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Healthcare of Atlanta

Support of Sepsis/MOSF: ECMO and Plasma Exchange

James D. Fortenberry MD, FCCM, FAAP
Director, Critical Care Medicine and Pediatric ECMO/Advanced Technologies

Emory University School of Medicine
Children's Healthcare of Atlanta at Egleston
Atlanta, Georgia, USA

Overwhelming Sepsis: Desperate Times...

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

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



Potential Extracorporeal Devices for Sepsis

- CRRT
- Extracorporeal Membrane Oxygenation (ECMO)
 - Potential benefits
 - Experience
 - Expert recommendations
- Plasma Exchange/Plasmapheresis
 - Use in TAMOF
 - Development of study network
 - Early results

ECMO in Sepsis-Why Use It?

- Temporary cardiovascular support
- Temporary lung support
- Temporary renal support
- Dilution of cytokines
- “Platform” for other therapies

- Earlier view:
 - Sepsis a **CONTRAININDICATION** for use of ECMO in neonates and children
 - Concerns:
 - ◆ Cannula might perpetuate bacteremia
 - ◆ Foreign membranes might aggravate inflammatory response
 - ◆ Sepsis: pre-existing coagulopathy might increase bleeding complications

- Arensman, Extracorporeal Life Support, 1993 (1st ed.)

ECMO in Neonatal Sepsis: Clinical Experience

- Neonates: persistent pulmonary hypertension with Group B streptococcal sepsis
- ECMO used in this setting with good results
- Case series experience: 70-100% survival (McCune, J Ped Surg 1990; Hocker Peds 1992)
- ELSO registry review 1995: 1060 with sepsis (74% GBS): survival similar to nonseptic patients (Meyer, J Thorac Cardiovasc Surg, 1995)

ECMO in Neonatal Sepsis: Not A Contraindication

- “ECMO should not be withheld from neonates solely on the basis of sepsis”

-Meyer, J Thorac Cardiovasc Surg, 1995

ECMO in Neonatal Sepsis: Does It Improve Outcome?

- 1997 ECMO center survey
- 107 septic neonates on ECMO
- Gram positive infections (83%): 77% survival
- Gram negative infections (13%): 60% survival

ECMO in Neonatal Sepsis: Does It Improve Outcome?

- Neonates: ELSO Registry 2428 “sepsis” patients to present
- Mean run time: 138 hours
- 75% survival
- Difficult to know “how septic” from Registry
- Previous review: higher predicted risk of mortality than observed risk
- **Similar to overall ECMO survival**

ECMO in Neonatal Sepsis: Clinical Experience

- Septic neonates:
 - Higher incidence of intracranial hemorrhage
 - Higher incidence of VA support (89%)
 - Increasing use of VV ECMO could impact these outcomes

-Meyer, J Thorac Cardiovasc Surg, 1995

ECMO in Pediatric Sepsis: Clinical Experience

- More difficult to assess
- **Sepsis not listed** as a primary indication for ECMO in ELSO registry for pediatrics
- Coexisting sepsis in at least 12 % of pediatric ARF ECMO

ECMO in Pediatric Sepsis: Clinical Experience

- 1997 ELSO registry pediatric review
 - ECMO patients (univariate analysis)
 - With sepsis: 37% survival
 - Nonseptic 52% survival
 - But multivariate → Sepsis NOT an independent predictor of ECMO survival
- **Don't exclude from ECMO for sepsis**

ECMO in Pediatric Sepsis: Clinical Experience

- Increased likelihood of seizures, CNS complications with sepsis
- Sepsis survival decreased with advancing age
- 83% of patients on VA ECMO (? impact of increasing VV use)

-Meyer et al., Ann Thorac Surg 1997

ECMO in Pediatric Sepsis: Clinical Experience

- Our center:
 - Occasional use for refractory septic shock alone
 - ◆ 12 patients with primary or contributing indication (50% survival)
 - Sepsis a frequent coexisting diagnosis (40%)

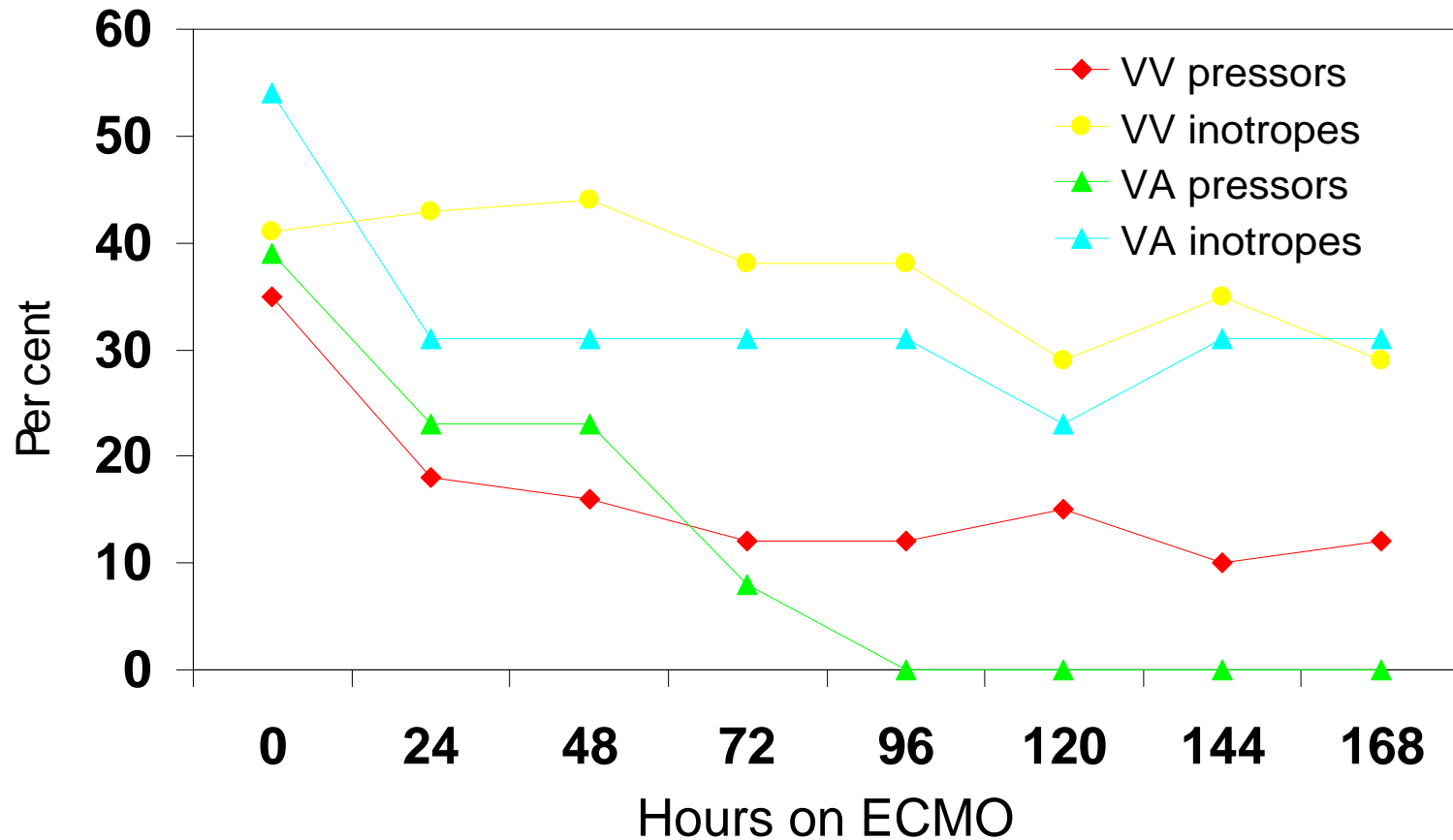
- Pettignano, Fortenberry et al.,
Pediatr Crit Care Med 2003

