2019 American Society for Apheresis
8th Special Edition of the Journal of Clinical Apheresis
Practical, Concise, Evidence-Based Recommendations for the Apheresis Practitioner

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For making and sharing slides
The American Society for Apheresis

• Founded in 1982
  – Society for Hemapheresis Specialists
  – American Society for Apheresis
• Society of physicians, scientists, and allied health professionals
  – Currently more than 1000 members from 35 countries
• Website: http://www.apheresis.org

The American Society for Apheresis

• Mission
  – To be the leader in apheresis medicine

• Vision
  – To advance apheresis medicine for patients, donors and practitioners through education, evidence-based practice, research and advocacy.

• Strategic Directions and Goals
  – In order to achieve the mission and vision, ASFA is focusing on the following strategic directions and goals:
    • Member Recruitment and Engagement
    • Education
    • Partnerships and Alliances
    • Organizational Structure
    • Research
Qualification in Apheresis (QIA)

ASFA is pleased to offer a Qualification in Apheresis (QIA) in partnership with The Board of Certification (BOC) of the American Society for Clinical Pathology (ASCP) as of January 2016.

Prove your competency in apheresis by taking the QIA exam! In order to add the letters QIA after your name, follow this link: https://www.ascp.org/content/board-of-certification/get-credentialed/qualifications/
What is the Special Edition of the *Journal of Clinical Apheresis*?

- *Journal of Clinical Apheresis*
  - Presents work in all aspects of basic and clinical research, practical applications, emerging technologies and regulation in apheresis.
  - **2018 impact factor of 3.088**

- ASFA Guidelines are published every three years
  - Provides a comprehensive literature review of the use of apheresis to treat disease
  - Objectively evaluates the science supporting or refuting the use of apheresis to treat disease
  - Provides practical recommendations

*Courtesy of Dr. Winters*
Why was the Special Issue of the Journal of Clinical Apheresis created?

- Very few randomized controlled trials of apheresis use
- 1976 to 1999*:
  - 592 published articles on the use of apheresis
  - 85 published randomized controlled trials
- 2000 to 2012**:
  - 7841 published articles on the use of apheresis
  - 53 published randomized controlled trials
- Quality of apheresis literature is limited
  - Randomized controlled trials frequently underpowered
  - For some diseases ONLY case studies or small series
- Need for evidence-based guidance


History of the Special Edition of the Journal of Clinical Apheresis

- 1986 - Edited by Dr. Harvey Klein
- 1993 – Edited by Dr. Ron Strauss
- 2000 – Edited by Dr. Bruce McLeod
  - ASFA Categories first introduced
  - 53 clinical indications categorized
History of the Special Edition of the *Journal of Clinical Apheresis*

- **2007** – Edited by Dr. Zbigniew Szczepiorkowski
  - Fact sheet format introduced
  - Strength of evidence for the use of apheresis provided
  - 54 clinical indications categorized
- **2010** – Edited by Drs. Beth Shaz and Zbigniew Szczepiorkowski
  - Category III definition revised
  - Recommendation grades for the use of apheresis provided
  - 68 clinical indications categorized

History of the Special Edition of the *Journal of Clinical Apheresis*

- **2013** – Edited by Joseph Schwartz and Beth Shaz
  - 78 indications categorized
- **2016** – Edited by Joseph Schwartz and Beth Shaz
  - 87 indications categorized
8th Special Edition of the *Journal of Clinical Apheresis*

- 2019 –Edited by Anand Padmanabhan and Nancy Dunbar; Guest Editor: Joseph Schwartz
  - 84 diseases and 157 indications categorized
  - Writing committee:
    - Anand Padmanabhan
    - Laura Connelly-Smith
    - Nicole Aqui
    - Rasheed A. Balogun
    - Reinhard Klingel
    - Erin Meyer
    - Huy P. Pham
    - Jennifer Schneiderman
    - Volker Witt
    - Yanyun Wu
    - Nicole D. Zantek
    - Nancy M. Dunbar

