Treatment of septic patients – guidelines into practice
oXiris filter tips and tricks in daily practice.

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Definition 21st century

Sepsis- life threatening organ dysfunction caused by dysregulated host response to infection

Septic Shock – subset of sepsis with circulatory and cellular/metabolic dysfunction associated with higher risk of mortality

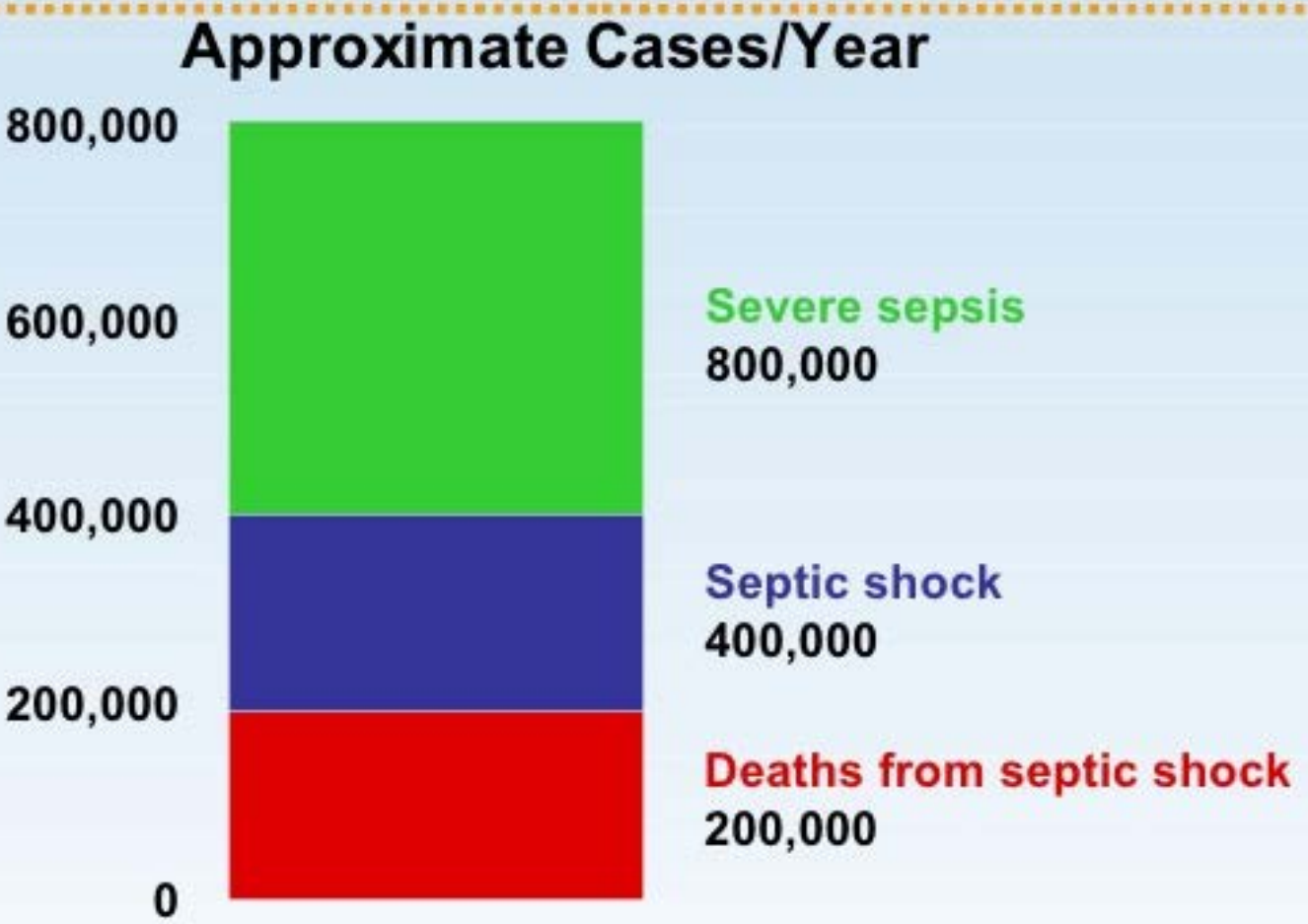
Organ dysfunction can be identified as an acute change in total SOFA score ≥2 points consequent to the infection

Clinical expression -

- **Hypotension - vasopressors to maintain MAP ≥65 mm Hg**
- **Serum lactate level >2 mmol/L (18mg/dL) despite adequate volume resuscitation.**
- **Mortality rate 40%.**

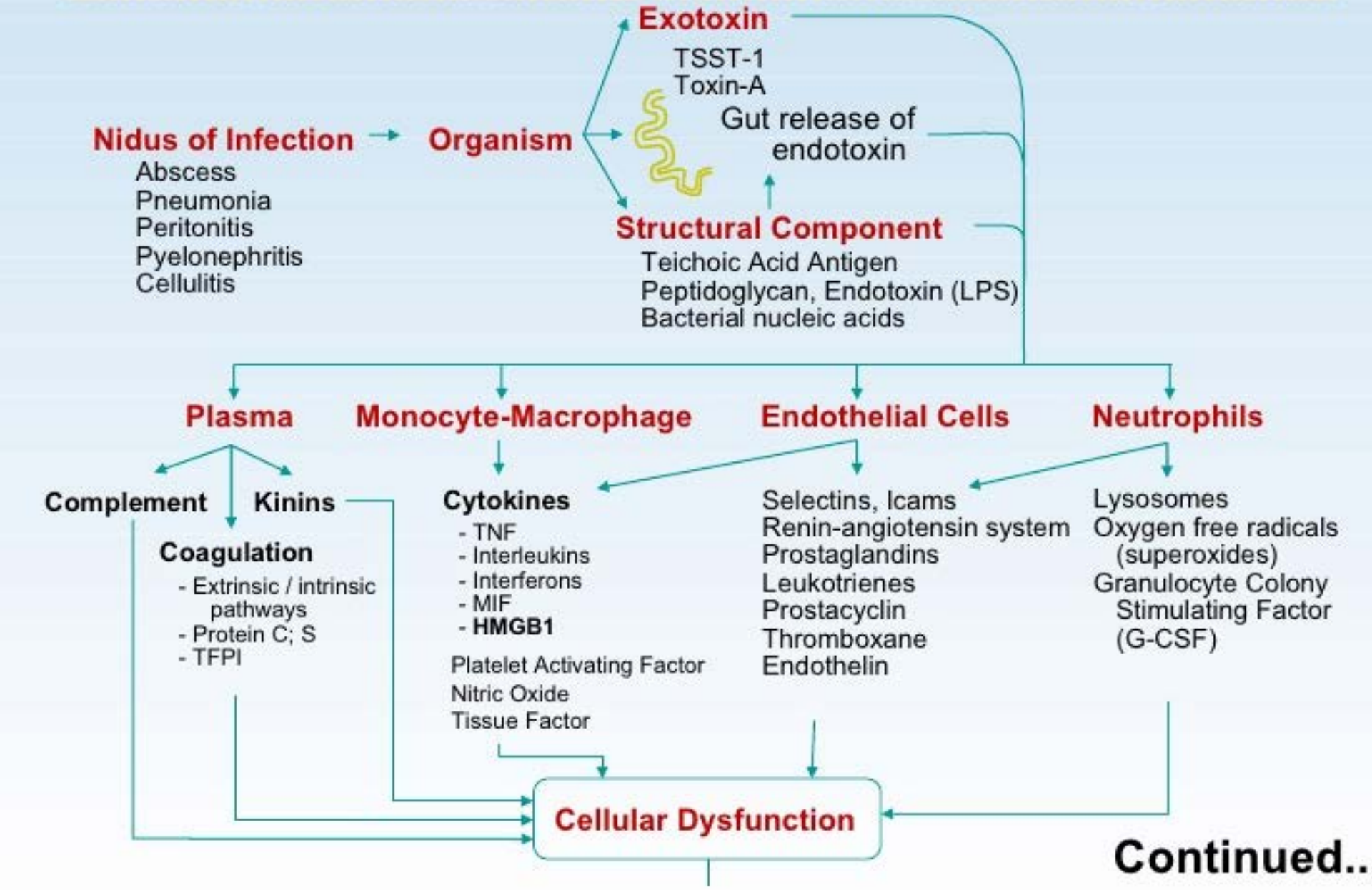
Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2018

Incidence of Severe Sepsis/Septic Shock



- Sepsis and sequelae are a leading cause of death in ICU
- Mortality in septic shock remains at 35 - 50%
  - -unchanged since advent of antibiotics (from 55 - 75%)

Pathogenesis of Septic Shock



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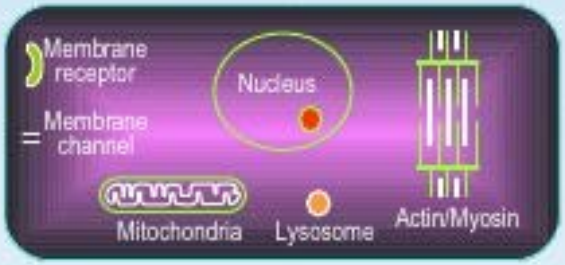
Pathogenesis of Septic Shock

Cellular Dysfunction



Vasculature

- Vasodilation
- Vasoconstriction
- Leukocyte aggregation
- Endothelial cell dysfunction

Organs

- Dysfunction
- Metabolic abnormalities

Myocardium

- Depression
- Dilatation

Shock

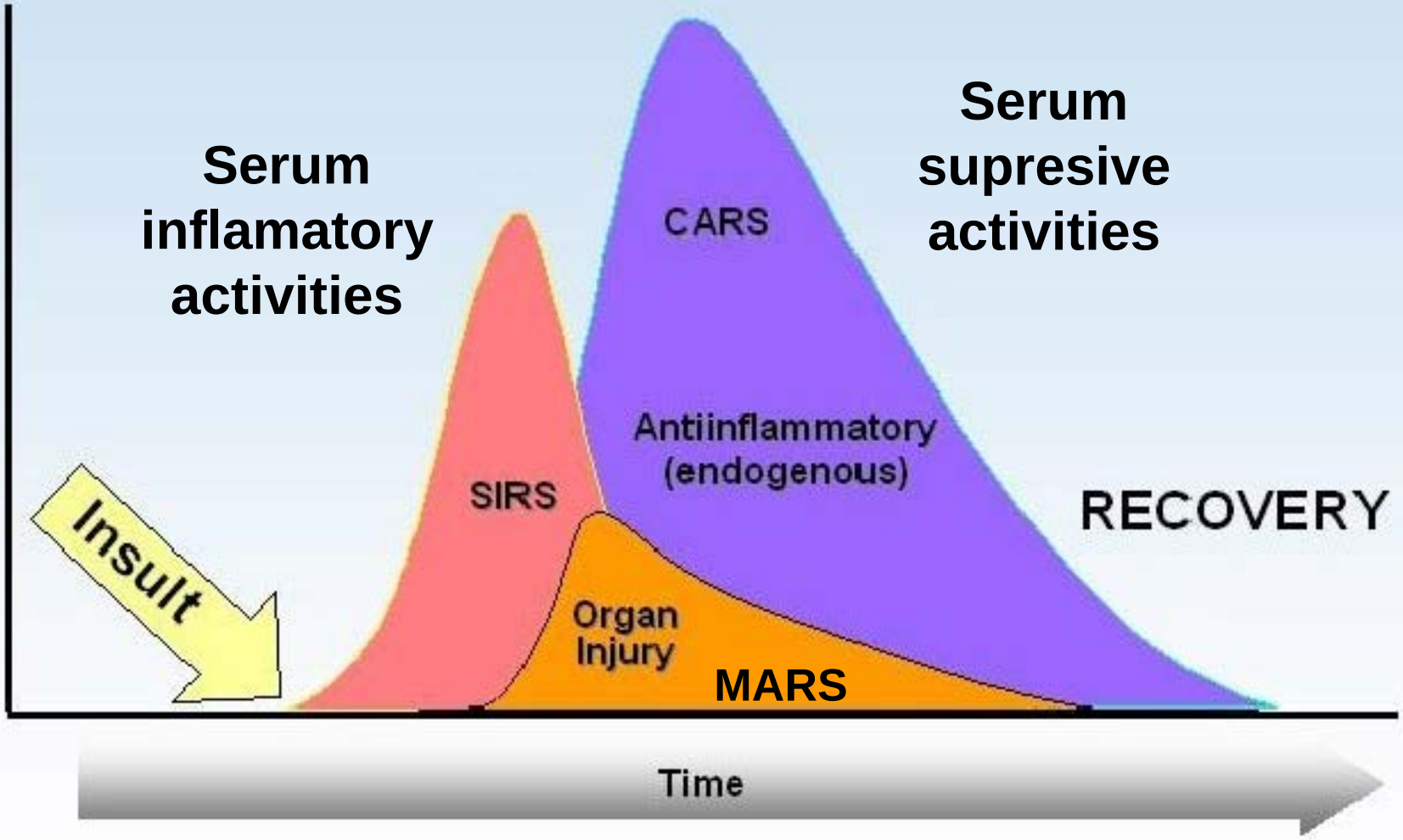
Refractory Hypotension

Multiple Organ Dysfunction

Recovery

Death

The Dynamic Nature of Sepsis



van der Poll T, van Deventer SJH. Infect Dis Clin N Am.

Society of Critical Care Medicine
The Intensive Care Professionals

Sepsis 2018

Initial Resuscitation

Goals during first 6 hours:

- Central venous pressure: 8–12 mm Hg
- Mean arterial pressure ≥ 65 mm Hg
- Urine output ≥ 0.5 mL kg^{-1}/hr^{-1}
- Central venous (superior vena cava) or mixed venous oxygen [SvO_2] saturation ≥ 70%

Grade B

Diagnosis

- Appropriate cultures
- Minimum 2 blood cultures
  - 1 percutaneous
  - 1 from each vascular access ≥ 48 hrs

Grade D

Initial Resuscitation

Goals during first 6 hours:

- Central venous or mixed venous O_2 sat < 70% after CVP of 8–12 mm Hg
  - Packed RBCs to Hct 30%
  - Dobutamine to max 20 µg/kg/min

Grade B

Antibiotic Therapy

- Begin intravenous antibiotics within first hour of recognition of severe sepsis.

Grade E

Reassess antimicrobial regimen at 48-72 hrs

- Microbiologic and clinical data
- Narrow-spectrum antibiotics
- Non-infectious cause identified
- Prevent resistance, reduce toxicity, reduce costs

The Surviving Sepsis Campaign Bundle: 2018 update Intensive Care Medicine
ISSN: 0342-4642 (Print) 1432-1238 (Online)

Fluid Therapy

- Fluid challenge over 30 min
  - 500–1000 ml crystalloid
  - 300–500 ml colloid
- Repeat based on response and tolerance

Grade E

Vasopressors

- Do not use low-dose dopamine for renal protection.

