Molina Clinical Policy
Therapeutic Apheresis: Policy No. 134

Last Approval: 10/12/2022
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DISCLAIMER

This Molina Clinical Policy (MCP) is intended to facilitate the Utilization Management process. Policies are not a supplementation or recommendation for treatment; Providers are solely responsible for the diagnosis, treatment and clinical recommendations for the Member. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (e.g., will be paid for by Molina) for a particular Member. The Member's benefit plan determines coverage – each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their Providers will need to consult the Member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a Member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid Members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this MCP and provide the directive for all Medicare members.[1] References included were accurate at the time of policy approval and publication.

OVERVIEW

Therapeutic apheresis is a treatment used to remove select cells (cytapheresis), components, or plasma (plasmapheresis or plasma exchange) from the blood. During the procedure, whole blood is removed from the patient and passed through a machine that separates the specific component being targeted for removal. The remainder of the constituents are then returned into circulation. In the case of plasma exchange, the plasma is discarded, and the remaining components are combined with a plasma substitute or donor plasma before being reinfused. The procedure is used to treat a variety of disorders such as Goodpasture's syndrome, myasthenia gravis, Guillain-Barré syndrome, and thrombotic thrombocytopenic purpura (Fridey & Kaplan, 2022).

COVERAGE POLICY

1. Therapeutic apheresis **may be considered medically necessary** as a first line therapy for **ANY** Category I condition as outlined by the American Society for Apheresis that including, but not limited to:
   a. Acute inflammatory demyelinating polyneuropathy (Guillain-Barré syndrome); **OR**
   b. Acute liver failure; **OR**
   c. ANCA-associated rapidly progressive vasculitis (granulomatosis with polyangiitis [Wegener's]) including **ONE** of the following:
      - Dialysis dependence; **OR**
      - Dialysis independence without DAH; **OR**
      - Diffuse alveolar hemorrhage (DAH)

   OR
   d. Anti-glomerular basement membrane disease (Goodpasture's syndrome) including **ONE** of the following:
      - Dialysis independence; **OR**
      - Diffuse alveolar hemorrhage
   e. Catastrophic antiphospholipid syndrome (CAPS); **OR**
   f. Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP); **OR**
   g. Cutaneous T cell lymphoma (CTCL); mycosis fungoides; Sézary syndrome (eythrodermic); **OR**
   h. Familial hypercholesterolemia (homozygotes with small blood volume); **OR**
   i. Focal segmental glomerulosclerosis (recurrent in transplanted kidney); **OR**
   j. Hereditary hemochromatosis; **OR**
   k. Hyperviscosity in monoclonal gammopathies (prophylaxis for rituximab or treatment of symptoms); **OR**
   l. Myasthenia gravis (acute short-term treatment); **OR**
   m. N-methyl-D-aspartate receptor antibody encephalitis; **OR**
   n. Paraproteinemic polyneuropathies (IgG/IgA or IgM); **OR**
   o. Polycythemia vera; **OR**
   p. Sickle cell disease (acute stroke or non-acute stroke prophylaxis); **OR**
   q. Transplantation, liver (desensitization, ABOi living donor); **OR**
   r. Transplantation, renal, ABO compatible (antibody mediated rejection or desensitization, living donor); **OR**
   s. Transplantation, renal, ABO incompatible (desensitization, living donor); **OR**

t. Thrombotic microangiopathy including the following:
   - Drug-associated (Ticlopidine); **OR**
   - Complement-mediated (Factor H autoantibody); **OR**
   - Thrombotic thrombocytopenic purpura (TTP, severe ADAMTS13 deficiency).