### ASFA Categories

#### Indications for Therapeutic Apheresis

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Disorders for which apheresis is accepted as first-line therapy, either as a primary standalone treatment or in conjunction with other modes of treatment.</td>
</tr>
<tr>
<td>II</td>
<td>Disorders for which apheresis is accepted as second-line therapy, either as a standalone treatment or in conjunction with other modes of treatment.</td>
</tr>
<tr>
<td>III</td>
<td>Optimum role of apheresis therapy is not established. Decision making should be individualized.</td>
</tr>
<tr>
<td>IV</td>
<td>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.</td>
</tr>
</tbody>
</table>
## Recommendation Grades

**Grading Recommendations Adopted from Guyatt et al**

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Description</th>
<th>Methodological Quality of Supporting Evidence</th>
<th>Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1A</td>
<td>strong recommendation, high-quality evidence</td>
<td>RCTs without important limitations or overwhelming evidence from observational studies</td>
<td>Strong recommendation, can apply to most patients in most circumstances without reservation</td>
</tr>
<tr>
<td>Grade 1B</td>
<td>strong recommendation, moderate quality evidence</td>
<td>RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies</td>
<td>Strong recommendation, can apply to most patients in most circumstances without reservation</td>
</tr>
<tr>
<td>Grade 1C</td>
<td>strong recommendation, low-quality or very low-quality evidence</td>
<td>Observational studies or case series</td>
<td>Strong recommendation but may change when higher quality evidence becomes available</td>
</tr>
<tr>
<td>Grade 2A</td>
<td>weak recommendation, high quality evidence</td>
<td>RCTs without important limitations or overwhelming evidence from observational studies</td>
<td>Weak recommendation, best action may differ depending on circumstances or patients’ or societal values</td>
</tr>
<tr>
<td>Grade 2B</td>
<td>weak recommendation, moderate-quality evidence</td>
<td>RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies</td>
<td>Weak recommendation, best action may differ depending on circumstances or patients’ or societal values</td>
</tr>
<tr>
<td>Grade 2C</td>
<td>weak recommendation, low-quality or very low quality evidence</td>
<td>Observational studies or case series</td>
<td>Very weak recommendations; other alternatives may be equally reasonable</td>
</tr>
</tbody>
</table>

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## Relationship Between Category and Recommendation Grade
2019 Guidelines – The Process

Table 1: Category and Grade Recommendations for Therapeutic Apheresis

<table>
<thead>
<tr>
<th>Disease</th>
<th>TA modality</th>
<th>Indication</th>
<th>Category</th>
<th>Grade</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute disseminated encephalomyelitis (ADEM)</td>
<td>TPE</td>
<td>Steroid Refractory</td>
<td>II</td>
<td>2C</td>
<td>187</td>
</tr>
<tr>
<td>Acute inflammatory demyelinating polyradiculoneuropathy (Guillain-</td>
<td>TPE</td>
<td>Primary Treatment</td>
<td>I</td>
<td>1A</td>
<td>189</td>
</tr>
<tr>
<td>Barre syndrome)</td>
<td>IA</td>
<td>Primary Treatment</td>
<td>I</td>
<td>1B</td>
<td></td>
</tr>
<tr>
<td>Acute liver failure</td>
<td>TPE-HIV</td>
<td></td>
<td>I</td>
<td>1A</td>
<td>191</td>
</tr>
<tr>
<td></td>
<td>TPE</td>
<td></td>
<td>III</td>
<td>2B</td>
<td></td>
</tr>
<tr>
<td>Age related macular degeneration, dry</td>
<td>Rhoephresis</td>
<td>High-risk</td>
<td>II</td>
<td>2B</td>
<td>193</td>
</tr>
<tr>
<td>Amyloidosis, systemic</td>
<td>β2-microglobulin column</td>
<td>Dialysis-related amyloidosis</td>
<td>II</td>
<td>2B</td>
<td>195</td>
</tr>
<tr>
<td></td>
<td>TPE</td>
<td>Other causes</td>
<td>IV</td>
<td>2C</td>
<td></td>
</tr>
<tr>
<td>Anti-glomerular basement membrane disease (Goodpasture syndrome)</td>
<td>TPE</td>
<td>Diffuse alveolar hemorrhage (DAH)</td>
<td>I</td>
<td>1C</td>
<td>197</td>
</tr>
<tr>
<td></td>
<td>TPE</td>
<td>Dialysis-independence</td>
<td>I</td>
<td>1B</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TPE</td>
<td>Dialysis-dependent, no DAH</td>
<td>III</td>
<td>2B</td>
<td></td>
</tr>
</tbody>
</table>
## Examples of Indications

