Extracorporeal Extravaganza: ECMO and Other Advanced Technologies

By Curt Froehlich, MD
Associate Professor
University of Texas Health Science Center at San Antonio

Disclosures

• Curt Froehlich, MD has NO financial relationships with commercial interest to disclose

• I WILL be discussing off label use of FDA approved equipment

• I WILL introduce equipment NOT FDA approved and will acknowledge when doing so

Disclosures

• I am a believer
• I believe in improving the availability of these services
• I AM NOT:
  • Nephrologist
  • Pathologist
  • Hematologist
  • Cardiologist
  • Surgeon

Learning Objectives

1. Understand the concept of extracorporeal therapies, how they are used to treat disease, and the rationale for grouping these therapies
2. Be able to name at least 4 extracorporeal therapies.
3. Be able to understand the history of extracorporeal therapies

Learning Objectives

4. Describe the cost of ECMO as it compares to other therapies such as organ transplantation and bone marrow transplantation.
5. Describe briefly some of the future applications of extracorporeal therapies including organ perfusion and prematurity
Extracorporeal Extravaganza

- History/Pitfalls
- Basics
- Continuous Renal Replacement Therapy (CRRT)
- Plasma Therapies
- Ventricular Assist Device (VAD)
- Hemoperfusion
- Extracorporeal Membrane Oxygenation (ECMO)
- Future Applications

Introduction

Diseases desperate grown
By desperate appliance are relieved, Or not at all.

- Claudius, King of Denmark
In Hamlet Act IV Scene 3
W. Shakespeare

Borrowed from Jim Fortenberry, MD

Haven’t I Heard this Before?

December 13, Washington had “taken a cold.” At 2 the next morning, he awoke and had difficulty breathing. By 6 a.m., he was febrile, with throat pain and respiratory distress. His aide, Colonel Tobias Lear, sent for Craik and bloodletter George Rawlins.

- At about 7:30 a.m., Rawlins removed 12 to 14 oz (355 to 414 ml) of blood, with Washington requesting additional bloodletting.
- Craik removed approximately 18 oz (532 ml) of blood at 9:30 a.m., with a similar amount removed at 11 a.m.

History of Extracorporeal Therapies

Morens December 9, 1999 NEJM

Arriving at 3 p.m., Dick argued that further bleeding might weaken Washington.

- Craik ordered a fourth bleeding, with the removal of 32 oz (946 ml) of blood.
- After the fourth bloodletting, Washington’s condition improved.
- However, around 5 p.m. his condition worsened. He continued to struggle for air. At around 10 p.m., Washington whispered burial instructions to Lear. He died at 10:20.

What Have We Learned?

- We now give some back!
- Our techniques have evolved from:
  - Cardiac bypass (1926)
  - Dialysis (1945)
  - Plasma Exchange (1963-1968)
  - ECMO (1971)
Extracorporeal Therapies in Tandem (2006)

Basics of Extracorporeal Therapies

Single Site
- Vascular access
- Blood pump
- Anticoagulation
- “Filter”
- Heater?
- Safety systems

Two or More Sites
- Vascular access
- Blood pump
- Anticoagulation
- “Filter”
- Heater?
- Safety systems
Basics of Extracorporeal Therapies

Similarities / Differences

- Vascular access
- Percutaneous
- Cutdown
- Blood Pump
- Roller
- Centrifugal
- Anticoagulation
- Regional
- Systemic
- Type of “Filter”
- Safety systems

Renal Dysfunction and Need for CRRT

- Leading Causes in Developed Countries
  - Ischemia associated with disease and advanced therapies
  - Congenital Heart Disease
  - Acute Tubular Necrosis (ATN)
  - Sepsis
  - Nephrotoxic Medications
- AEIOU
- CRRT
  - May allow more liberal use of “good” fluid

Continuous Renal Replacement Therapy

- Zobel
  - 36 neonates – 66% survival

- ppCRRT (344 multicenter patients)
  - Overall survival 58% (Symmans ClinAmSocNeph 2007)
  - mQIDS $1% survival (Goldstein Kid Int 2005)
  - <10 kg 43% (Asikainen J Peds 2012)

- Adults – range from 15-70% survival depending on population

Continuous Renal Replacement Therapy

Recovery of Function?

