Systematic Review

Therapeutic Plasmapheresis: A Systematic Review

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Abstract

Therapeutic plasmapheresis generally referred to as therapeutic plasma exchange (TPE), is an extracorporeal blood purification method which is used to remove pathogenic plasma constituents implicated in a wide range of immune-mediated, hematologic, neurologic, and renal disorders. In contrast to standard dialysis, TPE focus high molecular weight substances such as autoantibodies, immune complexes, paraproteins, and inflammatory mediators. This systematic review analyzes the functional basis, technical considerations, evidence based indications, clinical outcomes and complications of therapeutic plasmapheresis, with particular significance on the role of pathology and transfusion medicine services. A PRISMA guided literature search observed 70 relevant studies, including randomized controlled trials, meta-analyses, registries and international guidelines. Recent evidence strongly upholds TPE as first-line therapy in selected conditions such as immune mediated thrombotic thrombocytopenic purpura, Guillain–Barre syndrome and myasthenic crisis. Potent implementation requires close integration between clinicians, pathologists and transfusion services, especially in resource-restricted healthcare systems.

Keywords: Therapeutic plasmapheresis, therapeutic plasma exchange, apheresis, transfusion medicine, PRISMA guidelines.

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Introduction

Therapeutic plasmapheresis is a recognized extracorporeal procedure in which plasma containing disease associated macromolecules are removed and substituted with suitable fluids, while cellular blood components are restored to the patient. The procedure is especially important in conditions where pathogenic factors are limited predominantly to the intravascular compartment and are not efficiently removed by pharmacologic or renal replacement therapies. Across the past several decades, TPE has advanced from an experimental procedure into a systematised therapeutic method supported by evidence based guidelines.[1,2]

From pathology viewpoint, therapeutic plasmapheresis shows a laboratory centered involvement that relies mainly on accurate diagnosis, detection of circulating pathogenic factors and real time monitoring of hematologic and biochemical parameters. Transfusion medicine services are responsible for ensuring the adequate supply, safety and use of plasma products, particularly in conditions needing replacement of deficient plasma proteins. Additionally, the implementation of TPE in India should be in line with the regulatory policies such as the National Accreditation Board for Hospitals and Healthcare Providers (NABH) and the National AIDS Control Organisation (NACO) guidelines directing blood component therapy.[3,4]

Materials and Methods

Study Design and Reporting Standards: This systematic review was carried out in accordance with the PRISMA 2020 guidelines to ensure transparent and reproducible reporting.[1]

Data Sources and Search Strategy: A comprehensive literature search was done using PubMed, Medline, Embase and the Cochrane Library covering publications available up to December 2025. The search strategy included terms such as therapeutic plasmapheresis, therapeutic plasma exchange, apheresis, pathology and transfusion medicine. In addition, the latest American Society for Apheresis (ASFA) guidelines were reviewed and used as the primary reference standard for clinical indications and evidence grading.[2]

Eligibility Criteria: Randomized controlled trials, observational studies, registry data, systematic reviews and major clinical guidelines published in English were included. Case reports and narrative reviews without primary data were excluded unless they addressed rare or emerging indications.

PRISMA Flow of Study Selection: A total of 1,124 records were collected from electronic databases and an additional 46

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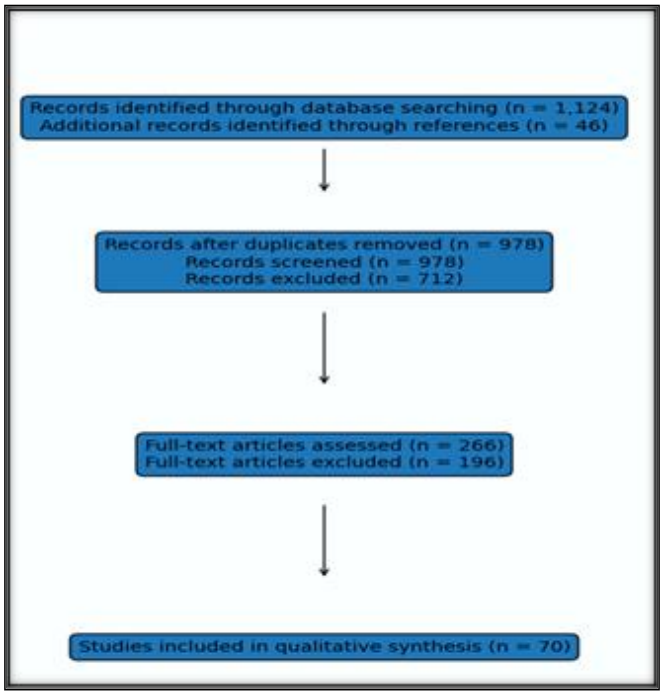
articles were identified through reference screening. After removing duplicates, 978 records remained for title and abstract screening, during which 712 studies were excluded as irrelevant. The full texts of 266 articles were then reviewed in detail, of which 196 were excluded due to inadequate data quality, narrative only design or language limitations. Finally, 70 studies were included in the qualitative synthesis [Figure 1].



