Urgent plasma exchange: how, where and when

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Introduction

Therapeutic apheresis has undergone a real technological revolution in recent years, with the adoption of procedures targeted at the most selective possible removal of pathological components present in the blood. These technological innovations and the ever more widespread adoption of evidence-based indications in the field of medicine have made it necessary for scientific societies to draw up guidelines on the clinical indications for the use of therapeutic apheresis[1].

Over the years, the Guidelines of the American Society for Apheresis (ASFA) have represented the main reference source for clinicians to evaluate the appropriateness of therapeutic apheresis. In 2010, only 3 years after the 2007 edition, the Fifth Edition of the Guidelines on the Use of Therapeutic Apheresis in Clinical Practice, drawn up by the Apheresis Application Committee of the ASFA, were published[2].

This new edition of the ASFA guidelines, like its preceding edition, used the methodological criteria of evidence-based medicine in evaluating the appropriateness of apheresis therapy, adopting the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system, which is used to evaluate scientific literature[3]. The GRADE system classifies the level of scientific evidence in relation to its scientific and methodological quality and translates it into recommendations of various strengths. This methodological updating of the guidelines enables the clinician to transfer the scientific evidence immediately into daily clinical practice.

Applying this method of evaluating scientific literature to the clinical use of therapeutic apheresis has been the key to overcoming the limitation inherent in the preceding definition of ASFA Categories of indications for apheresis, which was based on expert consensus. Using the GRADE system to redefine the criteria for assigning pathologies to treat into ASFA Categories has been particularly useful for overcoming the previously present dichotomy separating Categories I and II, seen as the only "real" indications for apheresis therapy, from Category III. The redefinition draws attention back to the pathologies in Category III which, in particular clinical situations, can have a strong grade of recommendation for therapy, even in the presence of lower levels of scientific evidence, such as that provided by series of clinical cases.

Furthermore, the consultation of the indications for treatment for individual diseases has been improved by the use of summary fact sheets in which the pathology, pharmacological treatment, and rationale and technical characteristics of the apheresis treatment are summarised and in which the ASFA Category with relative levels of evidence and recommendations are reported.

An examination of the ASFA 2010 guidelines shows that the traditional technique of therapeutic plasma exchange (TPE) is still the most widely used apheresis procedure because of its simplicity and cheapness, particularly in clinical situations in which therapeutic apheresis must be carried out urgently.

It should, however, be noted that the Apheresis Application Committee of the ASFA deliberately avoided, both in the introductory part and in the fact sheets dedicated to the individual diseases, dealing with the organisational aspects of managing critical situations by giving rules on the timing with which to carry out therapeutic apheresis (emergencies within a few hours, urgent cases within 24 hours, or planned treatment) since the presentation and progression of diseases requiring treatment differ in each patient.

The Apheresis Application Committee of the ASFA simply states that the patient's condition and clinical context must be considered individually

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when deciding the time to use apheresis treatment and that this decision must be taken on the basis of medical judgement after consultation between the clinician requesting the treatment and a doctor expert in apheresis. Since every patient is unique and there is a broad range of disease presentations and evolutions, it is not possible to categorise diseases and disorders to be treated with apheresis using the criterion of the timing of the treatment, even though there are pathologies in which therapeutic apheresis is among the acute treatments and should be carried out as soon as possible, such as thrombotic thrombocytopenic purpura, acute chest syndrome in sickle cell disease, thrombocytosis, hyperleucocytosis, hyperviscosity syndrome and malaria[2].

Returning to the statements of the ASFA, we can, therefore, define "urgent plasma exchange" as an apheresis treatment that is initiated as early as possible, and not beyond 24-36 hours after the clinical diagnosis, when the patient's life is threatened and there are no valid therapeutic alternatives. We believe that is useful to examine carefully some technical and organisational aspects presented in the guidelines on how, why and when to conduct an urgent TPE procedure.

How to evaluate a request for an "urgent "TPE?

The protocols and instruments used for therapeutic apheresis procedures work perfectly in patients with stable haemodynamic and physiological parameters. In patients in critical conditions with unstable haemodynamics and markedly pathological parameters, apheresis procedures can be less effective and poorly tolerated. For this reason it is important that the clinical and nursing management of the patient occurs in the context of close collaboration between the team caring for the patient and the team carrying out the therapeutic apheresis[4].

It is fundamental that the apheresis expert personally evaluates the patient and the clinical documentation. Plasma exchange must only be used in emergency/urgent situations after discussion among specialists with the aim of agreeing on the diagnosis and the possible indication for the apheresis therapy.