- Lotta
  - 24 children, 9 survivors
  - Recovery of renal function in all patients
- Barton
  - 250 adult patients, 132 surviving to discharge
  - 128 (97%) recovery of renal function
- Lin
  - 242 surgical CRRT patients, 83 surviving to 90 days
  - 73 (88%) had recovery of renal function

When to Start CRRT?

Leite et al. Critical Care 2013, 17:R62
When to Start CRRT?

<table>
<thead>
<tr>
<th>Meta-Analysis: All 15 studies</th>
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<tbody>
<tr>
<td>Study name</td>
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<tr>
<td>Study 1</td>
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<td>Study 2</td>
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<td>Study 3</td>
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Plasma Therapies

- First used by Michael Rubinstein in 1959 to treat an adolescent boy with TTP.
- Modern plasma therapies owe their origins to the National Cancer Institute and the dairy cream separator technology from 1963-1968.
- Can be used to separate:
  - Plasma
  - Red Cells
  - White Cells
  - Platelets

Basics of Extracorporeal Therapies

- Plasma Therapies
  - Vascular access
  - Blood pump
  - Anticoagulation
  - Centrifuge
  - Safety systems

Thrombotic Thrombocytopenic Purpura (TTP)

- Class 1 Disease
- Incidence 0.37/100,000/year
- Systemic thrombotic illness with ADAMTS-13 deficiency
- 7 RCTs / 301 patients
- Disease from universally fatal to <10% mortality
- Single to 1.5 volume exchange daily until platelet recovery (>150,000) and normal LDH for 2-3 days
- FFP is used as replacement (albumin alone is less effective)

ADAMTS-13 Deficiency Predicts Adult Sepsis Survival Independent of DIC

- 72 septic adults
- 36 with ADAMTS-13 deficiency
- Group 1: no DIC or low ADAMTS-13
- Group 2: DIC or ADAMTS-13 < 30
- Group 3: both DIC and ADAMTS-13 < 30
- Independent from DIC
Plasmapheresis in Severe Sepsis and Septic Shock

- PRCT, Russian adult ICU
- 106 sepsis patients randomized to:
  - Standard therapy
  - Addition of plasmapheresis (1/2 FFP, 1/2 albumin)
- Decreased mortality with plasma exchange

- Busund et al., Intensive Care Medicine 2002;28:1410

PELOD Scores Decrease Greater With Plasma Exchange

Ventricular Assist Device

- Most common circulatory assist remains ECMO
- 12,209 neonatal and pediatric patients have been supported with approx 45% survival to discharge
- Complications of ECMO may increase after 14 days of support
- Need for greater mobility and prolonged support

Basics of Extracorporeal Therapies

- Ventricular Assist Device (VAD)
  - Vascular access
  - Blood pump
  - Anticoagulation
  - Safety systems

Ventricular Assist Device

- Limited availability in pediatric patients
- Currently most pediatric experience is with the Berlin Heart EXCOR
  - Pulsatile pump
  - Can be configured for single ventricle or 2-ventricle support
  - Works by pneumatic compression
  - Indications: dilated cardiomyopathy, congenital heart disease, and restrictive cardiomyopathy

Berlin Heart EXCOR
Trial of a Pediatric Ventricular Assist Device

- Berlin Heart use was divided into 2 groups
- Matched to ECMO controls

<table>
<thead>
<tr>
<th>COHORT 1 (n=24)</th>
<th>COHORT 2 (n=24)</th>
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<tbody>
<tr>
<td>(85 kg &lt; 0.7 m²)</td>
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<td>Median survival = 174 days vs. 13 days matched ECMO</td>
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Fraser et al. N Engl J Med 367;6

Polymyxin B: EUPHAS Trial

- Early Use of Polymyxin B Hemoperfusion in Abdominal Sepsis (EUPHAS)
- Italy: adults with abdominal sepsis requiring surgery
- Randomized, unblinded
- Within 6 hours post-op:
  - Standard
  - Treatment (2 courses of hemoperfusion with polymyxin B column)
- Most common organisms: E.coli, Pseudomonas, Enterobacter

-Cruz et al., JAMA, 2009

Hemoperfusion

- Similar to CRRT
- Can be used to remove mediators of sepsis from blood
  - Cytokines
  - Chemokines
  - Superantigens
  - Modulators of apoptosis
  - Endotoxin
- Use cartridges containing materials such as resin-coated beads or fibers that bind the desired mediators.