Mechanistic Basis of Therapeutic Plasmapheresis

Removal of Pathogenic Plasma Constituents: The primary therapeutic benefit of TPE comes from removing circulating pathogenic substances, containing autoantibodies, immune complexes, cryoglobulins and monoclonal immunoglobulins. Exchanging roughly one plasma volume generally reduces the intravascular levels of these substances by 60–65%, with additional reductions achieved through sequential procedures.[5]

Plasma Replacement and Functional Repletion: In certain disorders, especially immune mediated thrombotic thrombocytopenic purpura (iTTP), therapeutic benefit of TPE comes not only from removal of inhibitory antibodies but also from replacing deficient plasma proteins such as ADAMTS13 using fresh frozen plasma.[6]

Immunomodulatory Effects: Beyond the direct removal of pathogenic substances, TPE influences more extensive immunologic effects by altering cytokine profiles, reducing complement activation and changing immune cell signaling. These mechanisms are thought to contribute to the sustained clinical improvement in autoimmune and inflammatory diseases.[7]

Technical and Transfusion Medicine Considerations: Therapeutic plasmapheresis is done using either centrifugal or membrane based separation techniques. Adequate vascular access via central venous catheters is required for achieving target flow rates. Anticoagulation is done using citrate requiring monitoring of ionized calcium levels to avoid hypocalcemia.[8]

Replacement Fluids: Choosing appropriate replacement fluid is a crucial transfusion medicine decision. Albumin solutions are preferred for most autoimmune and neurologic indications whereas plasma is crucial when coagulation factors or specific enzymes need to be replenished. In the Indian setting, plasma components must adhere with NACO standards and be issued from NABH accredited blood centres.[3,4]

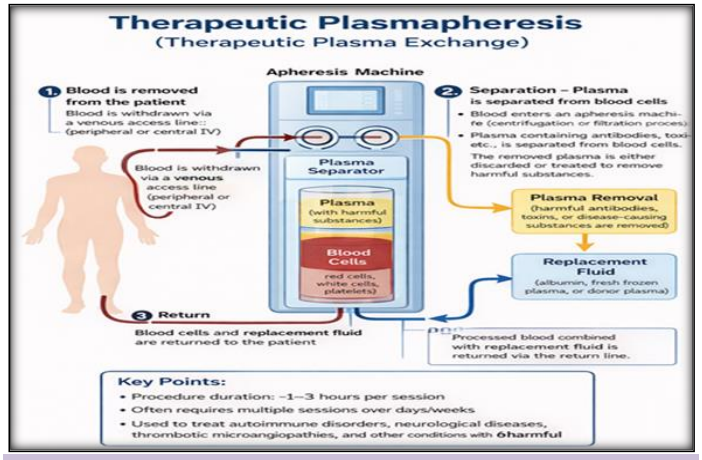


Figure 1: Therapeutic Plasmapheresis (Therapeutic Plasma Exchange): Detailed Schematic Workflow

This figure depicts the complete extracorporeal circuit and functional steps involved in therapeutic plasmapheresis. The procedure begins with blood withdrawal from the patient through a peripheral or central venous access line, ensuring continuous flow into the apheresis system. The blood is then processed within an apheresis machine (blood cell separator), where separation occurs via centrifugation or membrane-based filtration.

Inside the separator, whole blood is fractionated into plasma and cellular components. The plasma layer contains pathogenic substances such as autoantibodies, immune complexes, toxins, and abnormal proteins, while the cellular fraction consists of red blood cells, white blood cells, and platelets. The separated plasma is directed toward a plasma removal pathway, where it is either discarded or subjected to selective filtration techniques for removal of harmful constituents.

To maintain circulatory volume and oncotic balance, the removed plasma is replaced with appropriate replacement fluids, including albumin, fresh frozen plasma, or isotonic saline, depending on clinical indication. The retained cellular components are then recombined with the replacement fluid.

Finally, the processed blood is reinfused into the patient through a return intravenous line, completing the closed-loop system. The diagram highlights the bidirectional flow (withdrawal and return), integration of replacement therapy, and the continuous nature of the procedure. This technique is widely utilized for rapid clearance of circulating pathogenic factors in autoimmune, neurological, and hematological disorders.

