Indications and Rationale for Acute and Chronic Red Blood Cell Exchange

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Red Blood Cell Function

• Tissue oxygen delivery

• Tissue hypoxia occurs when
  • Decrease or Increase in RBC mass
  • Abnormal Hb that does not deliver oxygen to tissues
  • Abnormal Hb that occludes the microvessels
Rationale for RBC exchange - correcting tissue hypoxia

- Polycythemia or erythrocytosis
  - Increased RBC mass,
  - Increased viscosity

- Hemochromatosis
  - Iron overload

- Intrinsic RBC disorders:
  - Congenital - SICKLE CELL DISEASE
  - Acquired - Malaria, Babesiosis

- Deplete RBC or iron stores with non RBC replacement usually crystalloids or plasma

- Remove abnormal RBCs and replace with donor RBCs

Types of RBC exchange

- Acute: treat severe or life threatening complications of RBC disorders
- Chronic: prevent new or recurrent adverse events or progression of organ dysfunction
- Manual or Automated

- LIMITED LARGE CLINICAL TRIALS
### Indications for RBC exchange

<table>
<thead>
<tr>
<th>Disease</th>
<th>ASFA Category</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Babesiosis, severe</td>
<td>2</td>
<td>2C</td>
</tr>
<tr>
<td>Erythropoeitic protoporphyria, liver disease</td>
<td>3</td>
<td>2C</td>
</tr>
<tr>
<td>Hereditary Hemochromatosis</td>
<td>1</td>
<td>1B</td>
</tr>
<tr>
<td>Malaria, severe</td>
<td>3</td>
<td>2B</td>
</tr>
<tr>
<td>PVera</td>
<td>1</td>
<td>1B</td>
</tr>
<tr>
<td>Erythrocytosis</td>
<td>3</td>
<td>1C</td>
</tr>
<tr>
<td>HSC transplant ABO incompatible</td>
<td>3</td>
<td>2C</td>
</tr>
<tr>
<td>CO poisoning</td>
<td>None, likely 3</td>
<td></td>
</tr>
<tr>
<td>Drug/chemical overdose</td>
<td>None, likely 3</td>
<td></td>
</tr>
<tr>
<td>High affinity Hb (pre op)</td>
<td>None, likely 3</td>
<td></td>
</tr>
<tr>
<td>Methemoglobinemia, severe</td>
<td>None, likely 3</td>
<td></td>
</tr>
</tbody>
</table>

Padmanabhan et. al, J Clin Apheresis 2019

### Sickle Cell Disease and RBC Exchange
Sickle cell genotypes

Kato et al, Nature Reviews 2018

Geographic distribution
Molecular Pathophysiology of Sickle cell Disease

Sundbl et al., Annual review of pathology 2019

Manifestations of SCD

Kato et al., Nature Reviews 2018
Age distribution of SCD complications

Kato et al, Nature Reviews 2018

Therapeutics in SCD

Sundd et. al, Annual review of pathology 2019
Rationale for RBC exchange in SCD

- Decrease blood viscosity
- Correction of anemia
- Reduction of HbS (to < 30%)
- Suppression of defective RBC and HbS production (chronic)
- Reduction of hemolysis (chronic)
- Few effective medications known to affect the natural history of the disease

Sarode et al., J Clinical Apheresis 2016

Rationale for erythrocytapheresis/automated RBC exchange

No RCTs supporting simple or exchange transfusions in SCT

- Rapid lowering of HbS levels, without raising Hb
- More efficient removal/replacement of sickle RBCs
- Beneficial effects on blood viscosity, vessel relaxation time and reduction of adhesion molecules
- Decreases iron overload
## ASFA Indications for RBC exchange in SCD

<table>
<thead>
<tr>
<th>Setting</th>
<th>Indication</th>
<th>Category</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACUTE</td>
<td>Acute Stroke</td>
<td>I</td>
<td>1C</td>
</tr>
<tr>
<td></td>
<td>Acute chest syndrome, severe</td>
<td>II</td>
<td>1C</td>
</tr>
<tr>
<td></td>
<td>Others- cholestasis, multi-organ failure</td>
<td>III</td>
<td>2C</td>
</tr>
<tr>
<td>CHRONIC</td>
<td>Stoke prophylaxis</td>
<td>I</td>
<td>1A</td>
</tr>
<tr>
<td></td>
<td>Pregnancy</td>
<td>II</td>
<td>2B</td>
</tr>
<tr>
<td></td>
<td>Recurrent VOC</td>
<td>II</td>
<td>2B</td>
</tr>
<tr>
<td></td>
<td>Pre- op management</td>
<td>III</td>
<td>2A</td>
</tr>
</tbody>
</table>

Padmanabhan et. al, J Clin Apheresis 2019

## RBC exchange and CNS complications in SCD

Category I
Neurologic complications of sickle cell disease

- Cerebral ischemia
- Cerebral hemorrhage
- Silent cerebral ischemia
- Neurocognitive decline
- 10% of sickle cell patients can develop CVA in their lifetime in the absence of preventative therapies
- 20-35% may have silent stroke
- 30-40% can develop Moya Moya syndrome
- Recurrence rates are 46-90%

Transfusions and Stroke in SCD

- Primary Stroke prevention
- Secondary Stroke prevention
- Primary therapy after primary stroke
- Transfusion for silent stroke
Transfusions and stroke in SCD- key studies

- Maintain HbS< 30%
- No prospective trials comparing types of transfusions/ exchange
- STOP 1 trial- simple transfusions showed a 90% stroke prevention rate in children with elevated TCD velocity
- STOP2 trial- stopping transfusions leads to increased recurrent stroke risk
- SIT trial- RBC transfusions decrease the risk of recurrent infarcts in children with SCI
- Exchange transfusions have lower rate of subsequent strokes


Targets in sickle cell disease/ stroke

• For acute stroke- decrease HbS to < 30% as quickly as possible – erythrocyptheresis is preferred, maintain Hct 27-30%
• For secondary stroke prevention- goal is to prevent stroke while balancing iron overload risk
  • Select cases where there is no progression of vasculopathy, consider HbS target of < 50%, post Hct 30-35%

• Downside-
  • Erythrocytapheresis requires more blood than simple or exchange transfusions: RBC depletion incorporated when possible
RBC exchange and Acute Chest Syndrome in SCD

Category II

Acute Chest Syndrome in SCD

- National Acute Chest Study Group definition-
  - a new infiltrate on chest X-rays accompanied by at least one of the following:
    - chest pain; fever 38.5°C; and respiratory findings such as tachypnea, cough, or wheezing
  - Can rapidly progress to respiratory distress, severe hypoxia and respiratory failure
  - Most common cause of death in adults with SCD, 25% of deaths in SCD
  - Second most common cause of hospitalization
  - Pulmonary thrombosis, fat emboli syndrome (64% mortality!)
RBC exchange in Acute Chest Syndrome

Role for exchange controversial, transfusions may be of benefit

- NHLBI 2014- strong recommendations if O2< 90%, worsening infiltrate, decreased Hb
- ASFA 2019 category 2
- ASH 2020 suggests erythrocytapheresis for severe ACS

- In pediatrics- retrospective studies have shown improved outcomes with RBC transfusion< 24 hours of hospitalizations, others no benefit

In general, if symptoms are severe are presentation or progressive symptoms despite simple transfusion, or severe symptoms, consider exchange transfusion

Chronic transfusions to prevent ACS:
- decrease in ACS event rate in CVA studies
- patients with two or more ACS episodes in 24 months despite maximal hydrea therapy

RBC exchange in pregnancy

- ASFA category III in 2016, switched to category II in 2019
  - Double center retrospective cross sectional study-46 women
  - Early Erythrocytapheresis treated patients
    - no VOC, pre eclampsia, eclampsia
    - Normal umbilical artery impedance
    - Improved newborn birthweight
    - 3 women started later had adverse outcomes with late fetal loss

- ASH recommends simple transfusions at regular intervals or as needed when symptomatic
Vaso-occlusive crises

- Pain is the most common manifestation of SCD

- 2 studies looking at effects of red cell exchange in preventing recurrent VOC (trigger change from ASFA category III to II)
  - Erythrocytapheresis in 12 patients with recurrent hospitalization for pain showed a dramatic decrease in number of admissions (8 median pre, to 11 total post)
  - No stroke, multiorgan dysfunction or end organ dysfunction when on the program
  - Similar benefits described by another group looking at 43 patients
  - Symptoms worse when off program

Pre – operative management

- TAPS RCT- pre op transfusion decreased peri op complications (39% non-transfused vs 15%)
- Transfuse to Hb greater than 10 g/dL prior to surgery
- For patients with Hb> 10 (HbSC and HbS/beta thal), exchange is the preferred method to decrease HbS
- Consider erythrocytapheresis when available to bring down HbS, esp with major surgery
Acute multi organ failure

- Defined as acute failure of 2 organs- lung, liver or kidney
- Very rare, but life threatening and seen in patients with relatively high Hb
- Transfusions can reverse organ dysfunction and mortality
- Erythrocytapheresis when available associated with faster organ recovery and earlier discharge


Intrahepatic cholestasis

- Uncommon complication, associated with fulminant hepatic failure
- Severe subgroup with very high bilirubin and mortality of over 60%
- Erythrocytapheresis commonly advocated as therapeutic option
Uncategorized indications

- Pulmonary hypertension
- End stage renal disease

2020 ASH guidelines for transfusions in SCD

- Suggests using automated RCE over simple transfusion or manual RCE in patients with SCD (all genotypes) receiving chronic transfusions
- Suggests automated RCE or manual RCE over simple transfusions in patients with SCD and severe acute chest syndrome
- Suggests either red cell exchange with isovolemic hemodilution (IHD-RCE) or conventional RCE in patients with SCD (all genotypes) receiving chronic transfusions

Chou et. al, Blood Advances, 2020
Thank you!

