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THERAPEUTIC PLASMA EXCHANGE IN CLINICAL PRACTICE: LONG-TERM SINGLE CENTRE EXPERIENCE

Kes P, Bašić-Jukić N, Brunetta Gavranić B

Department of Nephrology, Arterial Hypertension and Dialysis, Department of Internal Medicine, University Hospital Centre Zagreb, Zagreb, Croatia

Abstract: Therapeutic plasma exchange (TPE) is a powerful tool in the treatment of a whole host of diseases and there is hardly any organ for which TPE has not been shown to have some beneficial effects. In most instances, TPE is indicated only as a last resort treatment if all conservative measures have failed. However, there are lifethreatening conditions where TPE is the primary mode of acute treatment. Results from recent randomized prospective controlled trials caused a narrowing of the spectrum of indications for use of TPE, while advances in the various fields of medicine and technology have enabled wider clinical application of this procedure and generated several new indications.

To define the current role of TPE, we retrospectively analysed changes in indications for TPE in our database, that contains information on all TPEs conducted during 27 years at University Hospital Centre Zagreb (a national referral centre for therapeutic apheresis, which covers approximately 90–95% of all TPEs performed in Croatia). The number of patients, including children and elderly people) who underwent this procedure and TPEs increased several-fold over 27 years of follow-up despite changes in the pattern of indications and the emergence of new, more selective therapeutic options (LDL-apheresis, immunoadsorption, etc.). With wider application of TPE, fear of its complications have diminished, which may be the reason for the more frequent treatment of very young children and very old patients. Our results derived from a large number of treatments indicate that TPE is a relatively safe method of treatment, providing it is carried out by experienced staff, and used for appropriate indications with all necessary precautions. Despite the development of more selective methods, TPE is still a widely applicable and useful procedure, possibly experiencing a *renesance* in this century.

Key words: Adult, Children, Complication, Elderly, Haematological disorder, Indication, Nefrological disorder, Neurological disorder, Therapeutic plasma exchange.

Therapeutic plasma exchange (TPE) is a powerful tool in the treatment of a whole host of diseases and there is hardly any organ for which TPE has not been shown to have some beneficial effects. In most instances, TPE is indicated only as a last resort treatment if all conservative measures have failed which as a rule are based on medical drug administration. The reasons for this are: 1. TPE is an extracorporeal blood purification method and therefore implies complex and expensive technology; 2. the need for large-bore venous blood access and in-hospital treatment; 3. often time-limited beneficial effects so that in some chronic diseases long-term extracorporeal therapy is required, and 4. high cost [1].

Since the introduction of TPE into clinical routine in Europe in 1978, and and very early thereafter in Croatia (February 1982), this technique has developed into a powerful interventional tool. The evolution of TPE might be viewed as a three-stage process.

The first phase was characterized by an enthusiastic welcome of this new tool which resulted in a rapid increase in indications for usage. It has been used extensively in the treatment of a broad range of immunological, neurological, haematological, nephrological and even dermatological or endocrinological diseases [2]. The evidence of its benefit was based mainly on uncontrolled, retrospective studies comprising only a few patients.

In the second phase, new technical developments tried to make unselective TPE more specific. The goal was to remove exclusively the target pathogenic (agents) while preserving most of the other valuable proteins, thereby avoiding the substitution of human albumin or fresh frozen plasma (FFP) and its possible side-effects. Cascade filtration using a second filter of smaller pore size in the plasma circuit improved the selectivity of IgM removal in Waldenström's disease or low density lipoprotein (LDL) cholesterol elimination in lipid apheresis. Most selective procedures were based on adsorption techniques. Protein A columns for selective IgG adsorption were applied in immunological diseases like systemic lupus erythematosus (SLE) or oncological diseases like AIDS-associated Karposi sarcoma. Neurological diseases such as myasthenia gravis (MG) or Guillain Barré syndrome (GBS) were treatable by immobilized tryptophan or phenylalanine. The selective removal of LDL-cholesterol and lipoprotein(a) (Lp/a/) was performed by procedures based on immunological or electrostatic interactions of the adsorber column with these atherogenic lipoproteins [3].

In the third phase, more sophisticated trials were performed to evaluate the clinical effects of TPE by using prospective, randomized, and prospective studies in larger patient groups. This led to a consolidation of indications. Finally, in 1993 members of *the Clinical Applications Committee of the American Society for Apheresis* (ASFA) specified for the first time the "hard" indications for performing TPE and related techniques [4]. The Fifth Edition of the ASFA Special Issue *Guidelines on the Use of Therapeutic Apheresis in Clinical Practice-Evidence-Based Approach* was published in 2010. This issue includes analysis based on the quality of evidence and the strength of recommendation derived from this evidence. The evidence-based approach is designed to achieve several objectives: 1. provides uniformity to category assignment and disease discussion while minimizing personal bias; 2. provides the strength of recommendation; and 3. provides comprehensive, yet condensed, information which could be shared with patients and clinical services requesting the use of TPE [5].

From the perspective of this historical background, there has been a shift from unselective TPE to selective procedures and from acute to chronic disease treatment. The reason are severe limitations in unselective TPE: 1. limited efficacy by restricted plasma volume that can be exchanged in a single session; 2. the elimination not only of the pathogenic proteins) which are normally present only in very small amounts, but also large quantities of beneficial, physiological proteins like immunoglobulins, albumin, and coagulation factors; and 3. substitution fluids are required which can cause allergic reactions or give rise to viral infections [6, 7]. Therefore, whenever possible, different technologies for selective removal of pathogen(s) should be applied. In this setting, high plasma or blood volumes may be treated which optimizes the clinical efficacy and minimizes adverse events (there is no need for substitution fluid) [8].

In our institution, University Hospital Centre Zagreb at Zagreb, Croatia as well as in most European Union countries, up to half of the TPE sessions performed are devoted to the mostly secondary prevention of atherosclerosis in hypercholesterolaemic patients. Although technologies for selective removal of LDL-cholesterol and Lp/a/ were initially performed exclusively in patients with familiar hypercholesterolaemia primary prevention of atherosclerosis) and in coronary patients, recent papers report on its beneficial effects on overt atherosclerosis of the lower limbs and the carotid arteries (secondary prevention of atherosclerosis) [9, 10] (Figure 1).