Grade B

Bellomo R, et al. *Lancet* 2000; 356:2139-2143

Vasopressors

- Either norepinephrine or dopamine administered through a central catheter is the initial vasopressor of choice.
  - Failure of fluid resuscitation
  - During fluid resuscitation

Grade D

Therapeutic Endpoints

- Capillary refill < 2 sec
- Warm extremities
- Urine output > 1 ml/kg/hr
- Normal mental status
- Decreased lactate
- Central venous O_2 saturation > 70%

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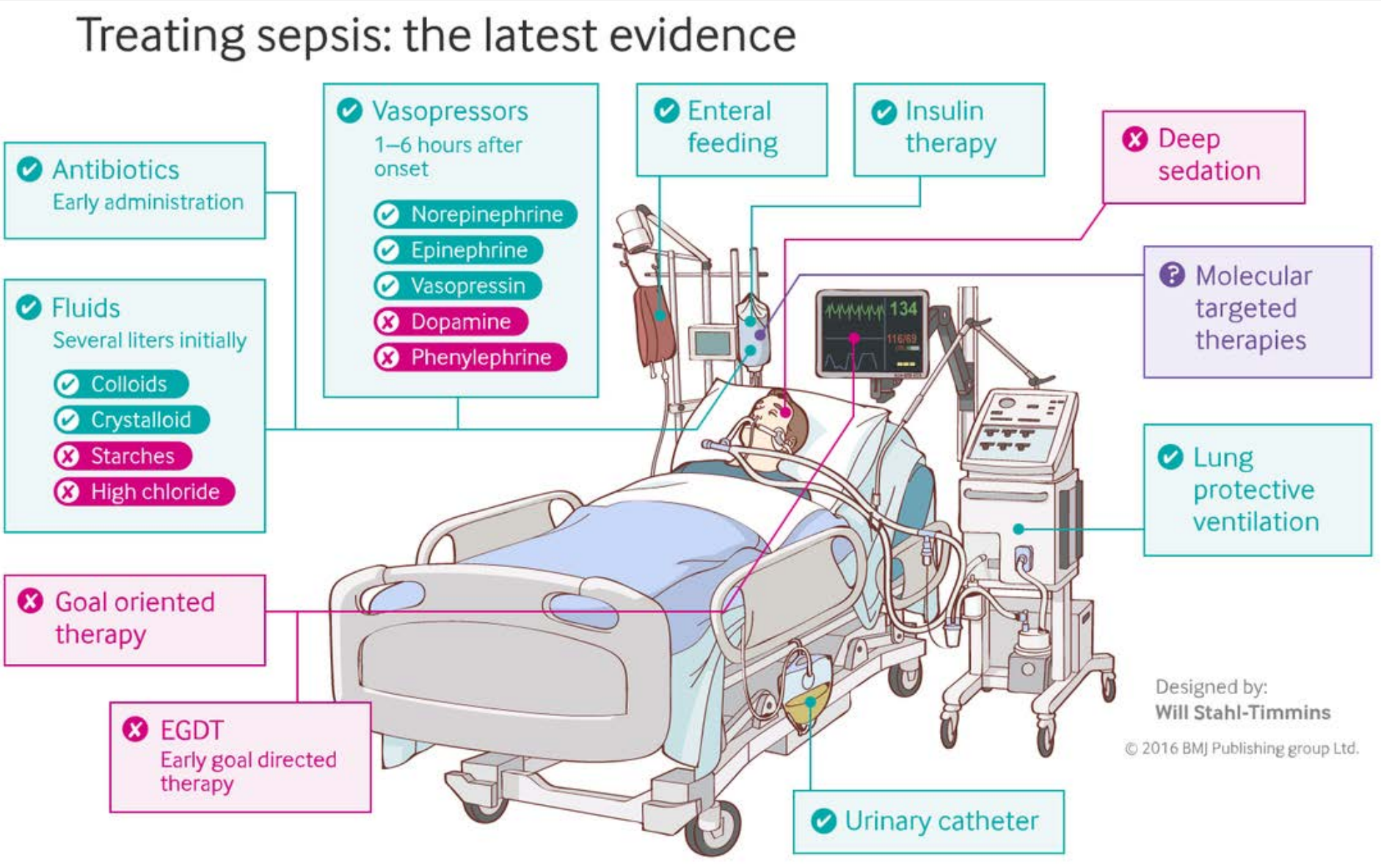


Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: 2016

CRRT possibilities for extracorporeal blood purification in septic patients

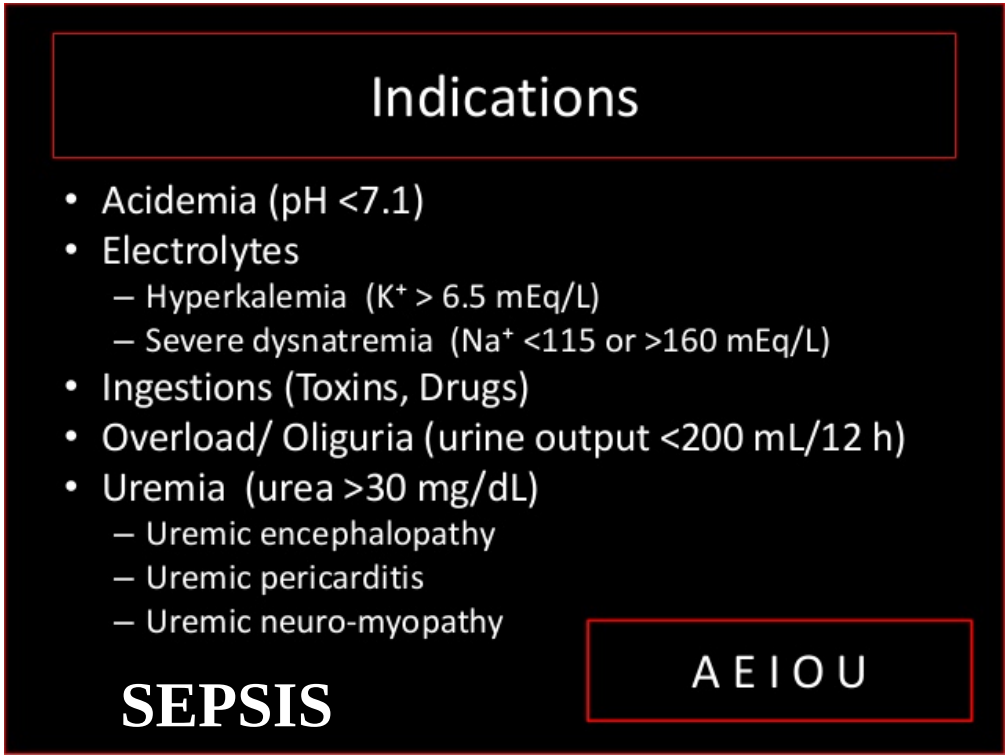
ZAN MITREV CLINIC

CRRT may modulate inappropriate tissue inflammation by eliminating inflammatory mediators

CRRT may not only be supportive but rather therapeutic

Which kind of filters , which kind of CRRT protocol

When to start (Between SIRS and MARS – the best result)



CRRT benefits in septic patient

Removal of small,meaddle to large molecule septic medijators by convection and adsorption including TNF α, IL-1,IL-6,IL-8, IL-10
Removal of excess fluid and waste products
Maintenance of acide-base balance
Improvement of cardiovascular hemodynamic- removal od cardiodepressants (caused by inflammatory mediators)
Termoregulation

Possible disadvantages

The use of biocompatible membranes may generate mediators of inflammation.

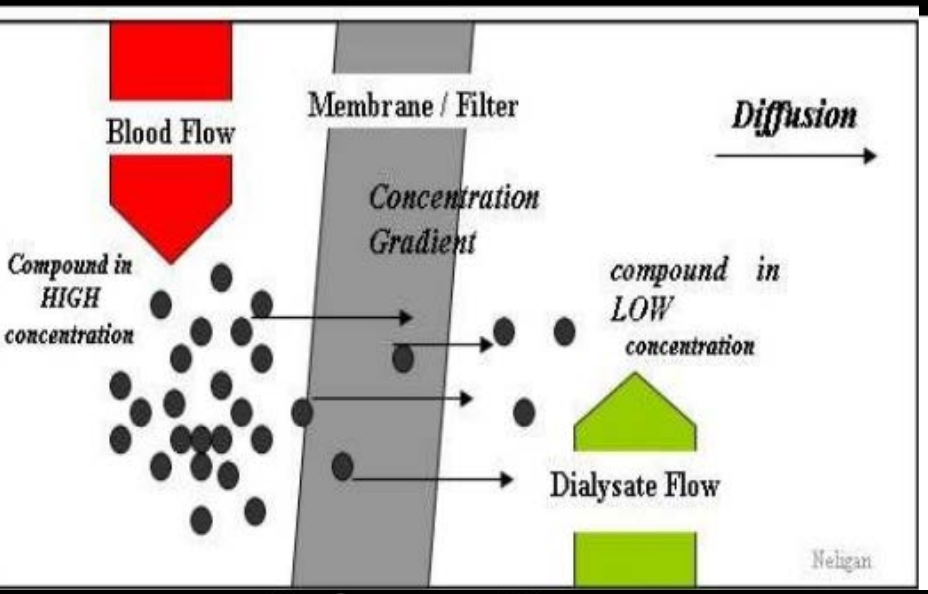
- Hemofiltration is an invasive technique that requires the placement of catheters and continuous anticoagulation, and,

- CRRT are expensive and represent a significant workload

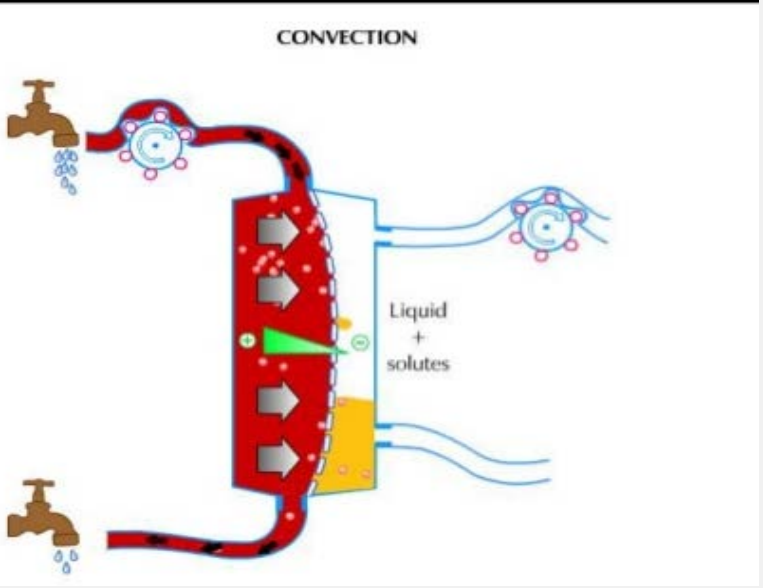
CRRT as Immunomodulatory therapy

- Mechanism of cytokine removal
  - Convective
    - High flux membranes cut-off 30 – 40 kD
    - Should remove many cytokines (17 – 30 kD)
    - Is removal rate significant given high production?
  - Adsorption
    - Filter dependent: higher with polyacrylonitrile (AN69) than with polysulfone membranes

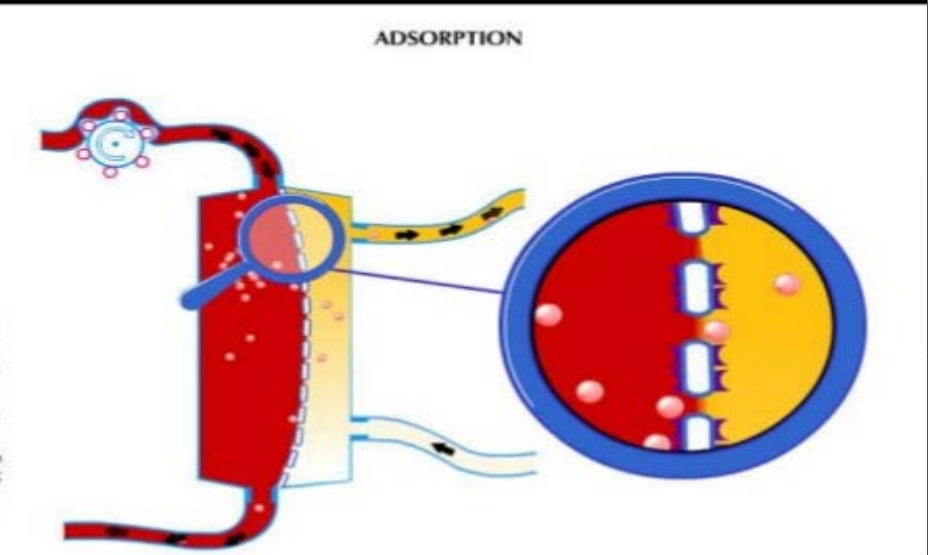
Diffusion/Dialysis



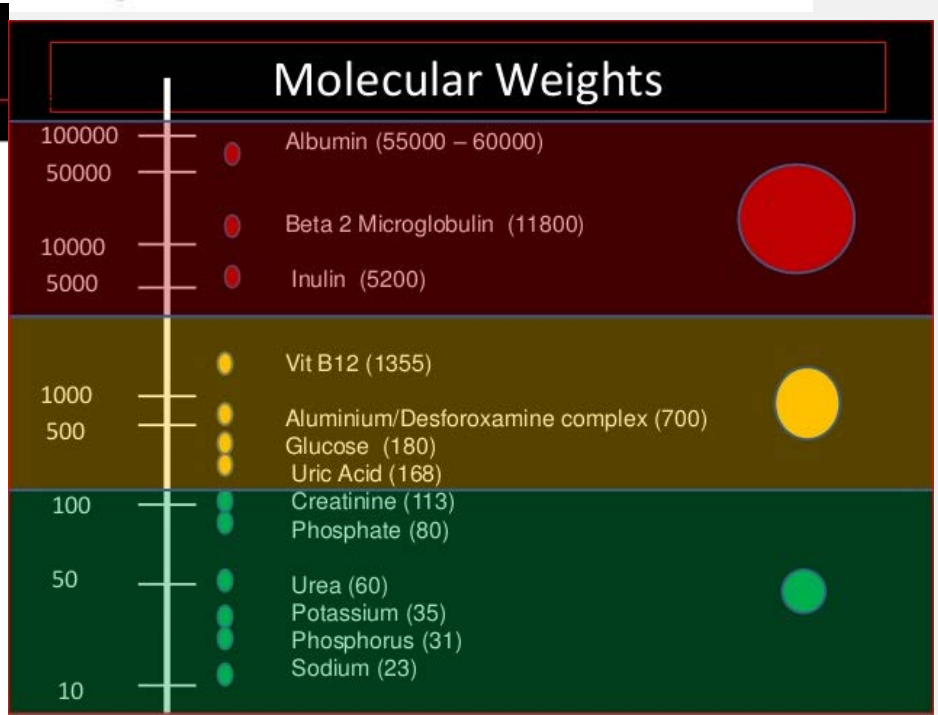
Convection



Adsorption



Molecular Weights



Different types of filters

2- Nonselective adsorptive membranes: *Polyacrylonitrile and AN69 ST (Surface Treated)*

Effectively adsorb high-mobility group box 1 protein (HMGB-1) which is a very upstream mediator liberated by macrophages and can activate the production of a bunch of cytokines.

The molecular weight is around 30 kDa and therefore is not eliminated through filtration

Able to remove molecules with molecular weight beyond the membrane cutoff

3- Semiselective Adsorptive CRRT Membranes:

Polyacrylonitrile and AN69 Oxiris

- Modified membrane surface polarity with a positive charge allowing catching endotoxins with negative charges
- No comparable studies on human septic shock

Polymethylmethacrylate PMMA

- In a recent cohort study, evaluating 43 patients with septic shock exhibiting hypercytokinemia (IL-6), CRRT using PMMA membranes was associated with improvement of hemodynamics and reduction of organ failure.

Toraymyxin Endotoxin adsorption (not a CRRT membrane, can be used in hemoperfusion)

Prosorba is a kind of sorbent used in apheresis

4- Polymyxin B [PMX] (antibiotic coated) adsorbs endotoxin

Can run on a hemoperfusion device

Cantaluppi et al. investigated in 2007, the effects of PMX therapy on the prevention of AKI during septic shock. 16 patients with gram-negative sepsis were randomly divided into two groups having standard treatment versus standard treatment plus PMX therapy. The plasma was collected and incubated with renal tubular cells and glomerular podocytes.

The use of PMX therapy was able to reduce the proapoptotic activity of septic plasma on renal tubular cells and glomerular podocytes.

Sepsis can directly induce AKI without the need of hemodynamic instability!

The Early Use of Polymyxin B Hemoperfusion in Abdominal Sepsis **(EUPHAS)**
Sixty-four patients with surgical sepsis were randomly assigned to receive either standard treatment or standard treatment plus two sessions of PMX therapy.

Beneficial hemodynamic effects, significant improvement in SOFA score and in 28 day mortality

JAMA 301: 2445–2452, 2009

5-Cytokine-adsorbing columns: CytoSorb, CYT-860-DHP, Lixelle, CTR-001, and MPCF-X

Adsorptive columns and sorbents are not anymore membranes but are seen as cartridges because the surface is extremely huge,
They can run with an hemoperfusion device

They have enormous surface (8,500 m2) when compared with that of classical CRRT membranes (1.5 m2)

CytoSorb seems to be very promising although it is not able to capture endotoxin and IL-10

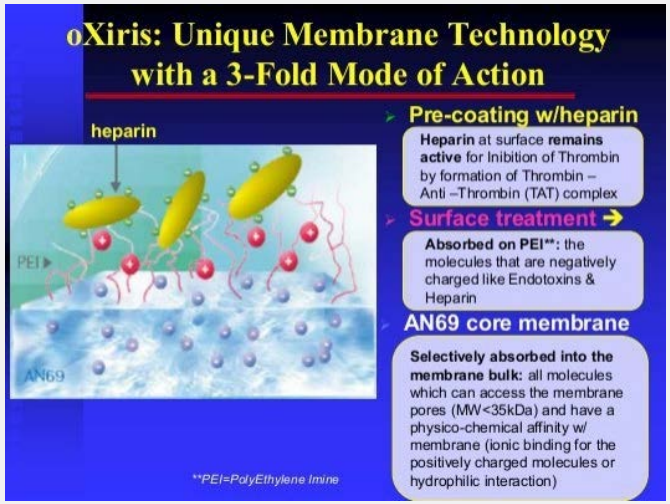
We still dont know which membrane or which sorbent will be the most useful in adjunctive treatment in patients with sepsis.

