Extra-corporeal Techniques to Remove Humoral Factors in Sepsis

The evidence

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Published literature

- Haemofiltration
- Plasmafiltration
  - In sepsis / SIRS

- Excluded:
  - not sepsis, subgroup analysis unclear

Principles

- Systemic Inflammatory Response Syndrome
  - Toxins
  - Inflammatory response
- Remove the “evil humors”
  - Bacterial toxins
    - Lipo-polysaccharide endotoxin
    - Exotoxins
  - Pro-inflammatory cytokines
    - e.g. TNFa, IL1/2/8, PAF, C3a/5a, etc
- +/- replace consumed factors
    - e.g. IL6/10, Ig, protein C

Variables

Fluids
- Crystalloid
- Albumin
- Plasma

Access
- Arterio – venous
- Veno – venous

Infective agent
- route

Animal

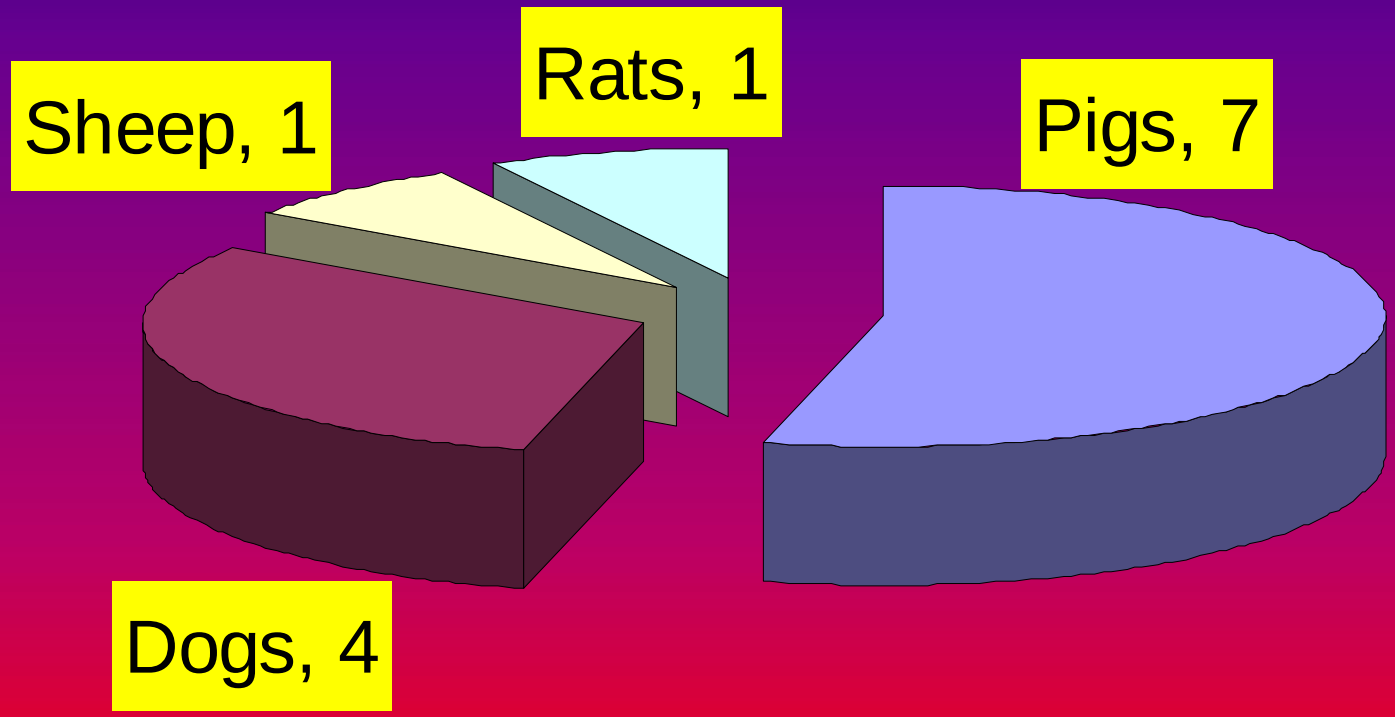
Duration

Flow rates
- Filtration rate
- Blood flow

Additional techniques
- Dialysis
- Adsorption

Outcome measures
- Survival
- Clinical
- Immunological

Haemofiltration animals



Haemofiltration animals

- Infective agent
  - Endotoxin
  - Bacterial culture (*E. coli, S. aureus, P. aerug)*
  - IV, intraperitoneal clot, inhalation
  - Sup. Mesenteric Art / caecal ligation
- Access:
  - CAVH 8; CVVH 5
- Start time: before ?BP vs after