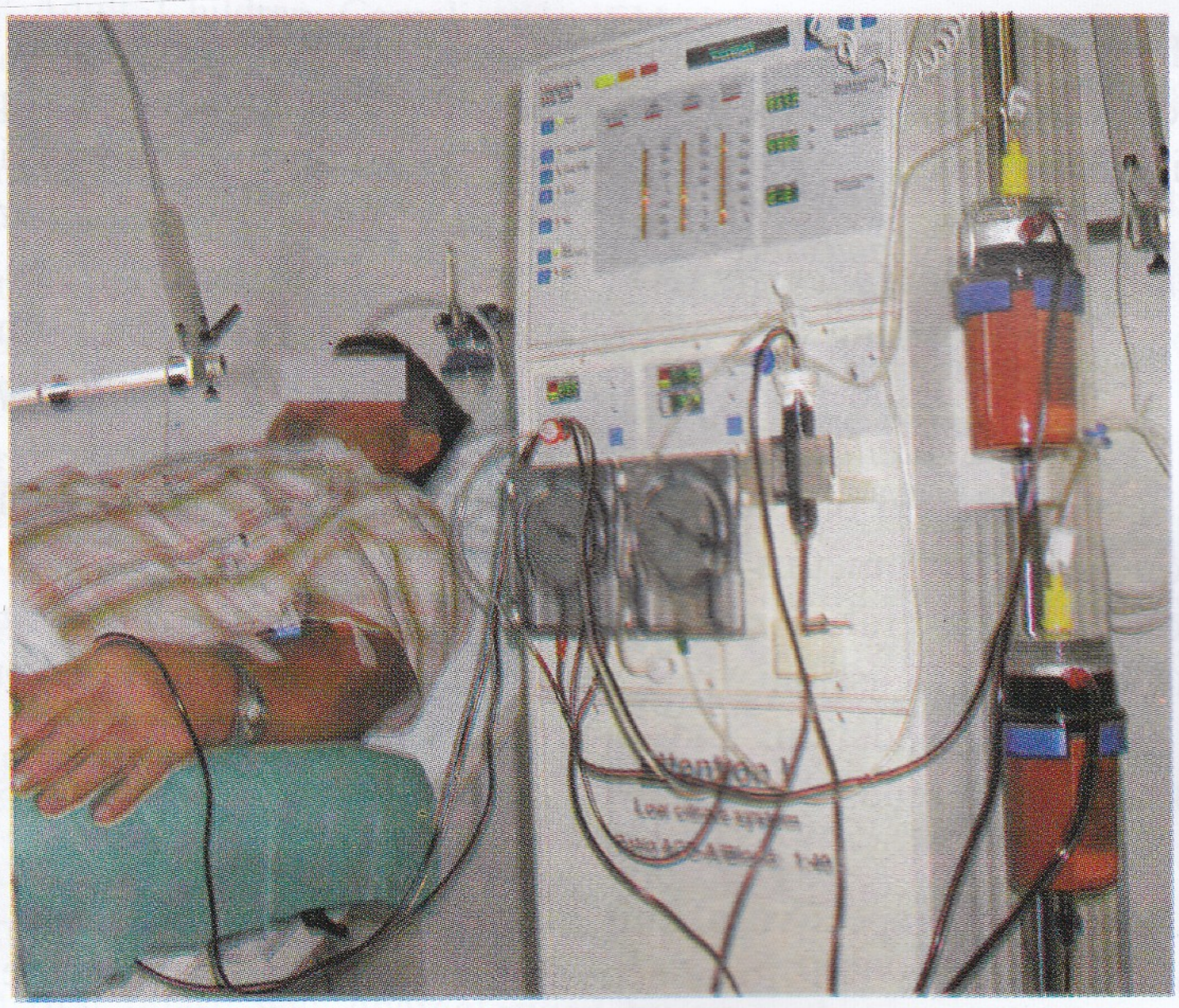

Figure 1 – LDL-apheresis in adult patient with severe hypercholesterolemia (LDL-Cholesterol ≥ 7.76 mmoL/L) in whom maximal dietary and drug therapy for more than one year has failed to lower cholesterol sufficiently (University Hospital Centre Zagreb, Croatia)

Direct adsorption of lipids DALI) apheresis is the first LDL-hemoperfusion technology allowing the adsorption of LDL and Lpa) directly from whole blood. Thus, no primary plasma separation is required which renders the treatment rapid and easy. Different adsorber sizes are used to tailor the LDL removal capacity to the needs of the patient.

Changes in indications for therapeutic plasma exchange

Results from recent randomized prospective controlled trials caused a narrowing of the spectrum of indications for use of TPE, while advances in the fields of medicine and medical technology have enabled wider clinical application of this procedure and generated several new indications.

Detailed records of therapeutic sessions and patient information have been maintained since the beginning of TPE treatments in the University Hospital Centre Zagreb, Croatia. We analysed data from the database of TPE in our department retrospectively from February 1982 to December 2008 for changes in indications for this therapeutic method and epidemiological information. The University Hospital Centre Zagreb is a national referral centre for TPE, and covers approximately 90–95% of all TPEs performed in Croatia. The changes in the number of TPE procedures and the number of treated patients per year, the number of TPEs per patient and the mean age of the patients has been analysed.

Indications for TPE were grouped according to medical specialty and correlated according to their frequency and the year that they were done. Special attention was given to the 5 most common indications for TPE during the first 5 years (1982–6) and the last 5 years (2004–8) of follow-up. We also calculated the percentage of the top 5 most common indications for TPE and compared changes over the years.

From 1982 to 2008, we performed 6,596 TPEs for 49 conditions. Altogether 678 patients were treated with TPE, with 194 treated on several occasions over years due to relapse of their disease. The numbers of TPEs and patients treated with this procedure increased several-fold over the years (Figure 2), yet there was no statistically significant difference in the mean number of TPEs performed per patient per year (mean 6.6; range, 11.3–4.2 TPEs/patient). The mean age of the patients was 35.3 years (range, 1–83 years) and it has increased significantly over the years [11].

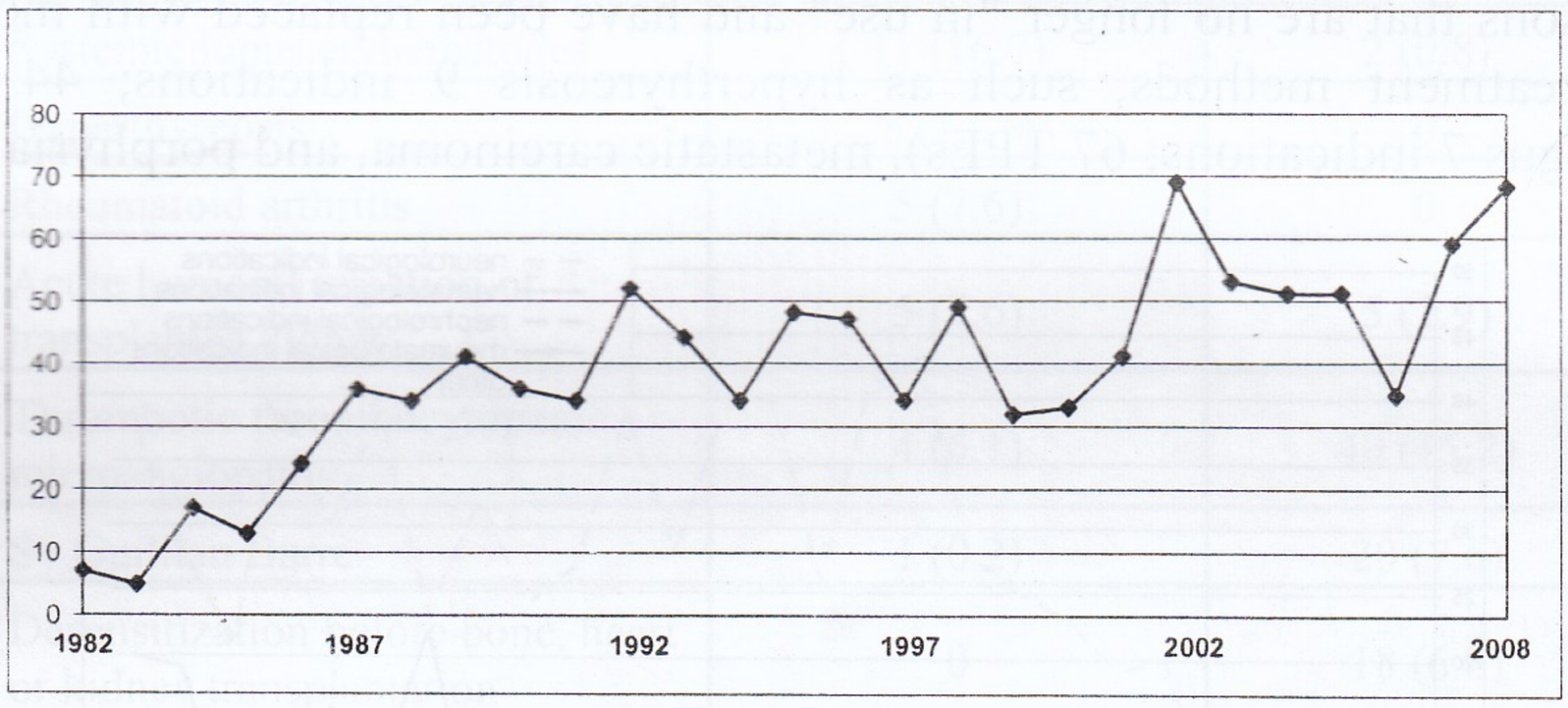

Figure 2 – Number of treted patients per year

The numbers of patients treated with TPE procedure increased several-fold over 27 years of follow-up.

The disorder that most frequently resulted in an indication for TPE was myasthenia gravis (577 indications; 55% of all indications), with 2,783 procedures done over 27 years. The second most common indication for TPE was (thrombotic thrombocytopenic microangiopathy thrombotic thrombocytopenic purpura and haemolytic uremic syndrome) with 91 indications and 1,060 TPE procedures. The third was Guillain-Barré syndrome (84 indications; 498 procedures). The number of TPEs performed for desensitization before bone marrow transplantation and for hyperviscosity syndrome due to Waldenström macroglobulinaemia and multiple myeloma also increased significantly in the last decade (41 indications, 83 TPEs; 25 indications, 161 TPEs, respectively). Only 6% of all TPEs were done for renal diseases, but in the 6 most recent years, we recorded a clear increase in their number. This is the consequence of the higher number of kidney transplantations in the last few years in our Centre and their

complications: acute humoral rejection of transplanted kidney (25 patients; 169 TPE), post-transplant recurrence of focal segmental glomerulonephritis (9 indications; 85 TPE) and desensitization before kidney transplantation. It is interesting that we also recorded a comparable increase in the number of patients who needed TPE for rapidly progressive glomerulonephritis (28 patients; 280 TPE) [11] Figure 3).