ECMO in Pediatric Sepsis: Clinical Experience

- **35% of VV** respiratory failure (36% of VA) patients **on significant pressors** prior to cannulation
- Able to wean rapidly off pressors even on VV ECMO

- Pettignano, Fortenberry et al.,
Pediatr Crit Care Med 2003;4:291

ECMO in Pediatric Sepsis: Vasopressors in VV vs. VA ECMO



- Pettignano, Fortenberry et al.,
Pediatr Crit Care Med 2003;4:291

ELS For Intractable Cardiorespiratory Failure Due to Meningococcal Disease: **Good News**

- ECMO in 12 children with meningococccemia
- 7 for intractable shock within 36 hours (5 ARDS)
- 6/12 required CPR pre-ECMO
- **8/12 survived**
 - 4/7 with shock
 - 4/5 with ARDS
- 6 functionally normal

- Goldman et al., Lancet 1997;349:466

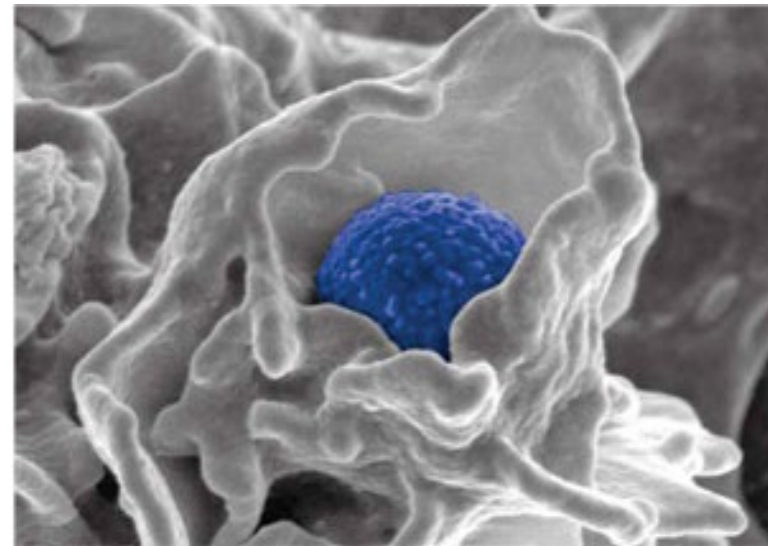
ECMO for Meningococcal Sepsis: **Not-So-Good News**

- 11 children (prognostic scores 90% mortality) treated with ECMO
- Overall survival 55 percent
 - 5 with ARDS (4/5 VV, time to initiation 946 hours): **all survived**
 - 6 with refractory shock and organ failure (all VA, time to initiation 8.5 hours): **only 1/6 survived** (survivor cannulated at 74 hours)

- Luyt et al., Acta Pediatr 2004

Methicillin-Resistant Staphylococcus Aureus (MRSA)

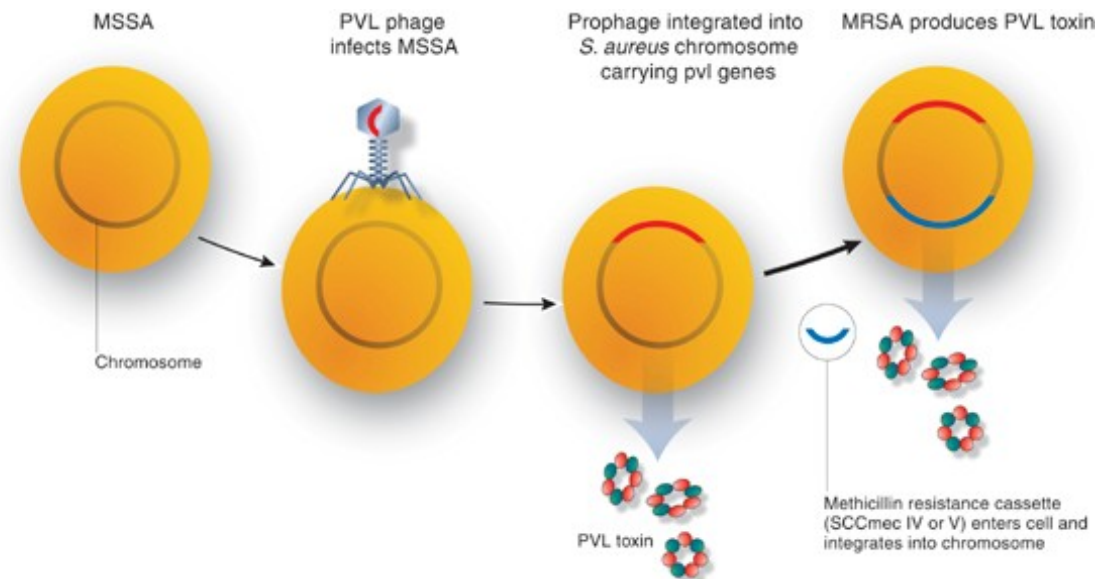
- New scourge
 - Community acquired vs. hospital acquired
 - Marked increase
 - Immunocompetent
 - Adolescents
 - Associated with skin, soft tissue infections
 - Increased osteo, empyema, DVT
 - Profound sepsis



Methicillin-Resistant Staphylococcus Aureus (MRSA)