Questions?
Red Blood Cell Exchange Basics: Prescription, Goals, and Monitoring

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Medical Director of Apheresis Unit
University of California San Diego

Disclosures

- Adult nephrologist & apheresis practitioner
Red Blood Cell Exchange or Erythrocytapheresis

- Goal: removal of RBCs +/- replacement with "normal" donor RBCs
  - If replacement is saline or albumin = erythrocytapheresis
- Can be done manually (blood letting followed by transfusion) or with an automated centrifugal system
- Can use PIVs or central access (certain ports, dialysis-type catheters, AVF/AVG)
  - Typically need dual access but new software available for single needle RBCx

Indications for RBCx or Erythrocytapheresis

<table>
<thead>
<tr>
<th>Disease</th>
<th>Therapeutic apheresis modality</th>
<th>Level of evidence</th>
<th>Indication category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sickle cell disease, acute complications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute stroke</td>
<td>RBC exchange</td>
<td>1C</td>
<td>I</td>
</tr>
<tr>
<td>Acute chest syndrome</td>
<td>RBC exchange</td>
<td>1C</td>
<td>I</td>
</tr>
<tr>
<td>Priapism</td>
<td>RBC exchange</td>
<td>2C</td>
<td>III</td>
</tr>
<tr>
<td>Multorgan failure</td>
<td>RBC exchange</td>
<td>2C</td>
<td>III</td>
</tr>
<tr>
<td>Splenic/hepatic sequestration</td>
<td>RBC exchange</td>
<td>2C</td>
<td>III</td>
</tr>
<tr>
<td>Sickle cell disease, chronic complications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke prophylaxis</td>
<td>RBC exchange</td>
<td>1A</td>
<td>I</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>RBC exchange</td>
<td>2B</td>
<td>II</td>
</tr>
<tr>
<td>Recurrent vaso-occlusive pain crisis</td>
<td>RBC exchange</td>
<td>2B</td>
<td>II</td>
</tr>
<tr>
<td>Preoperative management</td>
<td>RBC exchange</td>
<td>2A</td>
<td>III</td>
</tr>
<tr>
<td>Allogeneic HSCT</td>
<td>RBC exchange</td>
<td>2C</td>
<td>III</td>
</tr>
<tr>
<td>Minor, prevention PLS</td>
<td>RBC exchange</td>
<td>2B</td>
<td>III</td>
</tr>
<tr>
<td>Infections</td>
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</tr>
<tr>
<td>Malaria</td>
<td>RBC exchange</td>
<td>2B</td>
<td>III</td>
</tr>
<tr>
<td>Babesiosis</td>
<td>RBC exchange</td>
<td>2C</td>
<td>II</td>
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<tr>
<td>Polycythemia vera</td>
<td>Erythrocytapheresis</td>
<td>1B</td>
<td>I</td>
</tr>
<tr>
<td>Secondary erythrocytosis</td>
<td>Erythrocytapheresis</td>
<td>1C</td>
<td>III</td>
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<td>Hereditary hemochromatosis</td>
<td>Erythrocytapheresis</td>
<td>1B</td>
<td>I</td>
</tr>
<tr>
<td>Prevention and treatment of RhD alloimmunization</td>
<td>RBC exchange</td>
<td>2C</td>
<td>II</td>
</tr>
<tr>
<td>Thalassaemia, liver disease</td>
<td>RBC exchange</td>
<td>2C</td>
<td>II</td>
</tr>
</tbody>
</table>

Stussi et al Transfusion Medicine and Hemotherapy 2019;46:407-416
For any given Hct, viscosity is higher in a patient with SCD

- Increased viscosity limits blood flow and oxygen transport
- Increased blood viscosity can cause complications with Hgb > 10 g/dL

Deoxygenated sickle blood has 10x greater viscosity than normal blood

- Increased viscosity further promotes the physiology of sickling
- Flow of blood even slower through the smallest vessels/venules
  - More opportunity for sickling

### Main Objectives of Transfusion Therapy in SCD

- Correction of anemia
  - Should not exceed baseline of patient (avoid hyperviscosity)
- Reduction of sickle cell hemoglobin (HbS)
- Suppression of defective RBC and thus HbS production
- Reduction of hemolysis
Transfusion Therapy Options in Sickle Cell Disease

<table>
<thead>
<tr>
<th></th>
<th>Simple Transfusion</th>
<th>Manual RBCx</th>
<th>Automated RBCx</th>
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</thead>
<tbody>
<tr>
<td>Availability</td>
<td>widespread</td>
<td>widespread</td>
<td>limited</td>
</tr>
<tr>
<td>Staff training</td>
<td>minimal</td>
<td>required</td>
<td>required</td>
</tr>
<tr>
<td># PRBCs</td>
<td>low</td>
<td>intermediate</td>
<td>high</td>
</tr>
<tr>
<td>Cost</td>
<td>low</td>
<td>intermediate</td>
<td>high</td>
</tr>
<tr>
<td>† viscosity</td>
<td>significant</td>
<td>minimal</td>
<td>minimal</td>
</tr>
<tr>
<td>HbS control</td>
<td>limited</td>
<td>intermediate</td>
<td>best control</td>
</tr>
<tr>
<td>Procedure time</td>
<td>long</td>
<td>long</td>
<td>rapid</td>
</tr>
<tr>
<td>Procedure freq.</td>
<td>short intervals</td>
<td>intermediate</td>
<td>long (4-6 wks)</td>
</tr>
<tr>
<td>Iron overload</td>
<td>high risk</td>
<td>intermediate</td>
<td>low risk</td>
</tr>
</tbody>
</table>

Sickle Cell Disease – Rationale for Automated RBC Exchange

- Red cell exchange is effective in both acute and chronic complications of sickle cell disease
  - Improves O2 carrying capacity while reducing viscosity of blood
  - Removes sickled cells from participating in new vaso-occlusive events
  - Reduces hemolytic complications
  - Safe in pregnancy
  - Molecular matching has made antibody production less common
    - Must weigh risks/benefits in a particular patient
- Disadvantages
  - Cost(?)/availability, vascular access, exposure to more blood products over time, special equipment & training required
Acute Indications For RBC Exchange in SCD

- Useful when you want to prevent further vaso-occlusion
  - Acute stroke, acute chest, multi-organ failure
  - May not be able to reverse pre-existing vaso-occlusion
- Can rapidly decrease the rate of hemolysis
  - ↓ liver processing of bilirubin, damage to renal tubules & scavenging of nitric oxide by free Hgb released from sickle cells
- Rapidly improve oxygen carrying capacity
- Quickly decrease the [HbS] without volume overload or increase in viscosity

Acute RBC Exchange in Sickle Cell Disease

- Goal is to reduce HbS <30% (in patients with SCD-SS) while keeping Hgb <10
  - To reach this goal, usually need one 1-1.5 x RCV "exchange"
  - Simple transfusion alone would only be able to achieve this if Hgb was ~3
- Can choose your end procedure Hct target
Non-Acute Indications for RBCx in SCD

- Chronic RBC exchange
  - Stroke Prophylaxis – Category I, Grade 1A
    - 2 RCTs (326 patients), 1 controlled trial
  - Pregnancy – Category II, Grade 2B
    - 5 controlled trials (170 patients)
  - Recurrent vaso-occlusive pain crisis - Category II, Grade 2B
    - 1 RCT (130 patients), 1 CT, 5 case series
    - Decreased frequency of VOC with monthly RBC exchange
- RBC exchange once (non-acute)
  - Pre-operative management – Category III, Grade 2A
    - 3 RCT (1035 patients), 1 CT

Chronic RBC Exchange

- Chronic RBCx throughout childhood & into adulthood can have profound impact on growth, neuropsychological development, & overall adult health
- Avoids the iron overload of simple transfusions
- Alloimmunization rates have actually been shown to be similar or lower than simple transfusions despite larger number of units of PRBCs*
- Phenotyping policies, at minimum, should screen and match for C, c, E, e, Kell, as well as ABO & Rh
  - More extensive phenotyping should be implemented in patients with an identified antibody
- Goals of chronic RBCx program in general:
  - Keep HbS <30% & decrease iron overload

*Wahl et al. Transfusion 52(12), 2012, pp2671-6
Example Ferritin Reduction with RBC Exchange

Principles of Prescription for RBCx
RBC Exchange Prescription & Monitoring

- Optimal pre-treatment Hb not clearly defined (~9)
  - Hb in lowest quartile (<7.6 g/dL) compared with highest quartile (≥8.6 g/dL) had significantly ↑ risk of a silent cerebral infarct (DeBaun et al Blood 2012)
  - Another controlled trial of transfusions for SCI used Hb >9 as target

- In general, goal HbS pre-treatment for both acute and chronic RBCx should be <30%
  - STOPPI & II – reduced primary strokes if HbS maintained <30%

RBC Exchange Prescription & Monitoring

- Goal post-treatment Hb
  - Not clearly defined, but must consider viscosity, iron overload, oxygen delivery
  - Post-exchange Hb ≥ 12 in children with priapism led to ↑ neurologic events
  - 2014 NIH guidelines recommend a post-exchange Hb level of 10 in children & adults with sickle cell anemia prior to surgery with general anesthesia
  - To avoid iron overload, you wouldn’t want the post Hb > pre Hb if possible
  - If pre Hb has been <9, ok to increase post Hb to ≥ 9 (but <12)
  - Post procedure Hct goal should be ≤30-33% to reduce viscosity & risk for vaso-occlusion
RBC Exchange Prescription & Monitoring

- Goal post-treatment HbS
  - Must first establish the pre treatment goals to achieve the post treatment goals
  - If interval is being lengthened between treatments, should target a lower HbS post treatment

Other Patient Care Issues

- Recommend Hepatitis B immunization if not already immune
- Pediatric patients may require a blood prime
  - If ECV >15% TBV
  - <20kg regardless of Hb level
  - If any reduction in circulating RCV undesirable (severe anemia, hypoxia, hemodynamic instability, etc)
- Some patients are sensitized, with multiple antibodies, may take >24 hours to match and find appropriate number of units for an RBCx
  - Have patient do blood draw/typing 2 days prior to planned procedure for chronic outpatient procedures
How Much Blood Should I Exchange?

