Paediatric Intensive Care Unit

Therapeutic Plasma Exchange UHL Childrens Intensive Care Guideline

Staff relevant to:	PICU/CICU and ECMO medical and nursing staff in the application of Therapeutic Plasma Exchange in paediatric patients
Approval date:	March 2023
Version:	5
Revision due:	March 2026
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Trust Ref:	C117/2016

Contents

1. Introduction and Who Guideline applies to

This guideline serves to aid PICU/CICU and ECMO medical and nursing staff in their understanding and application of Therapeutic Plasma Exchange in paediatric patients
This guideline provides background information and practical advice, based on best current evidence and practice, to aid nursing and medical staff on PICU and CICU, in considering, prescribing and administering therapeutic plasma exchange in appropriate patients.

2. Guideline Standards and Procedures

Prescribing Therapeutic Plasma Exchange

Patient receiving plasma exchange will require the insertion of an appropriately sized haemofiltration catheter. If already on Haemofiltration or ECMO, existing catheter will be utilised.
Plasma exchange will be performed using the Prismaflex™.
Prescription should be written on the haemofiltration prescription chart and circuit set up should be as per **haemofiltration guidelines** except for the use of the MPS 05 plasmafilter.
The Plasma Exchange Prescription calculator can be accessed on the S drive (K:\1. GUIDELINES\FORMS & PAPERWORK) and used to calculate prescription (as below) based on weight of child.

Blood flows should be prescribed as per haemofiltration, usually 5-10mls/kg/min but can be as much as IV access/circuit size allows.

Prescribe a 2x Plasma volume exchange over 4hrs

Plasma volume = (80 X weight (kg)) x (1-HCT)

E.g. For a 10kg child with Haematocrit of 0.3
Plasma volume = 800 x 0.7 = 560mls
Double plasma exchange volume = 560 x 2 = 1120mls
Over 4 hours this would require a rate of 1120/4 =280mls/hr

In plasma exchange, unlike haemofiltration, replacement fluid is given post filter. Therefore prescribe in the post dilution column.

Replacement fluid should be given as 4.5% human Albumin Solution and FFP/Octaplas in a combination of 2/3 HAS and 1/3 FFP. In patients who require a higher proportion of FFP (ALF patients), use FFP rather than Octaplas to prevent clotting of the haemofilter.

Full blood count and coagulation screen should be performed at the end of each plasma exchange. May require further blood, platelet, FFP or cryoprecipitate infusion.

If a specific measureable substrate is being removed, this should also be measured at the end of plasma exchange.

Subsequent plasma exchanges should be single plasma volume.

Daily treatment should be considered according to clinical response (see below).

In autoimmune disease, concurrent immunosuppression treatment should be continued.

Definitions

Plasmapheresis (from the Greek *πλάσμα* - *plasma*, something moulded, and *ἀφαίρεσις* - *aphairesis*, taking away) is the removal, treatment, and return of (components of) blood plasma from blood circulation. It is thus an extracorporeal therapy.

During plasmapheresis, blood is initially taken out of the body through a previously implanted catheter. Plasma is then removed from the blood by a cell separator. Three procedures are commonly used to separate the plasma from the blood cells:

- Discontinuous flow centrifugation: One venous catheter line is required. Typically, a 300 ml batch of blood is removed at a time and centrifuged to separate plasma from blood cells.
- Continuous flow centrifugation: Two venous lines are used. This method requires slightly less blood volume to be out of the body at any one time as it is able to continuously spin out plasma.
- **Plasma filtration**: Two venous lines are used. The plasma is filtered using standard haemodialysis equipment. This continuous process requires less than 100 ml of blood to be outside the body at one time.

After plasma separation, the blood cells are returned to the person undergoing treatment, while the plasma, which contains the antibodies, is first treated and then returned to the patient.

In **Therapeutic Plasma Exchange (TPE)**, the removed plasma is discarded and the patient receives replacement donor plasma, albumin or Plasmalyte with added proteins.

Removal of substances by plasma exchange is most efficient early in the procedure (Table 1)

Plasma Exchange Volume	%Substance removed
0	0
0.5	39.3
1	63.2
1.5	77.7
2	86.5
2.5	91.8

1 plasma volume exchange can be done in 1-2hrs, hence minimises time and reduces risk of complications to the patient

2-3 plasma volume exchanges result of greater diminution of substance but increases time and risk

Goals of therapeutic plasma exchange

Removal of very large plasma proteins (the molecular weight spectrum removed by plasmafiltration is up to 3million Daltons)

- Immune complexes
- Antibodies
- Poisons
- Inflammatory mediators

Correction of plasma deficiencies

Maintenance of normovolaemia by replacing plasma volume removed

Note: in autoimmune disorders, Plasma Exchange offers the quickest short-term answer to removing harmful autoantibodies; however, the production of autoantibodies by the immune system must also be suppressed, usually by the use of medications such as Prednisone, Ciclosporin, Rituximab or a mixture of these.