OR

u. Vasculitis, ANCA-associated (AAV) including the following:
   - Microscopic polyangiitis (MPA)/granulomatous polyangiitis (GPA)/renal limited vasculitis (RLV): RPGN, Cr ≥5.7; **OR**
   - MPA/GPA/RLV: DAH

OR

v. Wilson disease, fulminant

2. Therapeutic apheresis **may be considered medically necessary** as an adjunctive secondary therapy Category II condition as outlined by the American Society for Apheresis when response to conventional therapy (e.g., corticosteroids or intravenous immunoglobulins [IVIG]) has failed that includes, but is not limited to:
   a. Acute disseminated encephalomyelitis (steroid refractory); **OR**
   b. Age-related macular degeneration, dry (high-risk); **OR**
   c. Amyloidosis, systemic (dialysis-related amyloidosis); **OR**
   d. Autoimmune Hemolytic Anemia (AIHA) – cold agglutinin disease (life-threatening); **OR**
   e. Babesiosis (severe); **OR**
   f. Cryoglobulinemia (severe/symptomatic); **OR**
   g. Dilated cardiomyopathy, idiopathic (NYHA II-IV); **OR**
   h. Familial Hypercholesterolemia (heterozygotes, homozygotes/heterozygotes); **OR**
   i. Focal segmental glomerulosclerosis (recurrent in kidney transplant/steroid resistant in native kidney); **OR**
   j. Graft-versus-host disease (GVHD) – acute or chronic; **OR**
   k. Hyperleukocytosis (symptomatic); **OR**
   l. Lambert-Eaton Myasthenic Syndrome; **OR**
   m. Lipoprotein(a) Hyperlipoproteinemia (progressive atherosclerotic cardiovascular disease); **OR**
   n. Multiple Sclerosis (acute attack or relapse); **OR**
   o. Myasthenia Gravis (long-term treatment); **OR**
   p. Myeloma Cast Nephropathy; **OR**
   q. Neuromyelitis Optica (Devic's syndrome) – acute attack/relapse; **OR**
   r. Overdose, venoms, and poisoning (mushroom poisoning); **OR**
   s. Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS), exacerbation; **OR**
   t. Peripheral vascular diseases; **OR**
   u. Phytanic acid storage disease (Refsum's disease); **OR**
   v. Sickle cell disease (acute chest syndrome, non-acute pregnancy, non-acute recurrent vaso-occlusive pain); **OR**
   w. Steroid-responsive encephalopathy associated with autoimmune thyroiditis (Hashimoto encephalopathy); **OR**
   x. Systemic lupus erythematosus, severe (e.g., cerebritis, diffuse alveolar hemorrhage); **OR**
   y. Thrombocytosis (symptomatic); **OR**
   z. Thyroid storm; **OR**
   aa. Transplantation, cardiac (cellular/recurrent rejection, rejection prophylaxis, desensitization); **OR**
   bb. Transplantation, hematopoietic stem cell, ABO incompatible (ABOi) including either of the following:
      - Major ABOi hematopoietic cells obtained from bone marrow; **OR**
      - Major ABOi hematopoietic cells obtained by apheresis.

   OR

   cc. Transplantation, lung (bronchiolitis obliterans syndrome); **OR**
   dd. Transplantation, renal, ABO incompatible (antibody-mediated rejection); **OR**
   ee. Vasculitis, other (Behçet disease, Hepatitis B polyarteritis nodosa); **OR**
   ff. Voltage gated potassium channel antibodies.

Limitations and Exclusions

Therapeutic apheresis **is considered experimental and investigational** for all other indications because the medical literature does not support the clinical efficacy that includes any category III or IV condition as outlined by the American Society for Apheresis.

DOCUMENTATION REQUIREMENTS. Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

SUMMARY OF MEDICAL EVIDENCE

Renal Indications

Baweja et al. (2011) performed a systematic review on the indications for treatment in renal disease. Results from several randomized controlled trials, meta-analyses, and prospective studies have shown plasmapheresis may be of benefit in various renal diseases. A multicenter trial by the European Vasculitis Study Group found that it is the preferred additional form of therapy for patients with anti-neutrophil cytoplasmic antibody-associated glomerulonephritis and severe renal failure. A study conducted at Mayo Clinic also found it effective at reversing renal failure from myeloma-related cast nephropathy if serum free light chain levels were reduced by at least 50%. A Cochrane review analyzed the available evidence for its use in thrombotic thrombocytopenic purpura and hemolytic uremic syndrome.