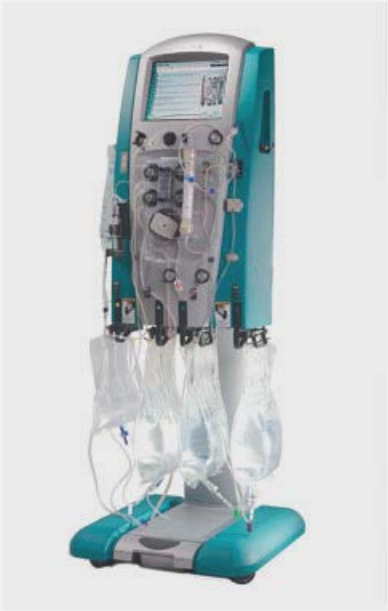
oXiris™

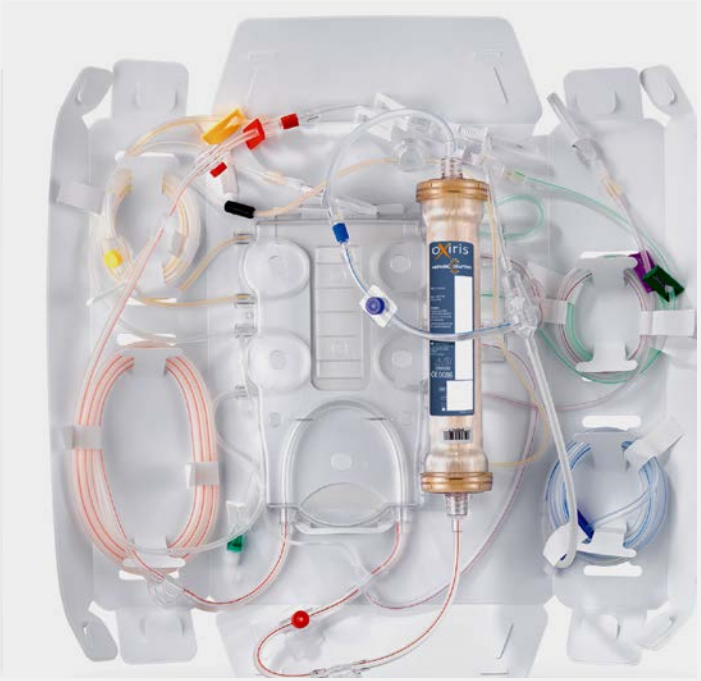
Removes larger molecular weight molecules by membrane binding,

Type of membrane - oXiris set is AN69™
Unique AN69 property - adsorption (membrane binding) – inflammatory mediators
Specific modification of the membrane, for adsorptive removal is related to endotoxin. These endotoxin fragments act as an inflammatory stimulus in many septic episodes. Finally, with consideration of the increased bleeding risk of the AKI population receiving CRRT, heparin is immobilized to the blood-contacting surface of the oXiris membrane.

The new Prismaflex eXeed™ system -- septeX™ and oXiris™.







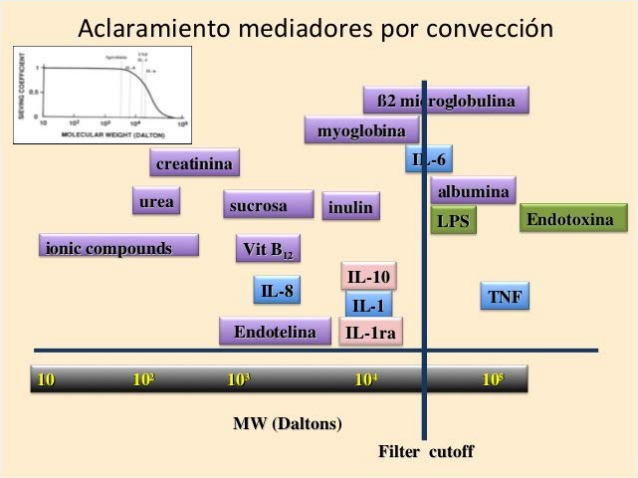
Continuous Renal Replacement Therapy in Sepsis and Multisystem Organ Failure

Michael Joannidis Intensive Care Unit, Department of Internal Medicine I, Medical University Innsbruck, Austria

this study was unable to demonstrate any clinical benefit by this approach. Thus, on basis of the current evidence, use of standard CRRT in the absence of AKI can not be recommended routinely.

ClinicalTrials.gov Identifier: NCT02600312

IVOIRE, SMART –oXiris AN69 ST150
EUPHAS II – POLIMIXIN
EUPHRATES



Ongoing trial

Comparing Cytokines, Toxins Adsorbing oXiris Filter to ST150 Filter During CRRT in Patients With Septic Shock (oXiris) – Marcus Broman Sweden

33rd International Symposium on Intensive Care and Emergency Medicine
•Poster presentation
•Open Access

Continuous renal replacement therapy with the adsorbent membrane oXiris in septic patients: a clinical experience

•F Turani, F Candidi, R Barchetta, E Grilli, A Belli, E Papi, A di Marzio and M Falco

*Critical Care*201317 (Suppl 2) :P6 https://doi.org/10.1186/cc12001 Published: 19 March 2013

In septic/septic shock patients with renal failure, CRRT with a new treated heparin-coated membrane (oXiris; Gambro) is clinically feasible, and has a positive effect on renal function and hemodynamics. An adsorbing effect on proinflammatory mediators may have a role in these results.
These data and the trend toward a decrease of endotoxin during the treatment warrant further investigation.

Newly designed CRRT membranes for sepsis and SIRS--a pragmatic approach for bedside intensivists summarizing the more recent advances: a systematic structured review.

Honore PM[1], Jacobs R, Joannes-Boyau O, De Regt J, De Waele E, van Gorp V, Boer W, Verfaillie L, Spapen HD. ASAIO J. 2013 Mar-Apr;59(2):99-106. doi: 10.1097/MAT.0b013e3182816a75

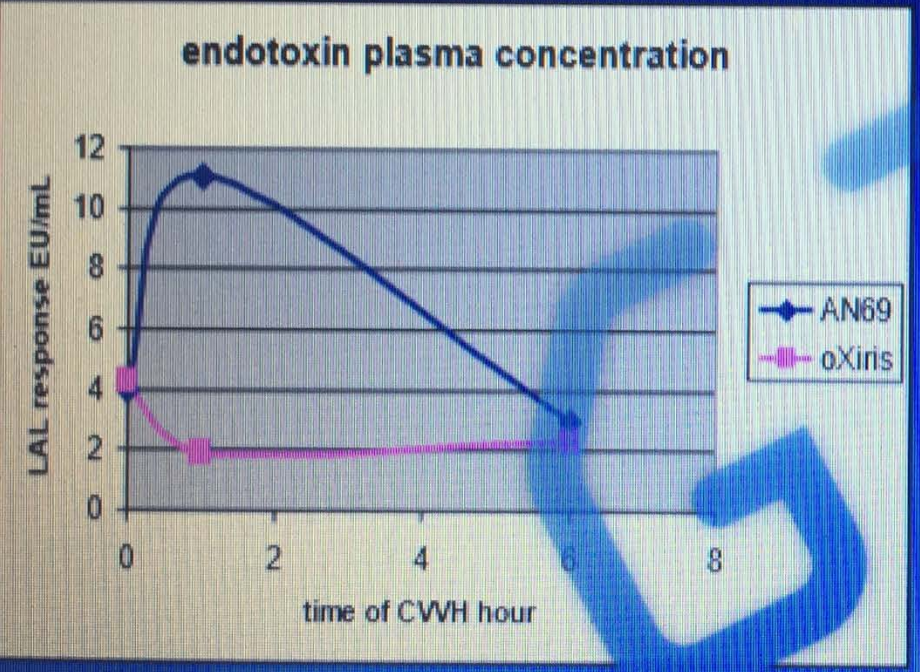
oXiris –advantages – capture endotoxin, IL 10 , eliminate fluid

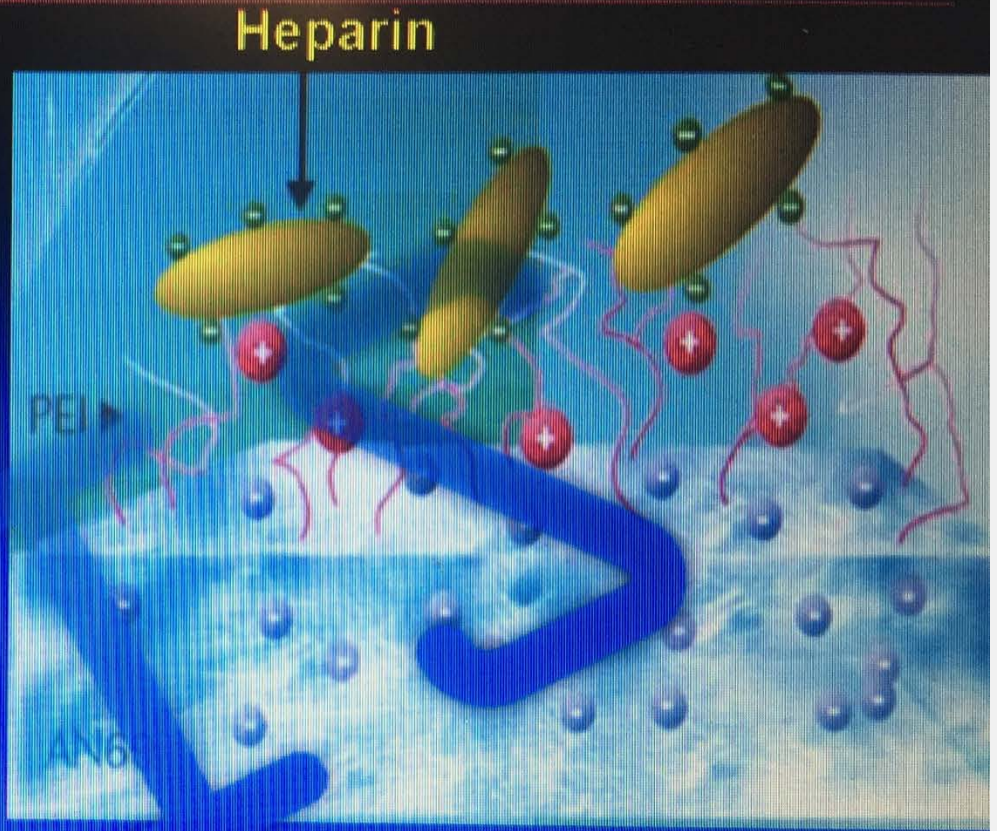
IVOIRE TRIAL 200 pts early septic shock
HEMODIAFE TRIAL –AN 69 ST-150 I.E /m2 heparin

There is a Shift in Paradigm : Convection Dose is no Longer the Key but Membrane Adsorption seems a valid Option…

- **High Volume (Above 35 ml/kg/h) is No Longer Recommended in Septic AKI…..**
- **As A consequence , the Prescribed Dose Should be 30-35 in order to Deliver 25 ml/kg….**
- **Starting at Rifle Injury Stage in Septic AKI could be Better …..**
- **Highly Adsorptive Membranes Could Be the Therapy of the Future……..Looks at HMGB-1..and Probably Others…**
- **oXiris AN 69 Membranes can Capture Endotoxin and Running at the Same Time CRRT…..when comparing to PMx..**
- **Adsorption as a lonely Modality could Be a Valuable strategy to Address Sepsis …but The Future will tell us…**

AN 69-oXiris :High Adsorption +LPS





*: PEI=PolyEthylene Imine

10,000 UI/m² grafted heparin

Honore PM et al.ASAIO J 2013 ;59:99-106

Rimmele T et al.NDT 2009 ;24 :354-357

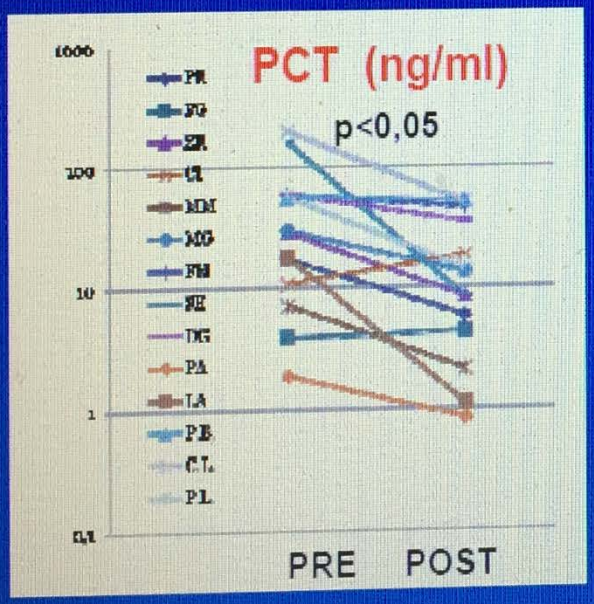
Removal of Endoxins and Cytokines during CRRT

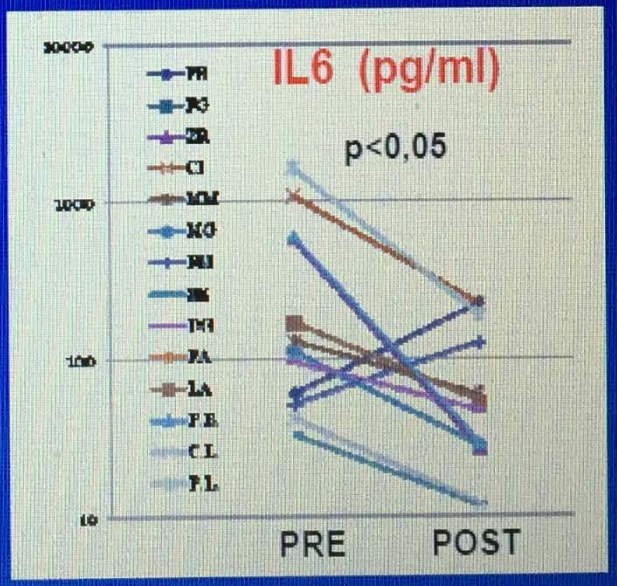
- Oxiris, AN 69 membrane treated with a polyethyleneimmine (PEI) and grafted with heparin with increased absorption of endotoxins
- CVVHDF with effluent dose of 50 ml/kg/h (60% convective)
- 14 patients with AKI having severe sepsis (n=7) or septic shock (n=7) from gram negative bacterial infection

Results:

SOFA from 13.2±2.5 to 8.8±4.3 ($p<0.05$);
MAP from 65±20 to 81±16 mmHg ($p<0.01$),
URINE OUTPUT from 0.7±0.6 to 1±0.6 L/12h ($p<0.05$),
NORADRENALINE from 0.3±0.3 to 0.03±0.04 γ/Kg/h ($p<0.05$)

Outcome: Survival 78% (11/14),
Renal recovery 81% (9/11)





Caravetta et. al – SMART 2010

The optimal timing of dialysis for AKI is not defined

5.1.1: Initiate RRT emergently when life-threatening changes in fluid, electrolyte, and acid-base balance exist. (*Not Graded*)

- Fluid overload (refractory to medical measures)
- Hyperkalemia (refractory to medical measures)
- Severe metabolic acidosis (refractory to medical measures)
- Signs of uremia (such as pericarditis, neuropathy, or an otherwise unexplained decline in mental status)
- Certain alcohol and drug intoxications

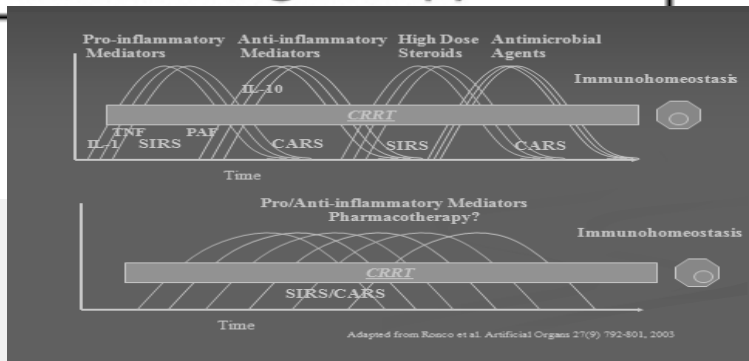
Kidney International Supplements (2012) 2, 89–115

5.1.2: Consider the broader clinical context, the presence of conditions that can be modified with RRT, and trends of laboratory tests—rather than single BUN and creatinine thresholds alone—when making the decision to start RRT. (*Not Graded*)

Other factors that might influence the decision of when to start RRT are:

- the severity of the underlying disease (affecting the likelihood of recovery of kidney function),
- the degree of dysfunction in other organs (affecting the tolerance e.g., fluid overload),
- the prevalent or expected solute burden (e.g.,in tumor lysis syndrome),
- the need for fluid input related to nutrition or drug therapy

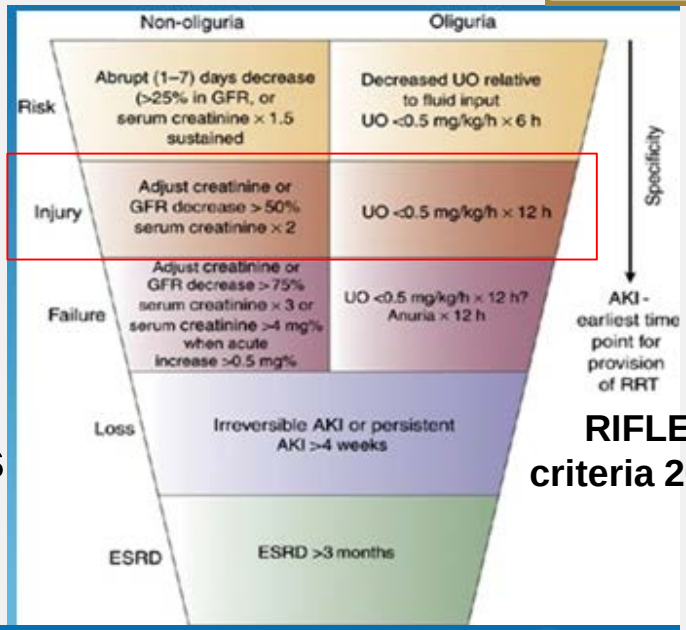
Kidney International Supplements (2012) 2, 89–115



What is EARLY and what is LATE

Wang C et all Nephrology 2017; 22:7-18

Presence/absence of clinical symptoms
Timing from ICU admission
BUN levels
Serum creatinine
Urine Output
Combination of BUN, SrCr and UO
RIFLE criteria; KDIGO stages; AKIN stages
Low UO despite diuretics administration



RIFLE criteria 2005

RIFLE v AKIN

	RIFLE		AKIN
R	Cr increased by 50-100%	1	Cr increased by 0.3 or 50-100%
I	Cr increased by 100-200%	2	Cr increased by 100-200%
F	Cr increased by more than 200% or Cr > 4	3	Cr increased by more than 200%, Cr > 4, or renal replacement therapy
L			
E			

KDIGO Classification of AKI (2012)

Stage	Serum creatinine	Urine output
1	1.5-1.9× baseline OR >0.3 mg/dL ↑	<0.5 ml/kg/hr for 6-12 hrs
2	2-2.9× baseline	<0.5 ml/kg/hr > 12 hrs
3	3 times baseline OR increase in Cr to ≥4.0 mg/dL OR Initiation of RRT	<0.3 ml/kg/hr > 24 hrs OR Anuria > 12 hrs

KDIGO Clinical Practice Guideline for AKI. Kidney Int 2012

When to initiate? Early vs Late

What is meant by EARLY?