### Table 5: Category IV Recommendations for Therapeutic Apheresis

<table>
<thead>
<tr>
<th>Disease</th>
<th>Procedure</th>
<th>Full Fact Sheet in JCA Special Edition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amyotrophic lateral sclerosis</td>
<td>TPE</td>
<td>2013</td>
</tr>
<tr>
<td>Dermatomyositis/polymyositis</td>
<td>TPE, ECP</td>
<td>2016</td>
</tr>
<tr>
<td>Inclusion body myositis</td>
<td>TPE, Leukocytapheresis</td>
<td>2013</td>
</tr>
<tr>
<td>POEMS syndrome</td>
<td>TPE</td>
<td>2013</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>TPE</td>
<td>2010</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>TPE</td>
<td>2013</td>
</tr>
</tbody>
</table>


## Diseases considered for new fact sheets in 2019

### Table 6: Diseases considered for new fact sheets in 2019

<table>
<thead>
<tr>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer’s disease</td>
</tr>
<tr>
<td>Antisynthetase syndrome</td>
</tr>
<tr>
<td>Autoimmune myofasciitis</td>
</tr>
<tr>
<td>Composite tissue transplantation</td>
</tr>
<tr>
<td>Fulminant meningococcemia</td>
</tr>
<tr>
<td>Mechanical red cell hemolysis</td>
</tr>
<tr>
<td>Methemoglobinemia</td>
</tr>
<tr>
<td>Necrotizing myopathy</td>
</tr>
<tr>
<td>Pancreatic transplantation</td>
</tr>
<tr>
<td>Platelet transfusion allorefactoriness</td>
</tr>
<tr>
<td>Pre-eclampsia</td>
</tr>
<tr>
<td>Recurrent pregnancy loss</td>
</tr>
</tbody>
</table>

Criteria for NEW Fact Sheets (2019)

- Minimum of 10 cases published in the last decade in peer-reviewed journals, ideally by more than one group.
- No NEW facts sheets in the 2019 edition

Diseases considered for new fact sheets
- Alzheimer’s disease
- Antisynthetase syndrome
- Autoimmune myofasciitis
- Composite tissue transplantation
- Fulminant meningococcemia
- Mechanical red cell hemolysis
- Methemoglobinemia
- Necrotizing myopathy
- Pancreatic transplantation
- Platelet transfusion allorefractoriness
- Pre-eclampsia
- Recurrent pregnancy loss

EVOLUTION OF ASFA GUIDELINES

2019: If more than one type of apheresis modality was used for the same clinical indication within the same disease, and if the assigned recommendation grade and category were identical for each modality, it was assigned as a single indication
Fact Sheet Structure

- Diseases listed in alphabetical order
- Single Page
- Consistent layout and information for each disease
- Goal is to be practical
Fact Sheet Structure

**ACUTE DISSEMINATED ENCEPHALOMYELITIS (ADEM)**

<table>
<thead>
<tr>
<th>Disease name</th>
<th>Incidence</th>
<th>Procedure</th>
<th>GRADE recommendation</th>
<th>ASFA Category</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Internal Refractory</td>
<td>T1FL</td>
<td>Grade 2C</td>
</tr>
</tbody>
</table>

**Description of the disease**

ADEM is an inflammatory demyelinating disease that typically affects the central nervous system, causing symptoms such as fever, headache, and neurological deficits. The disease often occurs after an viral or bacterial infection. It is characterized by the presence of inflammatory cells, demyelination, and axonal loss in the central nervous system. ADEM can be acute, subacute, or chronic, lasting from a few days to several months. The prognosis varies depending on the severity and duration of the illness.

**Current management treatment**

There is no specific cure for ADEM, but treatment is aimed at managing symptoms and preventing further damage to the central nervous system. Corticosteroids, such as methylprednisolone, are commonly used to reduce inflammation and swelling. Supportive care, including pain management and physical therapy, is also important.