Walsh et al. (2011) performed a systematic review and meta-analysis of randomized controlled trials of plasma exchange in adults with idiopathic renal vasculitis or rapidly progressive glomerulonephritis. Randomized controlled trials that compared standard care with standard care plus adjuvant plasma exchange in adult patients with either renal vasculitis or idiopathic rapidly progressive glomerulonephritis were reviewed. Nine trials with 387 patients were found. In a fixed-effects model, the pooled RR for end-stage renal disease or death was 0.80 for patients treated with adjunctive plasma exchange compared with standard care alone (95% CI, 0.65-0.99; P = 0.04). No significant heterogeneity was detected (P = 0.5; I(2) = 0%). The effect of plasma exchange did not differ significantly across the range of baseline serum creatinine values (P = 0.7) or number of plasma exchange treatments (P = 0.8). The RR for end-stage renal disease was 0.64 (95% CI, 0.47-0.88; P = 0.006), whereas the RR for death alone was 1.01 (95% CI, 0.71-1.4; P = 0.9). The reviewers concluded that plasma exchange may decrease the composite end point of end-stage renal disease or death in patients with renal vasculitis.

Cui et al. (2011) conducted a retrospective survey of 221 consecutive patients seen from 1998 to 2008 in one hospital and reported on the patient and renal survival and the risk factors affecting the outcomes. The effects of 3 different treatment regimens were compared: 1) combination therapy of plasmapheresis and immunosuppression, 2) steroids and cytotoxic agents, and 3) steroids alone. The patient and renal survival rates were 72.7% and 25.0%, respectively, at 1 year after disease presentation. The serum level of anti-GBM antibodies (increased by 20 U/mL; hazard ratio [HR], 1.16; p = 0.009) and the presentation of positive antineutrophil cytoplasmic antibodies (ANCA) (HR, 2.18; p = 0.028) were independent predictors for patient death. The serum creatinine at presentation (doubling from 1.5 mg/dL; HR, 2.07; p < 0.001) was an independent predictor for renal failure. The combination therapy of plasmapheresis plus corticosteroids and cyclophosphamide had an overall beneficial effect on both patient survival (HR for patient mortality, 0.31; p = 0.001) and renal survival (HR for renal failure, 0.60; p = 0.032), particularly patient survival for those with Goodpasture syndrome (HR for patient mortality, 0.29; p = 0.004) and renal survival for those with anti-GBM nephritis with initial serum creatinine over 6.8 mg/dL (HR for renal failure, 0.52; p = 0.014). The treatment with corticosteroids plus cyclophosphamide was found not to improve the renal outcome of disease (p = 0.73). In conclusion, the combination therapy was preferred for patients with anti-GBM disease, especially those with pulmonary hemorrhage or severe renal damage. Early diagnosis was crucial to improving outcomes.

Walters et al. (2010) conducted a systematic review to determine the benefits and harms of interventions for the treatment of renal vasculitis in adults. Statistical analyses were performed using a random effects model and results expressed as risk ratio with 95% confidence intervals for dichotomous outcomes or mean difference for continuous outcomes. Twenty-two studies (1674 patients) were included. Plasma exchange as adjunctive therapy significantly

reduces the risk of end-stage kidney disease at 12 months (five studies: RR 0.47, CI 0.30 to 0.75). Four studies compared the use of pulse and continuous administration of cyclophosphamide. Remission rates were equivalent, but pulse treatment causes an increased risk of relapse (4 studies: RR 1.79, CI 1.11 to 2.87) compared with continuous cyclophosphamide. Azathioprine has equivalent efficacy as a maintenance agent to cyclophosphamide with fewer episodes of leukopenia. Mycophenolate mofetil may be equivalent to cyclophosphamide as an induction agent but resulted in a higher relapse rate when tested against Azathioprine in remission maintenance. Rituximab is an effective remission induction agent. Methotrexate or Leflunomide are potential choices in remission maintenance therapy. Oral co-trimoxazole did not reduce relapses significantly in Wegener's granulomatosis. Authors concluded that plasma exchange is effective in patients with severe ARF secondary to vasculitis. Pulse cyclophosphamide results in an increased risk of relapse when compared to continuous oral use but a reduced total dose. Whilst cyclophosphamide is standard induction treatment, rituximab and mycophenolate mofetil are also effective. Azathioprine, methotrexate and leflunomide are effective as maintenance therapy. Further studies are required to more clearly delineate the appropriate place of newer agents within an evidence-based therapeutic strategy.