- Three ways to decide:
  1. Enter patient’s actual (pre) HbS% & final desired (post) HbS% or
  2. Enter the fraction of cells remaining (FCR): the % of original RBCs remaining in the patient at the end of procedure or
  3. The volume in milliliters of RBCs that will be used as replacement fluid

- Number of units needed to be ordered depends on:
  - Calculated 1-1.5x red cell volume to exchange
  - Desired end procedure Hct
  - Desired reduction in HbS

Where do you want the HbS%?

- Pre-procedure HbS% should be ≤30% to prevent morbidity & mortality of SCD
- A 10% post-procedure HbS has been described as a desirable goal in order to achieve the pre-procedure HbS target

Fraction of Cells Remaining (FCR)
- FCR is the percentage of original RBC volume remaining in the patients body at the end of the procedure
  - 100 – FCR = % of RBC exchanged
  - A lower FCR% results in a lower final HbS%
Fraction of Cells Remaining (FCR)

- If your goal is a post procedure HbS of 10%, and your current HbS is 40%, then $\frac{10}{40} = 25$
  - Program an FCR of 25%
  - The patient height, current Hct & Hct of the replacement cells used in the procedure will impact the volume of cells needed to achieve an identified FCR
  - The machine will then tell you the volume of RBCs needed

\[
\frac{\text{Post-HbS} \%}{\text{Pre-HbS} \%} = \text{FCR} \%
\]
\[
\frac{10 \%}{40 \%} = 25\%
\]

Calculate a Red Cell Volume (RCV)

- If you don’t have HbS% available or volume available of RBCs is less than desired
  - 1.5 x RBC volume for first
  - 1 x RBC volume for subsequent
- Calculate the Total Blood Volume
  - Normal 70kg man, Hct of 30
    - 70kg x 70ml/kg = 4900 mL
    - RCV = 4900ml x Hct (0.3) = 1470 mL
    - One unit of blood 280-350ml (~300)
    - $\frac{1470}{300} = \approx 5U$ PRBCs
    - $\frac{(1470 \times 1.5)}{300} = \approx 7U$ PRBCs

Blood volume (mL/kg body weight)

<table>
<thead>
<tr>
<th>Patient</th>
<th>obese</th>
<th>thin</th>
<th>normal</th>
<th>muscular</th>
</tr>
</thead>
<tbody>
<tr>
<td>male</td>
<td>60</td>
<td>65</td>
<td>70</td>
<td>75</td>
</tr>
<tr>
<td>female</td>
<td>55</td>
<td>60</td>
<td>65</td>
<td>70</td>
</tr>
</tbody>
</table>

Glibcher’s Rule of Five

If volume of blood to exchange entered into machine, machine will tell you expected FCR
Hematocrit of Replacement Cells Varies

- In an automated exchange the Hct of the PRBCs removed is ~80%
- Important to note that Hct of donor PRBCs varies depending on the anticoagulant used – *not a one for one volume of exchange*
  - 21-day CPD “Hct 80%” we assume 78%
  - 35-day CPDA “Hct 80%” we assume 78%
  - 42-day AS-1 “Hct 55-65%” we assume 58%
  - 42-day AS-3 “Hct 55-65%” we assume 58%

Machine will have you input Hct of replacement cells:
input an average Hct calculated from the PRBC types received from blood bank

Choosing The Final Desired Patient Hct%

- You must specify the final desired patient Hct at end of the procedure
- For an “iron-neutral” procedure you would order a final Hct% that is equal to the patient’s starting Hct
- If patient is anemic beyond usual baseline or symptomatic from anemia, end procedure Hct can be higher than starting
- The higher the Hct you target, the more RBC units are needed to complete the exchange
- Post procedure Hct should be ~ ≤30% to reduce viscosity and risk for vaso-occlusion
Performing an initial “deplete” phase shown to reduce number of PRBCs needed & increase intervals between treatments

- Targets achieved more efficiently

**Two phases:**

1. **Isovolemic Hemodilution phase = “Deplete”**
   - Remove red cells, replace with saline or albumin.
   - Lowers Hct – You set how low

2. **RBC “Exchange” phase**
   - RBCs exchanged and Hct gradually raised to desired endpoint.

**How low can you go?**

**TABLE 1. Procedure Programming Targets**

<table>
<thead>
<tr>
<th>Pre-procedure Hct</th>
<th>Post-procedure IHD Hct</th>
<th>End-procedure Hct</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;23%</td>
<td>IHD not performed</td>
<td>27-30%</td>
</tr>
<tr>
<td>23-25%</td>
<td>20%</td>
<td>27-30%</td>
</tr>
<tr>
<td>26-30%</td>
<td>6% below Pre-Hct</td>
<td>Pre Hct + 2%*</td>
</tr>
<tr>
<td>≥31%</td>
<td>8% below Pre-Hct</td>
<td>Pre Hct (Max. 36%)</td>
</tr>
</tbody>
</table>

Hct, hematocrit; IHD, isovolemic hemodilution.

*Max. 32%, if pre-Hct ≤30%.
Isovolemic Hemodilution or Deplete/Exchange

- Goals
  - Decrease RBC utilization
    - PRBC savings of 0.5-1.7 units/procedure
  - Sarode et al. estimated 305 PRBC units over 10 yrs (about $200,000/pt)
  - Lower HbS more efficiently than standard RBCx
  - Increase interval between procedures (37 to 53 days)
  - Decrease cost

Isovolemic Hemodilution or Deplete/Exchange

- The short term and long term effects of acute anemia at the end of the deplete phase on brain & other organs are not known
- Decision to do isovolemic hemodilution – must decide first if patient is at increase risk for silent cerebral infarcts due to ↓O2 delivery during the brief induction of anemia
  - Children with SCD and normal MRI have been shown to have evidence of SCI in association with acute severe anemia (hb ≤5.5, or 30% ↓ from baseline)
  - ASIA: acute severe isovolemic anemia
Contraindications to IHD-RBCx

- Body weight <20 kg (low total red cell volume)
- Pre-Hct <27 in target HbS <30% group & Hct <24% if target <50%: deplete to ≥24% and ≥21% respectively
- Acute stroke in past 6 months
- Cardiopulmonary disease (CHF, PHT) esp with hypoxia
- Hemodynamic instability
- Recent changes in or unstable neuro status (CVA, TIAs, Has of unknown etiology, etc)
- Recent changes in brain imaging studies
- When any degree in reduction of circulating RCV is deemed undesirable

*Sarode et al ASFA 2015 Consensus Conference

Phone App Calculator Available (RBCXCalculation)

![Image of phone app calculator]

2018 ml ~7 units
Sample Prescription for RBC Exchange

- **Diagnosis:**
- **Frequency:**
- **Access:**
- **Maximum Blood Flow:**
- **Anticoagulation:**
- **Calcium:**
- **Vitals monitoring:**
- **Labs:**
  - Pre: cbc, iron/ferritin, Hb electrophoresis
  - Post: cbc, Hb electrophoresis
- **Exchange Only or Deplete Exchange:**
  - Perform deplete if Hct ≥:
  - Minimum Hct during deplete phase: *** or ***% below starting Hct
  - Replacement fluid during deplete:
  - Volume of cells to exchange or target HgbS:
  - Hct of PRBCs given: (take average if not given)
  - Desired end procedure Hct:
- **Fluid balance:**
Chronic RBC Exchange Program

- Multidisciplinary approach with hematologist, apheresis provider, and blood bank
- Potential quality improvement / performance measures:
  - Achieved end procedure Hct +/- 3% of target value
  - %HbS should be within 10% of the programmed FCR
  - Pre-HbS <30% (ok to be higher if patient stable)
  - Reduction in iron stores or need for chelators over time
  - Decreased number of veno-occlusive crises / ER visits

Erythrocytapheresis

- Automated reduction in red cell mass without RBC replacement
- Indications: To decrease viscosity (typically when Hct >50%)
  - Polycythemia vera, secondary erythrocytosis
- Indications: To reduce iron overload
  - Hereditary hemochromocytosis
  - Each tx removes 2-3x iron/RBCs than simple phlebotomy
- Rationale for automated erythrocytapheresis over phlebotomy:
  - Reduces the Hct more efficiently
  - Increase interval between procedures
  - Decrease number of procedures
  - May be tolerated better than phlebotomy if hemodynamically unstable
Erythrocytapheresis

- Prior to surgery shown to reduce risk of perioperative thrombotic complications if Hct >55%
- Shown to improve platelet function post treatment
- Can set the post procedure Hct target on the machine
- Calculates the volume of blood removal necessary to achieve the goal
- One study showed an exchange volume <15ml/kg and an inlet velocity <45 ml/min (esp in >55yo) decreases adverse events
- Saline boluses may be required to reduce blood viscosity in the circuit & avoid pressure alarms
- Frequency: polycythemia – often 1x, hemochromocytosis – q2-3 weeks until ferritin <50 ng/dl
- Replacement fluid: saline or albumin

Summary

- RBC exchange is useful in acute and chronic management of sickle cell disease
- In patients with SCD and history of stroke – high risk of recurrent stroke which is reduced with prophylactic RBC exchange
- RBCx allows for most effective, rapid, and isovolemic reduction in HbS without increasing viscosity or contributing to iron overload
- For sickle cell disease, in general the targets are Hct of ~30 and a HbS <30%
- You must also know the approximate Hct of the blood you are exchanging!
Do not continue simple transfusions in patients with stroke from sickle cell disease who have iron overload, if red blood cell exchange is available.