From 1982 to 1989, almost 20% of all diseases treated by TPE were from the field of rheumatology (systemic *lupus erythematosus* /SLE/, rheumatoid arthritis /RA/, systemic sclerosis, polymyositis, some forms of vasculitis, and Sjögren syndrome). After this period, there was a sharp decrease in the number of rheumatological indications for TPE. Nevertheless, SLE remains the fourth most common indication for TPE 43 indications; 593 procedures), and rheumatologic diseases represent 6% of all indications for TPE (Figure 3). During first decade of our follow-up, a significant number of TPEs were performed for reasons that are no longer "in use" and have been replaced with more efficient treatment methods, such as hyperthyreosis 9 indications; 44 TPEs), pemphigus 7 indications; 67 TPEs), metastatic carcinoma, and porphyria [11].

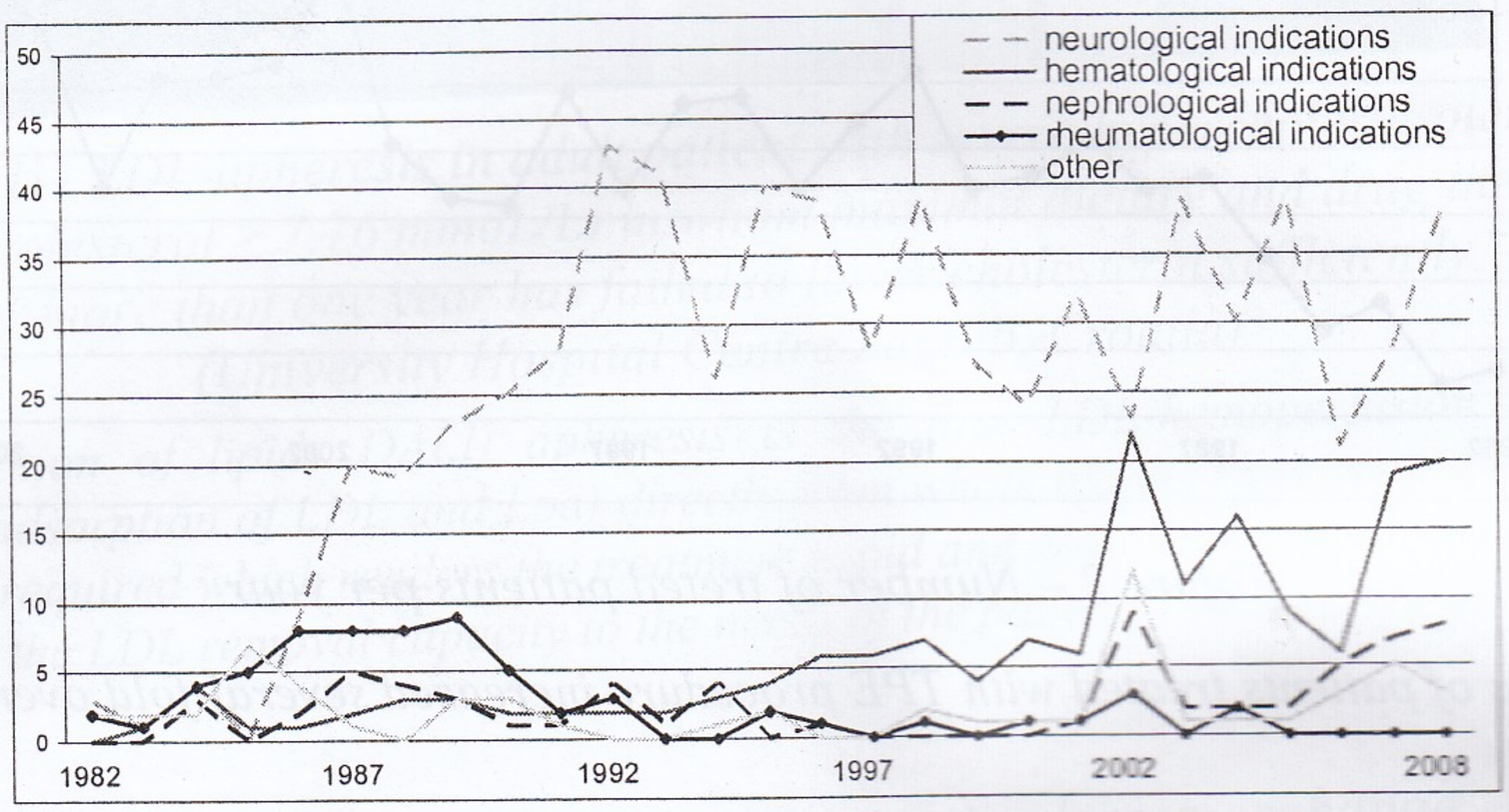

Figure 3 – Indications for therapeutic plasma exchange in a year according to field of medical speciality

The 5 most common indications for TPE during first 5 years of follow-up (1982–6) were compared with the 5 most common indications for TPE during last 5 years of follow-up (2004–8) (Table 1). The most common disorder *myasthenia gravis*) remained the same during both periods. Three disorders that were among the 5 most common indications for TPE during the first 5 years (SLE, RA, and hyperthyreosis) became obsolete. The fifth most common indicator from 1982–9, acute humoral kidney rejection, is still in use, but not as often as before. New indications such as thrombotic thrombocytopenic microangiopathy; desensitization before bone marrow, kidney, and heart transplantation; Guillain-Barré syndrome; and rapidly progressive glomerulonephritis

have emerged and are now prevalent as a result of new therapeutic procedures and knowledge gained in the field of medicine.

Table 1

Comparison of use of therapeutic plasma exchange during 1982–1986 and 2004–2008 for the five most frequent indications

Time period year) / Indication	1982–6	2004–8
	N (%)	N (%)
Myasthenia gravis	12 (18.2)	123 (46.6)
Systemic lupus eryhematodes	11 (16.7)	2 (0.8)
Hyperthyreosis	8 (12.1)	0
Rheumatoid arthritis	5 (7.6)	0
Acute humoral rejection of transplanted kidney	5 (7.6)	5 (1.9)
Thrombotic thrombocytopenic microangiopathy	4 (6.1)	40 (15.2)
Sy Guillian Barre	1 (0.2)	20 (7.6)
Desensitization before bone, heart or kidney transplantation	0	18 (6.8)
Rapidly progressive glomerulonephritis	0	10 (3.8)
Total	66 (62.2)	264 (79.9)

From 1982 to 1986, the 5 most frequent indications for TPE represented 62.2% of all indications, whereas during the last 5 years of follow-up, the percentage was 79.9%. The percentage that represent the 5 most frequent indications for TPE rises from the beginning of 1982 until 1992 when it comprises more than 90% of all TPE procedures. The numbers remain that way until 2000 after which the spectrum of indications grows again. The new indications belong primarily to Category I or II, according to the guidelines of *the American Society for Apheresis*. In the 90's 91.5% of indications belong to category I and II, and in this century, the percentage is almost the same (88.6%) [11] (Figure 4). Increase in the number and diversity of indications for TPE can be attributed to better medical diagnostics, validation of new indications, and wider application of new therapeutic procedures such as transplantation.