EUPHAS Trial: Survival

- Hazard Ratio 0.43 (0.21-0.90)

-Cruz et al., JAMA, 2009
What is ECMO?

- Stands for: ExtraCorporeal Membrane Oxygenation?
- Should it stand for Extremely Costly Midnight Operation?
- What is it?
  - A way in which the lungs or the heart and lungs can be artificially supported for prolonged periods of time
  - What is prolonged?
    - 2 weeks?
    - 3 months?
    - 9 months?

ECMO History

- Technology is not “new”
- Reports of first patients supported 1971 after development of long term “oxygenators”
- First Randomized Adult Study 1972
  - Used New ECMO centers
  - Many patients with influenza
  - Lots of bleeding
  - Showed conventional therapy better than “bad” ECMO

ECMO History

- Bartlett et al, Esperanza (Hope) first neonatal case 1976
  - “Abandoned newborn”
- Bartlett et al 1982 45 newborns, 90% predicted mortality >50% survival
- O’Rourke 1989 randomized neonatal trial: Stopped early due to ECMO benefit

Basics of Extracorporeal Therapies

- Extracorporeal Membrane Oxygenation (ECMO)
  - Vascular access
  - Blood pump
  - Anticoagulation
  - “Artificial” lung
  - Heater
  - Safety systems

ELSO

- Extracorporeal Life Support Organization
  - Organization of national and international centers
  - Formed by Dr. Bartlett and others in 1989
  - 223 international centers in 2014 and growing rapidly
  - Provides collaboration
  - Each patient a “data point”
Basics of Extracorporeal Therapies

(ECMO II)

- Vascular access
- Blood pump
- Anticoagulation
- “Artificial” lung
- Heater
- Safety systems

What about this?

ECMO Basics

- All mechanical ventilation causes acute lung injury (pressure, volume, jet, APRV, HFOV)
- ECMO provides support, it does not **FIX ANYTHING DIRECTLY!**
- Right therapy/Right Time
- ECMO support allows time to heal, optimizing fluid status and nutrition, restoration of acid/base status and normalizing oxygen delivery

ECMO Basics

- ECMO should be considered if the process is:
  - Severe
  - Acute
  - Potentially reversible
What has changed since 2010?

Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial

And in 2014?

Flu hitting adults hard, ECMO treatment helped save one man’s life

Active ECLS Centers

Overall Patient Outcomes

Neonatal Respiratory Cases

Neonatal Diagnoses and Survival
Future of ECMO?

- Past “contraindications”
  - Single ventricle
  - CPR in progress
  - Sepsis
  - Organ support
- “Acceptable” candidates are always evolving
  - HIV?
  - Malignancy?
  - Bridge to transplant?
  - Bridge to VAD?
  - Trauma?
  - Sepsis?

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**ELSO Registry January 2014**

**Pediatric Respiratory Cases**

**Pediatric Diagnoses and Survival**

**Adult Respiratory Cases**

**Adult Cases by Diagnosis**

- ** Runs  | % Surv **
  - Viral Pneumonia  407  | 66
  - Bacterial Pneumonia  858  | 61
  - Aspiration  125  | 64
  - ARDS  906  | 53
  - Acute Resp Failure, Non-ARDS  673  | 54
  - Other  2,309  | 54

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**Cumulative Runs**

**Annual Runs**

**Total Runs**

- Viral pneumonia  345
- Bacterial pneumonia  379
- Aspiration pneumonia  201
- ARDS  385
- Acute resp failure  584
- Other  1000
Retrospective review of the ELSO registry: outcomes of ECLS patients with neoplastic disease. 

Organization’s registry after 2007 to determine utilization and

Objective:
ECLS survey felt neoplastic disease was not a contraindication to community, he found that 95% of ECLS centers responding to a discharge. Demonstrating a change in attitude in the ECLS neoplastic disease (1994-2007) and found a 35% survival to Gow otherwise healthy patients; however, this dogma is changing.

