

# *Filtr Cytosorb u kriticky nemocných*

*- zkušenosti s více jak  
500 aplikacemi*

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**OA Dr. Stibor B.**

*ICU, Landeskrankenhaus Baden bei Wien, Austria*

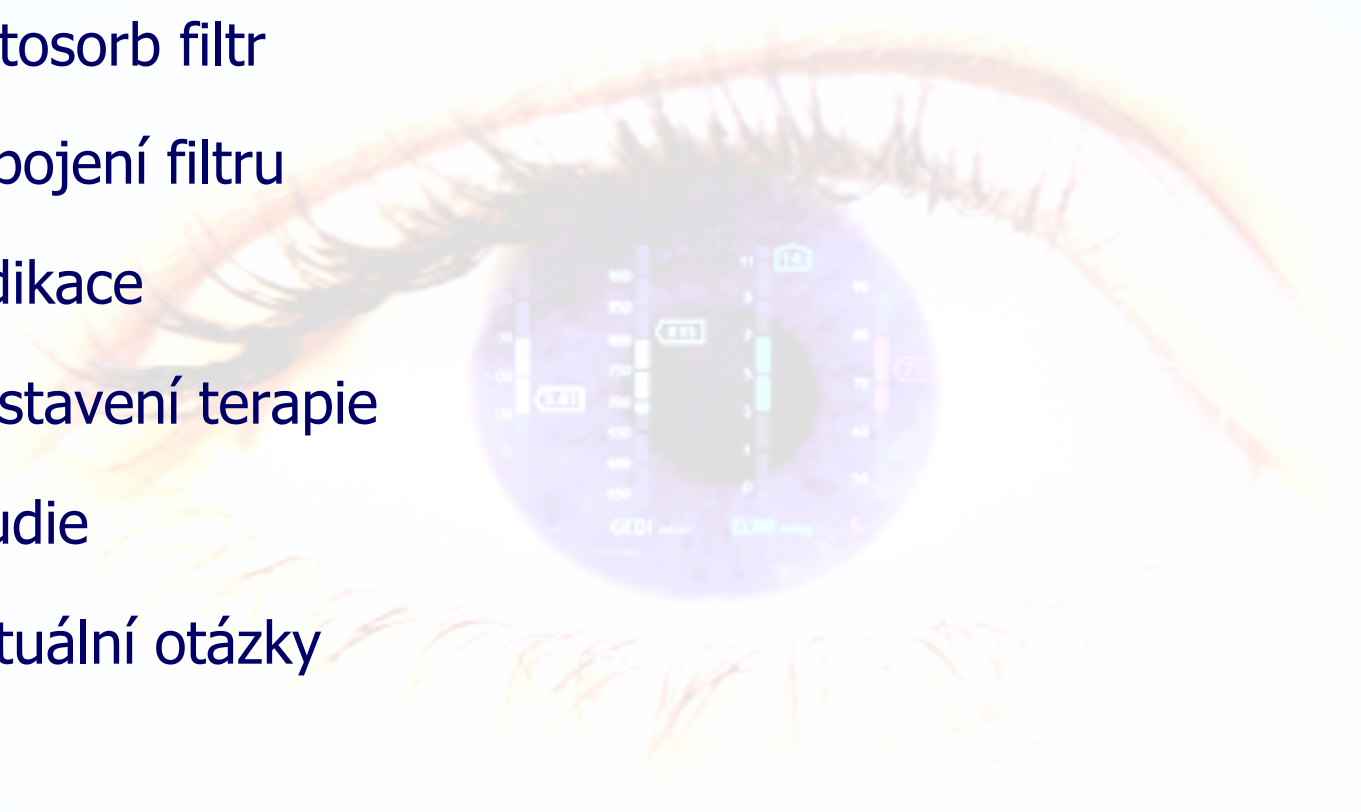
*no conflict of interest*

**OA Dr. Stibor B.**

*ICU, Landeskrankenhaus Baden bei Wien, Austria*

# přehled

1. Cytosorb filtr
2. zapojení filtru
3. indikace
4. nastavení terapie
5. studie
6. aktuální otázky



# Cytosorb filtr

- ✓ obsahuje vysoce porézní materiál
- ✓ je bio- a hemokompatibilní
- ✓ objem 150 ml
- ✓ krevní průtok 100 – 700 ml/min (optimální cca 150 ml/min)
- ✓ skladovatelnost 3 roky