Indications and ASFA Classification: The ASFA classification system remains the most widely accepted framework for

grouping indications for therapeutic plasmapheresis, as it integrates both the strength of evidence and clinical utility.[2] [Table 1] summarizes the ASFA 2023/2024 categories by integrating level of evidence, grade of recommendation and significance to pathology and transfusion medicine practice.

Table 1: ASFA 2023/2024 Classification of Therapeutic Plasmapheresis (Adapted for Indian Practice)

ASFA Category	Indication	LoE	GoR	Pathology / Transfusion Medicine Relevance
I	Immune-mediated thrombotic thrombocytopenic purpura	I	1A	Mandatory plasma exchange utilizing FFP for ADAMTS13 replenishment (ASFA 2023)[1]
	Guillain–Barré syndrome	I	1A	Removal of anti-ganglioside antibodies; alternative to IVIG in resource restricted settings[1]
	Myasthenia gravis (crisis / pre-thymectomy)	I	1A	Rapid antibody reduction; laboratory authentication of AChR/MuSK antibodies[1]
	Hyperviscosity syndrome (IgM/IgG paraproteinemia)	II	1B	Reduction of paraprotein load; viscosity monitoring by laboratory[1]
II	ANCA-associated vasculitis with rapidly progressive glomerulonephritis	II	2B	Adjunct to immunosuppression; ANCA titers monitored in pathology labs[1]
	Antibody-mediated solid organ transplant rejection	II	2B	Reduction of donor specific antibodies; coordinated with HLA laboratory[1]
	Catastrophic antiphospholipid syndrome	II	2C	Removal of antiphospholipid antibodies; adjunctive therapy only[1]
	Severe cryoglobulinemia	II	2B	Elimination of cryoglobulins resulting in vasculitis and hyperviscosity[1]
III	Sepsis with multiorgan dysfunction	III	2C	Cytokine removal; investigational use, demands ethics and institutional approval[1]
	Refractory lupus nephritis	III	2C	Immune complex reduction; individualized decision[1]
	Atypical hemolytic uremic syndrome	III	2C	Limited role in complement-inhibitor era; supportive indication[1]
IV	Typical (Shiga toxin–associated) hemolytic uremic syndrome	I	1D	No benefit; not recommended per ASFA and Indian practice[1]
	Chronic progressive multiple sclerosis	I	1D	Ineffective; procedure not justified[1]

LoE (Level of Evidence):

- I – Randomized controlled trials; II – Well-designed non-randomized studies; III – Case series/expert consensus
- GoR (Grade of Recommendation):
- 1 – Strong recommendation; 2 – Weak recommendation; A–D denote quality of evidence
- Procedures should be carried out in NABH-accredited blood centres, with plasma components sourced and documented as per NACO hemovigilance guidelines.[3,4]

ASFA Category I indications, for instance immune mediated TTP, Guillain Barre syndrome and myasthenic crisis are assisted by high quality evidence and demand prompt initiation of TPE.[2,6,9] Category II indications represent adjuvant use in severe diseases, while Category III indications validate individualized decision making. Category IV conditions have shown lack of benefit and should not be treated with TPE.[2]

Pathology and Transfusion Medicine Perspective: From a pathology viewpoint, therapeutic plasmapheresis is essentially a laboratory-driven intervention, requiring:

- Identification of pathogenic plasma constituents
- Selection of appropriate replacement fluids
- Constant monitoring of hematologic and biochemical parameters
- Integration with transfusion services and blood banks

Pathologists play a crucial role in indication validation, plasma product selection, monitoring of complications and quality assurance.

Table 2: Pathogenic Plasma Constituents Targeted by Therapeutic Plasmapheresis

Disease Category	Pathogenic Factor Removed	Pathology Relevance
Thrombotic thrombocytopenic purpura	Anti-ADAMTS13 antibodies, UL-vWF multimers	Microangiopathy, thrombocytopenia
Myasthenia gravis	Anti-ACh receptor antibodies	Autoimmune neuromuscular pathology
Guillain–Barré syndrome	Anti-ganglioside antibodies	Immune-mediated demyelination
Hyperviscosity syndromes	IgM, IgG paraproteins	Plasma cell dyscrasia
Cryoglobulinemia	Cryoglobulins	Vasculitis, immune complex deposition
Antibody-mediated rejection	Donor-specific antibodies	Transplant pathology

Technical Aspects: Transfusion Medicine Focus

Replacement Fluids and Plasma Products

The choice of replacement fluid is a critical transfusion decision:

5% Albumin

- Ideal in most autoimmune and neurologic indications
- Negligible risk of transfusion reactions
- Does not replenish coagulation factors