Panton Valentine Leukocidin (PVL) gene expression

- Risk factor for severity?
 - ◆ Local tissue invasion, DVT, severe systemic infection
- **75% mortality in PVL+** patients presenting in septic shock

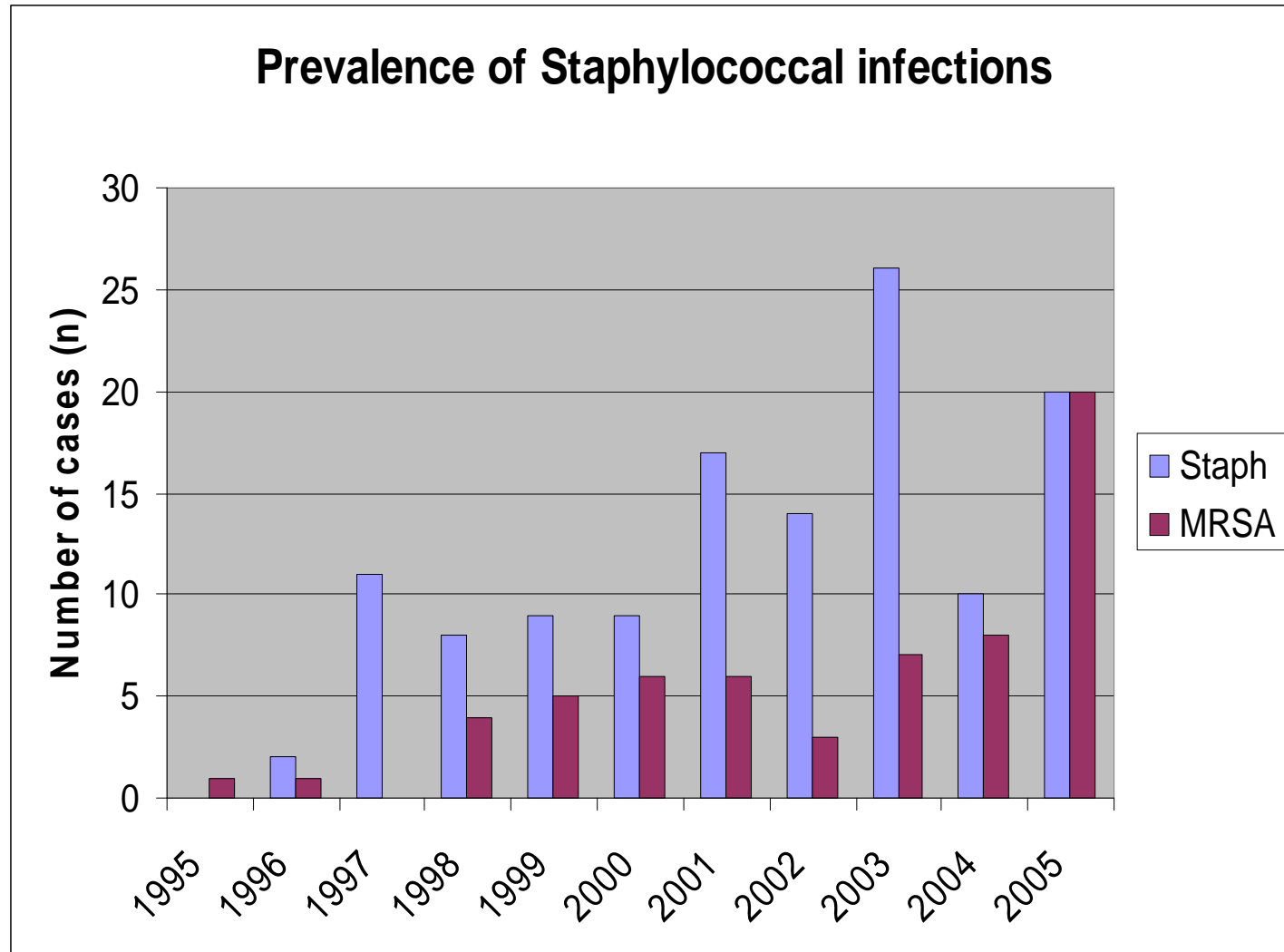


ECMO for MRSA Sepsis: ELSO Experience

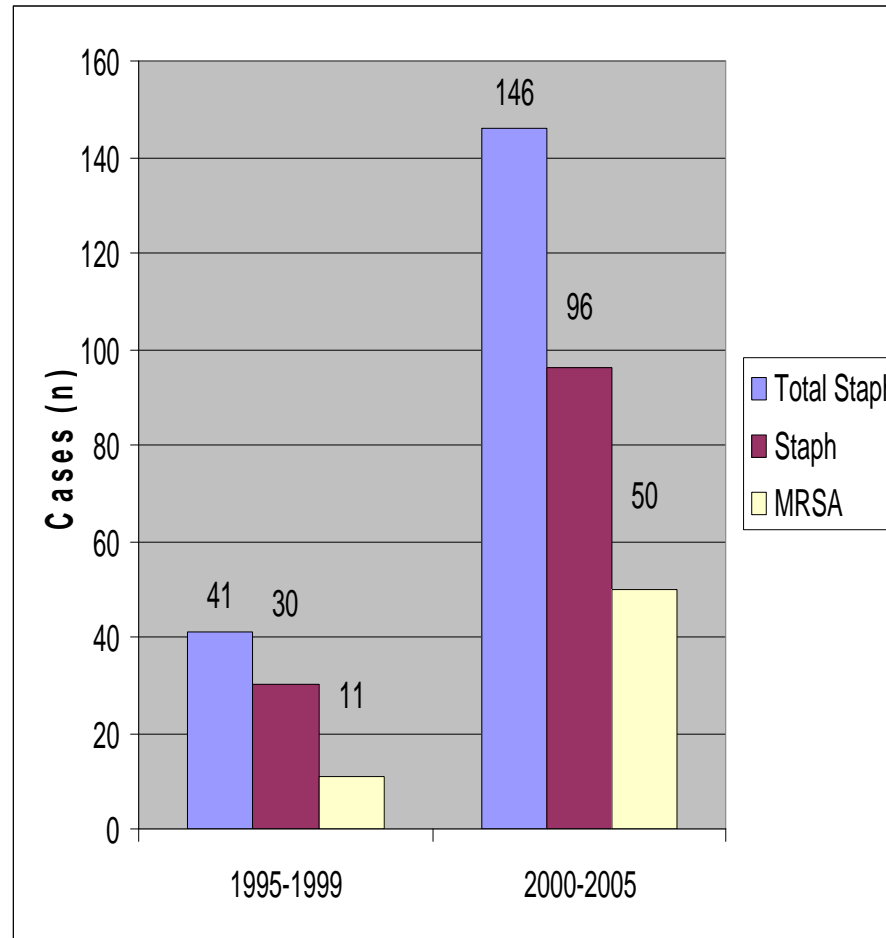
- Review of ELSO experience 1986-2005
- 123 *S. aureus* patients
- 45 MRSA
- 20 in 2004-2005 alone
- Median age 2.4 years
- Overall *S. aureus* survival 43% (vs. 57.3 overall peds)
- VA ECMO in 53% of patients