The apheresis expert has a precise role of consultant and intervenes in the therapeutic choices according to strict levels of decision: (i) indication for the use of apheresis that is consolidated and agreed upon, based on scientific evidence (ASFA Categories I and II), (ii) indication with limited scientific evidence for which apheresis is used only in the case of failure of other treatments (ASFA Category III), (iii) motivated refusal of the apheresis because of the lack of scientific evidence and lack of a therapeutic rationale (ASFA Category IV).

It is very important that plasma exchange is not used as a heroic treatment when "there is nothing left to offer".

Where to carry out "urgent" TPE?

In order to provide urgent plasma exchange it is important to have readily available medical and nursing staff expert in apheresis treatment and, likewise, rooms suitable for the treatment of patients who are often in a critical clinical condition. For this reason it is often necessary to carry out therapeutic apheresis in an intensive care unit. This compels the expert apheresis staff to share their skills and responsibilities with their colleagues in the intensive care units.

The collaboration between the various professional figures covers both clinical and technical aspects.

The intensive care physician must control the patient's metabolic function and, in particular, acid-base balance, respiratory function (above all in intubated patients), and cardiocirculatory function in view of the possible removal of drugs during the apheresis procedure.

The apheresis expert must control the heart rate and rhythm (with particular attention to any changes induced by the citrate used as anticoagulant or present in fresh-frozen plasma, if this is used as the fluid replacement), monitor blood pressure, evaluating both the apheresis flow velocity and volumes of reinfusion. It is also the duty of the apheresis expert: (i) to evaluate and control the peripheral venous accesses; (ii) decide whether to administer, during the procedure or prophylactically, calcium gluconate or calcium chloride to antagonise the effects of the citrate and corticosteroids or anti-histamine drugs if a transfusion reaction to fresh-frozen plasma occurs; and (iii) choose, on the basis of the pathology, clotting parameters, exchange volumes and frequency of treatment, which replacement therapy (albumin

4-5% or fresh-frozen plasma) to use. When blood components (fresh-frozen plasma, cryoprecipitate-poor plasma or red blood cells) are used for fluid replacement, careful monitoring is essential to pick up any signs of transfusion reactions or circulatory overload, given the rapid exchange times.

The intensive care specialist has the duty to determine whether the drugs necessary for the patient's treatment should be administered during the apheresis, although it is generally recommended that drugs are given after the apheresis treatment has been completed, and whether to position, when necessary, a large calibre, double-lumen central venous catheter which will not collapse under the high negative pressures at the sampling site and with the necessary characteristics to support apheresis therapy. In urgent procedures, particularly in children, it may be useful to position a femoral catheter[3].

When apheresis treatment is carried out "off site", an important aspect, besides the technical management of the plasma exchange, is the management of the venous accesses and of the central venous catheter. Venipuncture for peripheral venous accesses must be carried out by an apheresis nurse. The possibility of using already placed catheters, if of adequate calibre, for the reinfusion line should be evaluated. As far as concerns the use of a central venous catheter, it would be good practice for the apheresis staff to concord the maintenance procedures (washing of the catheter, dressing the insertion site) with the intensive care unit staff. The presence of expert medical apheresis staff at the start of procedure is essential in order to evaluate any corrections of the treatment protocol needed based on the evolution of the clinical state of the patient. It may be necessary, or requested by the nursing staff, for the apheresis expert to remain with the patient the whole duration of the procedure. It is fundamental that the expert apheresis nursing staff pick up the patient's reactions that are strictly of apheresis relevance (e.g., drop in blood pressure, hypocalcaemia, transfusion reaction to plasma).

Great care must be paid to differences in the ways of storing the materials needed for apheresis therapy between the intensive care unit and the apheresis staff's usual site of work in order to avoid errors in their use.

When to carry out urgent TPE?

For TPE to be effective, the clinical picture must be related to a high plasma concentration of a pathogenic substance whose rapid elimination can halt the evolution of the disease, there must not be valid therapeutic alternatives and the severity of the patient's conditions does not allow time to wait for a response to pharmacological therapy.