Gupta et al. performed a systematic review (2010) of three randomized controlled trials (RCTs) and multiple observational trials to evaluate the potential role of plasmapheresis in the management of multiple myeloma complicated by acute renal failure. This systematic review presents the results of these trials regarding survival benefits, recovery from dialysis, and improvement in renal function. A comprehensive search revealed 56 articles. Of these, only 8 articles met inclusion criteria (3 RCTs, 1 correction of results, and 4 observational trials). Two of the 3 RCTs showed no difference in survival benefit. Two of the 3 RCTs showed a greater percentage of patients stopping dialysis in the intervention group; however, these results were not reproduced in the largest trial. All the studies showed an improvement in renal function for patients receiving plasmapheresis; however, only 2 RCTs and 1 retrospective study showed a statistically significant improvement in renal function among patients who received plasmapheresis in comparison with a control group. The authors concluded that this systematic review does not suggest a benefit of plasmapheresis independent of chemotherapy for multiple myeloma patients with acute renal failure in terms of overall survival, recovery from dialysis, or improvement in renal function.

Tobian et al. (2008) performed a systematic review to evaluate the role of therapeutic plasma exchange (TPE) to remove ABO antibodies and permit ABO-incompatible (ABO-I) kidney transplants. The TPE treatment plan is based on ABO titers with the goal of a titer of 16 or less at the anti-human globulin (AHG) phase before surgery. Pretransplant therapy consists of every-other-day TPE followed immediately by cytomegalovirus hyperimmune globulin. ABO antibody titers are closely monitored before and after transplantation. After transplantation, TPE therapy is performed for to prevent rebound of anti-A and anti-B titers until tolerance or accommodation occurs. TPE is discontinued and reinstituted based on the clinical criteria of creatinine levels, biopsy results, and ABO titer. Fifty-three ABO-I kidney transplants have been completed with no episodes of hyperacute antibody-mediated rejection (AMR) and only three episodes of AMR. One-year death-censored graft survival is 100% and patient survival is 97.6%. The review concluded that while randomized clinical trials are needed to evaluate the optimal method and protocol to remove ABO antibodies, the literature and results indicate a critical role for TPE in ABO-I renal transplantation.

Non-Renal Indications

Huang et al. (2012) performed a prospective randomized controlled study to compare the therapeutic effect of molecular adsorbent re-circulating system (MARS) treatment (MARS group, n=60) with that of plasma exchange (PE) combined with MARS treatment (PE+MARS group, n=60) in patients with liver failure complicated with hepatic encephalopathy. The serum total bilirubin and blood ammonia levels were significantly decreased compared with pretreatment levels after 3 days of both the MARS treatment ($p=0.0001$, $p<0.001$) and PE+MARS treatment (both $p<0.0001$) and the Glasgow coma scale score was significantly increased (both $p<0.0001$). The 30-day mortality rate was 10.0% (6/60) in the MARS group and 11.7% (7/60) in the PE + MARS group. The per capita cost of treatment was significantly lower in the PE + MARS group than in the MARS group ($p=0.0003$). It was concluded that both MARS and PE + MARS therapy can safely and effectively be used to treat liver failure complicated with hepatic encephalopathy, but PE + MARS therapy reduces serum total bilirubin level more effectively and is cost-effective.