## **synonyma**

cytokine adsorption therapy

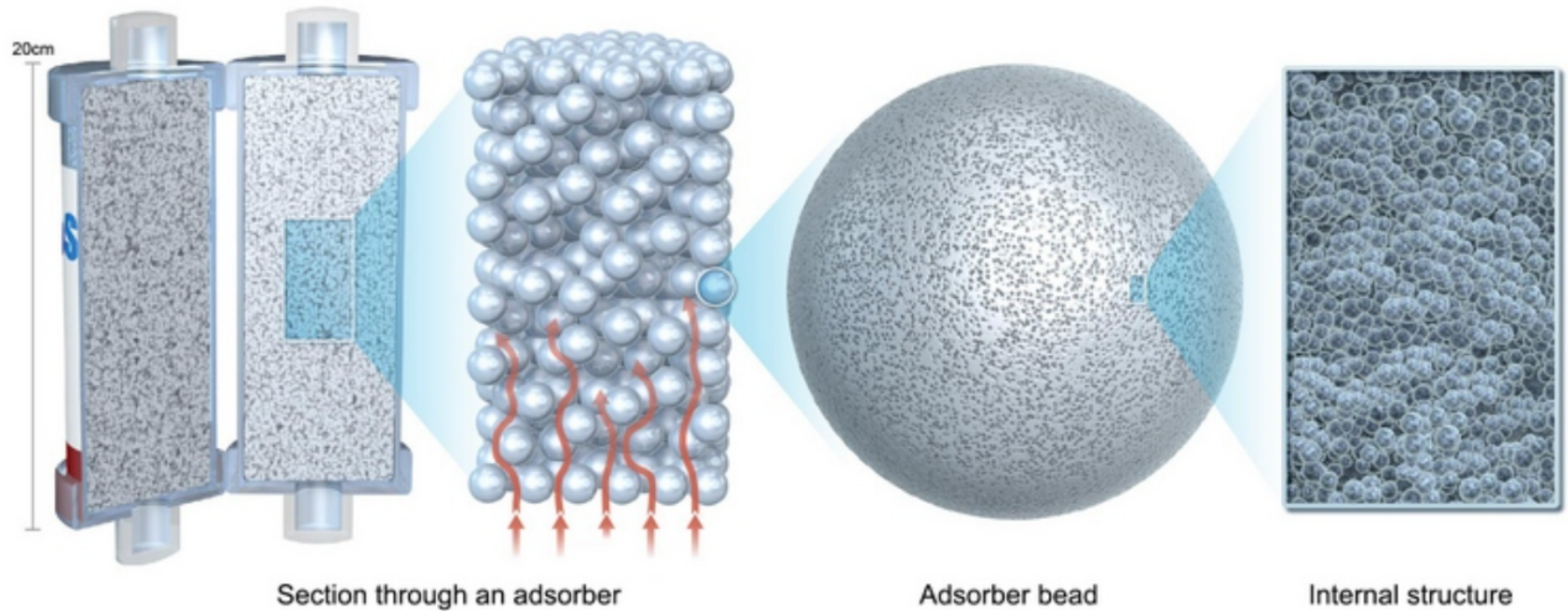
cytokine reduction

extracorporeal cytokine adsorption

haemoadsorption

cytokine removal therapy

# Cytosorb filtr



povrch  $>40.000 \text{ m}^2$  (cca 5 fotbalových hřišť)

# Cytosorb filtr

- ✓ zachycuje cytokiny a jiné mediátory
- ✓ antikoagulace: heparin, citrát, argatroban...
- ✓ max. délka terapie 24 hod (1 filtrem)
- ✓ zabuduje se do ECC (CRRT, kardiochirurgie)



# Cytosorb filtr

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- ✓ > 50.000 použití celosvětově  
(cca 9.000 kardiologie)
- ✓ > 600 ICUs ve více jak 43 zemích
- ✓ Landeskrankenhaus Baden: > 500 použití  
(od roku 2015)