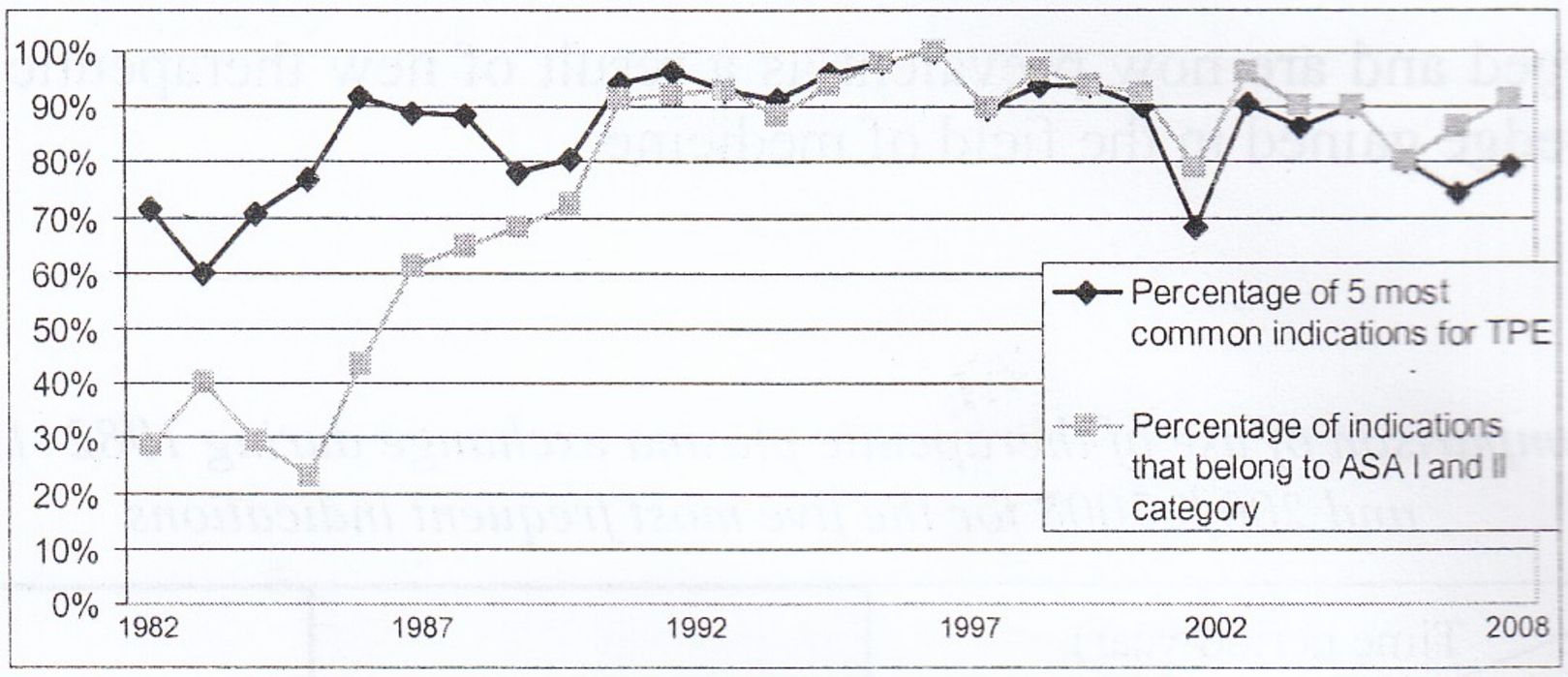

Figure 4 – Percentages of the 5 most frequent indications from all of the indications for TPE and percentage of indications that belong to Category I and II according to American Society for Apheresis of the total number of therapeutic plasma exchange

Despite the development of more selective methods and the elimination of some indications by the results of prospective randomized controlled trials, TPE is still a widely applicable and useful procedure, possibly experiencing a "renaissance" in this century.

Therapeutic plasma exchange in paediatric patients

Although the principles of the technique of TPE performed in children are the same as in adults, apheresis personnel who are not familiar with paediatric patients may be uncomfortable providing apheresis therapy for them. The use of TPE in paediatric patients remains limited for two reasons. The first is a lack of generally accepted indications and treatment schedules. Apheresis has not been perceived as a first-line therapeutic modality in paediatric patients, even in illnesses in which the efficacy in adults has been proven through controlled studies or clinical trials. The pathophysiology of a particular disease and the physiological responses to therapy may differ in children. A second reason for the limited usage of TPE in children is technical difficulty. Apheresis equipment was designed for adults and it is not possible for operators to perform safe procedures in infants and small children without modifying procedures [12]. In addition, difficulty in securing adequate vascular access may discourage or even prohibit a trial of TPE in children. Nevertheless, TPE has a definite role in the treatment of certain disorders in paediatric patients as a primary, standard therapy or as a first-line adjunct to primary therapy. If adequate vascular access can be established, children should not be denied TPE because they are very small, severely anaemic, or haemodynamically unstable.

Between 1982 and 2005, 61 consecutive children (33 male, 28 female) with a mean age of 5.1 ± 4.6 years (3 months to 15.4 years) and a mean weight of 19.9 ± 13.9 kg (5 to 52 kg), with renal and/or extra-renal diseases requiring TPE procedures have been treated in our centre. The overall number of proce-

dures performed were: 284 TPE and 66 LDL-apheresis sessions. Our therapeutic protocol involves blood flow of 20–100 ml/min and ultrafiltration of 5–20 ml/min. In each 70–120 minute session we exchanged plasmatic volume with FFP or with a solution of 5% albumin in lactated Ringer's, using heparin (10–20 UI/kg/h). We used Diapact monitor (B. Braun AG, Germany), Prisma Flux monitor (Hospal-Gambro, Sweden) and DALI monitor (Fresenius Medical Care, Germany). As plasma separator, we used a filter made of polypropylene, 0.2 m^2 surface, 30 ml priming (Hemaplex BT 900). DALI filter of 500 ml has been used for LDL-apheresis.

Haemolytic uremic syndrome was the most commonly treated disease (24/61 cases) with good results in 14/24 cases (Figure 5). We recorded good results in vasculitis as well, in one girl with focal glomerulosclerosis in transplanted kidney and rapid improvement in all children with Guillaine-Barré Syndrome. The treatment was effective in metabolic disorders such as tirosynemia and familiar hypercholesterolemia. Only 4/12 patients with acute liver failure due to viral hepatitis recovered. Therapeutic apheresis has also been used in the treatment of phalloid mushroom intoxication in 5 children (age 30 months to 12 years) (Figure 6). Since the toxins of *Amanita phalloides* are not demonstrable within plasma after 48 hours, TPE has been started early, within 20 and 36 hours. We had poor result in one of 5 cases.