-Creech et al., Ped Crit Care Med, 2007

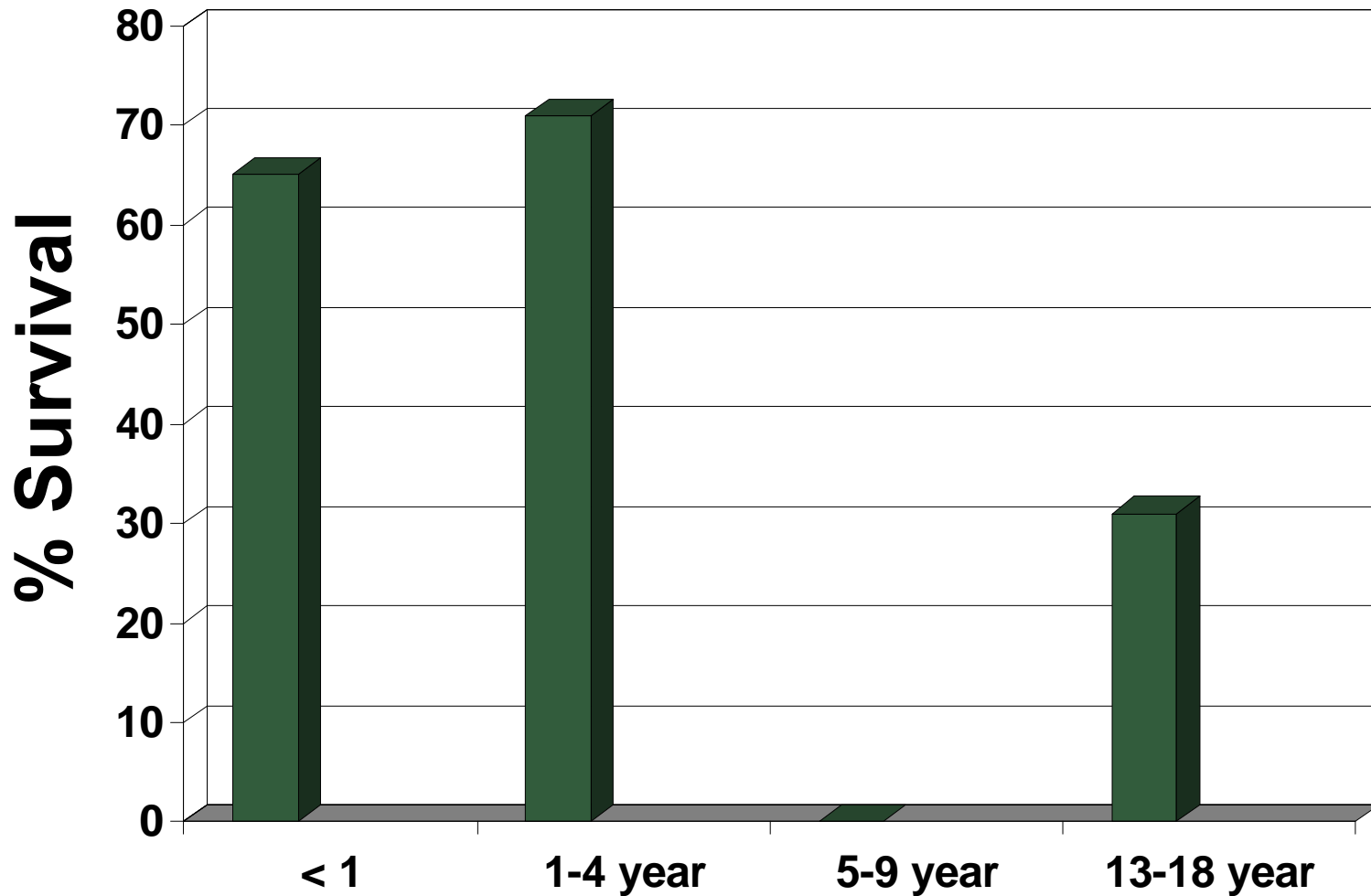
ELSO Registry: Staph Aureus Runs



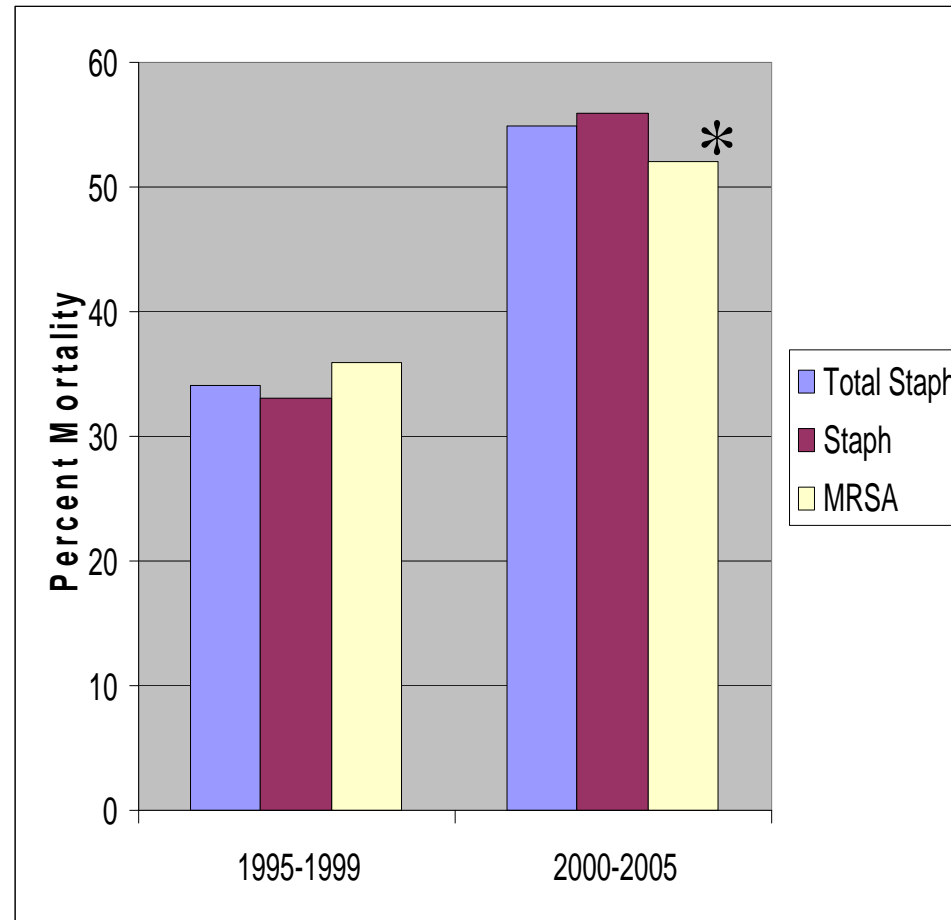
ELSO Registry Data: S. Aureus Cases Are Increasing