Thank You!

a6sanchez@ucsd.edu
RECOMMENDATION 1

- The ASH guideline panel suggests an extended red cell antigen profile by genotype or serology over only ABO/RhD typing for all patients with SCD (all genotypes) at the earliest opportunity (optimally before the first transfusion) (conditional recommendation)
  - An extended red cell antigen profile includes C/c, E/e, K, Jk\(\text{a}/\text{jk}^b\), Fy\(\text{a}/\text{Fyb}\), M/N and S/s at a minimum.
  - Red cell antigen profiles should be made available across hospital systems.
  - A serologic phenotype may be inaccurate if the patient has been transfused in the last 3 months.
  - Genotyping is preferred over serologic phenotyping, as it provides additional antigen information and provides increased accuracy for, among other things, C antigen determination and Fyb antigen matching.

RECOMMENDATION 2

- The ASH guideline panel recommends prophylactic red cell antigen matching for RH (C, E or C/c, E/e) and K antigens over only ABO/RhD matching for patients with SCD (all genotypes) receiving transfusions (strong recommendation)
  - The extended red cell antigen profile may be determined by genotype or serology
  - Extended red cell antigen matching (Jk\(\text{a}/\text{jk}^b\), Fy\(\text{a}/\text{Fyb}\), S/s) may provide further protection from alloimmunization
  - Patients who have a GATA mutation in the ACKR1 gene, which encodes Fy antigens, are not at risk for Anti-Fyb and do not require Fyb negative red cells.
  - Patients identified by genotype with the hybrid RHD*DIIIa-CE (4-7)-D or RHCE*Ce or *CE allele should be transfused with C-negative red cells to prevent allo-anti-C development.
RH ANTIGENS

- D, C/c and E/e
- 25 – 30 % of patients with SCD will become alloimmunized with chronic transfusion, in the absence of minor blood group antigen matching
- Antibodies to K, E, C and Jk^b constitute the majority of antibodies formed
- People of African ethnicity have different Rh antigen frequencies and can have different expression of Rh antigens compared to Caucasians
### Prevalence of the Principal HLA Haplotypes

<table>
<thead>
<tr>
<th>Haplotype</th>
<th>White</th>
<th>Black</th>
<th>Asian</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rh Positive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DCE</td>
<td>42</td>
<td>17</td>
<td>70</td>
</tr>
<tr>
<td>DcE</td>
<td>14</td>
<td>11</td>
<td>21</td>
</tr>
<tr>
<td>Dce</td>
<td>4</td>
<td>44</td>
<td>3</td>
</tr>
<tr>
<td>DCE</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>1</td>
</tr>
<tr>
<td>Rh Negative</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ce</td>
<td>37</td>
<td>26</td>
<td>3</td>
</tr>
<tr>
<td>Ce</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>cE</td>
<td>1</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>CE</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

**RH PROTEIN**
HYBRID ALLELES

RHD and RHCE encode RhD and RhCE proteins

**Genes**

<table>
<thead>
<tr>
<th>Rh positive</th>
<th>RHD</th>
<th>RHCE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>D antigen</td>
</tr>
<tr>
<td></td>
<td>5'</td>
<td>3'</td>
</tr>
</tbody>
</table>

**Proteins**

RhD

RhCE

RhD and RhCE differ by 32 to 35 amino acids

Adapted from: Westhoff CM, Semin Hematol. 2007;44:42-50
RHD AND RHCE GENES

IMPORTANCE OF MOLECULAR PHENOTYPING

- Individuals who make variant, hybrid or partial Rh antigens can type as positive for that antigen by serologic methods.
- Individuals with variant, hybrid or partial Rh antigens can make antibody to that antigen.
- Put another way, there is enough antigenic expression to type positive by serology, but, because that expression is not complete, antibodies can still be made.
- The only way to know, for certain, that one of these variant, hybrid or partial antigens is present, is to perform molecular phenotyping of the patient.
- Alternatively, you can suspect it in a person who makes antibody directed against an antigen for which they have typed positive.
THE DUFFY SYSTEM

• The Duffy glycoprotein is a red cell receptor for a variety of chemokines
• The purpose/function is not known
• Duffy antigens are expressed on endothelial cells lining post-capillary venules
• Fya and Fyb differ by a single amino acid change (Gly42 and Asp42)
• The Duffy glycoprotein is a receptor for merozoites of *Plasmodium vivax*
• Red blood cells that are Fy(a-b-) are resistant to invasion by *P. vivax* merozoites

DUFFY PHENOTYPES IN SELECTED POPULATIONS

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Frequency %</th>
<th>Caucasians</th>
<th>African Americans</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fy(a+b-)</td>
<td>20</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>Fy(a+b+)</td>
<td>48</td>
<td>3</td>
<td>20</td>
</tr>
<tr>
<td>Fy(a-b+)</td>
<td>32</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Fy(a-b-)</td>
<td>0</td>
<td>67</td>
<td>20</td>
</tr>
</tbody>
</table>
In people of African ethnicity Fy^b antigen is silenced by a mutation in the promoter region – 67T>C

Mutation disrupts the binding site for the erythroid-specific GATA-1 transcription factor and prevents Fy^b expression on red blood cells

Mutation does not affect expression on non-erythroid tissues

**DUFFY SYSTEM AND MOLECULAR TYPING**

- The majority of individuals who type as Fy(a-b-) by serology have the GATA-1 mutation
- Because these individuals express Fy^b on their endothelium, they do not make anti-Fy^b
- The only way to know if a person has the GATA-1 mutation is to perform molecular RBC typing
BEAD CHIP ASSAY

MOLECULAR TYPING OF RED BLOOD CELLS

- A molecular typing platform for RBCs has been approved by the US FDA
  - 35 antigens from 11 blood groups
    - Rh – c, C, e, E
    - Kell – K, k, Kpa, Kpb, Jsa, Jab
    - Kidd – Jka, Jkb
    - Duffy – Fya, Fyb
    - MNS – MNS
    - Lutheran – Lua, Lub
    - Diego – Dia, Dib
    - Colton – Coa, Cob
    - Dombrock – Doa, Dob, Jsa, Hy
    - Landstainer-Weiner – Lwa, Lwb
    - Scianna – Sc1, Sc2
    - Hemoglobin S
**RBC ANTIGEN TYPING**

**SEROLOGY**
- Quick (hours)
- Limited availability of typing sera for some antigens
- Unreliable if the patient has been transfused
- Only cheaper if typing a few antigens

**MOLECULAR**
- Longer turnaround (weeks)
- Typing for 35 antigens from 11 blood groups
- Not affected by transfusion
- Cheaper than serology if typing more than a few antigens
RECOMMENDATION 3

• The ASH guideline panel suggests immunosuppressive therapy (intravenous immunoglobulin (IVIg), steroids, and/or rituximab) over no immunosuppressive therapy in patients with SCD (all genotypes with an acute need for transfusion and at high risk for acute hemolytic transfusion reaction or with a history of multiple or life-threatening delayed hemolytic transfusion reactions (conditional recommendation)

RECOMMENDATION 4

• The ASH guideline panel suggests immunosuppressive therapy (IVIg, steroids, rituximab, and/or eculizumab) over no immunosuppressive therapy in patients with SCD (all genotypes) with a delayed hemolytic transfusion reaction and ongoing hyperhemolysis (conditional recommendation)
The cause and pathogenesis of hemolytic transfusion reactions in sickle-cell disease

France Pirene

Purpose of review
The current review aims to summarize the epidemiology, cause, pathophysiology, and management of hemolytic transfusion reactions in sickle-cell disease (SCD).

Recent findings
Patients undergoing occasional, isolated transfusions have been shown to have a higher risk of developing this condition. Despite the identification of well known risk factors, including alloimmunization, the pathophysiology of this syndrome remains unclear, as very severe forms with hyperhemolysis may develop in the absence of detectable antibodies, or with antibodies that are not considered to be clinically significant. Complement plays a crucial role in this reaction, particularly in cases of intravascular hemolysis. Complement triggers the reaction, but it also amplifies the inflammatory response and aggravates tissue damage. Free heme and hemoglobin are released and interact with complement, causing tissue damage.

DHTR IN PATIENTS WITH SCD

- Delayed hemolytic transfusion reactions are a life-threatening complication of transfusion in SCD
- Syndrome typically develops 3-5 days after transfusion
- Clinical symptoms mimic vaso-occlusive crisis
- Most severe cases present with hyperhemolysis
  - Decrease in Hb after transfusion to a level below that before transfusion
  - Profound anemia, destruction of transfused and autologous RBCs often accompanied by reticulocytopenia
  - Destruction of autologous RBCs may be due to activation of the complement cascade
HYPERHEMOLYSIS IN SCD

- In a cohort of adult SCD patients in France, hyperhemolysis accounted for 5% of deaths
- Prevention of antibody formation, DHTRs and hyperhemolysis syndrome is the most important reason to provide SCD patients with antigen matched blood

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A Patient’s Apheresis Journey

PRESENTER ~ RONA S. WIGGINS, MSW
SLIDE SHOW EDITOR ~ ANTWOINE WIGGINS

MY BABY PIC…February 1974
Who is Rona?

- Advocate  
- Novice Cook  
- Child of God  
- Traveler  
- Wife  
- Bonus Mom

- Poet  
- Writer  
- Cat Lover  
- Graduate of an HBCU  
- Motorcyclist  
- Redskin Fan

- Novice rock painter  
- Novice painter  
- Inspirational Speaker  
- Member of AKA, INC  
- College Graduate  
- Bigger than HgbSS & RRMS

Hey Sickle Cell, you Lose
SCDAA Advocacy Day

March 31, 2011

Presided by Keita Land, Venezuela and Edita Coleman

Polsinelli Shughart
ACCESS PORTS
SCDAAS CONFERENCE POSTER PRESENTATION – By Rona Brown and Howard FFrench
FIRST TIME SHOOTING…
SICKLE CELL WARRIORS...

A DOCTOR, A LAWYER AND A CPA...
ADVOCATE WARRIORS...

AN ACTOR...
A MOM AND ADVOCATE…

COUSIN BABY WARRIOR…
KID WARRIOR...
MOM ADVOCATE...