What is meant by LATE?

ZAN MITREV CLINIC

Studies aimed at determining the optimal time for starting RRT have evaluated various arbitrary cut-offs for:

- ser
- ser
- uri
- tim

When to initiate? Early vs Late

Serum Urea a

Lower urea better pr
Wu et al. *J Am Coll Surg 2007;205: 266–276*
Gettings et al. *Intensive Care Med 1999; 25: 805–813*
Carl et al. *Hemodial Int 2010; 14: 11–17*

When to initiate? Early vs Late

UOP as a trigger for RRT

Better prognosis	Early dialysis: Better results when UOP
Elahi et al. *Eur J Cardiothorac Surg 2004; 26: 1027–1031*	<100 mL in 8 h
Demirkilic et al. *J Card Surg 2004;19: 17–20*	<100 mL within 8 h
Sugahara et al. **RCT** *Hemodial Int 2004; 8: 320–325*	<30 mL/h for 3 h
Ji et al. *Heart Vessels 2011; 26: 183–189*	<0.5 mL/kg/h for <12h

NephroTube

Optimal timing for CRRT

ELAIN trial – conclusion -Among critically ill patients with AKI, early RRT compared with **ced mortality over the first 90 days. Fu** **ntervention are warranted.**
Zarbock A et al J A M

Timing

PRO Retrospective trials support early initiation of CVVH
Intensive Care Med 32:80–86, 2006
Intensive Care Med 25:805–813, 1999
Clin J Am Soc Nephrol 1:915–919,2006
Crit Care 9:R755–R763, 2005

CON Prospective, only one randomized trial: Early initiation of CRRT did not improve survival (mainly surgical patients with a very few sepsis)
Crit Care Med 30:2205–2211, 2002

Late is worse!

AKIKI trial – conclus **y ill patients with severe acute kidney injury, we found no significant difference with regard to mortality between an early and a delayed strategy for the initiation of renal-replacement therapy. A delayed strategy averted the need for renal-replacement therapy in an appreciable number of patients. (Funded by the French Ministry of Health; ClinicalTrials.gov number, NCT01932190.) Gaudry S et al N Eng J Med 2016; 375:122**

When to Stop?

5.2.1: Discontinue RRT when it is no longer required, either because intrinsic kidney function has recovered to the point that it is adequate to meet patient needs, or because RRT is no longer consistent with the goals of care. (*Not Graded*)

Creatinine Clearance

Urine Output

Kidney International Supplements (2012) 2, 89–115

Table 3: Systemic and brain hemodynamics, oxygenation and metabolic variables pre-CVVH and at 12 hours after CVVH start, by MODS causation

Group	Sepsis group (n=11)			Nonsepsis group (n=7)		
Variables	**Pre CVVH (X ± SD)**	**Post CVVH (X ± SD)**	**p Value**	**Pre CVVH (X ± SD)**	**Post CVVH (X ± SD)**	**p Value**
Systemic hemodynamics						
HR (beats/min)	124 (± 26.5)	101 (± 13.2)	0.023	104 (± 20.4)	87 (± 20.1)	0.237
MAP (mmHg)	75 (± 19.7)	89 (± 9.9)	0.086	73 (± 16.0)	74 (± 16.4)	0.866
Norepinephrine (µg/kg/min)	0.7 (± 0.7)	0.3 (± 0.3)	0.015	0.4 (± 0.6)	0.6 (± 0.7)	0.173
Brain hemodynamics						
Right MCA MFV (cm/s)	50 (± 20.7)	52 (± 10.5)	0.752	60 (± 15.9)	55 (± 25.3)	0.753
Right MCA PI	1.3 (± 0.3)	1.1 (± 0.2)	0.078	1.5 (± 0.6)	2.1 (± 2.4)	0.735
Oxygenation						
SaO_2 (%)	95 (± 4.8)	99 (± 0.6)	0.003	93 (± 4.0)	97 (± 3.4)	0.075
FiO_2 (%)	45 (± 4.4)	40 (± 3.7)	0.047	61 (± 19.0)	58 (± 21.7)	0.753
Metabolic						
Creatinine (mmol/L)	422 (± 235.5)	225 (± 127.5)	0.003	164 (± 57.5)	141 (± 58.2)	0.398
Urea (mmol/L)	28 (± 13.9)	19 (± 7.9)	0.003	13 (± 8.4)	11 (± 7.7)	0.237
Bicarbonate (meq/L)	19 (± 5.0)	23 (± 3.0)	0.013	18 (± 6.4)	18 (± 6.4)	0.933
Temperature (°C)	37.2 (± 1.1)	35.6 (± 0.5)	0.003	37 (± 1.2)	35 (± 1.1)	0.043

CVVH: Continuous venovenous hemodiafiltration
MAP: Mean arterial pressure
MODS: Multiple organ dysfunction syndrome
SD: Standard deviation
FiO_2: Inspired oxygen fraction
MCA: Middle cerebral artery
PI: Pulsatility index
X: Mean
HR: Heart rate
MFV: Mean flow velocity
SaO_2: Arterial oxygen saturation

Important to know-tricks from daily practice

Comparison Pre & Post Dilution

PRE-FILTER

- Increases filter life
- Increases convective transport
- Reduced solute clearance
- Some of delivered replacement fluid lost by hemofiltration
- Lower anticoagulation requirements
- Higher UF required given loss of replacement fluid through filter

POST-FILTER

- No solute dilution, improved diffusion and solute clearance
- Increased hemoconcentration
- Higher delivered dose of hemofiltration

Dialysable or Not

Dialysable

Barbiturates
Lithium
Alcohols, Amglcoside
Salicylates
Theophyllin
Penicillins,
Carbapenems, Cephalo

Non-Dialysable

Digoxin
Tricyclic
Antidepressents
Phenytoin
Benzodiazepines
B-blockers
(atenolol is removed)
Metformin

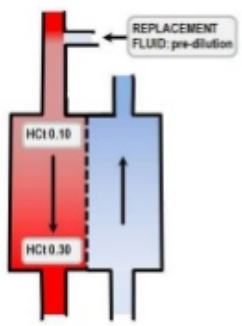
PC-B L A S T

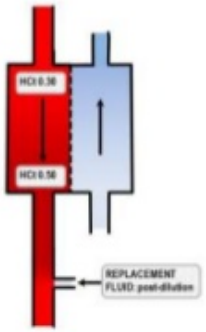
The following anti-infectives do NOT require dose adjustment during CRRT:

- Amphotericin
- Azithromycin
- Ceftriaxone
- Clindamycin
- Doxycycline
- Linezolid
- Metronidazole
- Micafungin
- Oxacillin
- Rifampin
- Tigecycline
- Voriconazole

Use list from ESICU for medicament CRRT dosage

Important to know-tricks from daily practice





Pre-dilution	Post-dilution
Low risk of clotting	High risk of clotting

No clinical study has definitively addressed when pre- or post-dilution HF should be used, so this decision is largely a matter of local experience and preference.

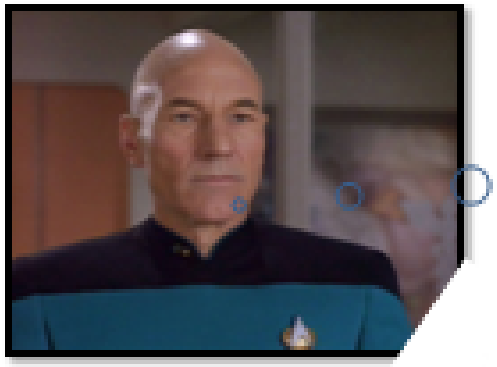
Ronco et al. Critical Care (2015) 19:146

- CRRT Dose
  = Delivered effluent volume of 20-25ml/kg/hr
  = Prescribed effluent volume of 25-30ml/kg/hr

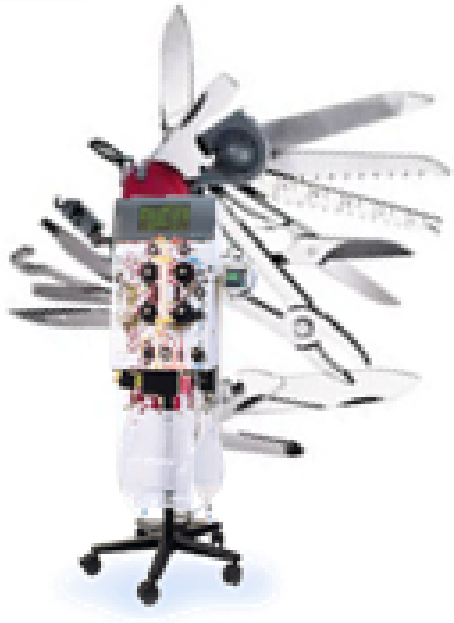
- Filtration fraction during CRRT must be < 30%

- No evidence that septic shock patients will benefit from higher effluent volumes

- Plasma Adsorption may have an important role in management of septic AKI patients



As machines and therapies improved, patients become more severely ill



MODS need MOST

OUR CLINICAL PRACTICE

MOST (multipleorgan support therapy): ECMO, CRRT, hemoperfusion, adsorption and plasmafiltration combined in a single device

Seminars in Dialysis 24(2), 2011

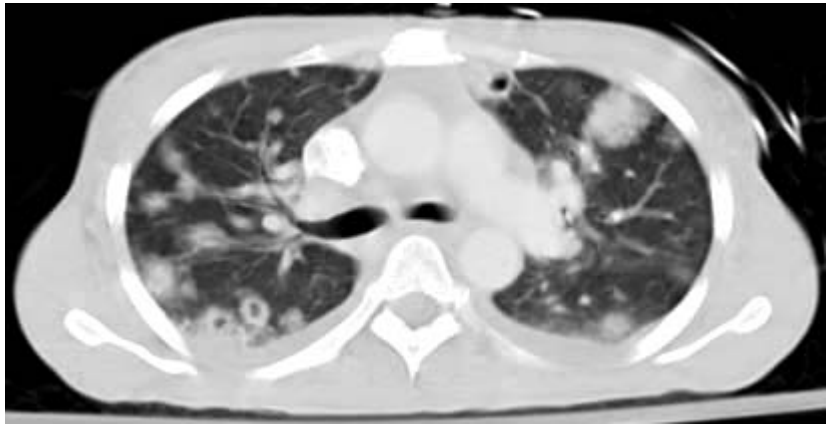
ZAN MITREV CLINIC

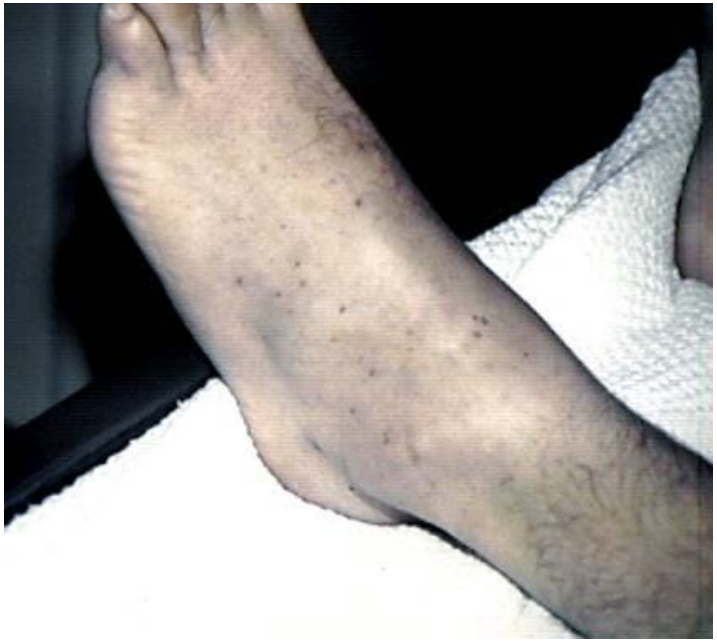
CLICAL DILEMA AND ANSWERS

1. **When to start with CRRT – OXIRIS?**
2. **Which parameters to follow before, during and post CRRT**
3. **How to treat, -blood pump, dyalisate, PBP, PostBP, Effluent???**
4. **Diuretics to stop or not???? – YES**
5. **Cathecholamines ???**
6. **Phoxilium 1,2mmol/l – benefit for septic patients**

Case 1: Acute endocarditis with septic shock and pulmonary edema

- **37 years old man** (A.S.) BW=87kg, BH=190cm
- **History:** 40 days history of febricity, sweating, dyspnea on exertion and loosing weight, coughing
- **Physical examination: bilateral basal pneumonia, systolo-diastolic murmur on the aortic valve, splenomegalia , Roth spots, Janeway lesion , petechia**
- **Transthoracic echocardiography:**
- **CT scan of the lung:**