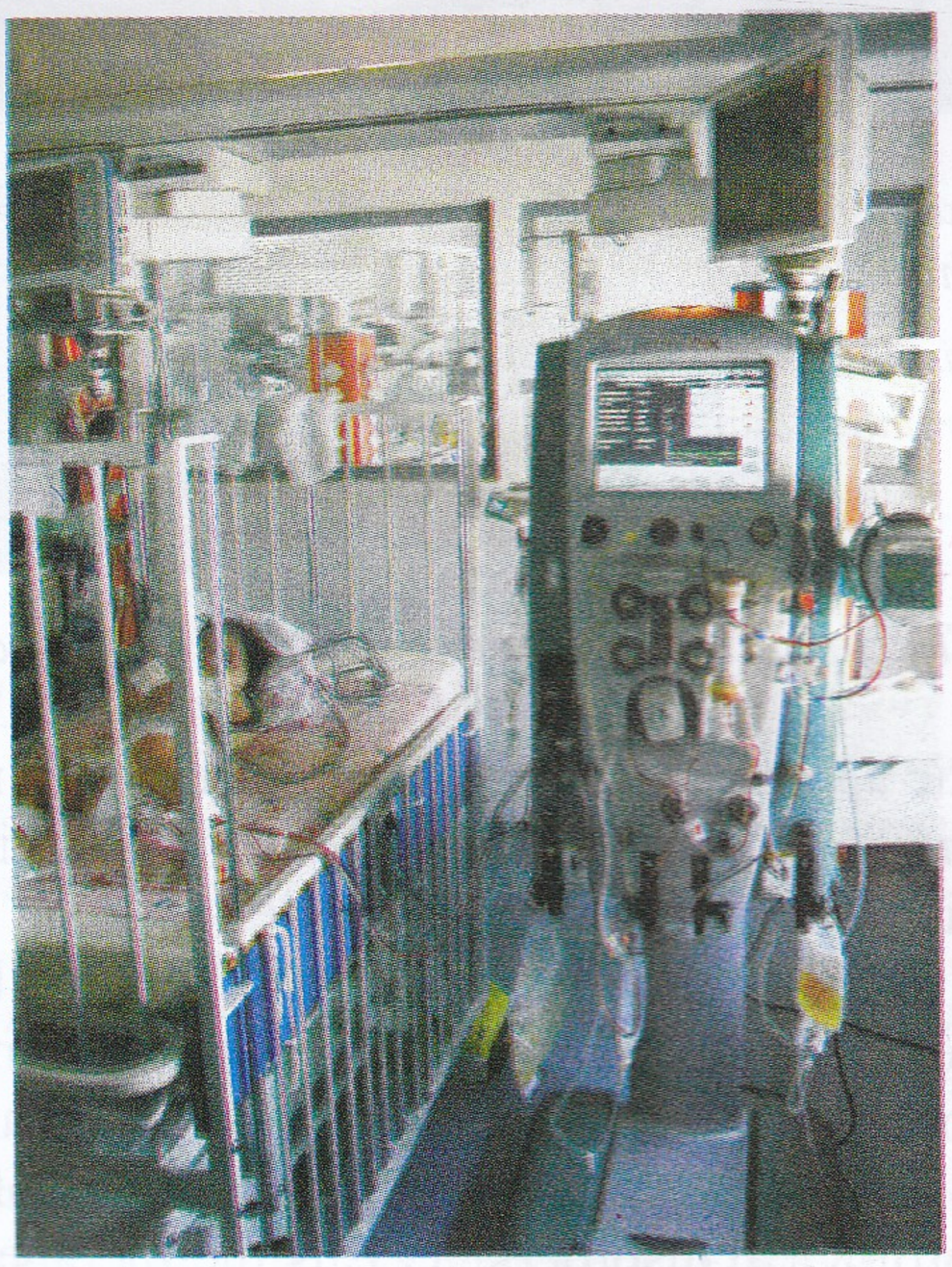

Figure 5 – Pediatric therapeutc plasma exchange in patient with hemolytic uremic syndrome University Hospital Centre Zagreb, Croatia)

Hemolytic uremic syndrome HUS) is a classic disease of nephrology, initially described as fatal renal cortical necrosis in children. It is defined by renal thrombotic microangiopathy, also the characteristic lesion of thrombotic thrombocytopenic purpura TTP), and by throm-

bocytopenia and microangiopathic hemolytic anemia. Its course also has changed since its initial description, with the recognition in 1982 of Shiga toxin-producing Escherichia coli typically 0157:H7) as a new human pathogen causing epidemic hemorrhagic colitis. These bacteria are now the predominant etiology of HUS in children.

Complications were rare and no viral infection was found in any patient. Our data show that it is possible to use TPE and LDL-apheresis in paediatric patients.

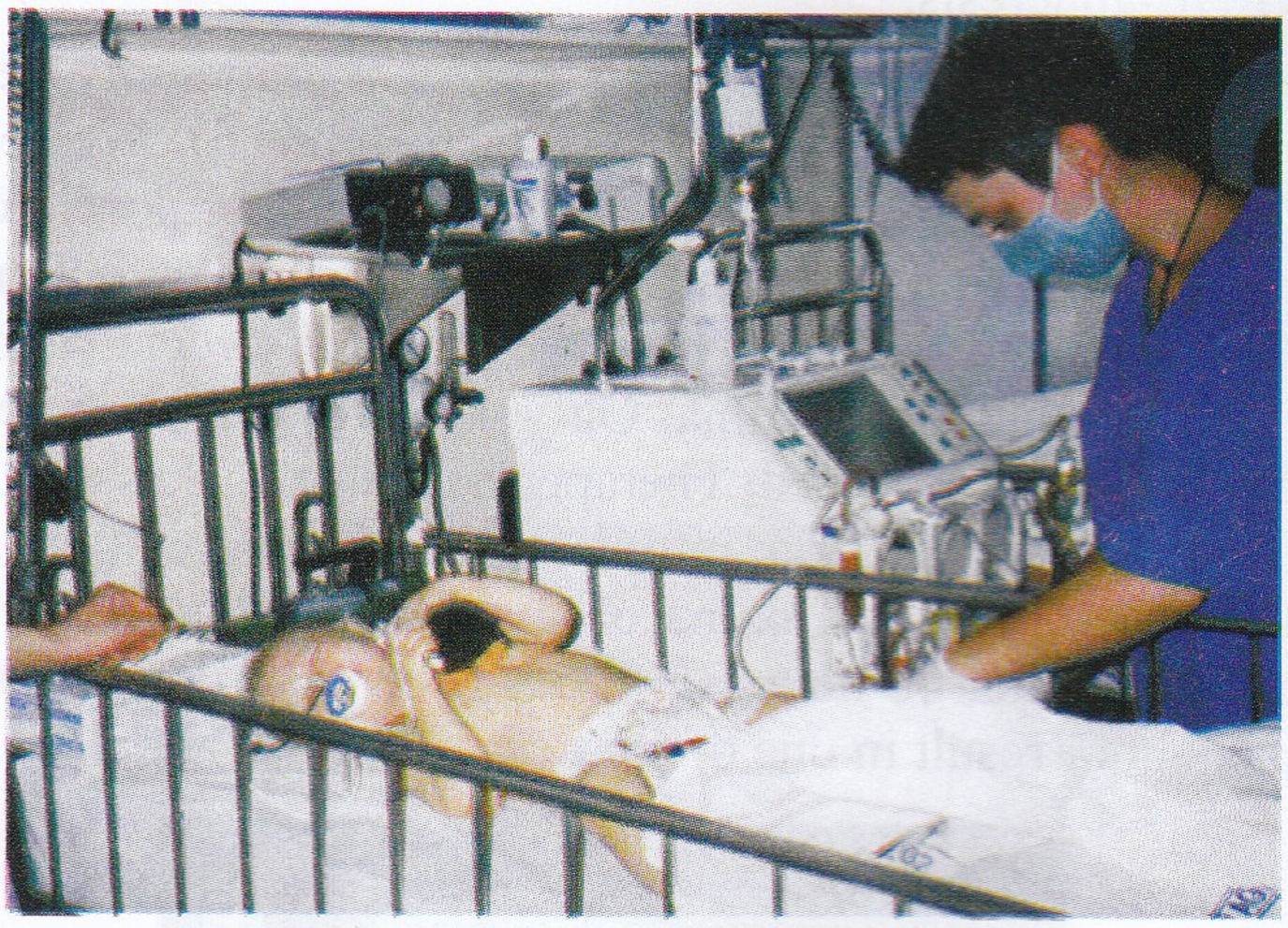

Figure 6 – The treatment of phalloid mushroom intoxication in one thirty months old child (University Hospital Centre Zagreb, Croatia)

Therapeutic apheresis has also been used in the treatment of phalloid mushroom intoxication. In this potentially fatal intoxication, TPE is at least as effective as hemoperfusion in reducing mortality from as high as 30–50% with conventional therapy, to less than 20%.

Therapeutic plasma exchange in adult patients

Therapeutic apheresis is used to treat diseases in many different medical specialties, but ***neurological*** disorders are currently leading indications for TPE in our registry as in other registries worldwide [13–15]. Therapeutic efficacy of plasma exchange in certain neurological conditions, including myasthenia gravis, Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, and paraproteinemic polyneuropathic disorders, has been demonstrated in large randomized controlled studies with a high level of evidence [16, 17]. In some of these neurological disorders, TPE is the therapeutic gold standard (Figure 7) to which new treatments are compared, whereas in other neurological disorders, the therapeutic value of plasma exchange remains less clear. The predominance of neurological indications started in 1987 with a sharp rise in the number until 1992. After that year and until the end of the follow-up period, the

number of neurological indications stagnated. Neurological indications still constitute the largest group of indications for TPE, but their number is not increasing. The cause is probably the use of high doses of intravenous immunoglobulin in the treatment of Guillain-Barré syndrome and myasthenia gravis, 2 leading neurological indications for TPE worldwide [18].

Two disorders, myasthenia gravis with 577 indications and 2,783 TPE procedures and Guillain-Barré syndrome with 84 indications and 498 TPE procedures, combined with other neurological indications (sclerosis multiplex, encephalitis, neuromyotonia, etc), constituted 66% of all indications in the adult population for therapeutic apheresis and gained predominance after 1987 [7].