**Factors that influence outcome**

The outcome of ADEM can vary depending on several factors, including the patient’s age, the duration and severity of the disease, and the presence of other medical conditions. Children and young adults tend to have better outcomes compared to older adults. Patients with severe or chronic ADEM may require long-term management and support.

**Summary of published evidence**

- RCT – Randomized controlled trials
- CT – Controlled trials
- CS – Case series
- CR – Case reports
Fact Sheet Structure

ACUTE DISSEMINATED ENCEPHALOMYELITIS (ADEM)

Description of the disease

Acute disseminated encephalomyelitis (ADEM) is an acute inflammatory, demyelinating disease that predominantly affects the white matter of the brain and spinal cord. Typically occurs after a viral or bacterial infection, or vaccination. ADEM may occur at any age, but is most common during childhood with substantial differences in reported incidence between USA, Europe, or Asia. This pathogenesis is thought to be the uncontrolled multifocal inflammation and pachymeningeal demyelination associated with transient autoimmune response against myelin oligodendrocyte glycoprotein or other autoantigens. It is believed that viral or bacterial primary ascending demyelination brings the capacity to activate multipolar and oligodendrocyte subsets through immune response, and thus can cause a clinical syndrome with non-species autoimmune response. ADEM typically begins within days to weeks of presenting with acute encephalopathy (change in mental status) accompanied by multifocal neurological deficits which improve slowly over the next days to months. MRI is the diagnostic imaging modality of choice for the demyelinating process. Characteristic lesions seen on MRI appear as back areas of increased signal intensity, with typical involvement of deep cerebral hemispheres and subcortical white matter, as well as lesions in the basal ganglia, gray-white junction, basis pontis, cerebellar, and spinal cord. The differentiation of ADEM from a first attack of multiple sclerosis (MS) has prognostic and therapeutic implications. ADEM has these features, which help to distinguish it from MS: B-cell polyfunctional presentation, lack of oligoclonal bands in the cerebrospinal fluid, predominance of MRI lesions in the subcortical regions with relative sparing of the periventricular area and complete or partial resolution of MRI lesions during convalescence. New Scans should not appear unless a clinical relapse has occurred. A rare hypervariable variant of ADEM, immune-mediated leucencephalopathy, is characterized by a rapidly progressive, fulminating hemorrhagic demyelination of white matter, usually associated with severe morbidity or death.

Current management/treatment

Once ADEM is diagnosed, the therapeutic aim is to abbreviate the CNS inflammatory reaction as quickly as possible, to aid in clinical recovery. Since there has been no RCTs for the treatment of ADEM, treatment are based on the experiences published in Case. Due to the postulated immune-mediated pathogenesis treatment is based on immunosuppressive agents. The use of high-dose intravenous corticosteroids, such as methylprednisolone 30-60 mg/kg/day (maximum 1 gram/day) for 3-5 days, has been suggested on the basis of their efficacy in treating other demyelinating conditions such as MS, and is widely accepted as first-line therapy. It may be followed by a prolonged oral prednisolone taper over 3-6 weeks. Corticosteroids are considered effective because of their anti-inflammatory and immunosuppressive effects with additional beneficial effect on cerebrospinal fluid. IVIG 2 g/kg total dose, given over 2-5 days, is typically reserved for patients who are severely hypotensive, but has also been rarely used as initial or concurrent therapy.

Fact Sheet Structure

ACUTE DISSEMINATED ENCEPHALOMYELITIS (ADEM)