MUSIC SOUND WARRIOR...
BIKER ROAD DOG...
AMAZING RUN FOR SICKLE CELL TROPHIES...
6 MONTHS OF ORDERS...
MY HOSPITAL CHILL... GOT THE FLU...
ULCER...NO, JUST INFECTED MOSQUITO BITES...
QUESTIONS/COMMENTS
ALONG MY JOURNEY…

“THEY BLEW MY PORTS ON MY FIRST TREATMENT.”
“WHAT IS THAT TREATMENT YOU ARE TALKING ABOUT, I HAVE NEVER HEARD OF IT.”

“DO THEY TAKE ALL OF YOUR BLOOD OUT AND PUT IT BACK IN?”
“Is it dialysis?”

“Does it hurt?”
“I have heard of it, but they don’t offer that where I live.”

“You said you get six bags of blood…that’s a lot of blood!”
“Do I have to get ports to have the treatment?”

“May I see your ports? Do they hurt?”
“I keloid, will this affect my treatment?”

“They are afraid to put heparin in both sides of my double lumen port!”
“Does your insurance pay for this treatment?”

“How long does it take?”
“I don’t like needles.”

“Aren’t you afraid of catching something from the blood?”
“What is Apheresis?”

Thank you all for your time. Now, it’s time for questions.
Advances in LDL Apheresis:
from Low density Lipoprotein & Lipoprotein(a)
to Focal Segmental Glomerulosclerosis

David M. Ward, MD, FRCP, HP(ASCP)
Professor Emeritus,
Division of Nephrology,
University of California San Diego

DISCLOSURES:
None
OUTLINE:

- Case report and clinical features
- Treatment of elevated LDL cholesterol (Low Density Lipoprotein)
- Treatment of elevated Lp(a) cholesterol ("Lipoprotein little a")
- Use for Focal Segmental Glomerulosclerosis (FSGS)

Case Report

16 year old boy.
- Age 4: nodules on his tendons.
- Age 9: cholesterol >600 mg/dl.
- Genetics: compound heterozygote (2 loci on LDL-R gene).
- Rx: atorvastatin, Zetia, Welchol. Niacin not tolerated.
- On meds, diet and exercise: LDL >300 mg/dL.
- Negative cardiac stress and carotid U/S.
- Rx: LDL-apheresis (Kaneka) at UCSD:
**LDL Apheresis for Familial Hypercholesterolemia (FH)**

- **Homozygous FH**
  - Rare disorder (1:1,000,000).
  - Virtual absence of cell-surface receptors that remove LDL from circulation
  - LDL often 500-1000 mg/dl
  - Severe atherosclerosis & coronary heart disease (CHD) in 1\textsuperscript{st} and 2\textsuperscript{nd} decades of life.

- **Heterozygous FH**
  - More common (1:500)
  - LDL twice normal; CHD in middle decades.

- **Double heterozygotes**
  - CHD in 1\textsuperscript{st} and 2\textsuperscript{nd} decades of life.

---

**Physical Characteristics of Familial Hypercholesterolemia**

- Xanthelasma of the eyelid in hetero-FH
- Arcus corneae and xanthelasma of the eyelid in hetero-FH
- Xanthoma on extensor tendons of the hand in hetero-FH
- Achilles tendon xanthoma in hetero-FH
- X-ray measurement of Achilles tendon thickness
Advances in LDL Apheresis

OUTLINE:

- Case report and clinical features
- Treatment of elevated LDL cholesterol (Low Density Lipoprotein)
- Treatment of elevated Lp(a) cholesterol (“Lipoprotein little a”)
- Use for Focal Segmental Glomerulosclerosis (FSGS)

Historical development of LDL-apheresis systems

First: Plasma Exchange (TPE)
- First reported use for hypercholesterolemia in France in 1967 (1)
- Then 1975 for 2 homozygous FH (2)

(2) Thompson et al Lancet. 1:1208-11, 1975
Sibling as control subject. All on nicotinic acid & lovastatin.

**TPE (Plasma Exchange)** q 2 weeks for 6-9 years:
- peak cholesterol decreased by 37%.
- regression of xanthomas & coronary lesions.
- survived 5.5 years longer than controls (p = 0.03).

*Thompson et al., British Medical Journal. 291:171-1673, 1985*

**Historical development of LDL-apheresis systems**

**TABLE 1. Extracorporeal methods for elimination of low-density lipoprotein cholesterol (36,37,38,39,40,41,42,43,44,45)**

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Method</th>
<th>Advantage</th>
<th>Disadvantage</th>
</tr>
</thead>
<tbody>
<tr>
<td>De Gennes (36)</td>
<td>1967</td>
<td>Plasmapheresis</td>
<td>Quick, considerable elimination of pathologic substances</td>
<td>Unselective, danger of infection, bleeding, sensitivity of human albumin</td>
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<tr>
<td>Thompson et al. (37)</td>
<td>1975</td>
<td>Plasmapheresis</td>
<td>Quick, considerable elimination of pathologic substances</td>
<td>Unselective, danger of infection, bleeding, sensitivity of human albumin</td>
</tr>
<tr>
<td>Agishi et al. (38)</td>
<td>1980</td>
<td>Cascadefiltration</td>
<td>Semiselective</td>
<td>Danger of infection, low effectiveness</td>
</tr>
<tr>
<td>Stoffel et al. (39)</td>
<td>1981</td>
<td>Immunoadsorption</td>
<td>Selective, effective, regenration, reusable</td>
<td>Expended technology</td>
</tr>
<tr>
<td>Borberg et al. (40)</td>
<td>1983</td>
<td>Immunoadsorption</td>
<td>Selective, effective, regenration, reusable</td>
<td>Expended technology</td>
</tr>
<tr>
<td>Wieland et al. (41)</td>
<td>1983</td>
<td>Heparin-induced LDL precipitation (HELP)</td>
<td>Selective, effective</td>
<td>Expended technology</td>
</tr>
<tr>
<td>Nosé et al. (42)</td>
<td>1995</td>
<td>Thermodiffilration</td>
<td>Selective, effective</td>
<td>Expended technology, behavior of macromolecules under heat unknown, not available</td>
</tr>
<tr>
<td>Bosch et al. (44)</td>
<td>1987</td>
<td>Dextran sulfate LDL adsorption</td>
<td>Selective, effective</td>
<td>Expended technology</td>
</tr>
<tr>
<td>Mabuchi et al. (45)</td>
<td>1993</td>
<td>LDL hemoperfusion</td>
<td>Selective, effective, simple technology</td>
<td>Unknown</td>
</tr>
<tr>
<td>Otto et al. (45)</td>
<td>2002</td>
<td>LDL hemoperfusion</td>
<td>Selective, effective, simple technology</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

*Bambauer et al. Therapeutic Apheresis & Dialysis. 7:382-390, 2003*
Historical development of LDL-apheresis systems

LDL removal from separated plasma
1. Adsorption
   • Liposorber (Dextran sulfate adsorption)
   • TheraSorb LDL (Anti-ApoB immunoadsorption)
2. Precipitation
   • H.E.L.P. (Heparin-induced precipitation)
3. Filtration
   • Double Filtration Plasmapheresis (DFPP)

Direct LDL adsorption from whole blood
• Liposorber D (Dextran sulfate adsorption)
• Direct Adsorption of Lipoprotein (DALI) (Polyacrylate adsorption)
### LDL removal from separated plasma

1. Adsorption
   - **Liposorber** (Dextran sulfate adsorption)
   - TheraSorb LDL (Anti-ApoB immuno-adsorption)
2. Precipitation
   - **H.E.L.P.** (Heparin-induced precipitation)
3. Filtration
   - Double Filtration Plasmapheresis (DFPP)

### Direct LDL adsorption from whole blood

- Liposorber D (Dextran sulfate adsorption)
- Direct Adsorption of Lipoprotein (DALI) (Polyacrylate adsorption)

---

**Kaneka Liposorber MA-03**

**Dextran Sulfate Adsorption**

- Processes 1.5 x plasma volume
- Extracorporeal volume: 170ml blood + 230 ml plasma
- First described in 1987
- FDA approved
  - 1996

**B. Braun HELP Plasmat Futura**

**Heparin-induced Extracorporeal Lipoprotein Precipitation**

- Processes 3 liters of plasma (capacity of precipitate filter)
- First developed in 1983
- FDA approved
  - 1997: Secura (no longer in use)
  - 2007: Plasmat® Futura

---

### Kaneka Liposorber MA-03
**Dextran Sulfate Adsorption**

- **Cost:** $2,000 to $2,200
- **Time:** 2 - 4 hours
- **Anticoagulation:** heparin

### B.Braun HELP Plasmat Futura
**Heparin-induced Extracorporeal Lipoprotein Precipitation**

- **Cost:** $2,000 to $2,200
- **Time:** 2 - 3 hours
- **Anticoagulation:** heparin

### Advantages
- No binding of HDL
- Low extracorporeal volume: 170ml blood + 230 ml plasma

### Disadvantages
- Bradykinin effect: patient must not be taking ACE inhibitor.
- Can’t use citrate (disrupts dextran sulfate binding)
- Reduction of platelets (17%) and fibrinogen (29%)
B.Braun HELP Plasmat Futura
Heparin-induced Extracorporeal Lipoprotein Precipitation

- **Advantages**
  - No bradykinin effect (patient can be on an ACE inhibitor)

- **Disadvantages**
  - Limited to 3L plasma processed (capacity of precipitate filter)
  - Non-selective removal of C3, C4, fibrinogen, plasminogen, and factor VIII
  - Some removal of HDL (6 - 21%)
  - Complex system

Comparison of B.Braun (HELP) and Kaneka Liposorber (DS)

**Compared:**
1) Braun HELP at 3 liters plasma processed “HELP”
2) Liposorber at 3 liters (same volume as Braun) “DS$_3$”
3) Liposorber final volume (1.5 x patient’s TPF) “DS$_F$”

**Reduction of Cholesterol:**

<table>
<thead>
<tr>
<th></th>
<th>HELP 3 liter</th>
<th>DS$_3$ 3 liter</th>
<th>DS$_F$ 1.5 PV</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL</td>
<td>- 63%</td>
<td>- 60%</td>
<td>- 70% *</td>
</tr>
<tr>
<td>Lp(a)</td>
<td>- 65%</td>
<td>- 65%</td>
<td>- 71%</td>
</tr>
<tr>
<td>HDL</td>
<td>- 21%</td>
<td>- 6% *</td>
<td>- 6% *</td>
</tr>
</tbody>
</table>

* All close to (within 12% off) predicted maximum for TPE of same volume
* Less LDL loss with DS (p<0.003)

* DS significantly better than HELP

### Indications for hypercholesterolemia:
- Homozygous FH . . . . . . . absolute indication.
- Heterozygous FH + CHD . . relative indication.