Weiss et al. (2012) conducted an 8-year retrospective cohort study of children (≤18 years) with an international classification of diseases-9-clinical modification (ICD-9-CM) discharge diagnosis indicating an ASFA Category I or II condition, or a procedure code indicating receipt of TPE during hospitalization. Results: TPE was performed during 4,190 hospitalizations of 3,449 patients, of whom 310 (9.0%) and 77 (2.2%) had a primary discharge diagnosis of an ASFA Category I or II condition, respectively. Rates of TPE use for Category I conditions were highest for children with thrombotic thrombocytopenic purpura (TTP), Goodpasture's syndrome, and myasthenia gravis. TPE use in children's

hospitals significantly increased from 2003 to 2010, but TPE was performed during only 13.4 and 9.3% of hospitalizations for ASFA Category I and II conditions, respectively. There was significant between-hospital variation in the use of TPE for Category I conditions as a group and individual Category I conditions including TTP. Authors found low levels of TPE use across hospitals for key indications, including TTP, a condition for which TPE is considered a first-line and life-saving procedure. The variation identified may contribute to varying clinical outcomes between hospitals, warrants further investigation, and represents an opportunity to improve quality of care.

El-Bayoumi et al. (2011) preformed prospective randomized study to compare the outcome of intravenous immunoglobulin (IVIG) and plasma exchange (PE) treatment in children with Guillain Barré syndrome (GBS) requiring mechanical ventilation. Forty-one children with GBS requiring endotracheal mechanical ventilation (MV) within 14 days from disease onset were included. The ages of the children ranged from 49 to 143 months. Randomly, 20 children received a five-day course of IVIG (0.4 g/kg/day) and 21 children received a five-day course of one volume PE daily. Lumbar puncture (LP) was performed in 36 patients (18 in each group). Both groups had comparable age (p = 0.764), weight (p = 0.764), duration of illness prior to MV (p = 0.854), preceding diarrhea (p = 0.751), cranial nerve involvement (p = 0.756), muscle power using Medical Research Council (MRC) sum score (p = 0.266) and cerebrospinal fluid (CSF) protein (p = 0.606).Children in the PE group had a shorter period of MV (median 11 days, IQR 11.0 to 13.0) compared to IVIG group (median 13 days, IQR 11.3 to 14.5) with p = 0.037.Those in the PE group had a tendency for a shorter Pediatric Intensive Care Unit (PICU) stay (p = 0.094).A total of 20/21 (95.2%) and 18/20 (90%) children in the PE and IVIG groups respectively could walk unaided within four weeks after PICU discharge (p = 0.606). There was a negative correlation between CSF protein and duration of mechanical ventilation in the PE group (p = 0.037), but not in the IVIG group (p = 0.132). Authors concluded that in children with GBS requiring MV, PE is superior to IVIG regarding the duration of MV but not PICU stay or the short-term neurological outcome. The negative correlation between CSF protein values and duration of MV in PE group requires further evaluation.

Martin et al. (2011) conducted a systematic review to evaluate the safety and efficacy of interventions for pemphigus vulgaris and pemphigus foliaceus. Randomized controlled trials including participants with the diagnosis of pemphigus vulgaris or pemphigus foliaceus confirmed with clinical, histopathological, and immunofluorescence criteria were selected. All interventions were considered. Primary outcomes studied were remission and mortality. Secondary outcomes included disease control, relapse, pemphigus severity score, time to disease control, cumulative glucocorticoid dose, serum antibody titers, adverse events, and quality of life. Eleven studies with a total of 404 participants were identified. Interventions assessed included prednisolone dose regimen, pulsed dexamethasone, azathioprine, cyclophosphamide, cyclosporine, dapsone, mycophenolate, plasma exchange, topical epidermal growth factor, and traditional Chinese medicine. We found some interventions to be superior for certain outcomes, although we were unable to conclude which treatments are superior overall. The authors concluded that there is inadequate evidence available at present to ascertain the optimal therapy for pemphigus vulgaris and pemphigus foliaceus. Further randomized controlled trials are required.