MRSA and ECMO: Age and Mortality



ELSO Registry Data: S. Aureus Mortality is Increasing



ECMO and Sepsis: Questions

- Current data difficult to assess
- When is ECMO used for “overwhelming” sepsis with C-R failure vs. respiratory failure alone?
- Need for more directed data collection (ELSO Registry)

ACCM Clinical Practice Parameters for Pediatric Septic Shock Support

- Recommendations for use of ECMO:
 - Newborns: Use for “refractory shock”
 - Pediatric: “Consider ECMO”
 - Both Level II = Reasonably justifiable by scientific evidence and strongly supported by expert critical care opinion

- Carcillo et al., CCM 2002; 30:1365

ACCM Clinical Practice Parameters for Neonatal Septic Shock Support

... persistent catecholamine-resistant shock



Refractory shock



Use ECMO

ACCM Clinical Practice Parameters for Pediatric Septic Shock Support

... persistent catecholamine-resistant shock



Place PA catheter and direct therapies to attain normal MAP-CVP and CI . 3.3 and < 6.0 L/min/m²



Refractory shock



Consider ECMO

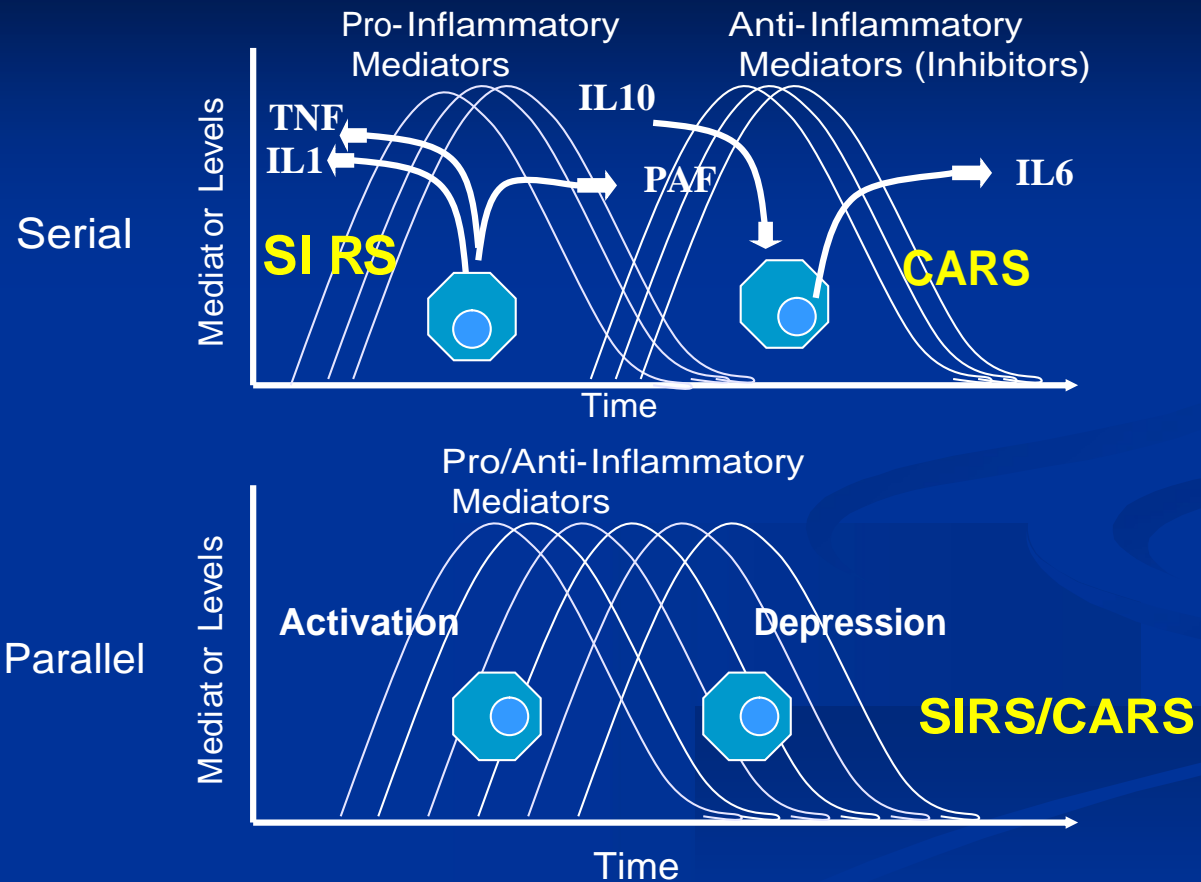
Benefits of ECMO in Sepsis: "Platform" for Immunomodulatory Therapies"?

- Allows for "easier" delivery of
 - ◆ Continuous renal replacement therapies (CRRT)
 - ◆ Plasmapheresis
 - ◆ Plasma exchange