Laboratory parameters

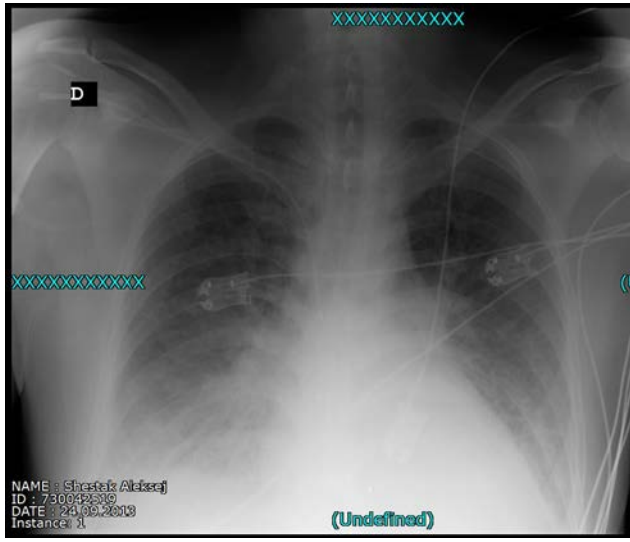
CRP >150

Neutrophylia – 28,43….9,63

IgG > 35…4,5, AST 2516…33, ALT 3151…49, BNP 1482

PCT 100…0,5

Microbyology- Streptococcus viridans MR,Pseudomonas aeruginosa



Treatment Linezolid i.v, EDGT

After 10 days- pulmonary edema

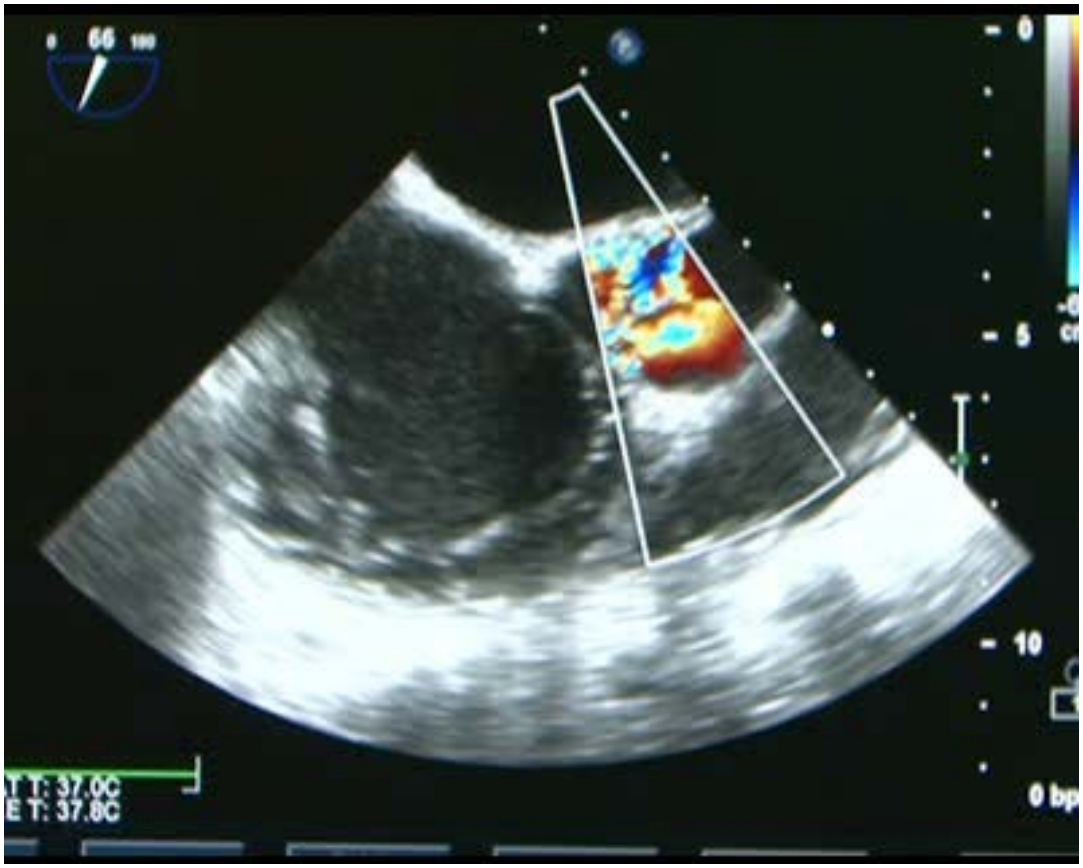
TEE-rupture of the non coronarial cusp – severe aortic regurgitation, LV failure

High fever, hemodynamic instability = shock

End goal directed therapy- non responder

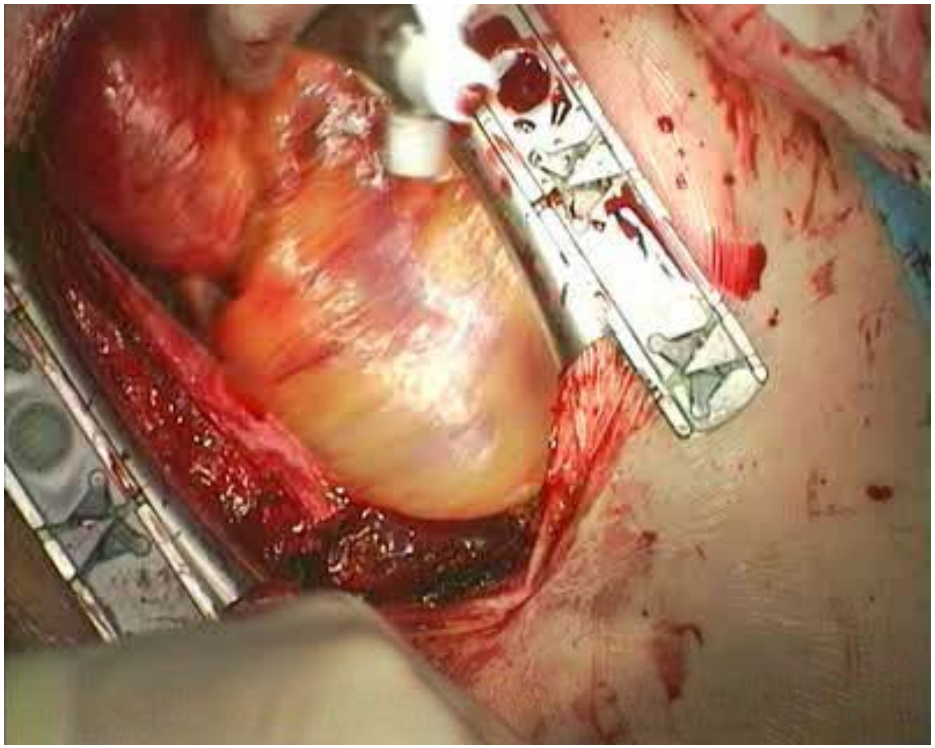
WHAT TO DO????

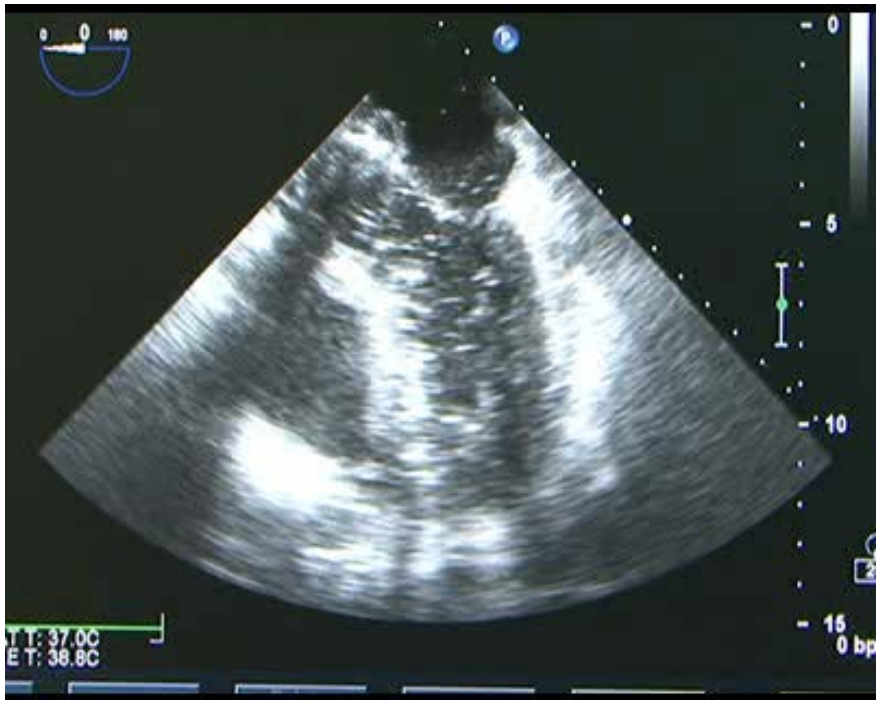
Transesophageal Echocardiography



great vegetations on the right and non-coronarial cusp with a aortic regurgitation +2

URGENT SURGERY 31.10.2013





Surgery:aortic valve extirpation
Reconstruction of the aortic root
Mechanical prostesis Sorin
25mm implantation

Intraoperative TEE

AFTER SURGERY

- Extremely high dosage of vassopresors with hemodynamic instability
- CRRT treatment with oXiris filter on Prisma-flex machine – immediately after surgery
- Linezolid i.v.+Imipenem i.v.
- 4 hours later hemodynamic stabilization
- Catecholamine excluded 2nd postop operative day
- Patient had been extubated after 58h.
- After 25 days he had been discharged at home – 25.11.2013.
- Follow up period 5,5 years

Skopje, 11.09.2018

CRRT protocol of treatment:

CVVHDF – Oxiris filter
Blood pump – 180ml/kg/h
Dyalisate 35 ml/kg/h,
Effluent 400ml/h, CVP 12-14
Continuous i.v Heparin target ACT – 140-180sec
P.B.P = 1160 ml
Post BP = 580 ml

1740ml

BW = 87kg
Total = 87 x 35 = 3045 ml
Dyalisate = 1305 ml
Replacement = 1740 ml
1-filter / 3 days

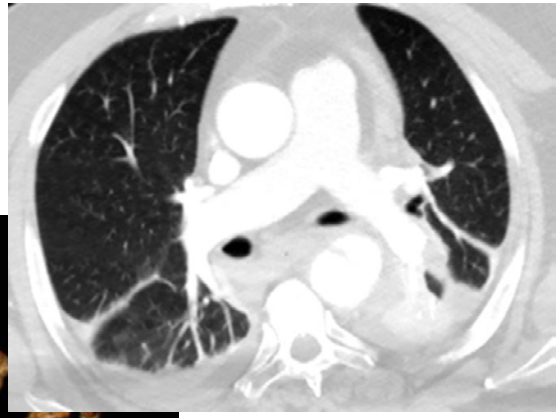
Follow up parameters

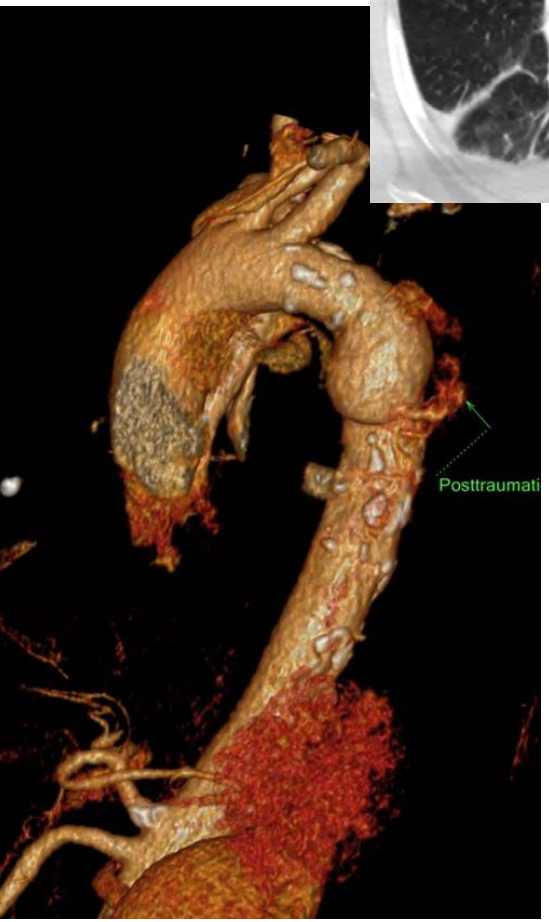
1. **CVP**
2. **BGA – K, glycaemia, lactate, BE**
3. **Urea,Creatinin, CRP,PCT**
4. **diuresis**

Case 2: Acute sepsis after car accident

- **64 years old man** (A.M.) BH=176cm, BW=97 kg
- **History: (04.01.2017)** 2 days after car accident accepted in our hospital, with clinical signs for multiorgan failure and sepsis
- **Physical examination:** fever – 39-40oC, dehidratation, tachypnea and crepitation on auscultation, tachycardia, severe pain spine, oliguria (400ml/24h)
- **Transthoracic echocardiography-** bilateral pleural effusion, LV EF 55%, hematoma in the area of descending aorta
- **X Ray –** Bilateral pleural effusion, F-ra on Xth rib right sided
- **Biochemistry**
- **Hb-10,0, Htc-28,8%** **CK –NAC 5334 U/l**
- **Le-i 13,7 x10^3** CK-MB 119 U/l
- **Urea 21mmol/l, creat 94,8mml/l** **PCT 75**
- **AST 91U/l** **glikemija 18,55**
- **ALT92 U/l** **Microbiology- Echerichia coli -sputum/Ciprofloxacin**

CT scan of the chest and abdomen:





Posttraumatic dissection of the descending aorta

25mm bellow left subclavian artery

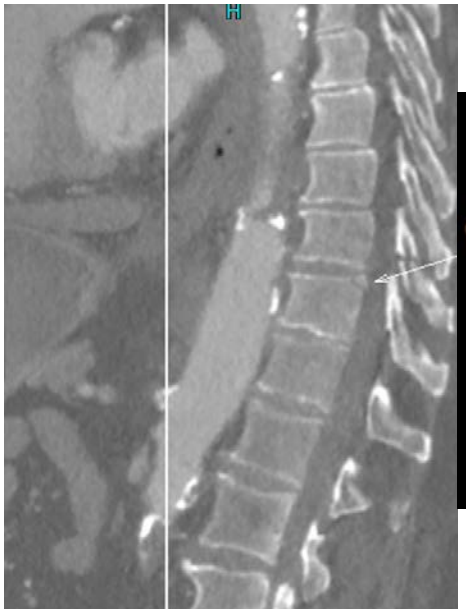
50mm below hematoma

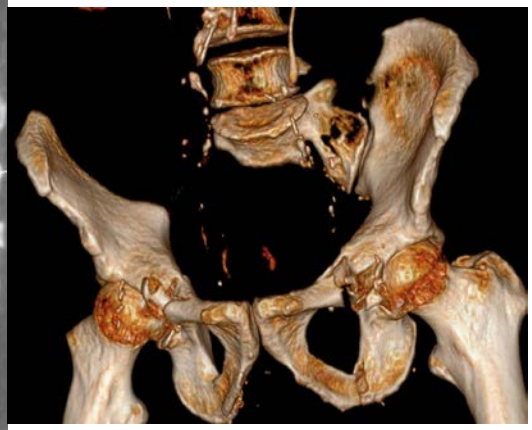
Pleural effusion with lung atelectasis

F-ra of the 7,8,9 rib left sided and 9th rib right sided

Spine bond – f-ra on the level of Th10/11, L4/5

F-ra ossis ilei,ishii , sacrum and alla ossae ilei left



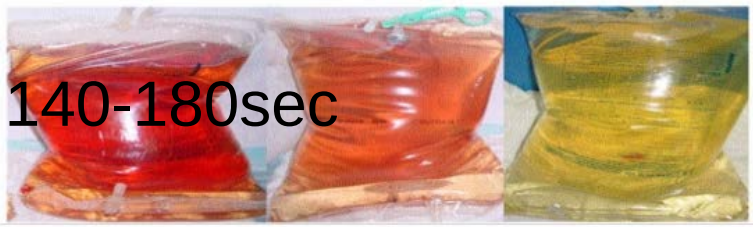


CRRT protocol of treatment:

CVVHDF – Oxiris filter
Blood pump – 180ml/kg/h
Dyalisate 30 ml/kg/h,
Effluent 400ml/h, CVP 12-14
Continuous i.v Heparin target ACT – 140-180sec
P.B.P = 970 ml
Post BP = 485 ml | **1455ml**

BW = 97kg
Total = 97 x 30 = 2910 ml
Dyalisate = 1455 ml
Replacement = 1455 ml
2-filter / 5 days

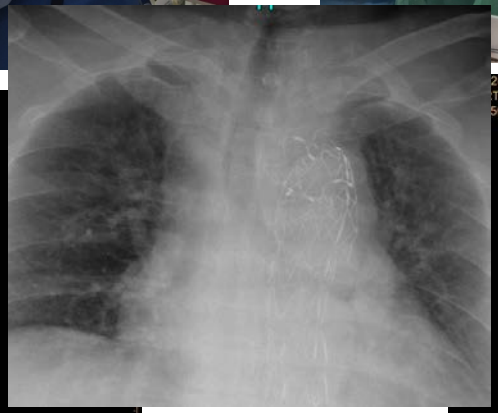
Follow up parameters
1. **CVP**
2. **BGA – K, glycaemia, lactate, BE**
3. **Urea,Creatinin,CRP,PCT**
4. **diuresis**

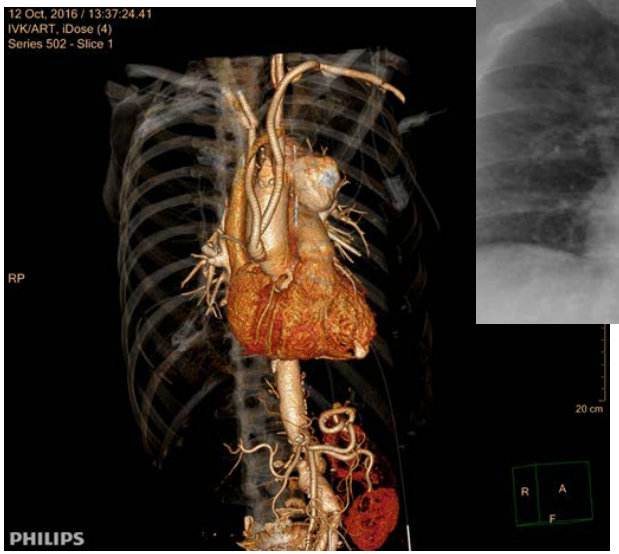


Antibiotics- Ciprofloxacin i.v /7 days
No need for catecholamine's

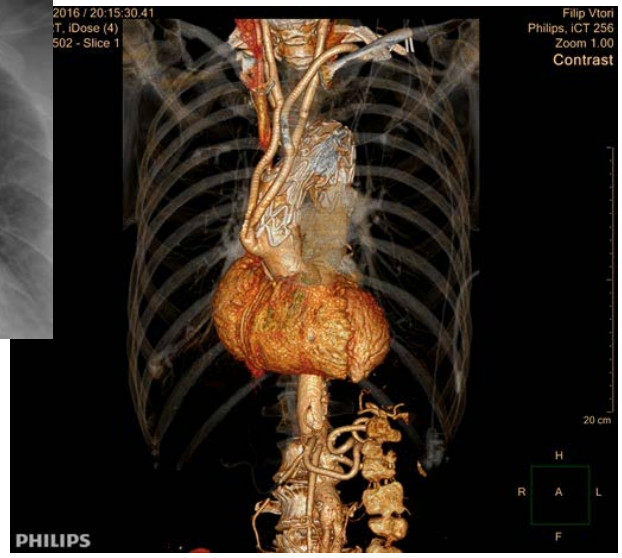
2 days later in a condition of CRRT patient was treated with TEVAR procedure in cath.lab.