Liu et al. (2010) performed a randomized controlled trial to investigate the effects of double-filtration plasmapheresis (DFPP), immunoadsorption (IA) and intravenous immunoglobulin (IVIg) in the treatment of late-onset myasthenia gravis (MG). A total of 40 late-onset MG patients were randomly divided into three groups: 15 patients were treated with DFPP; 10 patients were treated with IA; and 15 patients received IVIg. The titers of titin antibodies (Titin-ab), acetylcholine receptor antibodies (AChR-ab), presynaptic membrane antibody (Prsm-ab) were detected before and after the treatment, and the quantitative MG score (QMG score) was assessed by blinded examiners before and immediately after the entire course of treatment. The clinical efficacy, duration of respiratory support, hospital stay, and the correlation between the three antibodies and the QMG score were also analyzed. Compared to pre-treatment, the values of Titin-ab, AChR-ab, and PrsmR-ab were all dramatically decreased ($P < 0.05$); meanwhile the value of Titin-ab in the DFPP and IA groups decreased much more than in the IVIg group ($P < 0.01$); however, no statistical difference was found between the DFPP and IA groups ($P > 0.05$). Although the QMG score significantly improved in all three groups, it decreased much more in both the DFPP and IA groups than that in the IVIg group ($P < 0.01$). Symptoms were also effectively ameliorated by all treatments, but the clinical efficacy of the DFPP and IA groups was higher than the IVIg group ($P < 0.05$), as was the remission time ($P < 0.01$), the duration of hospital stay ($P < 0.05$), and the number of respiratory supports required ($P < 0.05$). Using Pearson's correlation, the decrease of Titin-ab showed a longitudinal correlation with the decrease of QMG score ($r = 0.6107$, $P < 0.01$). The authors concluded that both DFPP and IA showed better short-term clinical effectiveness than immunoglobulin transfusion, rapidly and effectively clearing the pathogenic antibodies in late-onset MG patients, especially for Titin-ab.

Zechmeister et al. (2009) performed a systematic review to evaluate apheresis in patients with familial hypercholesterolemia who are resistant to drug therapy and whether the various apheresis techniques available result

in relevant improvement of clinical endpoints (cardiovascular morbidity and mortality, quality of life). Evidence from the ten studies included weakly indicates an improvement in angina symptoms and reduced mortality. However, due to limited study quality, no reliable answers are possible concerning the question whether LDL apheresis results in reduced cardiovascular morbidity/mortality or improved quality of life. The review concluded that the available evidence indicates a possible net benefit of LDL apheresis. Since the quality of the evidence is very low, treatment should be strictly restricted to patients with severe familial hypercholesterolemia who are resistant to standard care.

Bonnan et al. (2009) retrospectively studied the outcome of plasma exchange (PE) treated versus steroid-only treated spinal attacks in relapsing neuromyelitis optica (NMO) and extensive transverse myelitis (ETM). Ninety-six severe spinal attacks in 43 Afro-Caribbean patients were included in the study. PE was given as an add-on therapy in 29 attacks. Expanded disability status score (EDSS) was obtained before attack, during the acute and residual stage. We defined the DeltaEDSS as the rise from basal to residual EDSS. The DeltaEDSS was found to be lower in the PE-treated group (1.2 +/- 1.6 vs 2.6 +/- 2.3; P < 0.01). A low basal impairment is associated with a better outcome. Improvement was obtained in both NMO-IgG negative and positive NMO attacks. Minor adverse events manifested in seven PE sessions (24%). The authors concluded PE appears to be a safe add-on therapy that may be employed early in severe spinal attacks in the NMO spectrum disorders in order to maximize improvement rate. PE efficiency is independent of NMO-IgG positivity.