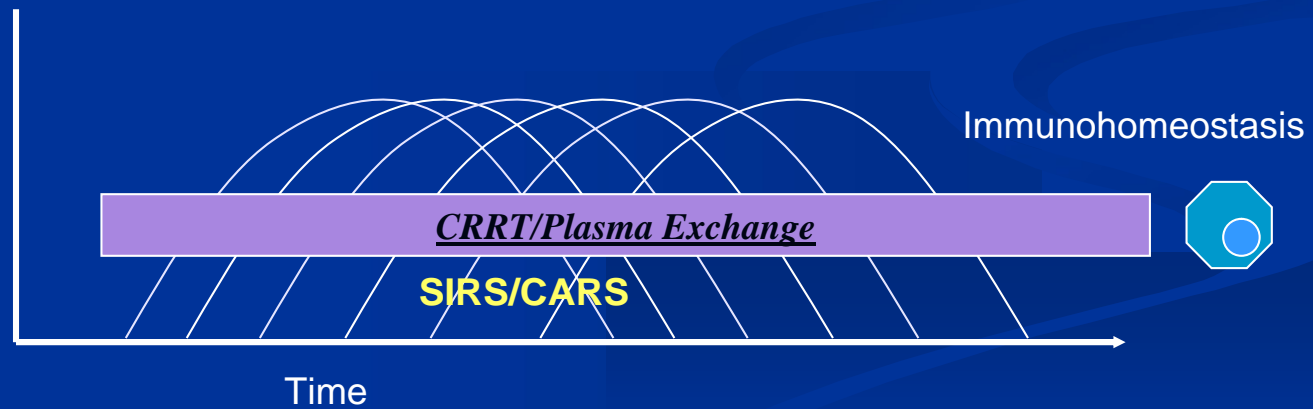
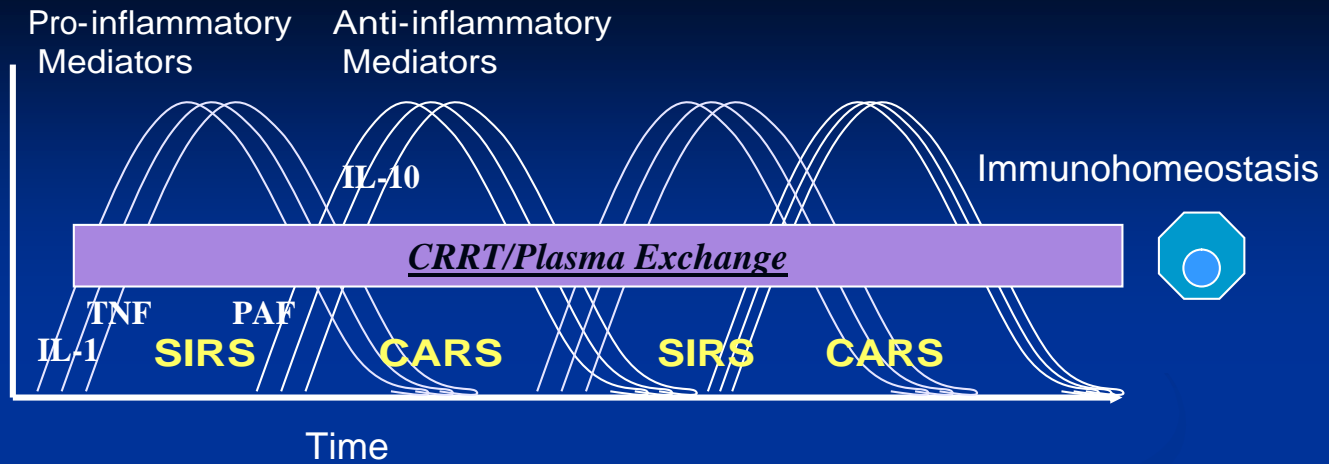
Plasma Exchange on ECMO



Peak Concentration Model of Sepsis



Peak Concentration Model of Sepsis



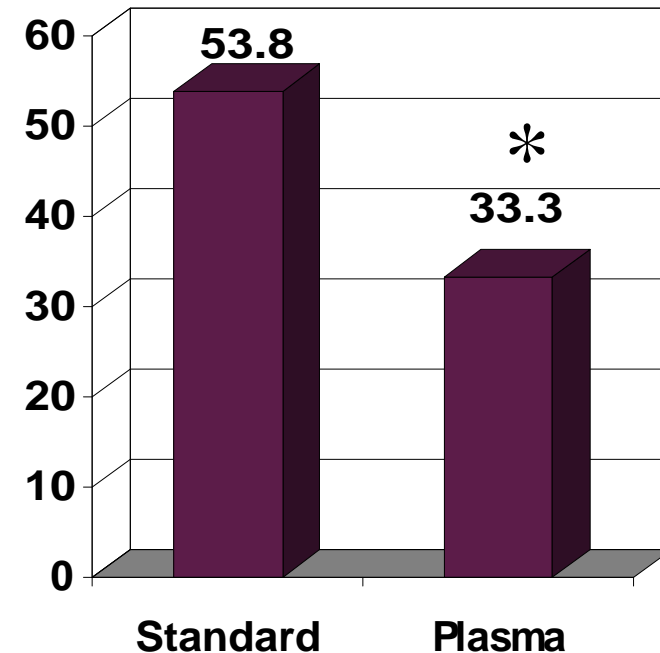
Adapted from Ronco et al. Artificial Organs 27(9) 792-801, 2003

Plasma Therapies

- Plasmapheresis: plasma removed → replaced with 5% albumin
- Plasma exchange: plasma removed → replaced with donor plasma
 - centrifugation
 - filtration