Haemofiltration dogs

Filtration ml/kg/hr	**Duration** hours	**Mortality treatment**	**Mortality control**	**Other effects of treatment**
33	3	0/12	0/26	Improved haemodynamics
50-80	2-3	0/8	0/14	Improved LV contractility
80	3	0/8	0/8	Higher mean blood pressure
60	6	6/7	11/14	None

Haemofiltration pigs

Filtration ml/kg/hr	**Duration** hours	**Mortality treatment**	**Mortality control**	**Other effects of treatment**
160	3.5	0/6	1/12	Improved haemodynamics
167	2.5	2/6	6/6	Improved haemodynamics
1.2-2.5	6	20/20	20/20	Longer survival
100-200	6	6/7	7/7	Longer survival with larger pore
20	4.5	4/10	7/10	Lung mechanics better
8	24	0/8	0/8	No clinical difference
25	24	0/7	0/14	None

Sheep

(Rogiers 2006)	Blood warmed	Control
BP (mmHg)	90	38
Cardiac output (l/min)	4.0	2.3
Mortality <16h	0/10	10/10

Metabolic acidosis & Lactate less in warmed

Immunological

- TNF & PGF1
  - ? (Bellomo 2000)
  - Not significantly different (Ishihara 1999)
- Pore size (Lee 1998)
  - 50 KD survival 56 hrs
  - 100 KD survival 103 hrs
- Ultrafiltrate (Grootendorst 1992)
  - Causes death on infusion to non-septic pigs

Study methods

- Control (Freeman 1995)
  - Not filtered (mortality 14%)
  - Filtered (mortality 29%)
  - +/- ultrafiltrate re-infused (Lee 1993)
- Outcome
  - 2 studies numbers too small for statistical significance
  - 8 benefit
  - 3 no benefit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Haemofiltration human case series

Blood flow ml/min	**Duration** hours	**Mortality**	**Effect of treatment**
100	-	0/1	Improved haemodynamic
450	4	11/20	Improved haemodynamic
300	4	2/24	Improved haemodynamic
-	36	1/1	Coagulopathy improved
400-750	-	7/9	None
2-145	26	14/19	None

Case studies

- Conditions
  - Sepsis +/- ARDS (Gotloib 1986)
    ARF (Tonnesen 1993)
- Outcomes
  - Cardiac index – improved 50%
  - SvO_2 – increased 25%
  - Inotropes – decreased requirement
    - Others no significant metabolic, resp, haem change
- Bias in reporting +ve outcomes

Human haemofiltration trials

- 9 prospective studies
  - 5 non-randomised cohort :
    - n = 5 (Hoffmann 1999)
      16 (Hoffmann 1995)
      18 (Bellomo 1995)
      10 (Kodama 1997)
      18 (Heering 1997)
- Conditions:
  - Sepsis (6), SIRS (3) +/-
    - MOF (Bellomo 1995)
    - ARF (Bellomo 1993; Heering 1997; Kellum 1998)
- Filtration rates
  - 0.4 – 2 L/hr (6 - 30 ml/kg/hr)

Controlled haemofiltration trials

- Outcome:
  - 4 cytokine levels (no clinical differences)
    - TNF & IL-1 in ultrafiltrate but levels unchanged (none in controls)
  - 2 effect of ultrafiltrate
    - ?myocyte contractility
    - Monocyte ?TNF,?IL-2 & IL-6
- Cohort mortality rates
  - 7/10 (Kodama 1997)
  - 12/18 (Heering 1997) Non-significant ? mortality