The indications for carrying out urgent plasma-exchange suggested by the ASFA 2010 guidelines are listed in Table I and include the pathologies for which evolution of the clinical picture can threaten the life of the patient[2]:

Table I - Indications for urgent Plasma Exchange (ASFA 2010 Guidelines)

Pathology	Category	Grade of recommendation
Thrombotic thrombocytopenic purpura	I	1A
Catastrophic antiphospholipid syndrome	II	2C
Acute pancreatitis due to hypertriglyceridaemia	III	1B
Intoxication by drugs or poisoning	II/III	2C
Hyperviscosity syndromes	I	1B
Acute fulminating hepatitis	III	2B
Acute inflammatory demyelinating polyneuropathy	I	1A
Myasthenia gravis	I	1A

In *thrombotic thrombocytopenic purpura*, the evolution of the disease can be rapidly fatal for the patient because of the neurological complications and for this reason plasma exchange is currently the only therapeutic procedure that can be used in an urgent situation. The rationale for plasma exchange lies in this procedure's dual mechanism of action of removing anti-ADAMTS 13 antibodies and in the infusion of active proteases present in the fresh-frozen plasma used as the replacement fluid in the forms in which ADAMTS 13 is lacking.

The apheresis treatment must be started as early as possible and in any case not more than 24 hours after the diagnosis has been made and continued daily until the patient's biochemical and clinical pictures have normalised. If apheresis is not immediately possible for organisational reasons, the patient can be

given an infusion of plasma, taking care not to cause haemodynamic overload. Published studies have not demonstrated a significant difference between the use of fresh-frozen plasma or cryoprecipitate-poor plasma as a replacement fluid[5]. The main complications of the use of plasma exchange in this condition are haemorrhage due to insertion of the central venous catheter and catheter-related sepsis. Care should also be taken with regards to possible anaphylactic reactions to plasma used as the replacement fluid[6].

Antiphospholipid syndrome presents clinically with vascular thrombosis and disorders of pregnancy. In the catastrophic form of antiphospholipid syndrome (CAPS) three or more organs are involved, with development of the manifestations simultaneously or within a week, histological confirmation of the occlusion of small vessels and serological evidence of the presence of antiphospholipid antibodies (anti-cardiolipin antibodies, anti-beta2-gp-I antibodies and lupus anticoagulant). There is often a combination of prolonged TTP with schistocytes (microangiopathic antiphospholipid syndrome, MAPS). This is a serious condition with a mortality rate of 50% due to myocardial thrombosis. The rationale for urgent apheresis treatment is the removal of pathogenic auto-antibodies and pro-coagulant factors[7]. Emergency plasma exchange should be carried out for 3 consecutive days, then on alternate days, with gradual suspension when the INR reaches 2.5-3.5 with remission of the thromboembolic disease and improvement of the organ pathology. Albumin can be used as the replacement fluid (also in the presence of microangiopathy) providing a supplement of antithrombin III at the end of the apheresis session (when the pre-treatment levels are borderline or below normal)[8].

Levels of triglycerides greater than 1,000 mg/dL, with consequent endothelial damage due to chemical irritation by free fatty acids, is often the cause of severe complications such as *acute hypertriglyceridaemia-induced pancreatitis*. Patients with this condition usually present with type IV or V hyperlipoproteinaemia, often associated with diabetes mellitus. The levels of triglycerides usually decrease when the patients starts to diet, but in some patients (with severe forms of hypertriglyceridaemia or pregnant women with acute pancreatitis) urgent plasma exchange can be a valid therapeutic option to reduce the blood levels of triglycerides rapidly. Plasma exchange carried out as early as possible produces a rapid improvement in the clinical and laboratory pictures, reducing morbidity and mortality. Ideally, the apheresis treatment should be started within 24 hours of the diagnosis; this treatment is able to reduce the triglyceride level by 70% through the exchange of one and a half volumes of plasma; the plasma exchange is suspended when the level of triglycerides reaches 500 mg/dL, although in most cases a single session is sufficient. Plasma exchange seems to be superior to cascade filtration because of the tendency of the chylomicrons and triglycerides to block the plasma filter. It can be useful to give fresh-frozen plasma as the fluid replacement in order to supply the lipoprotein lipases and apolipoproteins essential for the catabolism of triglycerides and to administer a bolus injection of heparin at the start of the procedure, given this drug's capacity to release lipoprotein lipases from the endothelium[9].

Plasma exchange is useful (within 36 hours) in cases of *poisoning* by *Amanita phalloides* and potentially useful in that due to heavy metals (mercury, cisplatin), chlorophenoxy derivatives, herbal products (e.g. kava kava/*Piper methysticum*) which cause acute fulminating hepatitis, whereas it has little effect in poisoning due to Paraquat. If there are any doubts on the toxicological characteristics (half-life, binding to plasma proteins) of the substance to be removed, a Poison Information Centre should be contacted.