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

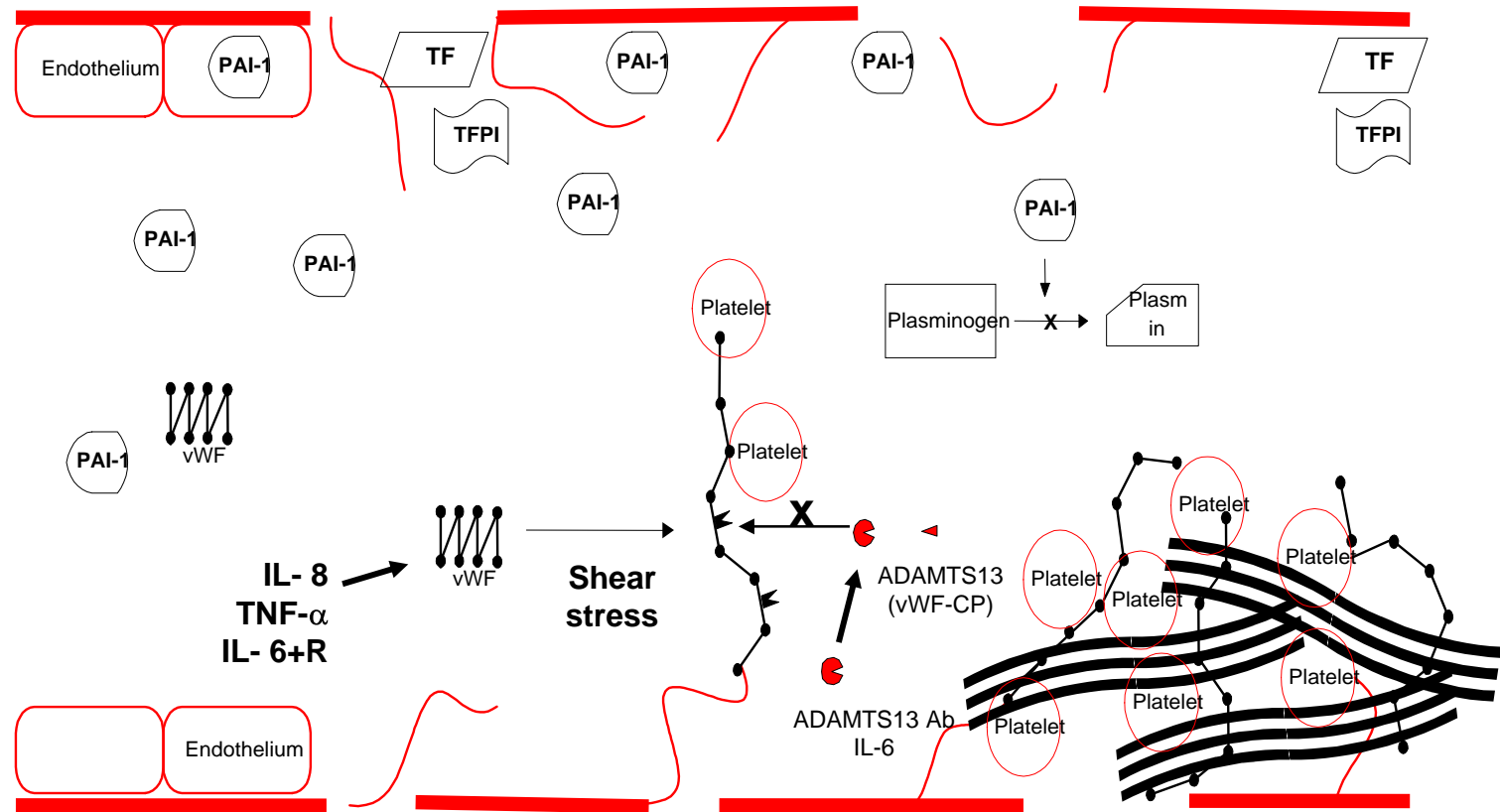
Plasma Exchange in Septic Shock

- Growing interest in use in children in sepsis
- TAMOF: particular subset
- Developed from interest in experience with TAMOF and plasma exchange at Children's Hospital of Pittsburgh
- 10 institution pediatric multicenter TAMOF study network- plasma exchange in 6 centers
- Includes use in ECMO

Thrombocytopenia-Associated Multiple Organ Failure (TAMOF)

- TAMOF
 - MOF > 2 organs
 - Platelet count < 100K
- Variant of TTP
- Primarily secondary to sepsis
- High mortality in children
- Deficient ADAMTS-13 (vWf cleaving protease), increased vWf-CP antibodies, increased ulvWf multimers
- Potential therapy: plasma exchange

Thrombotic Microangiopathy: TAMOF



CHP Pilot Data-Pediatric TAMOF

Pediatric Logistic Organ Dysfunction Score

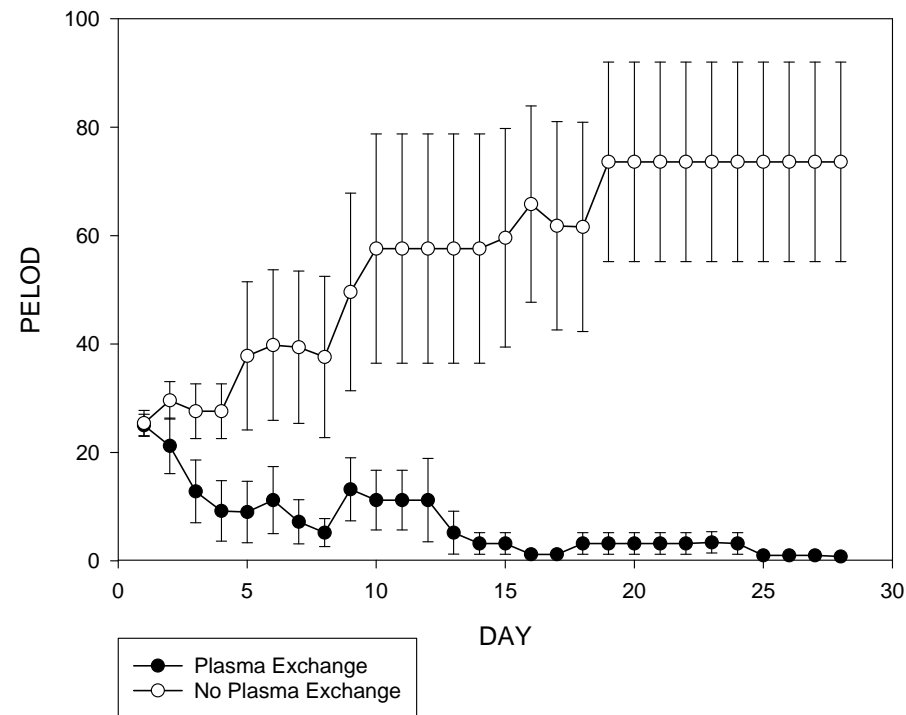


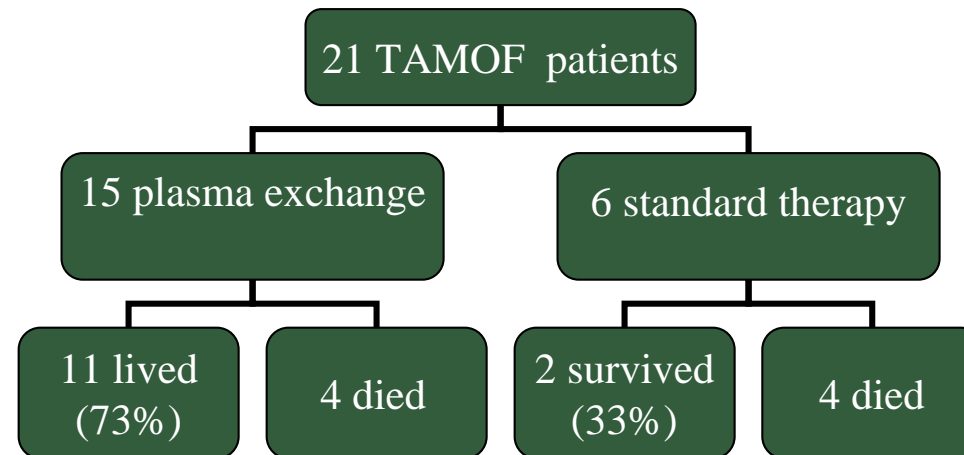
Figure 3. Pediatric Logistic Organ Dysfunction Score, Mean with standard error for patients who received plasma exchange therapy (N = 5) and who did not receive plasma exchange therapy (N = 5) for each day x 28 days.