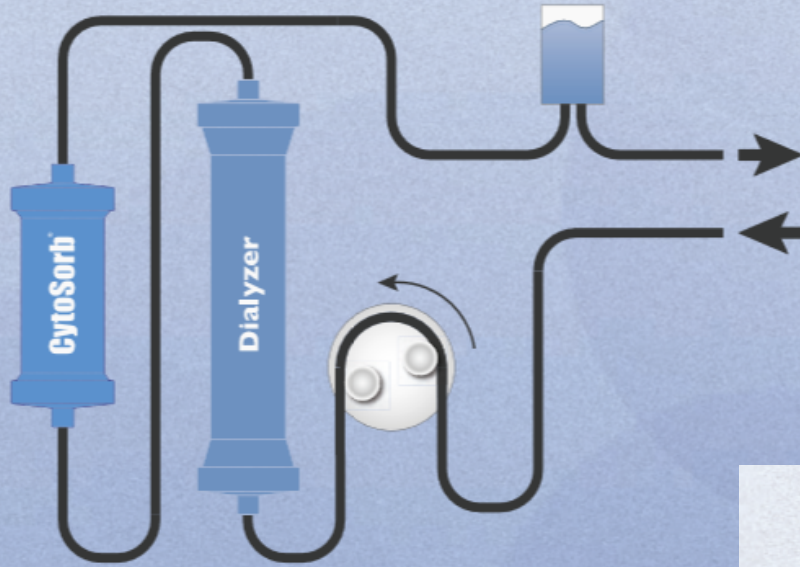


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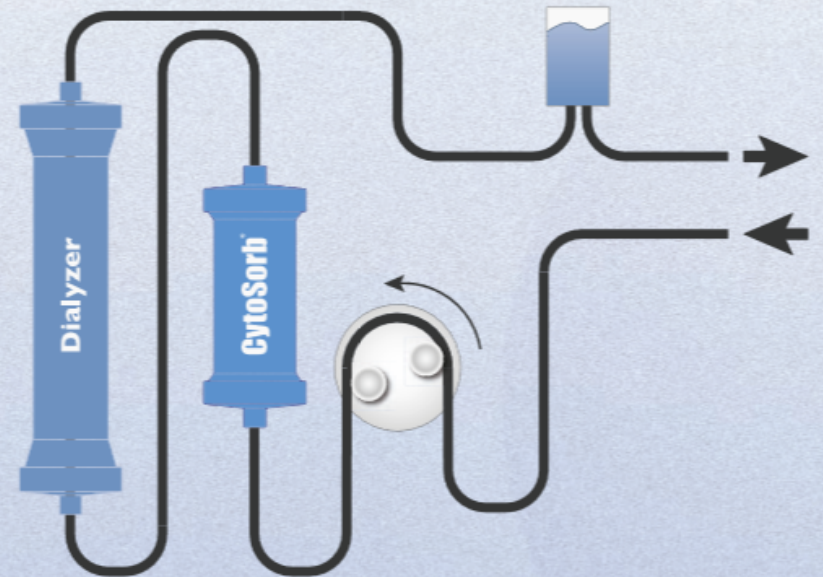
***zapojení  
filtru***

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### CytoSorb und CRRT, nach Dialysator \*