Endoscopic treatment of thoracic aneurysm TEVAR -06.01.2018





9month Follow up



Case 3: Acute myocarditis at patient with dilative cardiomyopathy

- **23 years old woman** (M.A.) BW= 46kg BH -160cm
- **History: (16.02.-21.03.2018) treated in our hospital.** She was transferred from Cardiology Clinik. 7 days before she was with high fever up to 40,oC, fatigue, breathless, tachycardia. During previous hospitalization CPR due to VF.
- **Physical examination:** fever – 39,5oC, dehidratation, tachypnea 22/min and crepitation on aulscutation, tachycardia- 138/min with VES, hepatomegalia, peripheral edema (global heart failure) oliguria – 450ml/24h.
- **Transthoracic echocardiography-** bilateral pleural effusion, LV EF 15%, LVd 70mm, LVs 61mm, Mreg +3
- **X Ray –** Bilateral pleural effusion, cardiomegalia
- **Biochemistry**
- **Hb-10,7, Htc-31,2%** **CK –NAC 291 U/l**
- **Le-i 2,4 x10^3** BNP 930 U/l
- **Urea 3,7mmol/l, creat 65,8mml/l** **PCT 0,45**
- **AST 61U/l**
- **ALT84 U/l**

- **Microbiology- MRSA – haemoculture on the cardiology clinic (Vanconycine/Nevaxone /6 days)**
- **In our hospital positive result for adenovirus and respiratory syncytial virus**

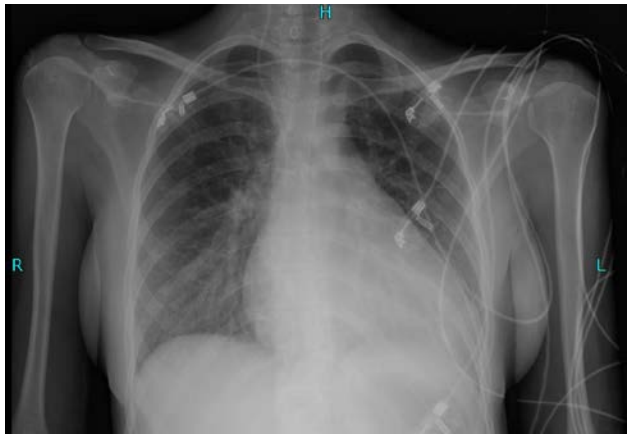
Patient treatment

1. Invasive lines (CVP -20-22, MAP 55, SaO_2 90%, SvO2 46%

2.Catecholamines i.v –Noradrenalin 5mck/kgTT/h,

3. Levosimendan

4. Furosemide i.v



3rd day patient developed pulmonary edema

CRRT- Oxyris –CVVHDF

CRRT protocol of treatment:

CVVHDF – Oxiris filter
Blood pump – 180ml/kg/h
Dyalisate 30 ml/kg/h,
Effluent 350ml/h, CVP 12-14
Continuous i.v Heparin target ACT – 140-180sec
P.B.P = 522 ml
Post BP = 261 ml

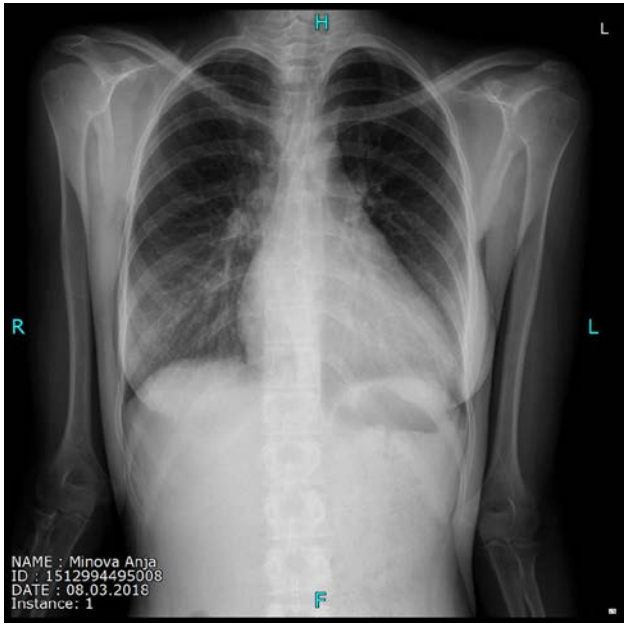
783 ml

BW = 46kg
Total = 46 x 30 = 1380 ml
Dyalisate = 591 ml
Replacement = 783 ml
4-filter / 4times x 2 days

Follow up parameters

1. CVP
2. BGA – K, glycaemia, lactate, BE
3.Urea,Creatinin,CRP,PCT
4. diuresis

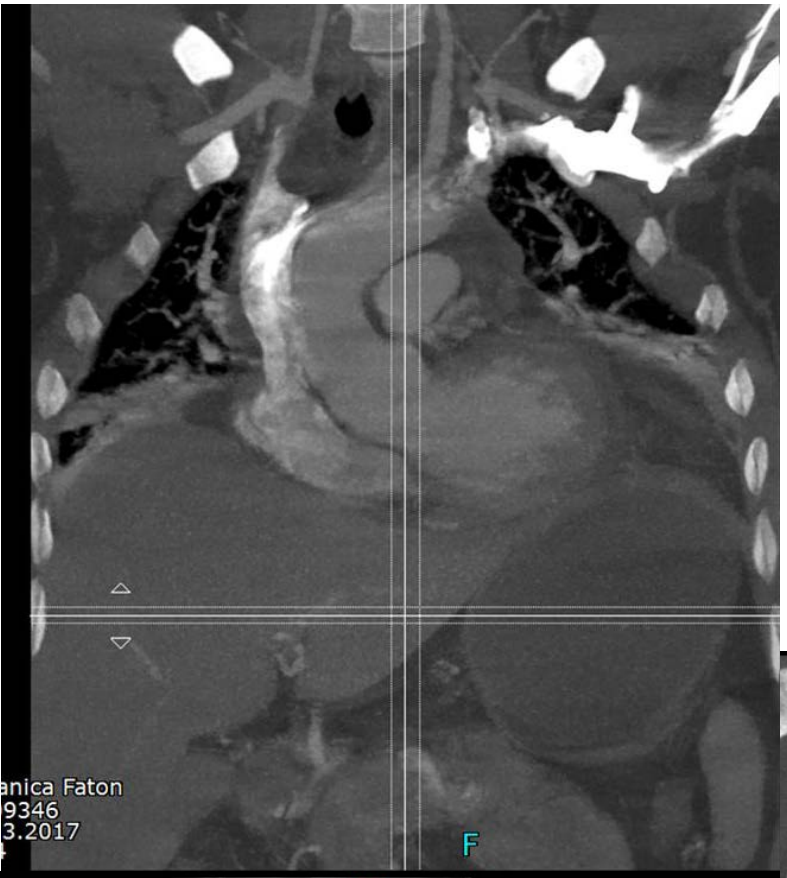
- 21.03. patient had been transported to Deutsche Hertz Centrum
- LVAD – Heart-ware was implanted 28.03.2018
- Follow up 13 months
- Control ultrasound 09.11.2018
- EF 37%, LVd 57mm, LVs 34mm
- No mitral regurgitation.

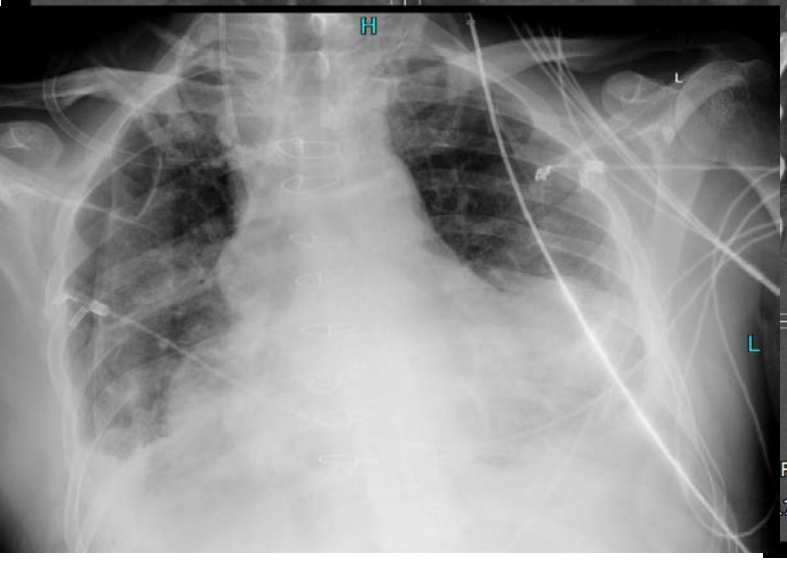


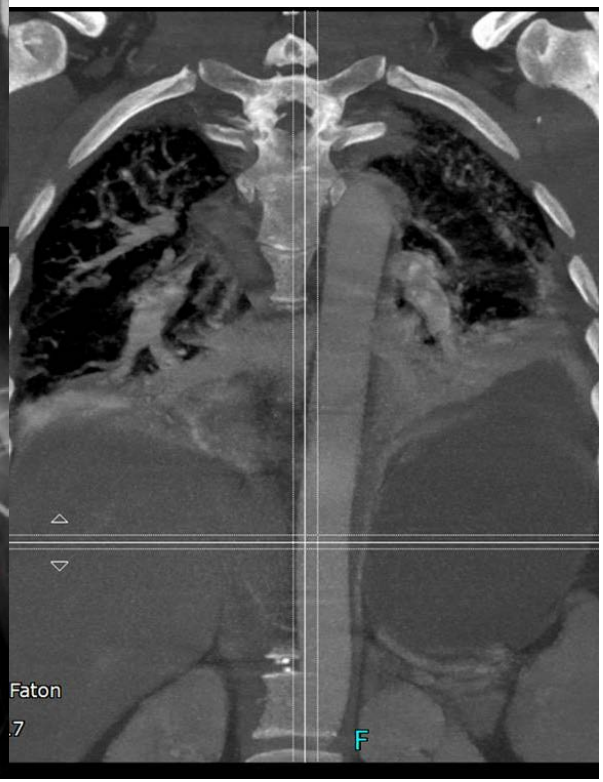
Case 4: Acute septic shock and mediastinitis

- **39 years old man** (T.F.) BH=180cm, BW = 90kg
- **History: (26.03.-03.05.2017) 2weeks before Plaut Vinccenti angina. 26.03.ina septic shock accepted in our hospital**
- **Physical examination:** fever -40oC, dehidratation, tachypnea 32/min and crepitation on auscultation, tachycardia-150/min, severe chest pain , hypotension (70/30mmHg), SaO2 75%, anuria
- **Transthoracic echocardiography-** bilateral pleural effusion, LV EF 60%,
- **Urgent CT – mediastinit**
- **Biochemistry SE 150/ , PCT 165**
- **Hb-10,2, Htc-29,8%** **CK –NAC 1255 U/l**
- **Le-i 11,05 x10^3** LDH 760, T.bil 65,6
- **Urea 10,6mmol/l, creat 109mml/l**
- **AST 73U/l** **glikemija 16,5**
- **ALT75 U/l**

Urgent CT scan and X Ray images







Treatment

- Hemodynamic stabilization :
  - intubation, IV lines and hemodynamic parameters (CVP 20, MAP 50mmHg, SvO2 86%)
  - hydration 15ml/kg/1 h, catecholamine – noradrenalin 4mkg/kg/h
  - antibiotic Ceftriaxon, continuous diuretic therapy
- 3 hours later anuria, pulmonary edema, severe hypotension
- CRRT Oxiris ,and increasing of catecholamine

CRRT protocol of treatment:

CVVHDF – Oxiris filter

Blood pump – 180ml/kg/h

Dyalisate 45 ml/kg/h,

Effluent 400ml/h, CVP 12-14

Continuous i.v Heparin target ACT – 140-180sec

P.B.P = 2100 ml

Post BP = 1050 ml

3150 ml

BW = 90kg

Total = 90 x 45 = 4050 ml

Dyalisate = 900 ml

Replacement = 3150 ml

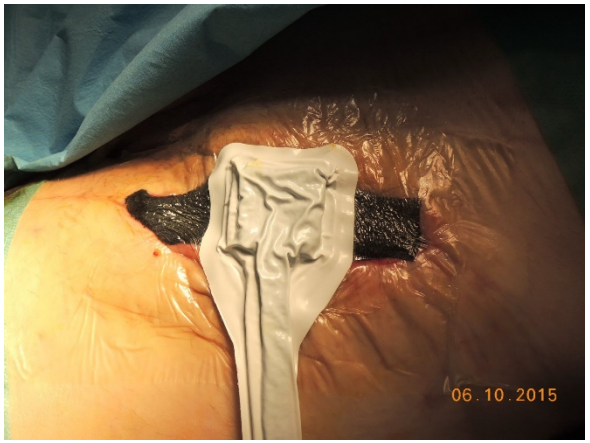
4 -filter / 10 days

2 times filter clotted

Follow up parameters

1. **CVP**
2. **BGA – K, glycaemia, lactate, BE**
3. **Urea,Creatinin,CRP,PCT**
4. **diuresis**

Surgery



- Median sternotomy
- Evacuation of the mediastinal abscess
- Antibiotics local flash
- Vacuum bandage every second day/ next 20 days
- Staphulococcus aureus and Pseudomonas

Treatment

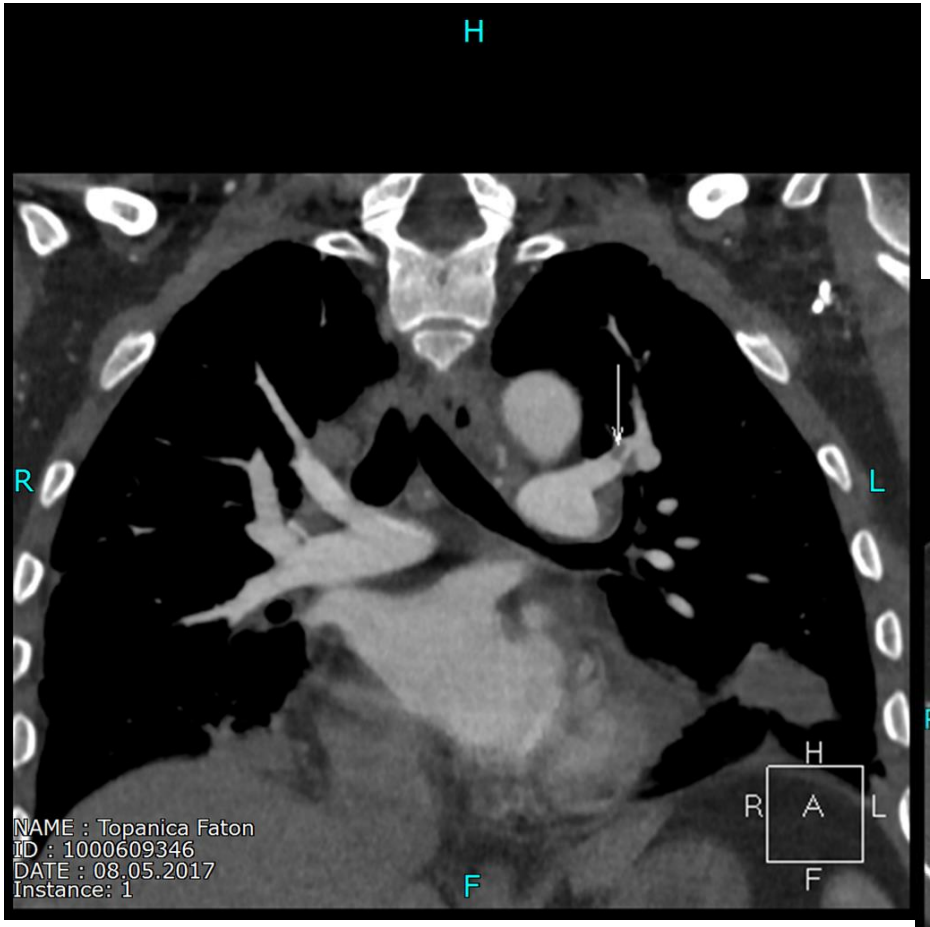
11.04.2018 – hematemesis, urgent gastroscopy and sclerosation on the gastric ulcer