Kaynar et al. (2008) performed a retrospective review of the medical records of 57 neurological patients consecutively treated with therapeutic plasma exchange (TPE). TPE indications in neurological diseases included Guillain-Barrè Syndrome (GBS) (n=41), myasthenia gravis (MG) (n=11), acute disseminated encephalomyelitis (ADEM) (n=3), chronic inflammatory demyelinating polyneuropathy (CIDP) (n=1) and multiple sclerosis (MS) (n=1). Patient median age was 49; there was a predominance of males. Twenty-two patients had a history of other therapy including intravenous immunoglobulin (IVIG), steroid, azothioprin, and pridostigmine prior to TPE. Another 35 patients had not received any treatment prior to TPE. All patients were classified according to the Hughes functional grading scores pre- and first day post-TPE for early clinical evaluation of patients. The TPE was carried out 1-1.5 times at the predicted plasma volume every other day. Two hundred and ninety-four procedures were performed on 57 patients. The median number of TPE sessions per patient was five, and the median processed plasma volume was 3075mL for each cycle. Although the pre-TPE median Hughes score of all patients was 4, it had decreased to grade 1 after TPE. While the pre-TPE median Hughes score for GBS and MG patients was 4, post-TPE scores were decreased to grade 1. Additionally, there was a statistically significant difference between post-TPE Hughes score for GBS patients with TPE as frontline therapy and patients receiving IVIG as frontline therapy (1 vs. 3.5; p=0.034). Although there was no post-TPE improvement in Hughes scores in patients with ADEM and CIDP, patients with MS had an improved Hughes score from 4 to 1. Mild and manageable complications such as hypotension and hypocalcemia were also observed. The authors concluded TPE may be preferable for controlling symptoms of neuroimmunological disorders in early stage of the disease, especially with GBS.

Ruma et al. (2007) conducted a retrospective multicenter case series. Patients with a history of early second-trimester fetal loss secondary to severe maternal red cell alloimmunization or patients with markedly elevated maternal antired cell titers felt to be consistent with poor fetal outcome were offered treatment. Therapy consisted of serial plasmapheresis followed by weekly infusions of intravenous immune globulin (IVIG). Maternal titers were measured before and after plasmapheresis. Pregnant patients with either a history of a previous perinatal loss (n = 7) or markedly elevated maternal antibody titers (n = 2) were treated with combined plasmapheresis and IVIG. All 9 fetuses subsequently required intrauterine transfusions (median 4; range 3-8). All infants survived with a mean gestational age at delivery of 34 weeks (range 26-38 weeks). Maternal antired cell titers were significantly reduced after plasmapheresis (P < .01) and remained decreased during IVIG therapy. Serial peak middle cerebral artery velocities remained below the threshold for moderate to severe fetal anemia during therapy. The authors concluded that combined immunomodulation with plasmapheresis and IVIG represents a successful approach to the treatment of severe maternal red cell alloimmunization.[23]

There are several Cochrane reports available on plasma exchange for various diseases as outlined below:

- **Guillain-Barré Syndrome.** There is moderate-quality evidence that shows significantly more improvement with plasma exchange than supportive care alone in adults with Guillain-Barré syndrome without a significant increase in serious adverse events (Raphaël et al., 2012).
- **Haemolytic Uraemic Syndrome and Thrombotic Thrombocytopenic Purpura:** PE with FFP is still the most effective treatment available for TTP.

- **Myasthenia Gravis.** Many studies with case series report short-term benefit from plasma exchange in myasthenia gravis, especially in myasthenic crisis (Gajdos et al., 2002).
- **Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP).** Moderate to high quality evidence from two small trials showed that plasma exchange provides significant short-term improvement in disability, clinical impairment and motor nerve conduction velocity in CIDP but deterioration may occur afterwards (Mehndiratta & Hughes, 2012).
- **Treatment for IgG and IgA Paraproteinaemic Neuropathy.** Modest short-term benefit of plasma exchange in IgG or IgA paraproteinaemic neuropathy, over a short follow-up period, when compared to sham plasma exchange (Allen et al., 2007).
- **Renal Vasculitis.** Plasma exchange is effective in patients with severe ARF secondary to vasculitis (Walters et al., 2008).
- **Bullous Pemphigoid (BP).** The effectiveness of adding plasma exchange, azathioprine or mycophenolate mofetil to corticosteroids, and combination treatment with tetracycline and nicotinamide needs further investigation (Kirtschig et al., 2010).