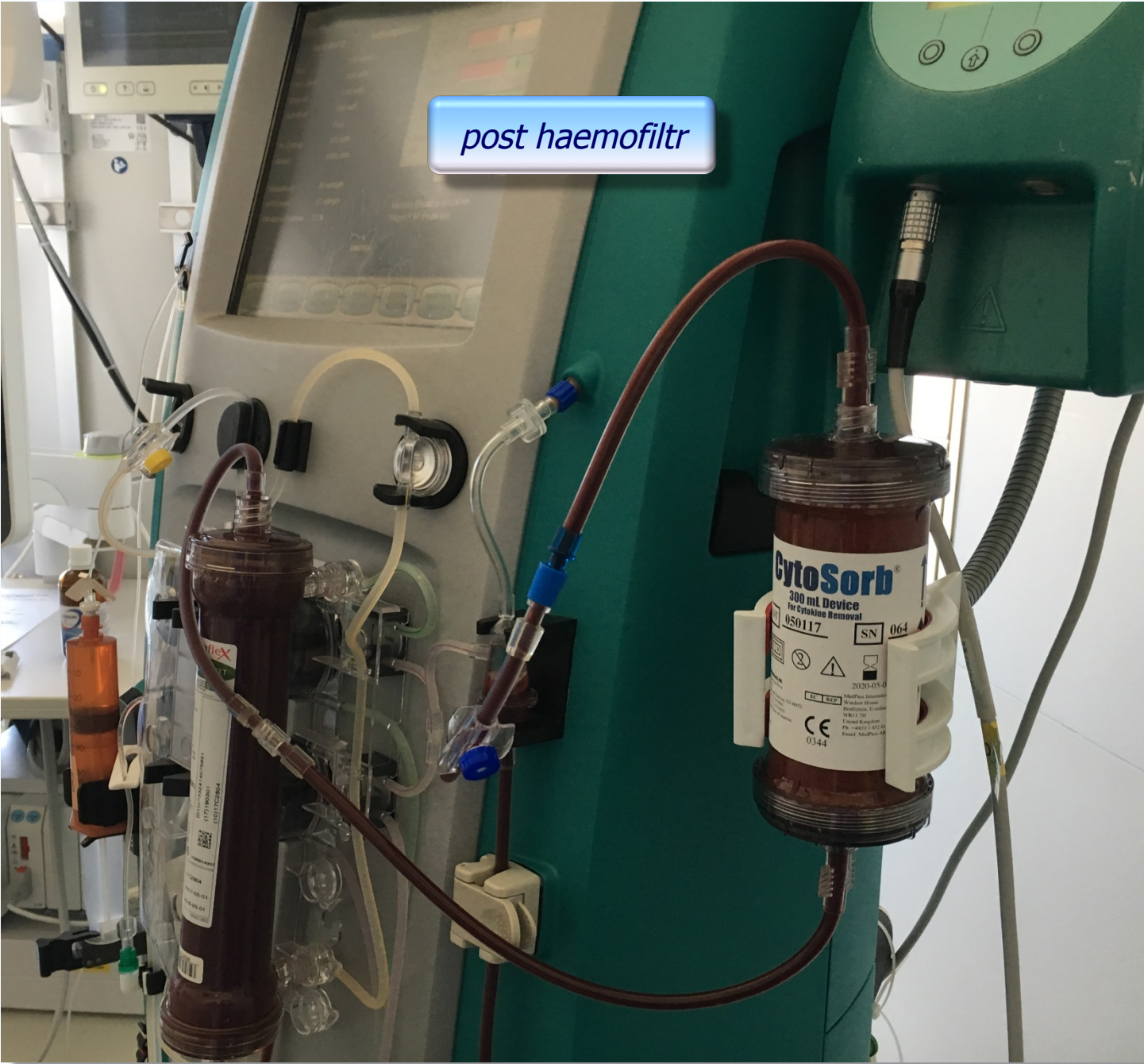


### CytoSorb und CRRT, vor Dialysator \*