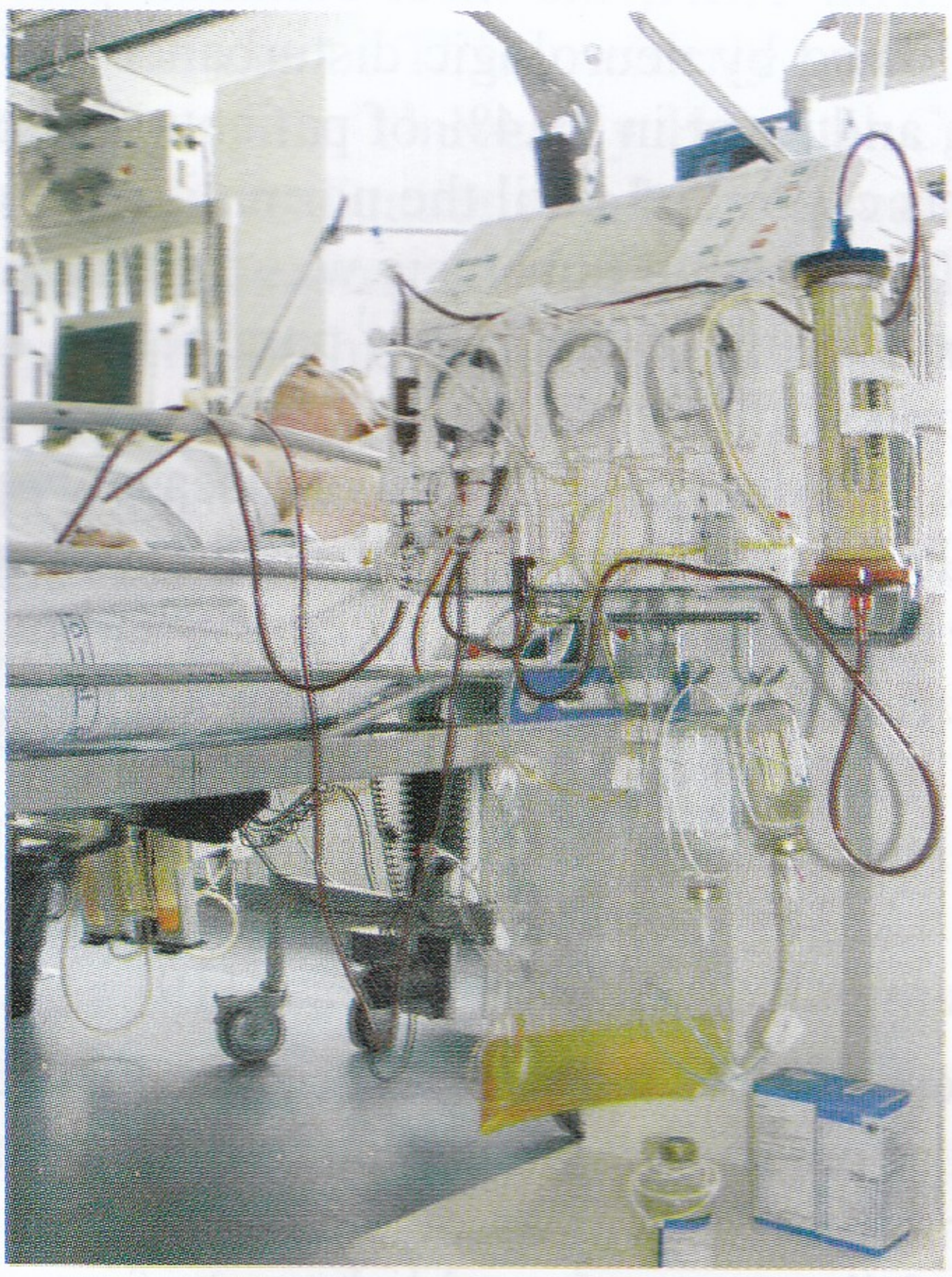

Figure 7 – Severely affected patient with Acute inflammatory demyelinating polyneuropathy (AIDP; Guillain-Barre syndrome) required mechanical ventilation and apheresis treatment in Neurologic intensive care unit
(University Hospital Centre Zagreb, Croatia)

Acute Inflammatory Demyelinating Polyneuropathy (AIDP) or the Guillain-Barre´ Syndrome is an acute progressive paralyzing illness affecting both motor and sensory peripheral nerves. Typically the disease begins with symmetrical muscle weakness and paresthesias that spread proximally. Progression, which can occur briskly over several weeks, may involve respiratory and oropharyngeal muscles in more severe cases. Thus, mechanical ventilation is required for approximately 25% of patients. Autonomic dysfunction can cause variability in blood pressure and heart rate. Spontaneous recovery may occur, however up to 75% of patients develop long-term neurologic deficits. Mortality is estimated at 5%. The results of several controlled trials comparing TPE to supportive care alone indicate TPE treatment can accelerate motor recovery, decrease time on the ventilator, and speed attainment of other clinical milestones. While recovery with TPE is improved, the

duration of disability from AIDP remains significant. For example in the French Cooperative Study, median time to wean from mechanical ventilation was 18 days versus 31 days for TPE compared to control, respectively. In the North American Trial the median time to walk without assistance was 53 days versus 85 days.

Thrombotic microangiopathy (TMA) is a syndrome characterized by thrombocythopenia, microangiopathic haemolytic anaemia, neurologic abnormalities, fever and renal dysfunction. In an retrospective analysis sought to determine the clinical characteristics and outcome of patients with TMA treated with TPE at the University Hospital Centre Zagreb, Croatia from 1983 to 2005. In 17 TMA patients (10 male and 7 female, age ranging from 18 to 74 years) have been diagnosed with TMA, the most common presenting symptom was purpura in 76.5%, followed by neurologic disturbance in 70.5%, renal function abnormality in 41.1%, and fever in 29.4% of patients. Patients were treated with a daily TPE, which was continued until the normalization of platelet count with minimal haemolysis. Therapeutic apheresis was first tapered and later discontinued with careful monitoring of laboratory parameters. Of the 17 patients, 13 achieved complete remission after 5 to 32 sessions, two had partial response, and 2 had no response and died of progressive disease. Four patients developed chronic relapsing TTP/HUS, and 3 of them progressed to end-stage renal disease. Survival at one year in our series exceeds 88%, but decreased with duration of follow-up. Overall, with the median follow-up of 5 years, 6 patients died from consequences of TTP/HUS 35.3%); 3 with chronic TTP/HUS, and 2 in the acute phase of progressive disease. Both of them had renal failure as one of the presenting symptoms. A 74-year-old man who developed TMA after prostate cancer died from disseminated malignant disease [19].

Our results demonstrate high incidence of renal function abnormalities in patients with TMA at presentation, but also in long term follow-up. Development of end-stage renal disease was associated with poor prognosis [19]. Further studies, long-term follow-up and establishment of international registries are needed to clarify many dilemmas associated with the diagnosis, treatment and outcomes of patients with TMA.

Within the next few years, haematology or nephrology may take the leading position, because they are progressing rapidly and creating new uses for TPE implementation. Included in this group are rapidly progressive glomerulonephritis (RPGN) often associated with the presence of autoantibodies, the glomerulonephritides associated with anti-GBM antibody (Goodpasture's syndrome), IgA mesangial deposition (the renal component of Henoch-Schönlein purpura), lupus erythematosus, cryoglobulinemia and the antineutrophil cytoplasmic antibody (ANCA)-associated pauci-immune group [20]. In each of these cases, apheresis may provide a therapeutically useful option. In kidney transplantation, TPE was performed for the following indications: acute humoral rejection, treatment of highly sensitized patients, crossmatch positive patients,

ABO incompatible recipients awaiting living donor kidney transplantation and recurrent focal segmental glomerulosclerosis (FSGS) [21].

Finally, there are renal diseases in which the immune component is less clearly involved with pathogenesis but for which TPE may offer a clear benefit, such as in the acute renal failure associated with 'cast nephropathy' (multiple myeloma) [22], or hyperviscosity syndrome in patients with plasma cell dyscrasias [23].

Therapeutic plasma exchange in elderly patients

Data regarding the use of TPE in elderly patients is lacking. Therefore we analyzed the database of the University Hospital Centre Zagreb (634 patients, 6,237 procedures) for indications and complications in patients aged ≥ 65 years or older who were submitted to TPE during the period from 1982 to 2007. A total of 50 patients in this age group were submitted to TPE, and their median age was 69 years (range 65–83) (Figure 8). This population underwent 323 episodes of TPE, mostly with albumin solution as the replacement fluid (94.0%), and blood access was usually via peripheral veins (72.0%). The number of TPE procedures ranged from 1 to 30 *per* patient (average 6.46), and the number of sets ranged from 1 to 6 (average 1.8).