### Insurance standards for LDL apheresis . . . if after 6 months of diet and maximum tolerated cholesterol-lowering drug therapy:
- LDL-C >100* mg/dl with documented CHD . . . every 2 weeks. *(Changed by FDA in April 2019 from >160 to >100)*
- LDL-C >300 mg/dl with documented CHD . . . every week.

### LDL Apheresis:
- Life-long therapy
- Continue statins, resins, niacin, fibrates, and diet (to help slow rebound and prolong intervals between LDL-Apheresis sessions).

### Clinical successes
- Cardiac survival
- Cardiovascular event rates
- Regression of coronary atherosclerosis
- Regional myocardial perfusion
- Exercise stress testing
- Endothelium-dependent coronary vasodilation
- Cerebral blood flow
- Carotid artery atherosclerosis
Reduction in major cardiovascular events

Mabuchi et al Am J Cardiol 82:1489-95, 1998
Increased myocardial perfusion

Figure 3. Bar graphs showing mean percent change in HMTT ± SEM (Hyperemic Mean Transit Time)

ST-depression on bicycle stress test

KD-apheresis

Maximal ST depression (blue lines)

Time to onset (histogram bars) (sec.)

Control group


Cerebral blood flow

LDL-Apheresis

Rubba et al. Stroke 24:1154-1161, 1993

Carotid artery atherosclerosis

Mean maximum IMT (mm year⁻¹)

FH (total; n = 11)  Homozygous FH (n = 2)  Heterozygous FH (n = 9)  Heterozygous FH (n = 10)

LDL apheresis group  Control group

P < 0.005

P = 0.0004

Koga et al. Journal of Internal Medicine 246:35-43, 1999
Renal deterioration after vascular interventions (35 cases):
- 11 (control group) received steroids
- 24 received steroids and LDL-apheresis (mean 4.3 +/- 1.8 apheresis treatments)
- eGFR rose from 15.0 to 19.6 in LDL-A group (p<0.05).
- At 1 year, eGFR higher in LDL-A versus controls (median 7.5 versus 2.2, p=0.019)
Follow-up series

The German Lipoprotein Apheresis Registry (GLAR) - almost 5 years on.

- 1435 patients, 15527 LDL-apheresis procedures.
- LDL reduction 67.5%.
- Major cardiovascular events reduced by 78%.

Long-term outcome in 53 patients with homozygous familial hypercholesterolaemia in a single centre in France.

- TPE and later LDL-apheresis for up to 38 years (53 patients).
- 28 patients had a major event.
- 4 died due to complications of major surgery
- 3 died of acute MI
- 1 died of stroke.

New anti-cholesterol drugs

- **Lomitapide**
  - FDA-approved 2012. Orphan drug (adjunctive) for Ho-FH.
  - Inhibits VLDL assembly.
  - Poorly tolerated (LFT elevations and fatty liver).

- **Mipomersen**
  - FDA-approved 2013. “Black box” warning (LFTs & fatty liver)
  - Antisense nucleotide – inhibits synthesis of Apo-B, so lowers LDL, VLDL and Lp(a).

- **PCSK9 inhibitors**
  - Are monoclonals, well-tolerated in many patients:
    - **alirocumab** = Praluent (Sanofi) (FDA-approved July 2015)
    - **evolocumab** = Repatha (Amgen) (FDA-approved August 2015)
  - Reduce plasma LDL levels by increasing density of LDL-R.
**PCSK9 (Proprotein convertase subtilisin/kexin type 9)**

- PCSK9 causes LDL-R to be internalized and degraded.
- Lower LDL-R density allows plasma LDL to increase.
- Inhibition of PCSK9 increases LDL-R and lowers plasma LDL.

**Addition of PCSK9 Inhibitor in Homozygous FH**

**The “TAUSSIG” Study:**

- 106 patients with Ho-FH – Interim analysis
- On treatment (including LDL-apheresis in 34 cases)
  - **Evolocumab (Repatha) q 2 wks**
  - Significant cardiovascular events in
    - 1 patient on apheresis
    - 3 not on apheresis
      (Mean follow-up of 1.7 years. No deaths.)
  - LDL reduction at 12 weeks was 20.6% (similar in apheresis and non-apheresis groups).
  - Some non-apheresis pts started injections q 4 weeks
    - those who switched to q 2 weeks (doubling dose)
    - had additional 8.3% reduction after 12 weeks.

PCSFK9 Inhibitor allowing discontinuation of LDL-Apheresis

“ODYSSEY ESCAPE” Trial (patients receiving LDL-apheresis):
- Double-blinded Alirocumab (Praluent) (randomized 2:1 to placebo)
- In 62 HeFH patients on LDL-apheresis (in USA & Germany).
- Withheld LDL-apheresis when LDL reduction of 30% from baseline.
- Adverse events rates similar in both groups.


PCSFK9 Inhibitor allowing discontinuation of LDL-Apheresis

“ODYSSEY ESCAPE” Trial (patients receiving LDL-apheresis):

63% of Alirocumab (Praluent) patients discontinued LDL-apheresis

Switch from LDL-Apheresis to PCSK9 Inhibitor


Evolocumab 140mg Q2W

Alirocumab after acute MI

Alirocumab after acute MI

Cumulative incidence of the primary end point, a composite of:
- death from coronary heart disease,
- nonfatal myocardial infarction,
- fatal or nonfatal ischemic stroke,
- unstable angina requiring hospitalization.


LDL Apheresis – in Pregnancy

- Statins and newer LDL drugs are contraindicated in pregnancy.
- 12 pregnancies in 7 patients with Ho-FH:
  - One patient who refused LDL-apheresis died from Acute MI.
  - Another poorly adherent patient also died from Acute MI.
  - One had to discontinue LDL-apheresis because of angina.
  - Another had bradykinin syndrome (nausea, hypotension, bradykinin) during dextran sulfate LDL-apheresis.
  - The other 3 (including 2 with CAD before pregnancy)
    - continued LDL-apheresis with good adherence
    - Delivered healthy infants with no adverse effects.
- Conclusion: LDL-apheresis essential for pregnant Ho-FH patients.

OUTLINE:

- Case report and clinical features
- Treatment of elevated LDL cholesterol (Low Density Lipoprotein)
- Treatment of elevated Lp(a) cholesterol (“Lipoprotein little a”)
- Use for Focal Segmental Glomerulosclerosis (FSGS)

“Lipoprotein little a” – Lp(a)

Lp(a) is an independent risk factor for CVD.

- Mortality, MI, stroke, and PAD still under investigation.
- Atherogenic levels >25-30 mg/dL.
- No FDA-approved drugs that specifically lower Lp(a)
- PCSK9 inhibitors sometimes lower Lp(a), unpredictably.
- LDL-Aph is the most effective way to lower Lp(a). (1,2)
  - Lp(a) not an FDA-approved indication for LDL-Aph.
  - Lp(a) >60 mg/dL (in absence of high LDL) approved in Germany (2008) (2)
- Device specific for Lp(a) – Lipopak® (Pocard, Moscow). (2,3)

LDL-apheresis for Lp(a) - UCSD case

- 65yo woman, diagnosed age 27, negative cath age 49, MI age 50.
- Intolerant of statins, but on Zetia, Niaspan & fish oil.
- Baseline LDL of 309 mg/dl.
- Baseline Lp(a) of 140 ("atherogenic" if >25 or 30).

Graph courtesy of Amber P. Sanchez MD

LDL-apheresis for Lp(a)

Pro(a)Life study:
- 170 cases of isolated Lp(a)-elevation + progressive CV disease
- Followed before and after starting LDL-apheresis

Major Adverse Coronary Events ("MACE")

118 patients with elevated LDL or Lp(a) or both (>36,000 treatments)
Overall MACE (Major Adverse Coronary Events) decreased by 79.7%
In 35 patients who had only Lp(a) elevation, MACE decreased by 90.4% (p<0.001)


From Cologne and Mainz:
- 170 consecutive LP(a) patients.
- 154 completed 5-year follow-up.

In Germany (written in 2016):

- 2,000 to 2,500 patients currently on LDL-apheresis.
- About 1,000 are for elevated LDL only.
- Of the remaining 1,000–1,500 subjects:
  - approx half for elevated Lp(a) only,
  - the other half for combined elevations of LDL and Lp(a).
- PCSK9 inhibitors will “most likely decrease the number of patients being treated for elevated LDL-C only very significantly (by approximately 80–90%)”.

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**OUTLINE:**

- Case report and clinical features
- Treatment of elevated LDL cholesterol (Low Density Lipoprotein)
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## FSGS Focal Segmental Glomerulosclerosis

### Normal foot processes vs. "Effacement"

- **Normal foot processes**: Normal appearance of podocyte foot processes.
- **"Effacement"**: Change caused by "Circulating Permeability Factor".

### In Minimal Change Glomerulopathy:
- Podocyte effacement is reversible by steroids.

### In Primary FSGS:
- Podocyte effacement progresses to podocyte cell death.
- Causes sclerosis of the glomerular capillary tuft.
- Heavy proteinuria, nephrotic syndrome, and progressive renal failure.