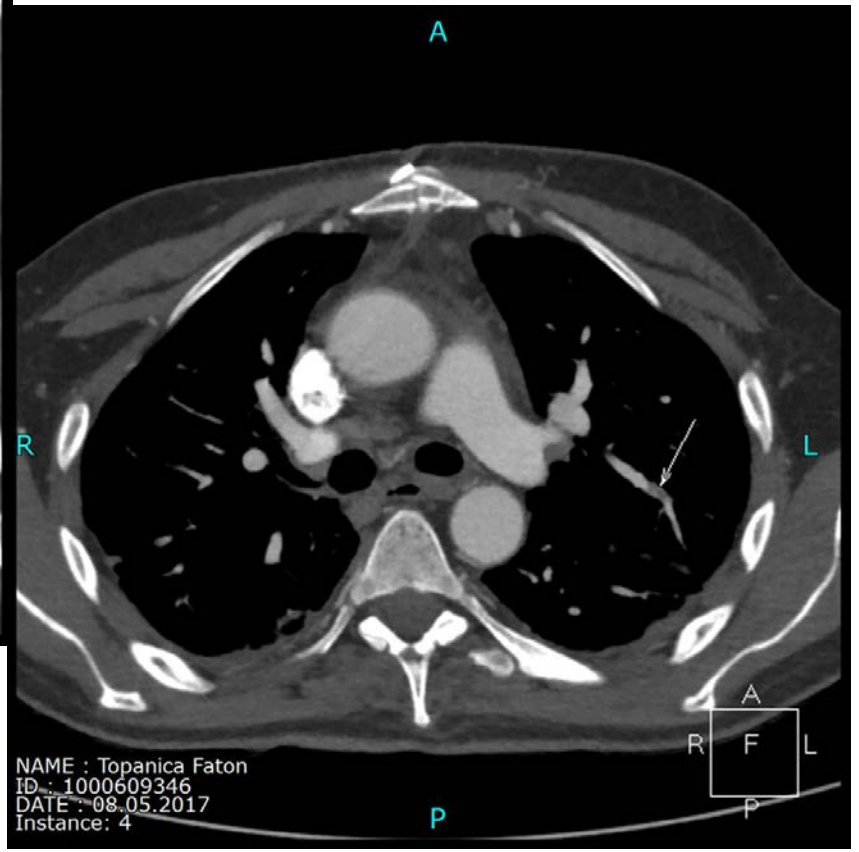
08.05.2018 – chest pain D-dimer 2900

CT scan –pulmonary embolism of the left pulmonary artery

09/2017 control CT in normal range

CT scan images of the pulmonary embolism of the left pulmonary artery





Clexane 0,8 I.E. x 2
Xarelto 20mg 1x1 / 6 months

Case 5: Acute enterocolitis, sepsis

- **65 years old man** (S.S.) BH=183cm, BW = 90kg
- **History: 16.03.2016-ACBPx4,2017 total prostatectomy, HBI (creat 222) Last 10 days high fever 39,0, diarrhea, severe dahidratation, anuria**
- **Physical examination:** fever -39oC, dehidratation, tachypnea 20/min tachycardia-115/min, SaO2 92%, anuria
- **Transthoracic echocardiography-** LV EF 55%, bilateral polycystic kidnies
- **Biochemistry SE 80/ , PCT 25. CRP 259**
- **Hb-14,2, Htc-41,2%** **CK –NAC 1255 U/l**
- **Le-i 8,9 x10^3** LDH 377,
- **Urea 47,9mmol/l, creat 1084mmol/l**
- **AST 24U/l** **glikemija 7,62**
- **ALT36U/l** **Potassium 6,2 mmol/l**

CRRT protocol of treatment:

CVVHDF – Oxiris filter

Blood pump – 180ml/kg/h

Dyalisate 35 ml/kg/h,

Effluent 400ml/h, CVP 12-14

Continuous i.v Heparin target ACT – 140-180sec

P.B.P = 2100 ml

Post BP = 1050 ml

3150 ml

BW = 90kg

Total = 90 x 35 = 3150 ml

Dyalisate = 1050 ml

Replacement = 3150 ml

2 -filter / 6 days

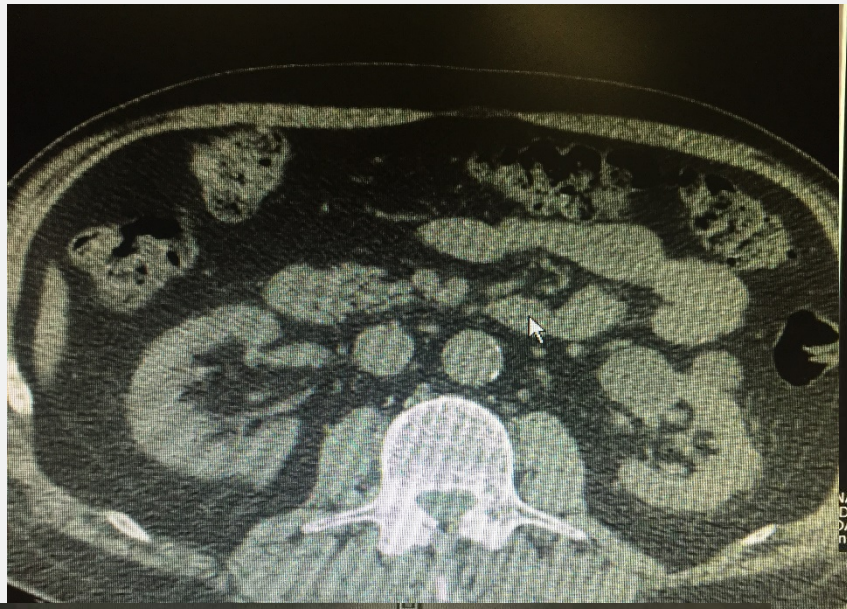
Follow up parameters

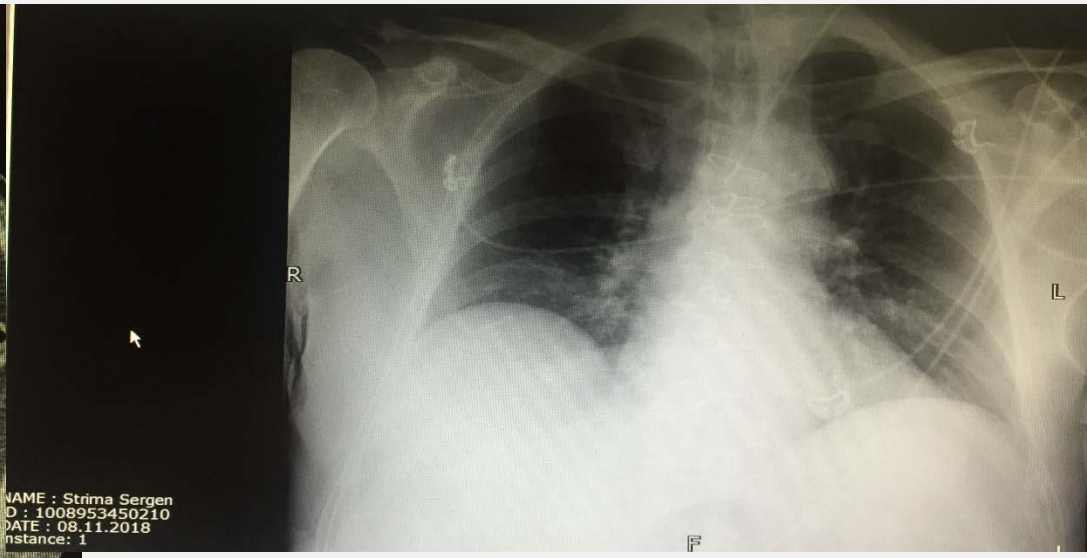
1. CVP

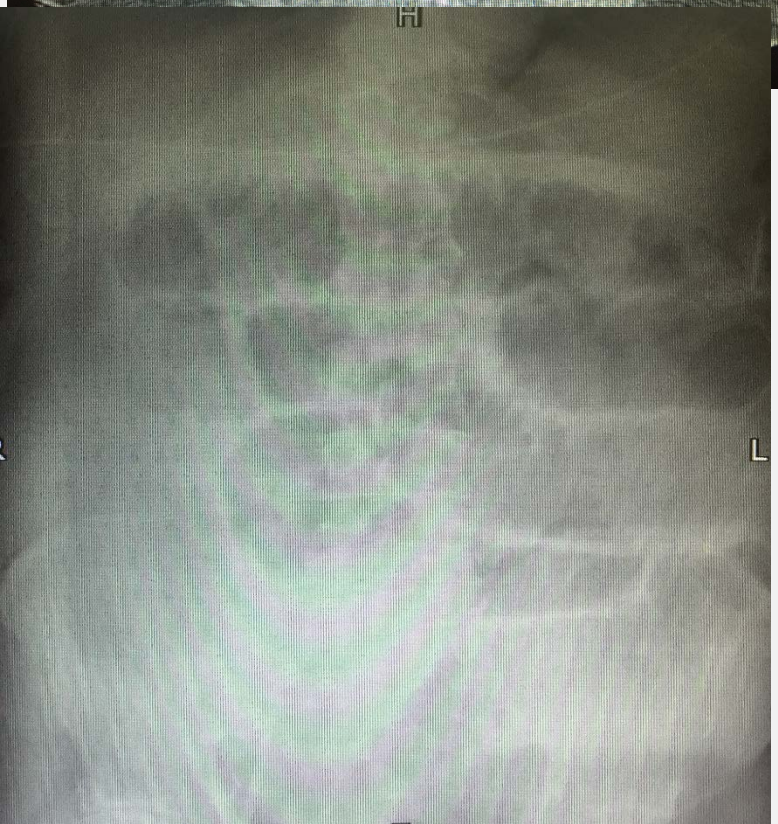
2. BGA – K, glycaemia, lactate, BE

3.Urea,Creatinin,CRP,PCT

4. diuresis







Control laboratory

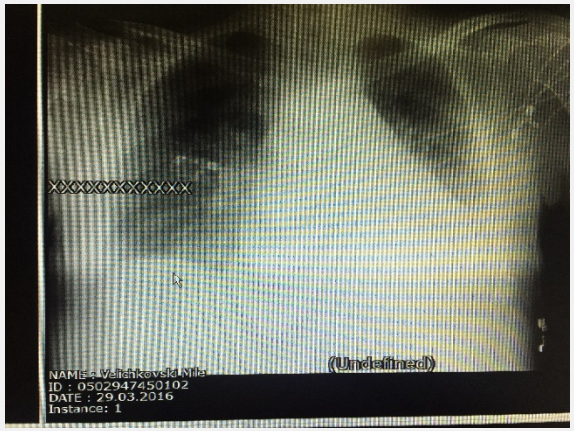
Creat – 458mmol/l, urea 23mmol/l, Potassium 4,5mmol/l, CRP 23, PCT 0,5

Patient was put on chronic program for HHD

Case 6: Acute prosthetic endocarditis with severe sepsis

- **69 years old man** (V.M.) BW=80kg, BH=180cm,BSA 2,0
- **History: 2**0 days history of febricity, dyspnea on exertion, coughing. 2014-got a prosthetic mechanical mitral valve due to anterior mitral valve prolapse. On ultrasound – severe prosthetic endocarditis with para valvular leakage.
- **Physical examination: bilateral pleural effusion, systolo-diastolic murmur on the ictus and Erb, hepatosplenomegaly ,**

Transthoracic echocardiography:



- **-paravalvular leakage**
- **And par annular abscesses**
- **Haemodynamic parameters**
- **-hypotensia, SB<85mmHg, SaO2 89%**
- **creat 189mmol/l, urea 13,6mmo/l,CRP 145, PCT 35**

- **Microbyology- enterococcus fecalis in blood, sensitive on Vancomycine.**
- **Urgent surgery – replacement of the mitral mechanical prosthesis with biological one, after debridement and reconstruction of the mitral annulus.**
- **After surgery**
- high dosage of vasopressors with hemodynamic instability
- CRRT treatment with Oxyris filter on Prisma-flex machine – immediately after surgery
- Vancomycine i.v.+Imipenem i.v.
- 2 hours later hemodynamic stabilization
- Catecholamine excluded 1st post operative day
- Patient had been extubated after 18h.
- After 30 days he had been discharged at home – 13.04.2016. 12/2016 we diagnosed CLL he was with hemiotherapy. Last year he expressed severe hypothyreosis.
- Follow up period 3- years after re-operation,5y.after first operation

CRRT protocol of treatment:

CVVHDF – Oxiris filter
Blood pump – 180ml/kg/h
Dyalisate 35 ml/kg/h,
Effluent 300ml/h, CVP 12-14
Continuous i.v Heparin target ACT – 140-180sec
P.B.P = 1200 ml
Post BP = 570 ml

1700ml

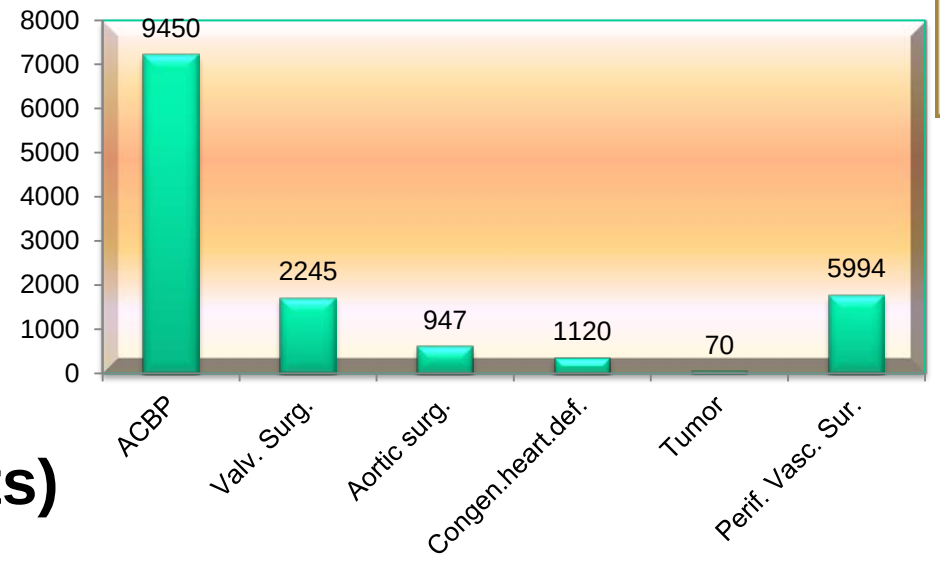
BW = 80kg
Total = 87 x 35 = 2800 ml
Dyalisate = 1100 ml
Replacement = 1700 ml
1-filter / 3,5 days

Follow up parameters

1. CVP
2. BGA – K, glycaemia, lactate, BE
3.Urea,Creatinin,CRP,PCT
4. diuresis

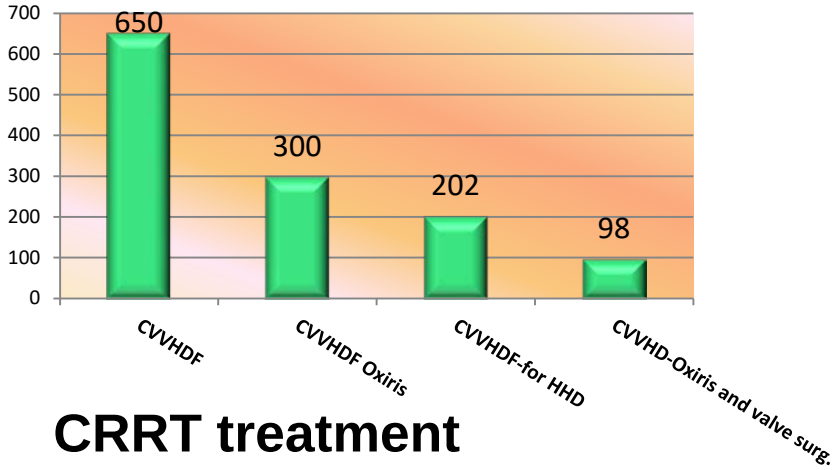
Statistical data

17 years – 19,7260 pts
Acute infective endocarditis - 234
Septic shock- 45
Mortality rate – 10% (23pts)



World literature mortality rate in infective endocarditis- 7,6-21%

Surgery for Infective Endocarditis Who and When? Bernard D. Prendergast, Pilar Tornos ; https://doi.org/10.1161/CIRCULATIONAHA.108.773598 Circulation. 2010;121:1141-1152
Originally published March 8, 2010



CRRT treatment

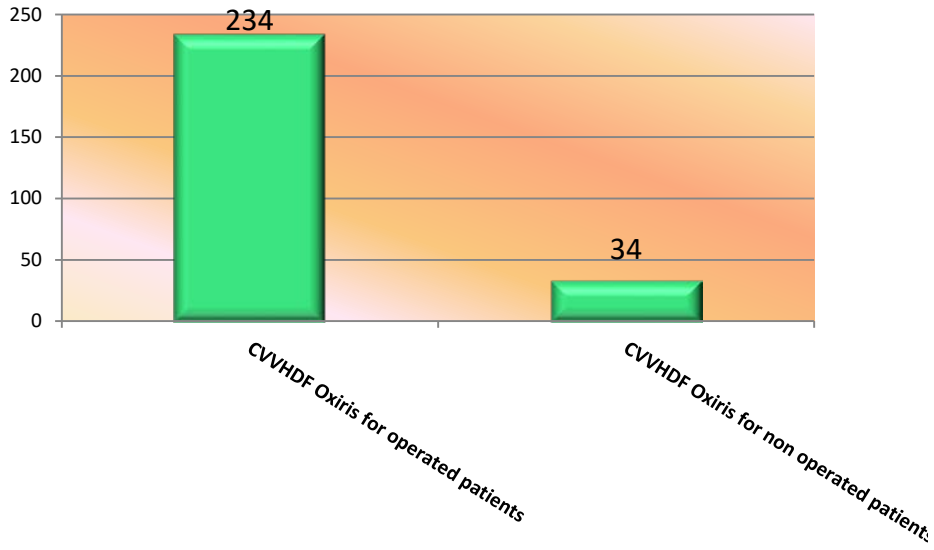
3 patients with aortic valve infective endocarditis, sepsis –urgent surgery (CRRT in combination with EKC) – 2 survived , 1 die 3rd postoperative day

Treatment of septic patients N= 278 1st OXIRIS tm filter used 2007

- **Treatment goals of the EGDT protocol were:**

- CVP = 8–12 mm Hg,
- MAP = 65–90 mm Hg,
- and $ScvO_2$ >70%
- APACHE II
- SAPSII
- SOFAII
- IL6,lacati
- Cahecholamines
- ICU mortality
- Duration of CVVHDF

No of treated patients n = 234 operated-45 in septic shock
n = 34 non operated



Patients data N= 278 pts.