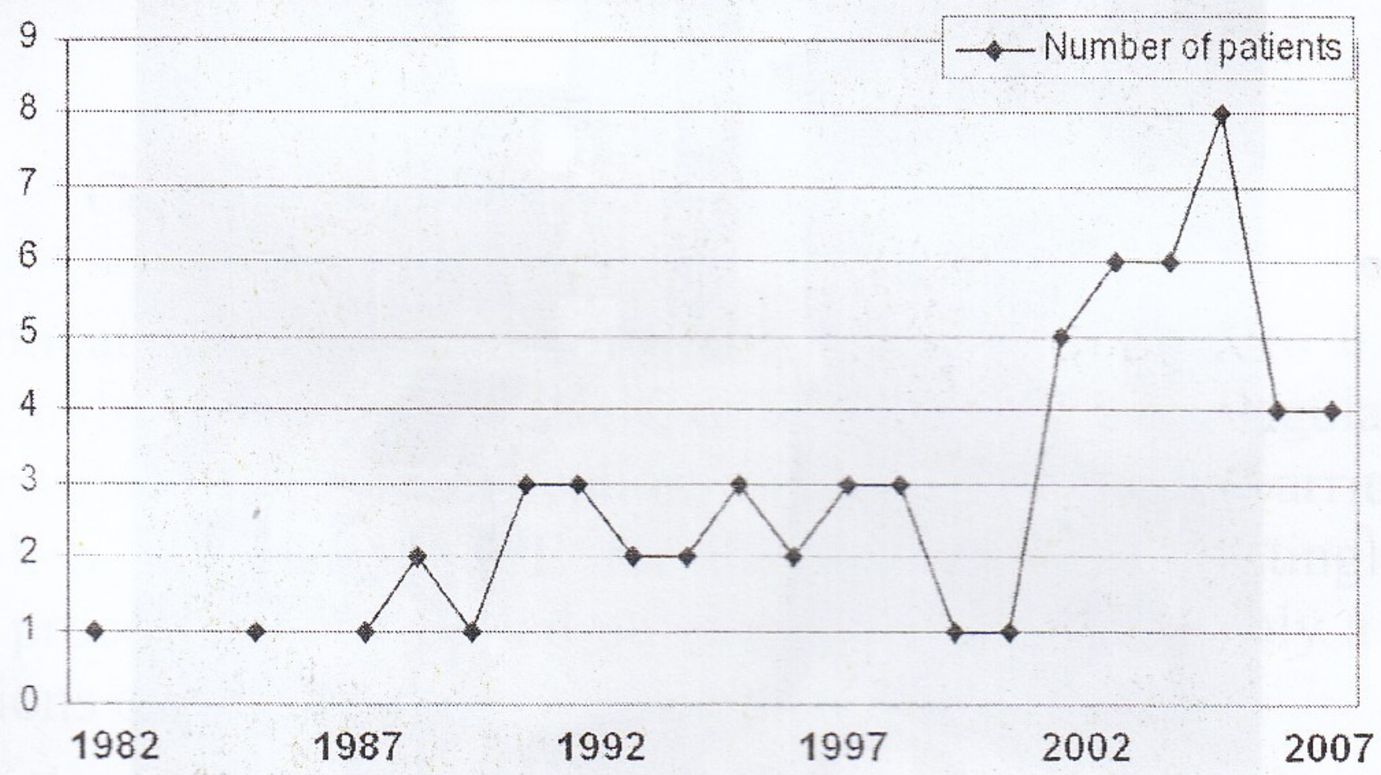

Figure 8 – Number of elderly patients submitted to therapeutic plasma exchange per year

An total of 50 (7.8%) elderly patients has been treated with TPE in the period from 1982 to 2007. Age (years) distributon: ≥ 65, 50 patienst; ≥ 75, 7 patients, and ≥ 80, 3 patients.

The most common indication for therapy (76.0%) was neurological (e.g. myasthenia gravis and Guillain–Barré syndrome), which was more common than in the entire population (i.e. of all age groups) 60%). The second most common indications were haematological diseases (Figure 9), followed by into-

xications and Goodpasture's syndrome. Ninety-four percent of patients showed improvement, 2 patients with Guillain–Barré syndrome died, and a patient with pemphigus vulgaris had no change in clinical status, compared with 75% of younger patients whose status improved after TPE. Complications occurred during 11.5% of treatments, compared to 3.9% in the younger group. Treatment protocol did not differ from the protocol used for younger patients. Careful and balanced substitution of potassium and calcium almost eliminated complications associated with electrolyte imbalance such as cardiac arrhythmias, paresthesia, and muscular cramps) [1, 7] that may be fatal in elderly patients. Heparin was used for anticoagulation in the majority of patients. For a significant proportion of patients, anticoagulant treatment was contraindicated. Clotting was the most common complication (3.7%), which also occurred in 2 out of 4 patients treated with nadroparin. It is possible that we used too small a drug dose (85–90 IU/kg). Circulatory problems were more frequent in elderly patients (1.20% vs. 0.17% in the younger group). This group of patients should be carefully followed up during the TPA procedure to recognize and treat cardiovascular complications. Frequent determinations of blood pressure during the procedure, balancing the replacement fluid rate with the plasma removal rate, replacement of calcium and potassium, and a relatively high percentage of protein in the replacement fluid are necessary to decrease the incidence of circulatory disturbances [1, 7].

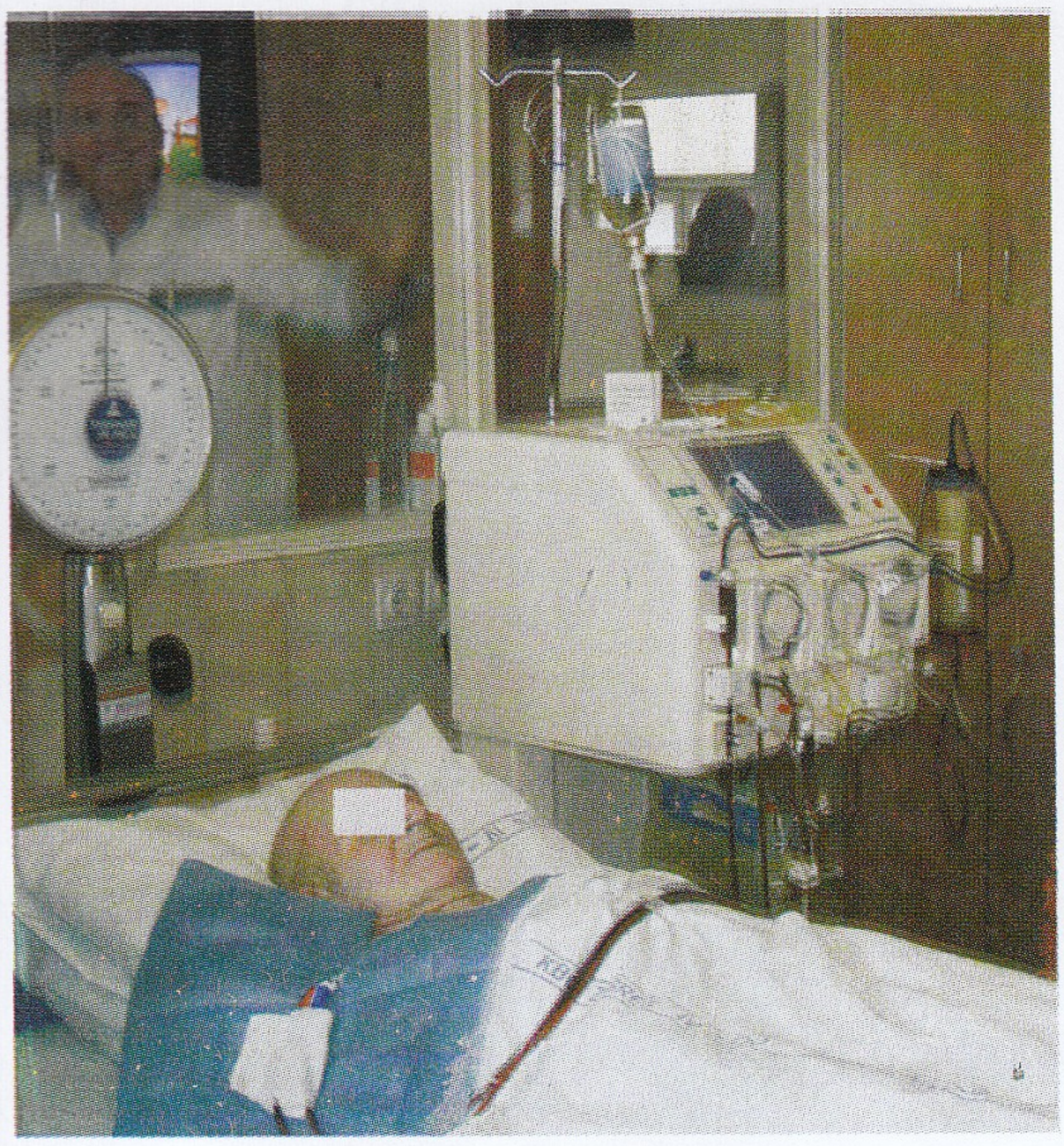

Figure 9 – 82-years male with Waldenström's macroglobulinemia and hyperviscosity syndrome (University Hospital Centre Zagreb, Croatia)

Because the offending protein in Waldenström's macroglobulinemia is a high molecular weight monoclonal IgM, TPE is very effective in its removal because 70% to 80% of IgM is

contained within the intravascular space. If symptomatic hyperviscosity is present, plasmapheresis becomes the treatment of choice. Daily or every other day, single plasma volume exchanges are generally used initially until symptoms are relieved. Delivered alone or in combination with drug therapy, TPE may be repeated on a less frequent basis, such as once per week, as needed for control of symptoms. This schedule of TPE may be needed during an initial course of cytotoxic drug therapy until the offending protein level is brought under control. Cytotoxic therapy with alkylating agents, including chlorambucil or cyclophosphamide, along with glucocorticoids, can be very effective in lowering the concentration of paraprotein in Waldenström's macroglobulinemia.