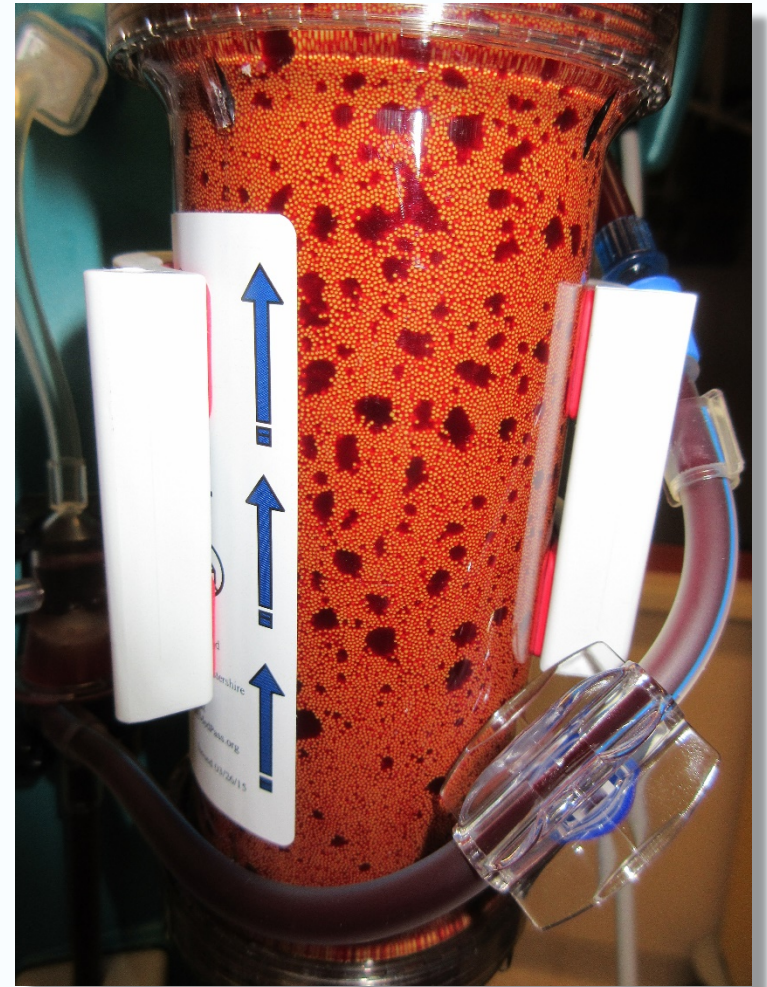
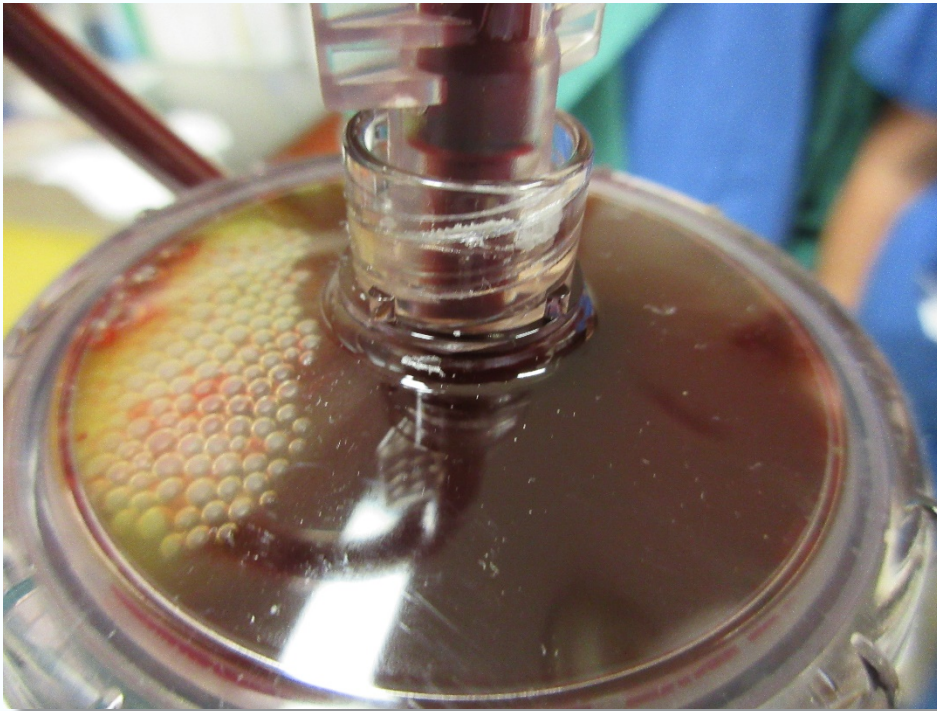