National and Specialty Organizations

In 2019, the **American Society for Apheresis (ASA)** published the eighth special edition of evidence-based guidelines for the practice of apheresis medicine. They classified the indications for apheresis into four categories (I-IV) based on the quality of the evidence and the strength of recommendations derived from the evidence. These categories rate the indications for PP by condition and include the following (Padmanabhan et al., 2019):

- Category I: Disorders for which apheresis is accepted as first-line therapy, either as a primary standalone treatment or in conjunction with other modes of treatment. (Example: plasma exchange in Guillain-Barre´ syndrome as first-line standalone therapy; plasma exchange in myasthenia gravis as first-line in conjunction with immunosuppression and cholinesterase inhibition).
- Category II: Disorders for which apheresis is accepted as second-line therapy, either as a standalone treatment or in conjunction with other modes of treatment. (Example: plasma exchange as standalone secondary treatment for acute disseminated encephalomyelitis after high-dose IV corticosteroid failure; extracorporeal photopheresis added to corticosteroids for unresponsive chronic graft-versus-host disease).
- Category III: Optimum role of apheresis therapy is not established. Decision making should be individualized. (Example: extracorporeal photopheresis for nephrogenic systemic fibrosis; plasma exchange in patients with sepsis and multiorgan failure).
- Category IV: Disorders in which published evidence demonstrates or suggests apheresis to be ineffective or harmful. IRB approval is desirable if apheresis treatment is undertaken in these circumstances. (Example: plasma exchange for active rheumatoid arthritis).

SUPPLEMENTAL INFORMATION

None.

CODING & BILLING INFORMATION

CPT Code

CPT	Description
36511	Therapeutic apheresis; for white blood cells
36512	Therapeutic apheresis; for red blood cells
36513	Therapeutic apheresis; for platelets
36514	Therapeutic apheresis; for plasmapheresis
36516	Therapeutic apheresis; with extracorporeal immunoadsorption, selective adsorption or selective filtration and plasma reinfusion

HCPCS Code

HCPCS	Description
S2120	Low density lipoprotein (LDL) apheresis using heparin-induced extracorporeal LDL precipitation

CODING DISCLAIMER. Codes listed in this policy are for reference purposes only and may not be all-inclusive. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement. Listing of a service or device code in this policy does not guarantee coverage. Coverage is determined by the benefit document. Molina adheres to Current Procedural Terminology (CPT®), a registered trademark of the American Medical Association (AMA). All CPT codes and descriptions are copyrighted by the AMA; this information is included for informational purposes only. Providers and facilities are expected to utilize industry standard coding practices for all submissions. When improper billing and coding is not followed, Molina has the right to reject/deny the claim and recover claim payment(s). Due to changing industry practices, Molina reserves the right to revise this policy as needed.

APPROVAL HISTORY

10/12/2022	Policy reviews, no changes to criteria. Updated policy title and policy verbiage to replace “Plasmapheresis” with “Therapeutic apheresis.” Updated coding table to include all codes associated with therapeutic apheresis.
10/13/2021	Policy reviewed, no changes to criteria, updated references.
09/16/2020	Policy reviewed, clinical criteria changed based on the American Society for Apheresis 2019 indications for therapeutic apheresis and cytapheresis procedures. Updated and references.
06/22/2017	Policy reviewed, no changes.
030/8/2018	Policy reviewed, no changes.
09/18/2019	Policy reviewed, no changes, updated references.
08/23/2016	Policy reviewed, updated to include revised criteria according to the 2016 American Society for Apheresis guidelines.
12/16/2015	Policy reviewed, no changes.
04/24/2013	New policy.

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APPENDIX

Reserved for State specific information. *Information includes, but is not limited to, State contract language, Medicaid criteria and other mandated criteria.*