Patient data	No (average ± SD)
Age (years)	68.6±11.9
Weight (kg)	57.6±12.2
Sex-male:female	120 : 158
Scoring of patients	No (%)
APACHE II	26,8±3,7
SAPS II	60,7±12,6
SOFA	23,1±2,4
Laboratory data before	
pH	7,34±0,17
Base excess(mmol/l)	7,8±7,2
Blood urea nitrogen (mmol/l)	16,8±7,9
Creatinine (mmol/l)	256±32,5
Urinary output pre CRRT (ml/hr)	41±13

Patients data N=278 pts.

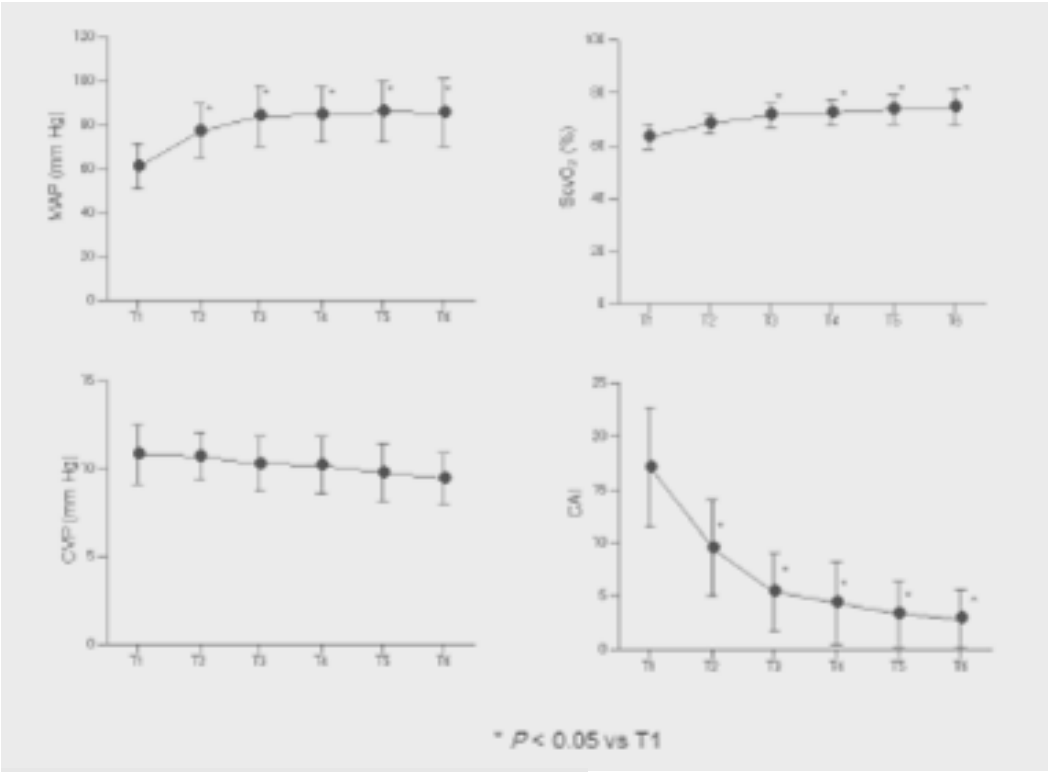
RIFLE CLASSIFICATION	No of pts
Risk	115
Injure	79
Failure	84
Blood culture positive	149
Gr negative	45
Gr positive	92
Fungus	2
Mixed	10

APACHE: Acute Physiology and Chronic Health Evaluation SAPS: Simplified Acute Physiology Score SOFA: Sequential Organ Failure Assessment CRRT: continuous renal replacement therapy
RIFLE: Risk, Injury, Failure, Loss, End-Stage Kidney Disease

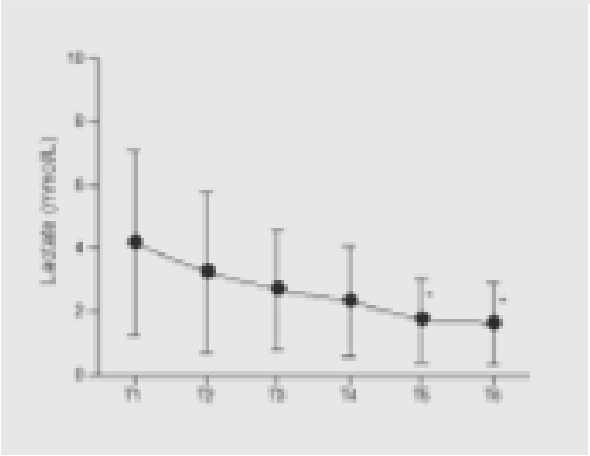
CRRT – Oxiris protocol

Blood pump -150-180ml/min
PreBP – if higher fervency is running
Dialysate 25-40ml/kg/min
Post BP (depends of CVP)
Effluent 250 -400ml/min
Every 4th bag is Phoxilium in cases with low level of phosphates

CRRT – Oxiris influence on patient's hemodynamic and metabolism



CAI= (dopamine dosagex1)+ (dobutamine dosage x1)+(epinephrine x100)+ (norepinephrinex100)+(phenylepinephrine x100)
CAI=cathecholamine index



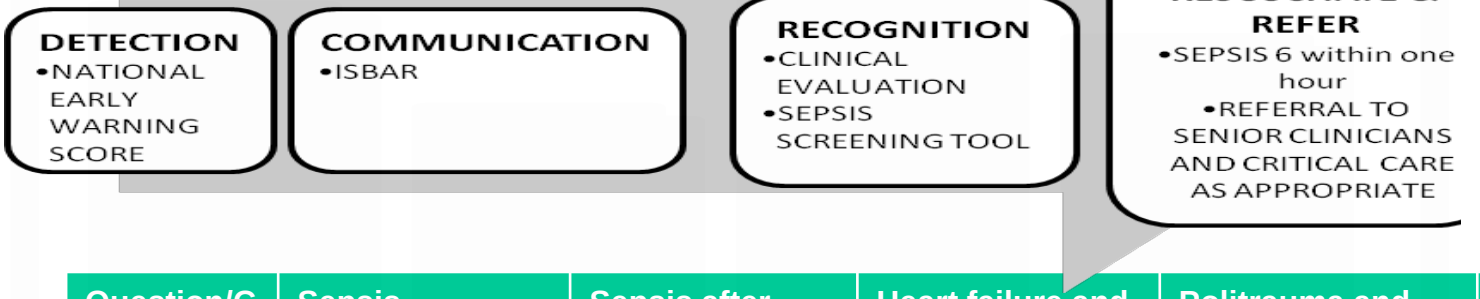
- **MAP increased significantly 3 hrs after CRRT began (Figure 1). obtain MAP at 65–90 mmHg.**
- **$ScvO_2$ began to increase significantly 6 hrs - maintained at >70%**
- **CVP did not change significantly during treatment,**
- **CAI decreased significantly after 3 hrs. Mean CAI was 17 before CRRT; 12 hrs after CRRT began it was possible to maintain CAI < 5.**
- **Serum lactate concentration - significantly lower 24 hrs after beginning CRRT compared with pretreatment levels (2.0±1.6 mmol/l vs. 4.1±2.9 mmol/l).**

Patients data N=278
Total mortality rate = 15,7% (44pts)

Hemopurification flow rate (ml/kg/h)	32.5 ± 7,3
CRRT (Oxiris) days	7,5 ± 4,2
ICU survival	234 (84,2%)
28-day survival	234 (84,2%)
Hospital survival	224 (80,6%)

- CRRT: continuous renal replacement therapy

INSTEAD OF CONCLUSIONS



Just remember

ZAN MITREV CLINIC

Question/Condition	Sepsis	Sepsis after surgery	Heart failure and sepsis	Politrauma and sepsis	Abdominal involvement and sepsis
When to start	Early	Early	Early	Early	Early
Which parameters to follow	CVP,glyc. K,BE,lactats,urea creat,urinoutput, CRP,PCT	CVP,glyc. K,BE,lactats,urea creat,urinoutput CRP,PCT	CVP,glyc. K,BE,lactats,urea creat,urinoutput, CRP,PCT	CVP,glyc. K,BE,lactats,urea creat,urinoutput, CRP,PCT	CVP,glyc. K,BE,lactats,urea creat,urinoutput CRP,PCT
How	CVVHDF/Oxiris	CVVHDF/Oxiris	CVVHDF/Oxiris	CVVHDF/Oxiris	CVVHDF/Oxiris
Blood pump	180-240	180	150	150-180	150-180
Dyalisate	30-35/kg/h(2/5)	30-35/kg/h (2/5)	30/kg/h (2/5)	30/kg/h (2/2)	30-35/kg/h (2/2)
PBP	2/3	2/3	2/3	2/3	2/3
Post BP	1/3	1/3	1/3	1/3	1/3
Total	dyalxBW	Dyal x BW	Dyl x BW	Dyal. X BW	Dyal. H BW
Effluent	200	200-400	400-500 /CVP?	200/CVP	200/CVP
When to stop	Metabol.stabil UO >1ml/kg TT/h	Metabol.stabil UO >1ml/kg TT/h	Metabol.stabil UO >1ml/kg TT/h	Metabol.stabil UO >1ml/kg TT/h	Metabol.stabil UO >1ml/kg TT/h

Gratitude to Baxter

Gratitude to Intercom – Skopje

Gratitude to Medicon - Belgrade

Gratitude to dr Vladimir Kojovic and dr Natasa

1st pediatric CRRT treatment in Macedonia 05.02.2017 E.A. 1 year old

6 months later

Exercise on Dosing

Mr. Smith, 60 kg, ARF

Required dose: 35ml/kg BW/hr

Mode: CVVHDF

- Pre: 66%
- Post:33%
- Dialysate: 900ml/hr

Calculation: 60kg x 35 ml/kg/h = 2100 ml/h

Flow rates

900 ml Dialysate

1200 ml Replacement

2100 ml Total

→ 400 ml Post-Replacement

→ 800 ml Pre-Dilution (PBP)

Exercise on Dosing

Mr.Tan, 120 kg, ARF, pulmonary edema, and sepsis

Required dose: 45 ml/kg BW/hr

Mode: CVVHDF

- Pre- Replacement: 66%
- Post- Replacement:33%
- Dialysate: 1200ml

Calculation: 120 kg x 45 ml/kg/h = 5400 ml/h

Flowrates:

1200 ml Dialysatee

4200 ml Replacement → 1400 ml Post-Dilution (Replacement)
4200 ml Replacement → 2800 ml Pre-Dilution (PBP)

5400 ml Total

Exercise on Dosing

Mrs. Jones, 100 kg, Polytrauma with Rhabdomyolysis

Required dose: 35ml/kg BW/hr

Mode: CVVH

- Pre-Replacement : 50%
- Post-Replacement :50%
- PBP: 500ml/hr

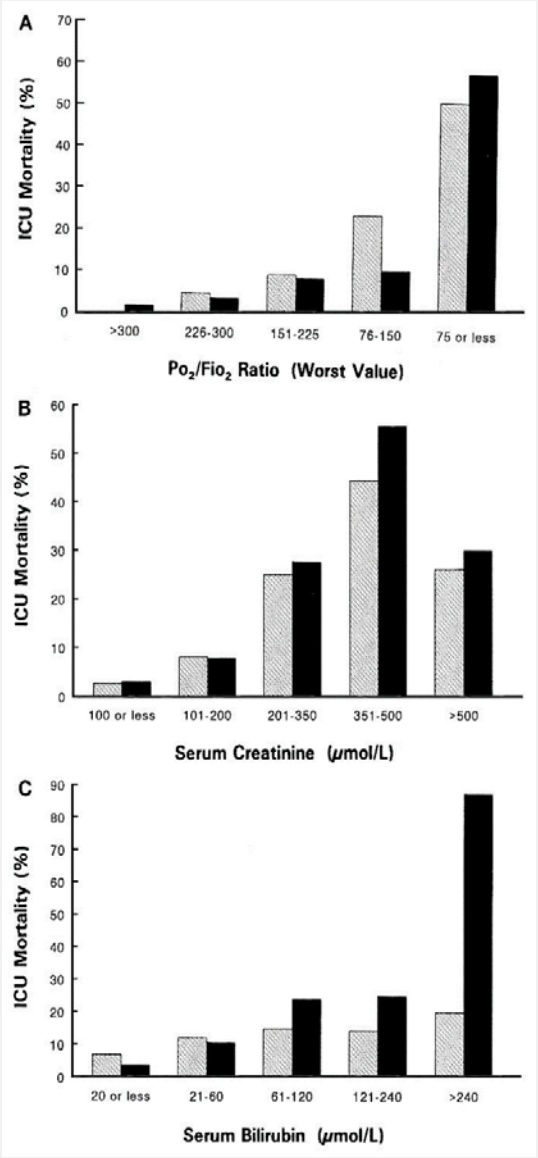
Calculation: 100kg x 35 ml/kg/h = 3500 ml/h

Flow rates:

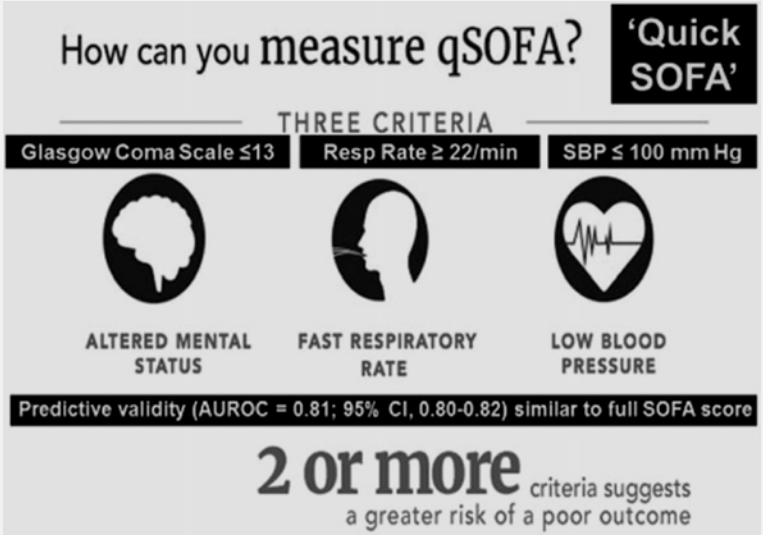
3500 ml Total Replacement →
- 1500 ml Post-Replacement
- 1500 ml Pre-Replacemnt
- 500ml PBP

Organ dysfunction and outcome

- SOFA score dinamics and outcome:
  - 0-1. day
  - CVS (p=0.0010)
  - Creat (p=0.0001)
  - PaO_2/FiO_2 (p=0.0469)
- Se creat increase and mortality
  - ~100µmol/24h p<0.05



Levy MM et al. *Crit Care Med* 2005; 33: 2194



Marshall JC et al. *Crit Care Med* 1995; 23: 1638