post haemofiltr







**WARNUNG: Filter ist geclottet**

17/August/16

Betrieb

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***indikace***

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# indikace

- sepsy a septický šok
- kardiochirurgické operace (odpojení od MO)
- rhabdomyolýza (*crush syndrom*)
- SIRS (st.p. CPR, akutní pankreatitida)
- intoxikace (lékové či jiné)
- *many others ...*

obecně přijímané indikace neexistují



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***nastavení  
terapie***

---

**CytoSorb**

post Dialysefilter

**dialysefilter**

ST 150, Oxiris

**bloodflow**

120 – 150 ml/min

**citrate**

18/0 mmol/l (Prismocitrate)

**dialysat +  
substitution**

Phoxilium

**Ca comp.**

Ca + Mg

**postfilter Ca**

0,30 – 0,35

**interval**

16 – 24 – 24 h



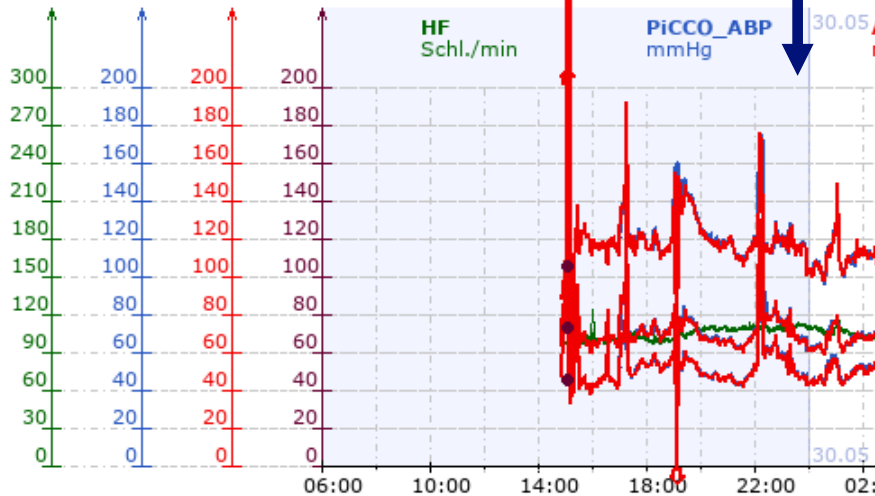
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***septický  
šok***

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# Cytosorb

## ✓ Vasoaktive Medikation



29.05.2018 - 31.05.2018

## Medikamente

Regelmässig

Solu-Cortef	1 mg/ml	100
NaCl 0.9 %	1 ml/ml	x

## Medikamenteninfusionen

Ziel

Empressin 20 i.E. / 50 NaCl 0.4 I.E./ml	4 !	4 !
Perfusor		
NORadrenalin 10mg Perfusor 0.2 mg/ml	8 !	7 ! 7 ! 8 !
Perfusor		
NORadrenalin 10mg Perfusor 0.2 mg/ml	7 !	7 ! 8 !
Perfusor		
Suprarenin 25mg-Perfusor 0.5 mg/ml		2 ! 1 !
Perfusor		
Simdax 0.23 mg/ml Glukose 5% 0.91 ml/ml 12,5mg/50ml		
Solu-Cortef 4 mg/ml NaCl 0.9 % 1 ml/ml	4 !	4 !
Perfusor		

## ✓ Infektionsparameter

23.05.2018 06:00 - 02.06.2018 0

Zeit	29.05.18
15:17	
PCT 0-0.5[ng/ml]	> 100.00
LEUKO 3.6-10.2[G/l]	24.8
CRP -0.5[mg/dl]	9.00
THRO 160-370[G/l]	347
KREACR 50-110[ml/min]	
GFR 0-70[ml/min]	30.00!
GFR Cystatin 0-90[ml/min]	28.00
IL-6 0-7[pg/mL]	> 50000.0