RCT haemofiltration trials

Trial design	**Flow** ml/min	**Duration** hrs	**Mortality**	**Effect**
RCT	150	48	9/13	Non-significant ? mortality
RCT	100-120	48	5/15	Non-significant ? mortality
RCT (adsorption)	-	2	17/37	Non-significant ? mortality
RCT (crossover)	-	24	12/13	None

molecular adsorbents recirculating system (MARS)

CVVH

Plasmapheresis animal studies

- Animals
  - Rats (Cohen 1987)
    - Can tolerate endotoxin > humans
  - Rabbits (Tetta 2000)
    - 109 rabbits in 9 arms
    - Similar sensitivity to LPS of *E. coli* as humans
- Toxin
  - Endotoxin (3), *E. coli* (IP Natanson 1993; IV Busund 1991)
- Adsorption
  - Polymyxin B (binds endotoxin) (Cohen 1987)
  - Reverse phase resin (Tetta 2000)

Plasmapheresis animal studies

Animal	**Method**	**Blood flow** ml/min	**Duration** hours	**Mortality treatment**	**Mortality control**	**Other effects of treatment**
Rats	PF & adsorptn	-	1.5	0/4	4/4	Haematological improved
Rabbit	PF & adsorptn	10	3	3/19	30/40	No difference haemodynamic
Dogs	PF	20	1.5	0/6	7/8	Haemodynamic improved
Dogs	PF	100	2	6/6	5/6	Haemodynamic worse
Pigs	PF	30	1.25	-	-	Haemodynamic improved

Plasmapheresis case reports (n=9)

- Condition
  - 6 Meningococcal
  - 2 Pneumococcal
  - 2 Sepsis including feb neut, VZV, HUS
- 3 single cases & 3 series of 3 cases
  - all survived
- 1 blood exchange (survived) (van Deuren 1992)
- Mortality: 2/6, 1/8, 6/9, 8/12, 0/3
- Haemodynamic
  - 1: Improvement SVRI, CI, LVEJ, DO_2 (Berlot 1997)
  - 1: No difference VI, A-a DO_2, inotropes (Reeves 1995)

Plasmapheresis and plasma exchange cohort studies

Technique	Condition treated	Mortality treatment	Mortality control	Difference
Plasma exchange	Meningo-coccaemia	1/13	6/10	P=0.025
Leuka-plasmapheresis	Meningo-coccaemia	3/13	7/9	P=0.02
Plasma exchange & CVVHF	Septic shock	1/7	8/21	P=0.25
Plasmapheresis	Surgical sepsis	11/19	13/24	P=0.94

Plasmapheresis and plasma exchange RCT

Mortality	Control	Plasmapheresis	
Reeves 1999	6/14	8/16	P=0.73

- No difference survival or number organs failing

Busund 2002	18/52	28/52	P=0.05

- 28d relative risk mortality 0.61
- Number needed to treat 4.9

CVVH +/- ECMO children

- PCCM 29 May 2007 Publish Ahead of Print Shaheen et al Nottingham, Sheffield, Leicester

CVVH +/- ECMO children

- Bacterial sepsis
  - 30 CVVH
  - 6 CVVH + ECMO
- Viral sepsis
  - 2 CVVH
  - 14 CVVH + ECMO
- All sepsis with MOF
  - 22/56 (39%) survived
- 4 meningococcal plasmafiltration
  - 2 survived

Case example

22.2.06 1y/o ?

- 150 ml/kg before admission
- Adrenaline 1.6 mcg/kg/min
- Noradrenaline 1 mcg/kg/min
- Milrinone 750 ng/kg/min
- Vasopressin
- pH 6.97, BE -20

- Anuric after 6hrs

CVVH

- Blood flow
  - 70 ml/min
- Replacement
  - 300 ml/hr
    (30 ml/kg/hr)
- Balance
  - neutral

Summary – The evidence

- Haemofiltration
  - Animals: 8 benefit vs 3 no benefit
  - Human: 3 case studies improved haemodynamics
    12 studies (inc 3 RCT) no ? mortality
- Plasmafitration
  - Animals: 3 improved, 1 worse
  - Human: retrospective – mortality lower 2; same 2
    prospective – mortality lower 1; same 1