Indications for Therapeutic Plasma Exchange

Category 1: (good evidence of treatment benefit)
Thrombotic Thrombocytopaenic Purpura
Guillain Barre Syndrome
Myasthemia Gravis,
Chronic Idiopathic Demyelinating Polyneuropathy

Category 2: (Some evidence to suggest a treatment benefit)
ABO incompatible organ transplant
Drug overdose
Haemolytic uraemic syndrome
Vasculitis

Category 3: (observational studies/expert opinion)
Failure of standard treatment
Active/progressive disease
There is a marker to follow
Agreed plan when to stop

Examples: Sepsis, Acute Liver failure

Therapeutic Plasma Exchange in sepsis

Significant debate exists:

Russian study[1]
106 patients
Plasmapharesis vs control in sepsis
28 day mortality in plasmapheresis group 33.3% vs 53.8% in control group
In first 24 hours APACHE score fell by 11pts in plasmapheresis vs 4pts in control group.

This represents a relative risk for fatal outcome in the plasmapheresis group of 0.61, an absolute risk reduction of 20.5% and a number of patients needed to treat of 4.9.
Significantly improved survival in abdominal sepsis (higher proportion of abdominal sepsis in TPE arm)

Review Article [2]
Looked at 76 patient with DIC and MODS who received TPE and compared with survival rates for sepsis in the literature at that time
Median 2 TPE (1-14)
82% survival with TPE vs 20%

Death in sepsis still related to degree of multiorgan failure. Emerging evidence of role of thrombotic microangiopathy in development of microcirculatory occlusive disorder, with platelet and VWF microthrombi predisposing to multiorgan failure (in combination with a deficiency of a disintegrin and metalloprotease with thrombospondin motifs-13(ADAMTS13), previously known as vWF cleaving protease)
In primary thrombotic microangiopathies, such as TTP, the use of Plasma Exchange has decreased mortality from 80-90% to 10% and this survival benefit is thought to be secondary to the removal of vWF multimers and replenishment of ADAMTS 13.[3]

TAMOF (thrombocytopaenia associated multiorgan failure) is a secondary thrombotic microangiopathy. Causes include sepsis, organ transplantation and chemotherapy.
Data starting to suggest relationship between TAMOF and ADAMTS 13 activity in paediatric sepsis

Preliminary paper[4]
Conclusions: Children with TAMOF syndrome can have VWF mediated thrombotic microangiopathy. Similar to adult experience, PEx can replenish ADAMTS-13 activity and reverse organ failure. As part of this review an IRB pilot RCT study was performed in University Hospital Pittsburgh.

- 10 children with TAMOF
- Decreased ADAMTS-13 (mean 33.3% of normal)
- Randomized trial: stopped after 10 patients: 28-day survival
- 1/5 standard therapy
- 5/5 plasma exchange ($p < .05$)

(Note 10 other children whose parents refused randomisation, 3 were not plasma exchanged and all died, 7 were plasma exchanged and all survived). Ongoing study in US by the Childrens TAMOF Network

Therapeutic Plasma exchange in Acute Liver Failure

Evidence suggests it may be a useful technique for correction of coagulopathy without volume overload (with additive effect of protecting renal function and preventing exacerbation of raised intracranial pressure associated with hepatic encephalopathy)

While toxin removal also seems a likely benefit there is no evidence that plasma exchange improves neurological outcome in these patients[5]

Replacement fluids

Evidence does not support one any one recipe for ideal plasma replacement.

It does suggest that using 2/3 Albumin solution and 1/3 FFP/Octaplas adequately restores clotting factors at the end of the procedure.

OCTAPLAS® is made from pooled plasma from voluntary donors. It contains human plasma proteins. The manufacturing process includes a solvent detergent treatment step using tributyl phosphate and Octoxinol 9 to reduce the potential for virus transmission.

OCTAPLAS® contains reduced concentrations of protein S compared to normal plasma. In clinical situations where large volumes of OCTAPLAS® are infused (e.g. plasma exchange for TTP or during liver transplantation), patient plasma protein S concentrations may be reduced, predisposing the patient to the development of deep venous thrombosis (DVT). Our own experience is that large volumes of Octaplas lead to clots within the plasmafilter and repeated failure of successive filters, resulting in interruption to plasma exchange, which is likely to reduce substrate removal.