## ✓ Infektionsparameter

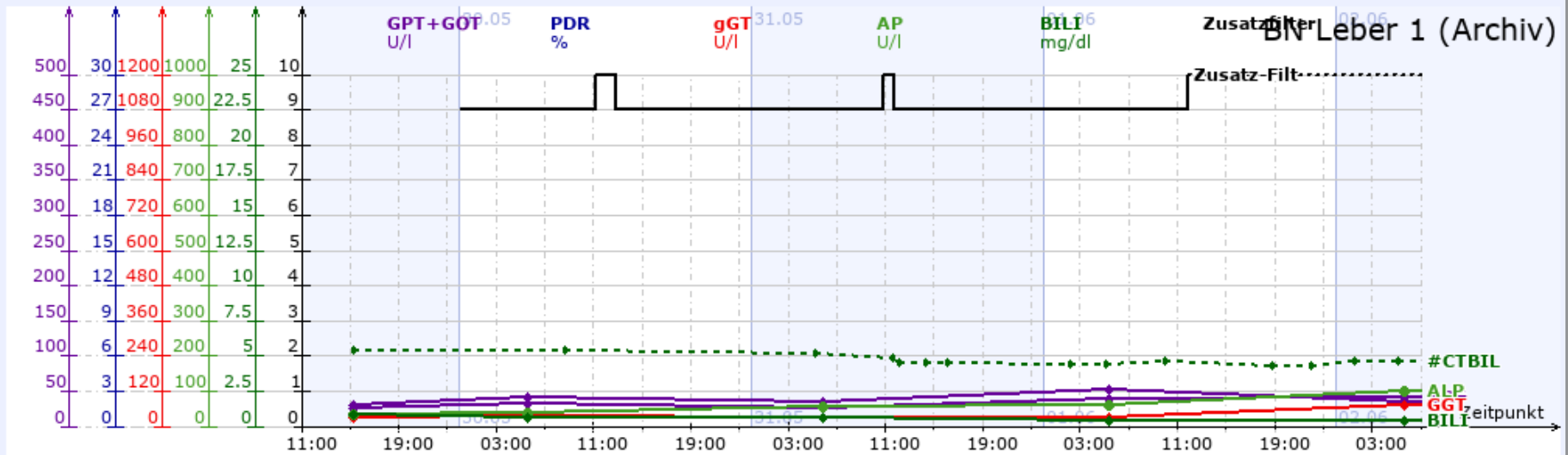
27.05.2018 00:00 - 02.06.2018 2

	27.05	28.05	29.05
Körperkerntemperatur [°C]			39
Axillary temperature [°C]			25.5

# Cytosorb Cytosorb Cytosorb

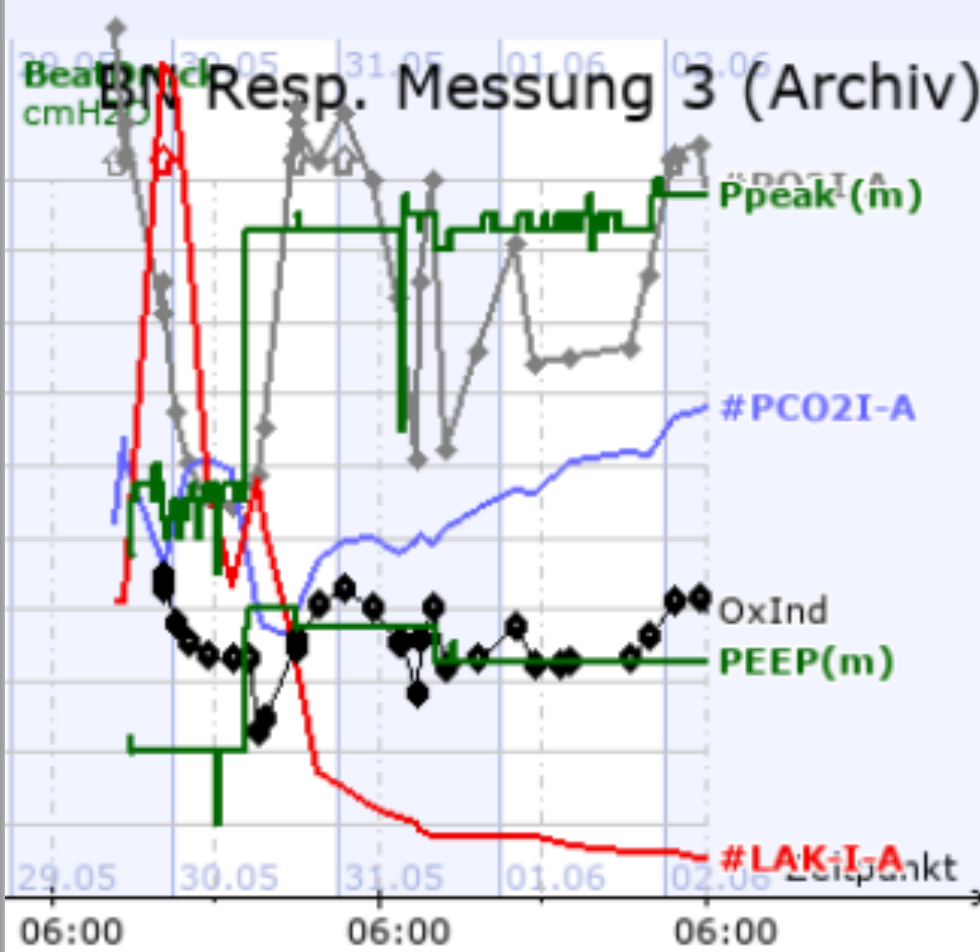
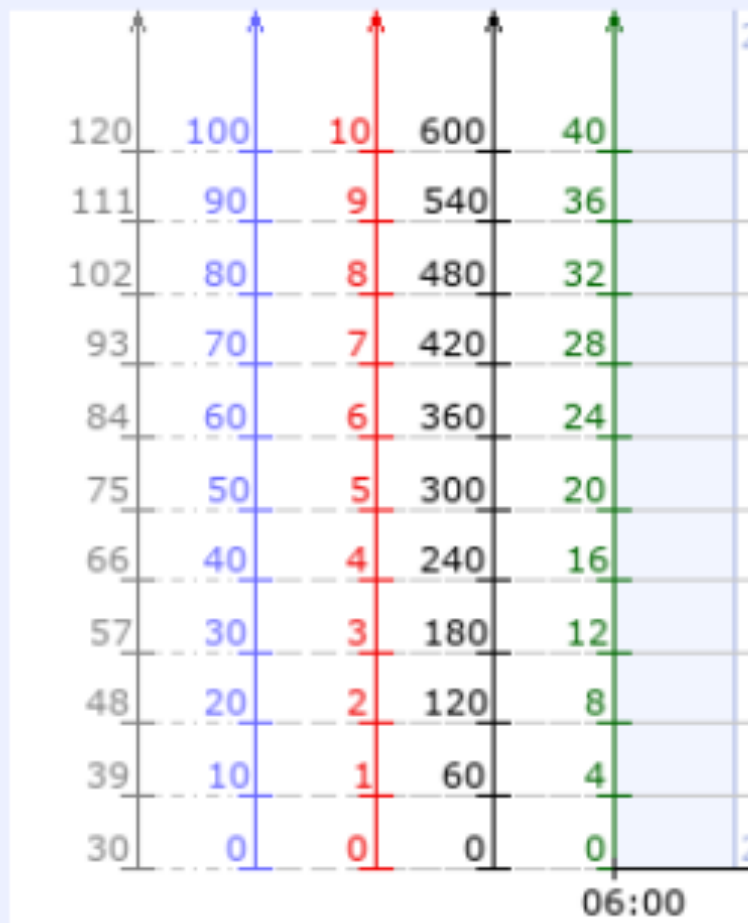
Leber1 ges