Description of the disease

Acute disseminated encephalomyelitis (ADEM) is an acute inflammatory, demyelinating disease that predominantly affects the white matter of the brain and spinal cord. Typically occurs after a viral or bacterial infection, or vaccination. ADEM may occur at any age, but is most common during childhood with substantial differences in reported incidence between USA, Europe, or Asia. This pathogenesis is thought to be the uncontrolled multifocal inflammation and pachymeningeal demyelination associated with transient autoimmune response against myelin oligodendrocyte glycoprotein or other autoantigens. It is believed that viral or bacterial primary ascending demyelination brings the capacity to activate multipolar and oligodendrocyte subsets through immune response, and thus can cause a clinical syndrome with non-species autoimmune response. ADEM typically begins within days to weeks of presenting with acute encephalopathy (change in mental status) accompanied by multifocal neurological deficits which improve slowly over the next days to months. MRI is the diagnostic imaging modality of choice for the demyelinating process. Characteristic lesions seen on MRI appear as back areas of increased signal intensity, with typical involvement of deep cerebral hemispheres and subcortical white matter, as well as lesions in the basal ganglia, gray-white junction, basis pontis, cerebellar, and spinal cord. The differentiation of ADEM from a first attack of multiple sclerosis (MS) has prognostic and therapeutic implications. ADEM has these features, which help to distinguish it from MS: B-cell polyfunctional presentation, lack of oligoclonal bands in the cerebrospinal fluid, predominance of MRI lesions in the subcortical regions with relative sparing of the periventricular area and complete or partial resolution of MRI lesions during convalescence. New Scans should not appear unless a clinical relapse has occurred. A rare hypervariable variant of ADEM, immune-mediated leucencephalopathy, is characterized by a rapidly progressive, fulminating hemorrhagic demyelination of white matter, usually associated with severe morbidity or death.

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Brief description of the non-apheresis treatments used to manage the disease

Not meant to be comprehensive nor a guide for the non-apheresis therapy
Fact Sheet Structure

Rationale for therapeutic apheresis

- Evidence supporting use of apheresis
- Summarizes most important publications
- Rationale for use of apheresis discussed in context of pathophysiology

Technical notes

- Includes description of:
  - Specific considerations for the disease
  - Volume of blood/plasma treated
  - Replacement fluid
  - Frequency of apheresis treatment
Fact Sheet Structure

ACUTE DISSEMINATED ENCEPHALOMYELITIS (ADEM) -

Duration and discontinuation of procedures -

- Describes the basic criteria for discontinuation of apheresis

References -

- Search terms used by the fact sheet author provided
- Date of search for references provided
- References provided at the end of the fact sheet
Fact Sheet Sample
(SICKLE CELL DISEASE, NON-ACUTE)

SICKLE CELL DISEASE, NON-ACUTE

<table>
<thead>
<tr>
<th>Incidence: 273/100,000 (1/375 for Hb SS, 1/835 for Hb SC, 1/1667 for Hb S/b-thalassemia)</th>
<th>Indication</th>
<th>Procedure</th>
<th>Recommendation</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke prophylaxis</td>
<td>RBC exchange</td>
<td>Grade 1A</td>
<td>I</td>
<td></td>
</tr>
<tr>
<td>Pregnancy</td>
<td>RBC exchange</td>
<td>Grade 2B</td>
<td>II</td>
<td></td>
</tr>
<tr>
<td>Recurrent vaso-occlusive pain crisis</td>
<td>RBC exchange</td>
<td>Grade 2B</td>
<td>II</td>
<td></td>
</tr>
<tr>
<td>Pre-operative management</td>
<td>RBC exchange</td>
<td>Grade 2A</td>
<td>III</td>
<td></td>
</tr>
</tbody>
</table>

# reported patients: >300

- RCT
- CT
- CS
- CR

| Stroke prophylaxis | 2(326) | 1(36) | NA | NA |
| Pregnancy | 0 | 5(170) | 1(5) | NA |
| Recurrent vaso-occlusive pain crisis | 1(130) | 1(21) | 5(45) | NA |
| Pre-operative management | 3(1035) | 4(184) | NA | NA |

*Includes patients who received RBC transfusion, manual RBC exchange or automated RBC exchange.