Fresh Frozen Plasma (FFP)

- Mandatory in TTP and coagulation factor deficiencies
- Restores ADAMTS13 and clotting proteins
- Increased risk of allergic reactions and TRALI

Cryosupernatant Plasma

- Used in selected centers for TTP
- Lower von Willebrand factor content

Table 3: Replacement Fluids in Therapeutic Plasmapheresis

Replacement Fluid	Indications	Advantages	Limitations
5% Albumin	Autoimmune, neurologic disorders	Low reaction rate	Coagulopathy risk
Fresh frozen plasma	TTP, coagulopathy	Replaces enzymes & factors	Transfusion reactions
Cryosupernatant plasma	TTP (selected centers)	Lower vWF	Limited availability
Combination therapy	Long-term TPE	Balanced approach	Complex logistics

Laboratory Monitoring and Quality Control

From a pathology perspective, the following parameters require close monitoring:

- Complete blood count (platelets, hemoglobin)
- Coagulation profile (PT, aPTT, fibrinogen)
- Serum calcium (citrate toxicity)
- Immunoglobulin levels during prolonged therapy

Table 4: Laboratory Parameters Monitored During TPE

Parameter	Clinical Significance
Platelet count	Bleeding risk, TTP response
Fibrinogen	Risk of hypofibrinogenemia
Ionized calcium	Citrate toxicity
Serum immunoglobulins	Infection risk
LDH	Disease activity (e.g., TTP)

Clinical Outcomes

Neurologic Disorders: Randomized trials have shown that TPE considerably improves short term functional outcomes in Guillain–Barré syndrome and gives rapid symptomatic relief in myasthenic crisis, with efficiency comparable to intravenous immunoglobulin.[9,10]

Hematologic Disorders: The introduction of plasma exchange has significantly reduced mortality in immune mediated TTP from over 90% to below 10%, depicting one of the most successful applications of therapeutic apheresis.[6]

Renal and Autoimmune Diseases: In abruptly progressive glomerulonephritis associated with ANCA vasculitis, TPE may postpone progression to end stage renal disease when used as a supplement to immunosuppressive therapy, although benefits are context dependent.[11]

Complications and Laboratory Monitoring: Therapeutic plasmapheresis is usually safe when done in experienced centres. However, complications such as hypotension, citrate toxicity, allergic reactions and coagulopathy may happen. From a pathology perspective, regular monitoring of platelet count, fibrinogen levels, coagulation parameters and serum calcium is essential to ensure the safety of the procedure.[8,12]

Complications: Pathology Relevant Considerations

Pathologists are often the first to identify complications related to therapeutic plasma exchange (TPE):

- Hypofibrinogenemia → bleeding tendency
- Dilutional thrombocytopenia
- Transfusion reactions (especially with plasma)
- Infection risk due to immunoglobulin depletion

Table 5: Complications of Therapeutic Plasmapheresis

Complication	Pathophysiology	Preventive Strategy
Hypotension	Volume shifts	Gradual exchange
Hypocalcemia	Citrate anticoagulation	Calcium supplementation
Bleeding	Loss of coagulation factors	Fibrinogen monitoring
Allergic reactions	Plasma proteins	Premedication
Catheter infections	Central venous access	Aseptic protocols

Role of Pathology and Transfusion Medicine Services

Pathologists play an important role in confirming indications, in differentiating between closely related clinical entities (e.g, thrombotic throbocytopenia purpura (TTP) versus hemolytic uremic syndrome) and assesssing laboratory response to therapy. Transfusion medicine teams support this process by ensuring the availability of safe plasma products, maintaining hemovigilance reporting and by supporting institutional apheresis governance. Strengthening of these services is essentially critical in resource limited healthcare systems.

Pathologists contributes by:

- Indication confirmation (e.g., TTP vs HUS)
- Selection of appropriate plasma products
- Monitoring laboratory trends for therapeutic response
- Participation in transfusion committees and audits
- Ensuring compliance with ASFA and institutional protocols

Future Directions: Future research should focus on conducting high quality randomized trials to evaluate emerging indications, improve exchange protocols and assess the role of selective adsorption technologies. In low and middle income countries cost effectiveness and infrastructure suitability remain important factor for developing access to therapeutic plasmapheresis.

Conclusion

Therapeutic plasmapheresis is an effective, evidence based procedure used in selected immune mediated and hematologic disorders. Its successful application depends on accurate laboratory diagnosis, appropriate transfusion support and close multidisciplinary cooperation. With ongoing refinement of clinical indications and protocols, therapeutic plasmapheresis will continue to play an important role in pathology guided

patient care.

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Conflicts of interest
There are no conflicts of interest.

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