The current ongoing study into TPE for TAMOF in children recommends a 50:50 ratio of Albumin Solution:FFP.

In coagulopathic patients with acute liver failure (where the liver is not synthesising new clotting factors) a higher proportion of FFP may be needed.

All patients may need cryoprecipitate or platelets in addition to FFP for restoration of platelet and fibrinogen levels at the end of the plasma exchange. This can be given as part of the exchange or as additional volume depending on the patients fluid volume status.

Number of therapeutic plasma exchanges to perform

Again debate exists

In Guillain -Barre syndrome therapeutic benefit occurs when tissue bound antibody leaches back into the circulation to replace that removed by plasma exchange. We therefore use 5 1-2 volume plasma exchanges over 2-5 consecutive days depending on severity of disease

Raphaël JC, Chevret S, Hughes RAC, Annane D. Plasma exchange for Guillain-Barré syndrome. Cochrane Database of Systematic Reviews 2002, Issue 2. Art. No.: CD001798

In TTP observational data suggests daily plasma exchange should be continued until platelet count returns to normal

In the ongoing trial: Patient Plasma Response and Outcomes in Thrombocytopenia-Associated Multiple Organ Failure (TAMOF) in Children: patients with platelet count <100 x 10^6 and OFI score (see below) >3 receive at least 5 and not more than 14 consecutive plasma exchanges. First TPE 1.5x Plasma volume, subsequently single volume plasma exchanges continued depending on response (response defined as Organ Function Index ((OFI) = number of organ systems failed) score <2 for 3 consecutive days)

In centres using Plasma exchange as supportive therapy for Acute Liver Failure plasma exchanges are continued according to clinical response (if no response, treatment discontinues, if improvement treatment continued).

Complications of therapeutic Plasma Exchange
Complications associated with insertion of Vascath -

Misplacement/Pneumothorax,

Haemothorax,

Thrombosis,

Infection

Bleeding complications (anticoagulation required as extracorporeal circuit)

Risk of transfusion reactions or transfusion associated diseases

Immunosupression / immunomodulation (removal of antibodies can lead to increased production)

3. Education and Training

No new training or education is required to implement this guideline.

4. Monitoring and Audit Criteria

What will be measured to monitor compliance	How will compliance be monitored	Monitoring Lead	Frequency	Reporting arrangements
Number/indications/ outcomes of TPE performed	Audit	C. Westrope	2yrs	PICU/CICU CPM

5. Supporting Documents and Key References

1. ICM 2002 Vol 28, No 10 1434-1439
Plasmapheresis in severe sepsis and septic shock: a prospective, randomised, controlled trial Busund R et al

2. Critical Care Medicine:
June 2003 - Volume 31 - Issue 6 - pp 1730-1736
Plasma exchange as rescue therapy in multiple organ failure including acute renal failure Stegmayr, Bernd G. MD, PhD; Banga, Ravjet; Berggren, Lars; Norda, Rut; Rydvall, Anders; Vikerfors, Tomas*

3. NEJM 2206 354:18

Thrombotic Thrombocytopenic Purpura
James N. George, M.D.

4. Critical Care medicine 2008 Vol 36 No.10
Intensive Plasma exchange increases a disintegrin and metalloprotease with thombospondin motifs-13 activity and reverses organ dysfunction in children in thrombocyopaenia associated multiorgan failure
Trung C. Nguyen, et al

5. Annals of Surgery 2001 Vol. 234, No. 3, 418–424
Role of Plasmapheresis in the Management of
Acute Hepatic Failure in Children
Andrew L. Singer et al

6. Key Words

Therapeutic Plasma Exchange, plasmapheresis, filtration

The Trust recognises the diversity of the local community it serves. Our aim therefore is to provide a safe environment free from discrimination and treat all individuals fairly with dignity and appropriately according to their needs.
As part of its development, this policy and its impact on equality have been reviewed and no detriment was identified.

CONTACT AND REVIEW DETAILS	
Guideline Lead (Name and Title) Claire Westrope – Consultant PICU/ECMO	**Executive Lead** **Chief Medical officer**
Details of Changes made during review: In **Therapeutic Plasma Exchange (TPE)**, the removed plasma is discarded and the patient receives replacement donor plasma, albumin or ~~saline~~ **Plasmalyte** with added proteins. Removed Sections – **Prescribing Therapeutic Plasma Exchange** **Plasma volume**	