In the case of *intoxication by drugs*, various factors affect elimination of the drug. The efficiency of removal of a drug is related to the drug's volume of distribution, plasma-protein binding, equilibrium between compartments and the amount of plasma exchanged. Furthermore, the drug's endogenous clearance (renal and hepatic) and its half-life should be evaluated in order to define the time to intervene. In general, the capacity of plasma exchange to remove drugs is overestimated because the procedure only acts on the intravascular compartment which is relatively small compared to the extravascular space. For the removal to be effective, it is important that the drug binds strongly to plasma proteins (>80%) and has a low volume of distribution (<0.2 L/kg weight)[10]. On the basis of these factors, plasma exchange has been demonstrated to be potentially useful in poisoning by

L-thyroxine, verapamil, diltiazem, carbamazepine, theophylline, cisplatin, vincristine, phenylbutazone, while it is not useful in poisoning by barbiturates, tricyclic antidepressants, benzodiazepines, phenytoin, and aminoquinolines (synthetic antimalarial drugs).

In *acute fulminating hepatitis* urgent plasma exchange is used to achieve rapid removal of the toxic factors responsible for the hepatic coma, such as aromatic amino acids, ammoniac, endotoxins, mercaptans and phenols and activated coagulation factors, tissue plasminogen activator, and fibrin degradation products; the haemostatic balance is also restored thanks to the use of fresh-frozen plasma as the replacement fluid[11]. With the introduction of cell-based hepatic support systems (bioartificial liver, extracorporeal liver perfusion, extracorporeal assist devices) or molecular-based ones (molecular adsorbents recirculation system, single-pass albumin dialysis) to bridge the gap while waiting for organ regeneration or a transplant, plasma exchange is now used in only sporadic cases.

With regards to the *hyperviscosity syndromes*, it is important to emphasise that, because of the individual response to plasma hyperviscosity, it is rarely necessary to carry out urgent plasma exchange in the syndromes characterised by the presence of M protein (Waldestrom's macroglobulinaemia, plasmacytoma) or kappa light chains, which tend to form asymmetrical, unstable, circulating polymers. Clinical manifestations of hyperviscosity syndromes can occur when the serum viscosity is more than 3 centipoise (cp) greater than water; with differences of 4 cp and 5 cp the prevalence of hyperviscosity syndrome rises to 67% and 75%, respectively. Urgent plasma exchange is indicated in the presence of severe neurological signs (convulsions or coma)[12]. A single session of plasma exchange reduces plasma viscosity by 20-30%; thus, the exchange of one plasma volume is sufficient to reduce the symptoms and normalise plasma viscosity when this is below 2.2 mPas, while three sessions are needed when the plasma viscosity is between 2.2 mPas and 6.0 mPas[13]. Still in the sphere of microcirculatory disorders related to plasma hyperviscosity, there is recently published evidence that selective apheresis treatments (cascade filtration, low density lipoprotein-apheresis) carried out within 24-48 hours can prevent irreversible auditory damage in sudden sensorineural hearing loss[14].

It is worth noting that the cellular causes of hyperviscosity (hyperleucocytosis, thrombocytosis), although rare, are associated with higher clinical risks, with severe effects on the central nervous system in particular. The treatment of choice is urgent therapeutic cytapheresis, which should be organised in the same way as previously described for plasma exchange[12].

It should also be remembered that therapeutic cytapheresis is used, albeit rarely, in the form of urgent red blood cell exchange in the treatment of cerebral malaria, babesiosis and acute chest syndrome in sickle cell disease[2].

Therapeutic apheresis is an alternative to the use of intravenous immunoglobulins, a consolidated therapeutic option for the treatment of autoimmune neurological disorders, as also confirmed by the 2011 Guidelines of the American Academy of Neurology[15].

Some of these disorders, in particular *acute inflammatory demyelinating polyneuropathy* or *Guillain-Barrè syndrome* and *myasthenia*, can present with severe neurological deficits (referred to as a myasthenic crisis in the case of myasthenia) and assisted ventilation and admission to an intensive care unit are sometimes necessary.

In these situations, urgent plasma exchange may be needed to facilitate the recovery of spontaneous ventilation[16].

Conclusions

The possibility of successful treatment of critical clinical conditions with urgent TPE procedures is limited to a few pathologies, so it is essential to follow guidelines based on published scientific evidence when choosing from therapeutic options in order to give the patient the appropriate treatment. It should, however, be emphasised that it is equally important for the management of emergencies with therapeutic apheresis to have organisational procedures that have been previously agreed between the clinicians who request a treatment and the medical experts in apheresis.

Since TPE is not without risks and complications, it should be carried out by staff who are skilled in procedures of therapeutic apheresis and in a suitable environment; these requisites are all the more important when a patient in a critical condition is treated urgently.

Keywords: therapeutic plasma exchange, TPE, emergency.

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