---

## FSGS: Focal Segmental Glomerulosclerosis

- **FSGS**: Only the "Primary" type recurs in kidney transplants.

### 1972

**Recurrent of Idiopathic Nephrotic Syndrome After Renal Transplantation**


### 2018

- Up to 50% do not recur in 2nd transplant despite prior recurrence in 1st transplant.
- Recurs post-transplant in:
  - ~ 23% of adults with primary FSGS.
  - Recurrence rates higher in children.
  - ~ 50% if previous transplant lost to recurrence.
TPE is first-line treatment for recurrence of Primary FSGS after renal transplantation.

Weeks or months after transplant, most patients no longer need TPE. This means that levels of "Proteinuric Factor" have declined.

(1) Zimmerman: Nephron, 1985
(2) Valdivia: Transplant Proc, 2005
(3) Schachter: Clin Nephrol, 2010
(4) Ponticelli, Glassock: CJASN, 2010
(5) Moroni: Transpl Int, 2010
(6) Gungor: Transplant Proc, 2011
(7) Tsagalis: Artif Organs, 2011
(9) Straatmann: Pediatr Transpl, 2014
(11) Fencl: Minerva Pediatr, 2015

Summary – use of apheresis for FSGS:

- The identity of circulating Glomerular Permeability Factor(s) remains unknown. Bioassays available in research labs only.
- For post-transplant recurrence of FSGS:
  - TPE + IS is first line treatment and of proven clinical benefit.
- For native-kidney FSGS:
  - Rituximab, corticosteroids and other IS can be effective.
  - Indications for adding TPE are less clear - selected cases.
- IA (Immunoadsorption of IgG); one positive report (France). (?)
- LDL-apheresis for FSGS:
  - Will be discussed in "LDL-Apheresis" talk.
FDA letter granting “Humanitarian Device Exemption” (HDE) for Kaneka Liposorber to treatment of pediatric FSGS.

(2018: extended to adult FSGS (post-transplant and refractory pre-transplant))

Dextran Sulfate Adsorption (Kaneka Liposorber®) for FSGS

Authorized by Federal (USA) law for use in the treatment of adult and pediatric patients with nephrotic syndrome associated with primary focal segmental glomerulosclerosis (FSGS) when:

- Standard treatment options, including corticosteroid and/or calcineurin inhibitors, are unsuccessful or not well tolerated and the patient’s glomerular filtration rate (GFR) ≥ 45 ml/min/1.73 m² or
- The patient is post renal transplantation.

The effectiveness of this device for this use has not been demonstrated.

Caution: Federal law restricts this device to sale by or on the order of a physician.

Carefully review the “LIPOSORB® LA-15 System Operator’s Manual for use in the treatment of adult and pediatric patients with primary focal segmental glomerulosclerosis (FSGS)” and use only under the direction of a licensed physician with appropriate training.

Distributed by
KANEKA PHARMA AMERICA LLC
548 Fifth Avenue, 21st Floor New York, New York 10036

https://www.accessdata.fda.gov/cdrh_docs/pdf17/H170002D.pdf
Dextran Sulfate Adsorption (Kaneka Liposorber®) for FSGS

- 11 children, biopsy-proven FSGS, all steroid resistant after 8 weeks (and prior cyclosporin-A).
- LDL apheresis (Kaneka Liposorber) 2x/wk for 3 wks, then weekly for 6 wks.
- 7 of 11 had marked reduction in proteinuria, or achieved remission.
- Appeared to improve response to steroids.


Dextran Sulfate Adsorption (Kaneka Liposorber®) for FSGS

The POLARIS Trial

- 58 patients with steroid resistant nephrotic syndrome, ages 18-84.
- All treated on Kaneka Liposorber system (dextran sulfate adsorption), for average of 9.6 LDL-Aph procedures
- Patients
  - 55% of courses were for FSGS.
  - 45% for other glomerular diseases.
- Proteinuria fell similarly in
  - FSGS cases (from $6.47 \pm 2.98$ to $3.26 \pm 3.13$)
  - non-FSGS cases ($6.13 \pm 3.41$ to $3.89 \pm 4.01$).

Mechanism of action of LDL-apheresis in FSGS

- Removes Glomerular Permeability factors (as efficiently as TPE)?
- Eliminates nephrotic syndrome in a majority of cases of primary FSGS?

- Reduces hypercholesterolemia that contributes to glomerular damage?
- Somewhat improves proteinuria in a variety of nephrotic diseases?

#1? Hattori, 2003
#2? Muso, 2015

1. Adults

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Patients</th>
<th>Study Design</th>
<th>Length of Follow-up</th>
<th>Clinical Outcomes</th>
<th>Pre-transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muso 2015 [1]</td>
<td>44 (26 with FSGS)</td>
<td>Prospective Multicenter Single arm</td>
<td>Immediate to 2 years after treatment</td>
<td>Urinary Protein (UP) decreased from 6.28 ± 3.33 to 2.7 ± 2.7 g/day.</td>
<td>Pre-transplant</td>
</tr>
<tr>
<td>Muso 2015 [2]</td>
<td>17 (14 with FSGS)</td>
<td>Prospective Multicenter Controlled</td>
<td>Immediate to 2 years after treatment</td>
<td>UP decreased from 6.2 ± 3.3 to 2.7 ± 2.7 g/day.</td>
<td>Pre-transplant</td>
</tr>
<tr>
<td>Muso 2001 [3]</td>
<td>6 (2 with FSGS, 1 treated with Liposorber®)</td>
<td>Prospective Single Center</td>
<td>Unknown</td>
<td>This was a prospective study of the effects of liposorber® in treating various forms of NS in 6 patients. One patient with FSGS failed to respond to one month of LIPOSORBER® treatment.</td>
<td>Pre-transplant</td>
</tr>
<tr>
<td>Nakamura 2006 [4]</td>
<td>8 FSGS</td>
<td>Prospective Single Center</td>
<td>2 weeks</td>
<td>UP decreased from 8.8 ± 4.2 g/day to 2.0 ± 1.2 g/day.</td>
<td>Pre-transplant</td>
</tr>
<tr>
<td>Muso 2007 [5]</td>
<td>41 FSGS</td>
<td>Retrospective</td>
<td>5 years</td>
<td>At 1 month after LDL apheresis, UP was significantly decreased. Remission of nephrotic syndrome was observed in 16/29 patients (55%) followed at 2 years and 13/17 patients (76%) followed at 5 years.</td>
<td>Pre-transplant</td>
</tr>
</tbody>
</table>

The continuation of this table lists 5 single-case publications

Table from "Liposorber® LA-15 LDL ADSORPTION COLUMNS, Instructions for use in adult and pediatric Focal Segmental Glomerulosclerosis (FSGS)”, Kaneka Pharma America LLC available on-line at: https://www.accessdata.fda.gov/cdrh_docs/pdf17/H170002D.pdf
Possible mechanisms of action of LDL-Apheresis:

- Removes Glomerular Permeability factor(s).
- Reduces LDL, etc., (incl. free fatty acids) that are elevated in all nephrotic patients and contribute to glomerular damage.
- Lowers plasma viscosity and improves endothelial function.
- Increases binding sites and effectiveness of corticosteroids.
- Increases uptake of cyclosporin into cells (40-60% is via LDL receptors which are up-regulated after LDL depletion).
- others.
Interim Conclusions for FSGS:

- TPE works for post-transplant & selected pre-transplant.
- LDL-Apheresis successes for FSGS reported.
- Data-collecting series underway in USA for refractory pre-transplant and post-transplant FSGS. (1)

Opinion:

- TPE still my first choice for post- and pre-transplant FSGS (2), but I will try LDL-A in resistant cases.
- LDL-Aph (Liposorber) benefit not fully defined or understood, needs to be subjected to a comparative trial with TPE.
- FSGS post-transplant often becomes inactive after weeks or months – so a sequential trial comparing TPE and LDL-A should randomize the order of these two modalities.

(1) Joshua Zaritsky MD PhD, Nemours Children’s Hospital, Delaware

Dextran Sulfate Adsorption (Kaneka Liposorber®) for FSGS

USA – Liposorber FSGS study sites:

- Alfred I. duPont Hospital (Wilmington) (Dr. Joshua Zaritsky – PI)
- Children's Boston
- Children's Pittsburgh
- Nemours Children's Orlando
- Univ. of Michigan
- Akron Children's
- Spectrum Health (Helen DeVos)
- MUSC (Charleston, SC)
- Cincinnati Children's Hospital
- Fresenius Indianapolis (St. Vincent)
- VCU Health System Children's (Richmond, VA)
- UNC (NC)
- Loma Linda (CA)
SUMMARY:

- Case report and clinical features
- Treatment of elevated LDL cholesterol (Low Density Lipoprotein)
- Treatment of elevated Lp(a) cholesterol (“Lipoprotein little a”)
- Use for Focal Segmental Glomerulosclerosis (FSGS)

Thank you for your attention

dmward@health.ucsd.edu
Mindfulness in Medicine: How to Avoid Physician and Nursing Burnout in a Demanding Field

Ni-Cheng Liang, MD
March 6, 2020
Director of Pulmonary Integrative Medicine
Coastal Pulmonary Associates
Scripps Health Partner
Voluntary Assistant Professor of Medicine
UC San Diego School of Medicine

Conflict of interest:
CEO of Ni-Cheng Liang, M.D., Inc
31 y.o. female physician...

