	2- to 3-Fold Decrease	Enhanced local microhemostasis
Pancreatic Tail Injury Rate	17.1%	4.4%	Avoided direct/crush tissue trauma
Postoperative Pancreatitis	4.3%	0.0%	Eliminated secondary enzyme leakage
Emergent Relaparotomy Rate	2.9%	0.0%	Structural security of vascular pedicle
Early Drain Removal (Day 1)	<50% of cases	92.0% of cases	Accelerated physical rehabilitation
Mean Plasma Transfusion Volume	84.5 mL/patient	30.5 mL/patient	Conserved 3,672 mL total plasma
Mean PRBC Transfusion Volume	152.0 mL/patient	44.0 mL/patient	Conserved 7,648 mL total PRBC mass
Early Clinical Improvement Rate	Lower Baseline Range	95.6%	Superior early recovery trajectory

Discussion

The results of this study demonstrate that replacing traditional systemic glucocorticosteroid options with targeted, cold-metered nebulized inhalation therapy via the "Boreal" system solves a major clinical dilemma in ATP management. Long-term systemic corticosteroid delivery poses a severe threat to gastrointestinal mucosal integrity.

When administered perorally, steroids directly disrupt the protective gastric mucus barrier, inhibit local prostaglandin synthesis, and increase gastric acid secretion, frequently causing severe gastroduodenitis, peptic ulcerations, and acute mucosal hemorrhage. This is particularly problematic

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in chronic ATP populations, where underlying thrombocytopenia multiplies the risk of catastrophic bleeding from these induced lesions.

Furthermore, intramuscular or repeated intravenous steroid injections in pediatric wards cause significant psychological distress, often manifesting as severe anxiety, crying episodes, and hysterical states. These responses elevate systemic blood pressure and increase the risk of microvascular rupture. Injections also carry an inherent risk of healthcare-associated parenteral cross-infections.

Nebulized GCS inhalation successfully avoids these complications due to its distinct pharmacokinetic profile. By delivering the fine aerosol cloud directly to the respiratory tree, the active compound achieves rapid systemic bioavailability via the pulmonary capillary network, inducing rapid anti-inflammatory and immunomodulatory effects.

The swallowed fraction is effectively neutralized by first-pass hepatic metabolism, preventing systemic gastrointestinal toxicity. This explains why the inhalation subgroup achieved a high overall efficacy rate and entered stable remission an average of 5.8 days faster, all while maintaining a 0% rate of therapy-induced gastrointestinal complications.

In the surgical arm, open splenectomy remains a highly effective definitive treatment for refractory chronic ATP, but the standard procedure carries significant risk. The main challenges for the operating surgeon include dissecting short gastric vessels within the superior pole's gastrosplenic ligament, safely mobilizing dense retroperitoneal attachments without causing capsular tears, and managing the splenic vascular pedicle near the tail of the pancreas.

In conventional open splenectomy, mass clamping of the hilar pedicle often compresses or lacerates the closely adjacent pancreatic tail, leading to localized tissue necrosis, postoperative pancreatic enzyme leakage, and acute pancreatitis (documented at 4.3% in our conventional cohort). Such complications often necessitate emergent relaparotomies. Additionally, sudden intraoperative tears of fragile splenic veins can lead to massive hemorrhage, requiring extensive transfusions of donor plasma and PRBC mass.

The modified splenectomy technique addresses these anatomical vulnerabilities. By avoiding mass clamping and instead carefully isolating and ligating individual vascular branches within the splenic hilum, the surgeon maintains excellent structural control. Preserving the anterior layer of the peritoneum near the hilum protects the underlying pancreatic tail from direct mechanical or ischemic trauma.

This microvascular approach reduced the pancreatic injury rate to 4.4% and completely eliminated postoperative pancreatitis (0%) and the need for relaparotomies (0%). Minimizing perioperative blood loss also eliminated the need for extensive blood product transfusions, conserving 11,280 mL of total blood products across the cohort and securing a 95.6% early postoperative improvement rate.

Conclusions

Nebulized inhalation delivery of GCS via a dedicated nebulizer system represents a significant advancement over traditional oral and parenteral steroid regimens for ATP. This approach eliminates therapy-induced gastrointestinal complications, prevents injection-related psychological trauma and pain in pediatric populations, and eliminates the risk of parenteral cross-infections.

Inhalation GCS therapy achieves rapid, high-yield therapeutic responses, inducing stable clinical-hematological remission in 81.0% of acute ATP cases and 88.0% of chronic ATP cases. It shortens the required hospitalization period by an average of 5.8 days compared to traditional systemic delivery options.

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Nebulized targeted hormone delivery provides clear clinical and economic advantages by lowering the total required pharmacological volume per patient course.

The modified surgical splenectomy technique minimizes operative trauma, reduces intraoperative hemorrhage, protects the tail of the pancreas from mechanical injury, and shortens overall operating room time. This technique lowers blood product consumption and ensures an early postoperative clinical recovery rate of 95.6%.

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