Description of the disease

- Sickle cell disease (SCD) affects approximately ~100,000 people in the US. It is caused by abnormal sickle hemoglobin, (HbS) that is formed by the substitution of valine for glutamic acid at β6. HbS polymerizes upon deoxygenation, causing RBC to become rigid and deformed; sickled RBCs occlude the microvasculature leading to tissue hypoxia and infarction.
- HbS RBCs have a shortened lifespan (~10-20 days), resulting in chronic hemolytic anemia. The overall SCD mortality rate is ~3% (0.5 deaths/100-person years) with peak at 1-3 years. The average life expectancy is ≥50 years.
- Leading causes of death include sepsis, acute chest syndrome (ACS), stroke, acute multiorgan failure (MOF), and pulmonary hypertension (PH).
Fact Sheet Sample
(SICKLE CELL DISEASE, NON-ACUTE)

Description of the disease, continued

- Chronic complications of SCD can begin in early age. These include recurrent vaso-occlusive crisis (VOC), end organ damage, avascular necrosis of bones, cholelithiasis, and pulmonary hypertension.
- Complications from chronic therapy, such as iron overload and alloimmunization, are also common, particularly from simple blood transfusions.
- Chronic VOC (>3 months) occurs in up to 55% of SCD patients with PH occurring in 6-10%.
- If chelation therapy is not used, many chronically transfused patients with SCD may become iron overloaded.

Fact Sheet Sample
(SICKLE CELL DISEASE, NON-ACUTE)

Current management/treatment

- RBC transfusion is one of the mainstays of long-term SCD therapy and supported by multiple RCTs.
- For stroke prevention there are several important studies.
- The STOP trial randomized children with elevated blood flow velocity, which predicts stroke risk, to standard supportive care without transfusion (control) versus chronic monthly transfusion for primary stroke prevention (Adams, 1998). The trial was terminated prematurely due to the marked (90%) stroke risk reduction by chronic transfusion.
- Another trial found that chronic RBC transfusion also was efficacious in secondary stroke prevention/progression in children with evidence of silent cerebral infarct on imaging (DeBaun, 2014).
- Transfusion withdrawal is associated with an increased risk of recurrent stroke.
Fact Sheet Sample
(SICKLE CELL DISEASE, NON-ACUTE)

Current management/treatment

- In the setting of chronic transfusion therapy during which time the patient is clinically stable, targeting a pre-transfusion threshold of 50% HbS may be as effective as 30%.
- Several studies have shown decreased frequency of recurrent VOC with monthly manual RBC exchange.
- Surgery is associated with high rates of SCD related complications. The TAPS RCT demonstrated that pre-op transfusion was associated with decreased perioperative complications (39% non-transfused vs 15% transfused; Howard, 2013). Pre-op transfusion should target a Hgb of 10 g/dL.
- For patients with high baseline Hgb such as in HbSC or HbSb1, RBC exchange may be used to avoid elevated blood viscosity, especially for high risk procedures (neurosurgery, prolonged anesthesia, cardiac bypass procedures).

- Hydroxyurea (HU), which increases HbF%, is another SCD therapy. HU reduces frequency of VOC episodes, ACS, and other complications, and is associated with less transfusion and hospital admissions.
- In pediatric patients with previous stroke, the SWiITCH RCT showed that HU therapy plus phlebotomy is not able to replace chronic RBC therapy for secondary stroke prevention (Ware, 2011). However, the TWiITCH trial demonstrated that HU can substitute for chronic transfusions to maintain TCD velocities in patients with abnormal TCD velocities and prevent primary stroke (Ware, 2016).
- Hematopoietic stem cell transplantation is a potentially curative therapy, however, indications, appropriate donor sources and preparative regimens are being defined to optimize outcomes.
Fact Sheet Sample
(SICKLE CELL DISEASE, NON-ACUTE)

Rationale for therapeutic apheresis

- Studies have shown automated RBC exchange results in a more efficient removal/replacement of HbS RBCs than manual exchange or simple transfusions.
- RBC exchange may also have beneficial effects on blood viscosity, vessel relaxation time, and reduction of adhesion molecule level like sVCAM-1.
- One report suggests that RBC exchange reduces cerebral blood flow and oxygen extraction fraction relieving cerebral metabolic stress mitigating infract risk (Guilliams, 2018).