Background:
Referring to stem cell or bone marrow transplantation during a diagnosis of neoplasm (International Classification of Excluded patients with diagnoses or procedure ICD-9 codes Required ECLS between 1/1/2008 and 12/31/2012 and carried Children (ages birth to 21 years)

Introduction

Methods

- Data were collected from the ELSO database
- Patients were excluded if they had neoplastic disease or procedure 1994-2007 ECLS use was used for temporary cardiac or pulmonary support when traditional means are unsuccessful. ECLS use has been traditionally restricted to

Demographics

Table 1: Demographics of Study Population and ECLS

<table>
<thead>
<tr>
<th>Type of support</th>
<th>Duration of ECLS (median [Q1, Q3, n])</th>
<th>Female gender</th>
<th>Pre-ECLS OI (median [Q1, Q3, n])</th>
<th>Weight (median, [Q1, Q3 and n])</th>
<th>Age at initiation (median, [Q1, Q3 and n])</th>
</tr>
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<tr>
<td>ECLS</td>
<td>6.4 days (2.8, 12.6, 174)</td>
<td>32% (57)</td>
<td>44.8 (21.3, 62.1, 114)</td>
<td>21 kg (11, 48, 165)</td>
<td>5.3 years (1.6, 13.4, 178)</td>
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<td>Pre-ECLS OI</td>
<td>3.0 days (1.5, 7.2, 55)</td>
<td>21% (37)</td>
<td>36.1 (20.7, 54.4, 105)</td>
<td>17 kg (10, 42, 163)</td>
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Results

- Survival to discharge is improved in this five-year era (48%)
- While ECLS use in cancer patients is still low (0.34% of all ECLS in 47.8% of patients survived to discharge
- 55.1% of patients survived their ECLS run
- No survival difference

Solid malignancy: 72 patients (40.4%)
Hematologic malignancy: 106 patients (59.6%)

Conclusions

- Additional work is needed to delineate which subpopulations will optimally benefit from survival for patients with neoplastic disease.
- Since 2007, ECLS is being used more often and with better survival to

What about Cost?

- Financial Obligation / Institutional Responsibilities (1993 analysis)
  - Average cost of ECMO patient: $50,000
  - Assuming accepted mortality and survival rates
  - Comparisons:
    - Renal Transplant - $16,300/life year saved
    - Heart Transplant - $26,900/life year saved
    - Liver Transplant - $43,500/life year saved
    - Bone-Marrow Transplant - $62,500/life year saved

ECLS Can Be Cost-Effective

Cost/Life-year-saved: Pediatric ECLS vs. Other Therapies

- Vats et al., Crit Care Med 1998

ECLS Research: Artificial Placenta

Slide courtesy of Bill Lynch

Pictures courtesy of George B. Mychaliska
ECLS Research: Cardiac Perfusion

How is this all applied?

- 17 year old male with Status Asthmaticus
  - Vent: 32/4, rate 10, FiO2 100%
  - 0220: 6.78/188/148/27/-11 (k 5.97, iCa 1.4)
  - 0250: 6.82/174/209/28/-10.7/ k 5.8/iCa 1.3
  - 0317: 6.76/187/81/26/-13.7/K 5.6/iCa 1.27
  - 0433: 6.78/-/125/-/-/k 5.6/iCa 1.24
  - 0602: 6.68/-/125/-/-/K 7.5/iCa 1.29
  - 0704: 6.56/190/54/17/-24.4/K 6.95/iCa1.2
  - 0902: 6.68/-/142/-/-/k 6.7/iCa1.18

Recent Success

- Pupils fixed and dilated

UHS Neonatal/Pediatric Extracorporeal Therapies

- Designed to maximize neonatal/pediatric experience
  - Neonatal ECMO (Available mid April)
  - Pediatric ECMO (Available mid April)
  - CRRT (Available now)
  - Plasmapheresis (Available now through pathology)
  - Call (210) 358-2500 for referrals
  - Future collaborations?

Conclusions

- Extracorporeal therapies for neonates/pediatric can be run out of a single department
- Technology is not “new”
- Extracorporeal therapies can be cost effective
- Application and development of extracorporeal therapies continues to evolve
Remember……

With Great Thanks!

• UHS Administration
• Pathology
• Hematology
• Nephrology
• Neonatology
• Cardiology
• Surgery
• Critical Care
• Jim Fortenberry
• Matt Paden
• Robert Bartlett
• ELSO
• Kendra
• Casey
• Perfusion
• All of our specialists

Questions?