What are her risk factors for burnout?
Nailed it!
Nightingale Pledge 1893

I solemnly pledge myself ... in the presence of this assembly, to pass my life in purity and to practice my profession faithfully. I will abstain from whatever is deleterious and mischievous, and will not take or knowingly administer any harmful drug. I will do all in my power to maintain and elevate the standard of my profession, and will hold in confidence all personal matters committed to my keeping and all family affairs coming to my knowledge in the practice of my calling. With loyalty will I endeavor to aid the physician, in his (or her) work, and devote myself to the welfare of those committed to my care.
Burnout

• “If your energy is in a long downward spiral and you are tapped out and unable to give your best at work ... you are most likely suffering from physician burnout”- The Happy MD

• Three components (Maslach)
  • Emotional exhaustion
  • Depersonalization
  • Low sense of personal accomplishment
Prevalence of Burnout Among Nurses

- Systematic review and meta-analysis of burnout symptoms in nurses worldwide
- 45,539 nurses worldwide in 49 countries
- Overall pooled-prevalence of burnout symptoms among global nurses was 11.23%.
- Sub-Saharan African region-highest, Europe and Central Asia-lowest.
- Pediatric nurses→highest, Geriatric care nurses→lowest
More Patients = More Nurse Burnout

- 10,000 nurses, 230,000 patients
- 168 hospitals in Pennsylvania
- Each additional patient assigned
  - 7% increase in 30-day patient mortality
  - 7% increase in failure-to-rescue rates
  - 15% increase in the likelihood of nursing job dissatisfaction
  - 23% increase in the likelihood of nurse burnout

"The system is what needs to change so we can promote thriving and well-being for our healthcare professionals."

-Lotte Dyrbye, MD MHPE
Table 2. Potential Interventions to Prevent and Treat Burnout Syndrome in the ICU

<table>
<thead>
<tr>
<th>Intervention Type</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Environmental interventions</td>
<td></td>
</tr>
<tr>
<td>Promoting healthy work environment</td>
<td></td>
</tr>
<tr>
<td>Communication training; appropriate staffing; meaningful recognition</td>
<td></td>
</tr>
<tr>
<td>ICU self-scheduling/time off</td>
<td></td>
</tr>
<tr>
<td>Limit the maximum number of days worked consecutively</td>
<td></td>
</tr>
<tr>
<td>Support groups</td>
<td></td>
</tr>
<tr>
<td>Cognitive-behavioral therapy</td>
<td></td>
</tr>
<tr>
<td>Team-based interventions</td>
<td></td>
</tr>
<tr>
<td>Team debriefings</td>
<td></td>
</tr>
<tr>
<td>Use of structured communication tools</td>
<td></td>
</tr>
<tr>
<td>Team-building and interpersonal skills training</td>
<td></td>
</tr>
<tr>
<td>Practitioner-focused interventions</td>
<td></td>
</tr>
<tr>
<td>Stress reduction training</td>
<td></td>
</tr>
<tr>
<td>Relaxation techniques</td>
<td></td>
</tr>
<tr>
<td>Time management</td>
<td></td>
</tr>
<tr>
<td>Assertiveness training</td>
<td></td>
</tr>
<tr>
<td>Meditation</td>
<td></td>
</tr>
<tr>
<td>Work-life balance measures: hobbies, family, and social activities</td>
<td></td>
</tr>
<tr>
<td>Self-care measures: ensuring adequate rest, exercise, healthy eating habits</td>
<td></td>
</tr>
<tr>
<td>Interventions to mitigate risk factors</td>
<td></td>
</tr>
<tr>
<td>Palliative care consultations</td>
<td></td>
</tr>
<tr>
<td>Ethics consultations</td>
<td></td>
</tr>
<tr>
<td>Establishing goals of care for every ICU patient</td>
<td></td>
</tr>
<tr>
<td>Family care conferencing within 72 h of ICU admission</td>
<td></td>
</tr>
<tr>
<td>Organizational measures</td>
<td>n (%)</td>
</tr>
<tr>
<td>Healthy food choices on campus</td>
<td>331 (55.8)</td>
</tr>
<tr>
<td>On-campus exercise/gym facilities</td>
<td>263 (44.5)</td>
</tr>
<tr>
<td>Self-scheduling</td>
<td>258 (43.5)</td>
</tr>
<tr>
<td>Ability to take personal/respite days</td>
<td>148 (25)</td>
</tr>
<tr>
<td>Interpersonal/communication training</td>
<td>131 (22.1)</td>
</tr>
<tr>
<td>Limit the maximum number of days to work consecutively in the ICU</td>
<td>114 (19.2)</td>
</tr>
<tr>
<td>Respite room</td>
<td>91 (15.3)</td>
</tr>
<tr>
<td>Staff support groups</td>
<td>66 (11.1)</td>
</tr>
<tr>
<td>ICU team building training</td>
<td>63 (10.6)</td>
</tr>
<tr>
<td>Individual measures</td>
<td>n (%)</td>
</tr>
<tr>
<td>Yoga class</td>
<td>115 (19.4)</td>
</tr>
<tr>
<td>Mindfulness-based stress reduction class</td>
<td>107 (18)</td>
</tr>
<tr>
<td>Meditation class</td>
<td>58 (9.8)</td>
</tr>
</tbody>
</table>
What do you do for your well-being?
Practicing Mindfulness

If your attention wanders a hundred times, simply bring it back a hundred times.

Mindfulness Practice Fosters Neuroplasticity

Increased gray matter:
- Left hippocampus
- Temporo-parietal junction

Compassion and empathy

Decreased gray matter:
- Amygdala

Mindfulness Reduces Burnout Amongst Physicians

- **2014 study at Mayo Clinic**
  - 1 hour biweekly sessions
  - Mindfulness
  - Reflection
  - Shared Experience
  - Small group learning
  - ~19 hours

- **2009, 70 primary care physicians**
  - CME Mindful Communication Course
    - 2.5 hour weekly classes x8
    - 7 hour day long session
    - 10 monthly sessions
    - ~52 hours
  - Mindfulness, empathy improved
  - Decreased characteristics of burnout
  - 12 and 15 month follow-up


Mindfulness Training Reduces Burnout in ICU

- Intensivists, nurses, nursing assistants
- Mindfulness workshop
- 8-week training program, short guided practices, virtual community on WhatsApp
- A weekly proposal in audio and text format, daily reminders with stimulating messages of practice
- Results: decrease in emotional exhaustion and an increase in self-compassion

Mindfulness in Nurses

- Meta-analysis, 17 articles, n= 632
- Mindfulness training decreased levels of burnout
  - Decreased emotional exhaustion
  - Decreased depersonalization
  - Increased personal accomplishment


Small-Group Curriculum Reduces Burnout

- 19 biweekly discussion groups: mindfulness, reflection, shared experience, learning for 9 months
- PROTECTED TIME: 1 hour of PAID time every other week
- Improvements in meaning, engagement, and reduced depersonalization
- Sustained results for 1 year after the study

Physician well-being (resilience – burnout) 

Mindful practice 

Quality of care (safety – errors) 

Quality of caring (empathy - detachment) 


© Mindful Practice Programs, University of Rochester, 2010

Let’s try mindfulness!
Invoke the Vagus Rule!!!
Pause and Check In

- What do you notice, having been through this experience?
- How do you see it affecting your own life and work?
- What are your thoughts about embedding mindfulness into your life?
- What are the barriers or challenges?

Please Check-in Here

Mindful Mnemonics

STOP
Stop, Take a Breath, Observe, Proceed

RAIN
Recognize, Allow, Investigate, Not Personal

AAA Card
Awareness, Acceptance, Action
Mobile Wellness for Healthcare Professionals by Ni-Cheng Liang, MD

• Password: Ucsdmindfulness
  
  Introduction - https://vimeo.com/217714368/4b81df773b
  Movement Practice – https://vimeo.com/230642078/845b267b29
  Awareness of Breath - https://vimeo.com/218659897/aabf02cb81
  Body Scan Practice - https://vimeo.com/218660073/8716691201
  Rain Practice - https://vimeo.com/218660664/b6cb686b62
  Loving Kindness Practice - https://vimeo.com/230641996/68c8d24d81
  Walking Practice - https://vimeo.com/230642005/430316f376
  Pause for Self Compassion - https://vimeo.com/230642071/4d04fdd39a

• Made possible by the Kaiser Teaching Award from the UCSD Academy of Clinician Scholars

@DrNiChengLiang

Incorporating mindfulness

• Your feet, your hands, stethoscope breaths
• Take Mindfulness Based Stress Reduction or Mindful Self-Compassion
• UCSD Center for Mindfulness website:
  Consider trying some of the guided meditations free on the website on your own
  • http://health.ucsd.edu/specialties/mindfulness/programs/mbsr/Pages/audio.aspx
  • U of Rochester Mindful Practice Programs
    https://www.urmc.rochester.edu/family-medicine/mindful-practice.aspx
  • Apps: Headspace, Calm, Insight Timer

@DrNiChengLiang
Summary

- The culture and systems of healthcare in the US need to change to prioritize healthcare professional wellness, establishing strong partnerships between organizational leaders and clinicians which in turn will promote a culture of safety and quality of care for patients.
- Cognitive behavioral therapy and mindfulness are proven methods to reduce burnout.
- Coaching is a promising intervention to reduce burnout.

https://www.thoracic.org/professionals/ats-wellbeing-collaborative/wellbeing-resources.php
Mindfulness Offerings

• Email info@ncliangmd.com for more info:
  • CME Online Mindful Doctor Course: 7 hours over 3 months
  • Pause: A Day-Long Retreat for Women in Healthcare (Green Gulch)

• Mindfulness Based Stress Reduction

To sign up and for free audio meditations:
www.ncliangmd.com
Thank you for your attention!

Questions?
Ni-Cheng Liang, MD
info@ncliangmd.com

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Director of Pulmonary Integrative Medicine
Coastal Pulmonary Associates, Scripps Health Partner
Campus Representative for Physician Burnout
Scripps Memorial Hospital Encinitas
Voluntary Assistant Professor of Medicine, UC San Diego School of Medicine

“YESTERDAY IS HISTORY, TOMORROW IS A MYSTERY, BUT TODAY IS A GIFT. THAT IS WHY IT’S CALLED THE PRESENT.”
-Master Oogway