Fact Sheet Sample
(SICKLE CELL DISEASE, NON-ACUTE)

Rationale for therapeutic apheresis

- Although iron overload can be treated with chelation or phlebotomy, its effectiveness has been limited by poor compliance. RBC exchange, particularly in conjunction with isovolumic hemodilution, can remove or keep iron stores steady.
- The 2015 ASFA Red Blood Cell Exchange consensus conference supports RBC exchange with and without isovolemic hemodilution to reduce or prevent iron overload.
- In 36 pediatric patients, long-term RBC exchange for a mean of 5 years was associated with improved growth velocity without increased risk of iron overload compared to matched controls (Bavle, 2014).
Rationale for therapeutic apheresis

- Chronic RBC exchange has also been described in several clinical settings.
- In pregnancy, RBC transfusion, and RBC exchange have been reported to be associated with lower risk of maternal and neonatal mortality, intrauterine growth restriction and other fetal complications, and decreased rate of maternal complications, although larger comparative studies are needed.
- RBC exchange has also been used to manage PH improving SaO2 and ability to execute activities of daily life.

Technical notes

- Chronic vascular access remains a concern in RBC exchange (Otrock, 2018). Vortex ports have been used successfully in adults though with longer procedures and more complications. A CS demonstrated feasibility with arterio-venous fistulas for long term access, but the risk/benefits need to be discussed (Delville, 2016).
- Apheresis equipment calculates the replacement RBC volume to achieve target HbS (fraction of RBCs remaining at procedure end ) and HCT.
- General guidelines are: (1) end HCT at 30+/3% (<33-36% to avoid hyperviscosity) and (2) HbS of 30% (or HbS+HbC of 30%, etc.).
- Modification of RBC exchange utilizing isovolemic hemodilution, which consists of RBC depletion with 0.9% NaCl replacement followed by standard RBC exchange, reduces replacement RBC volume and donor exposure, helping decrease transfusion related iron overload.
Duration and discontinuation/number of procedures

- Duration and number of RBC exchanges depend upon clinical indications; one time for pre-op, variable times for chronic pain, and life-long for stroke prevention.

### REFERENCES

As of December 5, 2018 using PubMed and the MeSH search terms sickle cell disease, red blood cell exchange transfusion, erythrocytapheresis for articles published in the English language. References of the identified articles were searched for additional cases and trials.


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Fact Sheet Sample

THROMBOTIC MICROANGIOPATHY, THROMBOTIC THROMBOCYTOPENIC PURPURA (TTP)

<table>
<thead>
<tr>
<th>Incidence: &lt;1/100,000/year</th>
<th>Procedure</th>
<th>Recommendation</th>
<th>Category</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>TPE</td>
<td>Grade IA</td>
<td>1</td>
</tr>
<tr>
<td># reported patients: &gt;300</td>
<td>RCT</td>
<td>CT</td>
<td>CR</td>
</tr>
<tr>
<td></td>
<td>7(901)</td>
<td>5(270)</td>
<td>NA</td>
</tr>
</tbody>
</table>

Description of the disease

- Thrombotic thrombocytopenic purpura (TTP), is a systemic thrombotic illness affecting mostly small vessels. It was originally defined by the pentad of severe thrombocytopenia, microangiopathic hemolytic anemia (MAHA), mental status changes, renal failure and fever. However, clinical findings of unexplained thrombocytopenia and MAHA are enough to make a presumptive diagnosis of TTP. Because TTP is potentially fatal if left untreated (~90% mortality), there should be a low threshold to treat presumed TTP. Treatment is usually initiated urgently within 4-8 hours of diagnostic suspicion, after other causes of systemic TMA have been considered unlikely.

Fact Sheet Sample (TTP)
**Fact Sheet Sample (TTP)**

**Description of the disease, continued**

- TTP is associated with a severe (<10%) deficiency of plasma ADAMTS13 enzyme activity, which is responsible for maintaining normal distribution of von Willebrand factor (vWF) multimers. The PLASMIC scoring system has been developed to predict severe ADAMTS13 deficiency and includes 5 independent variables identified as highly predictive by multivariable regression including platelet count <30 × 10^9/L, creatinine <2.0 mg/dL, INR <1.5, MCV <90 fL, and hemolysis. The PLASMIC scoring system has been validated in two different cohorts and when used in conjunction with clinical evaluation may help to quickly diagnose new TTP patients (Bendapudi, 2017).

- Congenital TTP comprises a minority of cases and is associated with somatic mutations resulting in severely deficient ADAMTS13 function. Most patients have immune-mediated TTP where autoantibody against ADAMTS13 is detected. IgG4 is the most common anti-ADAMTS13 IgG subclass and appears to be related to disease recurrence.