Two elderly patients with Guillain–Barré syndrome died from respiratory insufficiency. A patient with paraneoplastic cerebellar degeneration died 3 months after treatment with TPE from disseminated malignant disease, but free of neurological symptoms. A patient with pemphigus vulgaris had no change in clinical status after TPE. The clinical status of other patients improved after treatment with TPE (94%). Better treatment outcomes were recorded in elderly patients than in patients from the younger group, who responded in 75% of cases. However, the final outcome was determined by their overall status and concomitant diseases.

Therapeutic apheresis is rarely used in the elderly population. However, when carried out by experienced staff, it is a safe and efficient method that may significantly improve the outcome of elderly patients with appropriate indications.

Complications of therapeutic plasma exchange

Complications associated with TPE might be related to blood access, replacement fluids, the procedure itself, or to the use of anticoagulants. Awareness of the possible severe complications is one of the major barriers for some physicians when considering TPE for their patients. Interestingly, although thousands of procedures are carried out each year, there are only a few reports on complications of TA [23–25].

From the introduction of TPE to University Hospital Centre Zagreb in 1982, until the end of 2003, 509 patients (184 male and 325 female, with an age range of 2–82 years) were treated with 4,857 apheresis treatments, for a wide variety of medical conditions [7]. We retrospectively analysed our database to assess the incidence of complications associated with TA.

A total of 231 adverse reactions were recorded, indicating that complications were associated with 4.75% of TPE sessions. The incidence of adverse reactions was 3.8% and 8.5% in the procedures with albumin solution and FFP, respectively. Most complications were mild to moderate, and only 0.12%

of TPA procedures were associated with severe complications including five cases of anaphylactic reaction to FFP and one respiratory arrest. The most common complications were filter clotting and mild to moderate allergic reactions. Our anticoagulation protocol consisted of the initial administration of 2,500 IU heparin, followed by continuous infusion of 3,000–10,000 IU heparin. Regular, either oral or parenteral, replacement of calcium was responsible for a low incidence of the symptoms of hypocalcaemia (paresthesias, tingling) even in patients treated with FFP, which contains approximately 15% of citrate by volume. None of our patients experienced severe hypocalcaemia with the development of cardiac arrhythmia. Other studies report on the occurrence of hypocalcaemia symptoms in up to 11.1% of TPE treatments [23, 24]. Bleeding occurred in 3 patients (0.06% of procedures). Our experience further supports the use of FFP at the end of treatment in patients receiving multiple treatments over a short period. We use up to 700 mL FFP after five consecutive treatments in postoperative patients or in patients with bleeding. In our patients, infections were related to endovascular catheters (exit site infections without development of systemic response), rather than the TPE procedure. Allergic reactions which were characterized as mild or moderate complicated the course of TPE in 1.6% of treatments. A significantly higher incidence of allergic reactions was recorded in patients requiring FFP (9.5%). Our results are comparable with those reported from other studies, where most reactions were limited to rigor or urticaria [26]. Although most of these reactions were associated with the use of FFP, one should bear in mind that human serum albumin might contain trace amounts of globulins and other plasma constituents which might provoke anaphylactoid reaction. Anaphylactoid reaction in patients treated with albumin might also be the consequence of the formation of antibodies to albumin polymers, or might occur after the use of ACEi which block the degradation of bradykinins. ACEi should be withheld for at least 24 h before apheresis [7, 26]. Several investigators have reported deaths associated with therapeutic apheresis treatment [27]. The incidence of death associated with TA has been estimated at 0.05% [23]. These results were obtained by a review of published material including more than 15,000 cases.

Our results derived from a large number of treatments indicate that TPE is a relatively safe method of treatment, providing it is carried out by experienced staff, and used for appropriate indications with all necessary precautions. The use of FFP is associated with a higher rate of adverse reactions.

Conclusion

Therapeutic apheresis procedures should be performed in an environment that is safe for both patients and employees, and in which adequate backup is available to handle a severe adverse effect should one arise. There should

be a procedure manual that describes all routine activities, and records of each procedure should be created and maintained. Every patient is unique and there is a wide spectrum of presentation and progression for various diseases and conditions. The patient's clinical condition and situation should be considered when deciding the timing of treatment. This determination should be made through consultation between the requesting physician and the medical director of the dialysis/apheresis/intensive care unit using appropriate medical judgment. There are lifethreatening conditions where TPE is the primary mode of acute treatment. Comprehensive programmes should be in place for quality control and quality improvement, and to assure compliance with the guidelines.

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Резиме

ТЕРАПЕВТСКА ЗАМЕНА НА ПЛАЗМА ВО КЛИНИЧКАТА ПРАКТИКА: ДОЛГОРОЧНО ИСКУСТВО НА ЕДЕН ЦЕНТАР

Кес П., Башиќ-Јуќиќ Н., Брунета Гавраниќ Б.

Оддел за нефрологија, артериска хипертензија и дијализа, Катедра за интерна медицина, Универзитетски болнички центар, Загреб, Хрватска

Апстракт: Терапевтската замена на плазма (ТЗП) е моќен инструмент во третманот на цела низа болести и речиси нема орган за кој ТЗП не се покажа дека има некои корисни ефекти. Во повеќето случаи, ТЗП е индицирана само како последно средство за третман, ако сите конзервативни мерки не успеале. Меѓутоа, постојат животно загрозувачки услови кога ТЗП е примарен начин на акутен третман. Резултатите од последните рандомизирани проспективни контролирани обиди предизвикаа стеснување на спектарот на индикации за употреба на ТЗП, додека напредокот во различните области на медицината и технологијата овозможи поширока клиничка примена на оваа постапка и генерираше неколку нови индикации.

За да се дефинира тековната улога на ТЗП, ние ретроспективно ги анализиравме промените во индикациите за ТЗП во нашата база на податоци, која содржи информации за сите ТЗП спроведени во текот на 27 години во Универзитетскиот болнички центар во Загреб (Национален референтен центар за терапевтска афереза, кој опфаќа околу 90–95 % од сите ТЗП што се вршат во Хрватска). Бројот на пациентите (вклучувајќи ги и децата и постарите луѓе), кои биле подложени на оваа постапка и ТЗП се зголеми неколку пати во текот на 27 години следење, и покрај промените во моделот на индикации и појавата на нови, поселективни терапевтски опции (ЛДЛ-афереза, имуноадсорпција, итн.) Со поширока примена на ТЗП, стравот од нејзините компликации се намали, што може да биде причина за почест третман на многу мали деца и многу стари пациенти. Нашите резултати добиени од голем број на третмани укажуваат на тоа дека ТЗП е релативно безбеден метод на лекување, под услов да се врши од страна на искусен персонал и да се користи за соодветни индикации со сите неопходни мерки на претпазливост. И покрај развојот на поселективни методи, ТЗП сè уште е широко применлива и корисна постапка, можеби доживувајќи ренесанса во овој век.

Клучни зборови: возрасни, деца, компликација, постари, хематолошко нарушување, индикација, нефролошко нарушување, невролошко нарушување, терапевтска замена на плазма.

Correspodending Author:

Prof. Petar Kes, MD, PhD.
Department of Nephrology, Arterial Hypertension and Dialysis
Department of Internal Medicine
University Hospital Centre Zagreb
Kišpatićeva 12, 10000 Zagreb, Croatia
E-mail: kespetar@net.hr

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