Children's TAMOF Network

- Active centers:
 - Children's of Atlanta at Egleston: coordinating center
 - Children's of Atlanta at Scottish Rite
 - Children's of Pittsburgh
 - Cook Children's-Fort Worth
 - Vanderbilt Children's
 - Cincinnati Children's
 - Columbus Children's
 - LSU-Shreveport
 - Arkansas Children's
 - University of Michigan

Children's TAMOF Network Preliminary Data

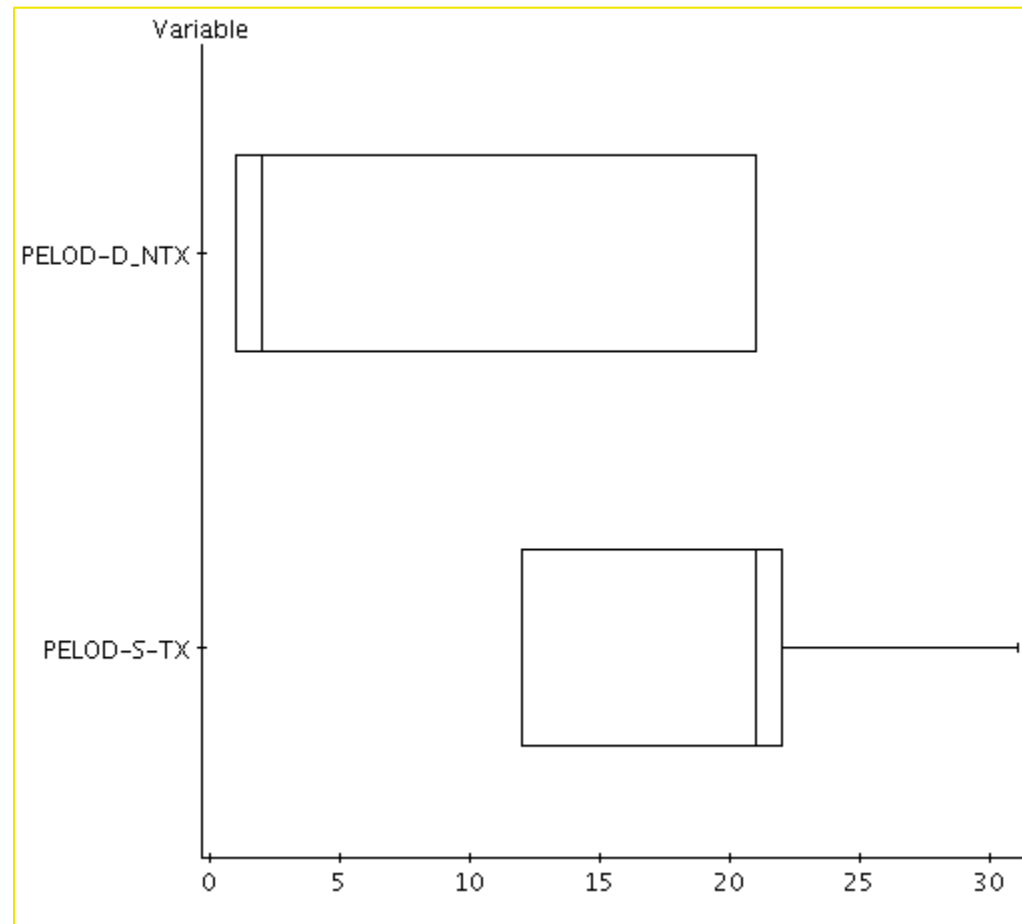
- 34 TAMOF patients registered to date-21 data complete
- Median age 12 years
- Median OFI: 4
- Similar PRISM, PELOD at admission



TAMOF Network Preliminary Data

Dying with
standard
therapy

Surviving
with
plasma
exchange



- Outcome evidence is suggestive of benefit of ECMO for sepsis in neonates
- Less convincing results in children/adults
- ECMO is potential alternative of last resort in sepsis and a platform for adjuncts of CRRT and plasma exchange
- Plasma exchange in sepsis/TAMOF promising but needs study

Alexis-A Success Story



Plasma Therapies in Sepsis-Why Use Them?

- General: exchange “transfer factors”
- Specific: control thrombotic microangiopathy (TMA)
- Slow progression of TMA-induced organ failure
- Treat coagulation abnormalities

CRRT in Sepsis-Why Use It?

- Remove/modulate cytokines, pro- and anti-inflammatory factors
 - ◆ Over 30 studies demonstrate removal by clearance/absorption
 - Most known mediators are water soluble
 - 500-60,000D “middle molecules”
- Manage septic ARF complications
- Manage fluid overload
- Multiple case reports, retrospective series: hemodynamic improvement, resolution of sepsis

Pediatric Patients Receiving CVVH

Factors Associated with Mortality

All Patients

Effect	β	SE	OR	95% CI	p
PRISM III	0.107	0.049	1.24	1.02, 1.50	0.03
% FO	0.032	0.018	1.37	0.97, 1.94	0.07

- Foland, Fortenberry et al., CCM 2004

Pediatric Patients Receiving CVVH

Factors Associated with Mortality

MODS & ≥ 3 Organ Involvement

Effect	β	SE	OR	95% CI	p
PRISM III	0.049	0.058	1.10	0.88, 1.39	0.4
% FO	0.058	0.023	1.78	1.13, 2.82	0.01

- Foland, Fortenberry et al., CCM 2004

Good Humours



Extracorporeal Support in Sepsis

There would seem to be a consensus in the movements of fluids and vapours. Thus the stronger draws and the weaker is evacuated.

- Claudius Galen, ca.
170 AD

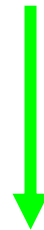


Back to “Bad Humours”

- Lots of interest in specific cytokine/factor control
- Animal experiments have not translated into human success
- Renewed interest in generalized control of immunologic stability-balancing inhibition of excessive inflammation with enhancement of anti-inflammatory and anti-thrombotic activity

Trends in Immune/Inflammatory Modulation Therapies for Sepsis

Specific: removal/blunting of proinflammatory factor



General: restoring immunologic stability → reduce both pro- and anti-inflammatory factors

-Kellum, Bellomo, Crit Care 2000

The Humours

Blood



Phlegm



**Yellow
Bile**



Black Bile