**Fact Sheet Sample (TTP)**

**Current management/treatment**

- TPE has decreased overall mortality of immune mediated TTP from nearly uniformly fatal to <10-20%. TPE should be initiated emergently once the diagnosis is recognized. If TPE is not immediately available, large dose plasma infusions (25-30 mL/kg), may be given if tolerated, until TPE can be initiated (Coppo, 2003). Corticosteroids should be used as an adjunct, either a daily prednisone dose at 1 mg/kg/day, pulsed methylprednisone for a few days, or a combination; however, no definitive trials proving their comparative efficacy have been performed.

- Rituximab is commonly used to treat refractory or relapsing TTP. Studies have also described the incorporation of rituximab as adjunctive agent with initial TPE. Since rituximab immediately binds to CD20-bearing lymphocytes, an 18-24-hour interval between its infusion and TPE is used in practice.
Current management/treatment

- Other adjuncts for refractory or relapsing TTP include cyclosporine, azathioprine, vincristine, bortezomib and other immunosuppressive agents.
- Splenectomy has been used in the past and may be considered for severe refractory cases.
- Caplacizumab is an anti-vWF nanobody directed against the platelet binding domain (A1) of vWF. When added to TPE plus immunosuppression in a phase II placebo-controlled RCT it induced a significantly faster resolution of acute TTP episode (Peyvandi, 2016). HERCULES, a phase III randomized, double-blind, placebo-controlled study demonstrated that patients with acquired TTP receiving caplacizumab were 1.5x more likely to normalize platelet count and had a 74% lower risk of a composite of TTP-related death, recurrence, or a major thromboembolic event while undergoing treatment compared to those patients receiving placebo (Scully, 2019).
- Other promising agents under evaluation include Nacetylcysteine and recombinant ADAMTS13.

Patients with TTP have a thrombotic rather than hemorrhagic tendency and bleeding, if present, is typically limited to skin and mucous membranes.
- Platelets should only be transfused if potential life-threatening bleeding is present. Because congenital TTP is characterized by constitutive deficiency of ADAMTS13 activity without an inhibitor, simple infusions of plasma (10-15 mL/kg) or cryoprecipitate (which contains ADAMTS13) or plasma derived vWF concentrates have been used.
Fact Sheet Sample (TTP)

Rationale for therapeutic apheresis
- TPE with plasma replacement has significantly improved patients’ clinical outcomes.
- One hypothesis is that TPE removes anti-ADAMTS13 autoantibody, while replacing ADAMTS 13 protease activity. However, clinical course does not always correlate with plasma ADAMTS13 activity or ADAMTS13 inhibitor levels.

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Technical notes
- Allergic reactions and citrate reactions are more frequent due to large volumes of plasma required. Since plasma has citrate as an anticoagulant, ACD-A can be used in a higher ratio (to whole blood) to minimize citrate reactions. Fibrinogen levels may decrease following serial TPE procedures with cryoprecipitate depleted plasma as replacement. A previous study demonstrated that the use of cryoprecipitate depleted plasma as replacement may be associated with more frequent acute exacerbations (Stefanello, 2014).
- Solvent detergent treated plasma may be used for patients with severe allergic reactions. In addition, combined use of 50% albumin and 50% plasma has been reported to result in similar treatment efficacy as compared to the replacement of 100% plasma with albumin being used for the initial portion (up to 50%) of replacement (O’Brien, 2013).
Duration and discontinuation/number of procedures

- TPE is generally performed daily until the platelet count is >150 \times 10^9/L, and LDH is near normal for 2-3 consecutive days. The role of tapering
- TPE over longer duration has not previously been studied prospectively but is currently being reviewed. A small retrospective study suggests a lower overall recurrence rate for 6 months with taper.
- A common taper strategy is three times a week for the first week, twice weekly the second and then once weekly the following week(s). Other taper approaches have been documented.

References

As of November 1, 2018 using PubMed and the MeSH search terms thrombotic thrombocytopenic purpura, plasma exchange, plasmapheresis, apheresis, rituximab for reports published in the English language. References of the identified articles were searched for additional cases and trials.
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