29.05.2018 11:00 - 02.06.2018 07:00



# ✓ Beatmung

19.05.2018 06:00 - 02.06.2018 06:00



✓ **Infektionsparameter**

**23.05.2018 06:00 - 02.06.2018 06:00**

**Cytosorb**

Variablen	Zeit	29.05.18	30.05.18	31.05.18	01.06.18	02.06.18
		15:17	05:38	05:51	05:26	05:38
PCT 0-0.5[ng/ml]		100.00	100.00	100.00	75.10	44.10
LEUKO 3.6-10.2[G/l]		24.8	32.1	22.5	19.5	18.9
CRP -0.5[mg/dl]		9.00	30.80	35.00	29.70	15.80
THRO 160-370[G/l]		347	366	250	189	188
KREACR 50-110[ml/min]			0.00!	24.80!	24.00!	24.70!
GFR 0-70[ml/min]		30.00!	22.00!	31.00!	40.00!	47.00!
GFR Cystatin 0-90[ml/min]		28.00	70.00	78.00	82.00	68.00
IL-6 0-7[pg/mL]		50000.0	1629.0	157.6	128.2	71.3

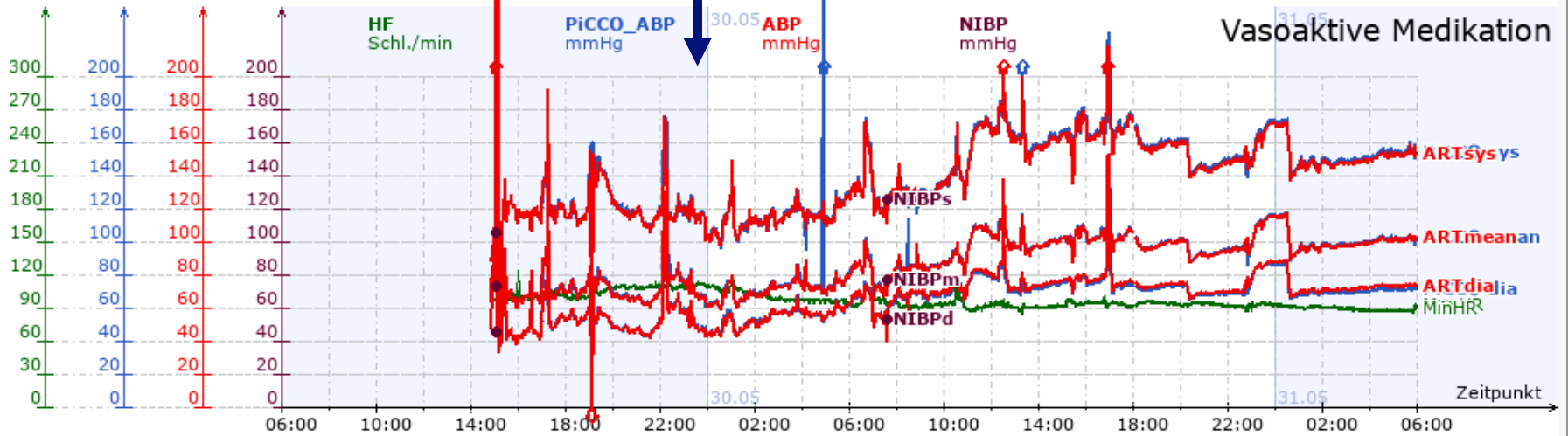
✓ **Infektionsparameter**

**27.05.2018 00:00 - 02.06.2018 23:59**

	27.05	28.05	29.05	30.05	31.05	01.06	02.06
Körperkerntemperatur [°C]			39	37.9	37.8	36.8	36.4
Axillary temperature [°C]			25.5	25.4			

# Cytosorb

Vasoaktive Medikation



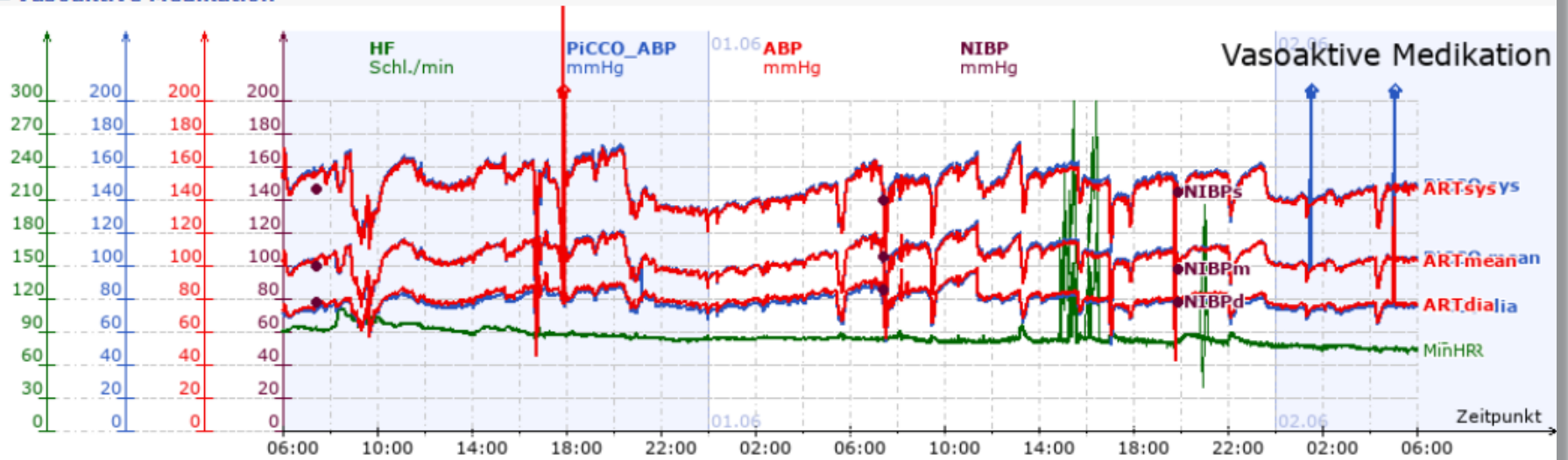
29.05.2018 - 31.05.2018	06	08	10	12	14	16	18	20	22	00	02	04	06	08	10	12	14	16	18	20	22	00	02	04	Gesamt
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Medikamente		Regelmässig																								Gesamt	
Solu-Cortef	1 mg/ml	100																								100 mg	
NaCl 0.9 %	1 ml/ml	x																								100 ml	

Medikamenteninfusionen		Ziel																								Gesamt	
Empressin 20 i.E. / 50 NaCl	0.4 I.E./ml	4 !																								53.9 I.E.	
NORadrenalin 10mg Perfusor	0.2 mg/ml	8 !	7 !	7 !	8 !	8 !	6 !	8 !	8 !	7	6	6 !	6 !	2 !	2 !	53.6 mg											
NORadrenalin 10mg Perfusor	0.2 mg/ml	7 !	7 !	8 !	8 !	10 !	6 !	6 !	4 !	3 !	2	2	47 mg														
Suprarenin 25mg-Perfusor	0.5 mg/ml	2 !																								20.5 mg	
Simdax	0.23 mg/ml	1 !																								7.33 mg	
Glukose 5%	0.91 ml/ml	0.025																								29.3 ml	
12,5mg/50ml		0.05																								[µg/kg/min]	
Solu-Cortef	4 mg/ml	4 !																								618 mg	
NaCl 0.9 %	1 ml/ml	4 !																								154 ml	



Vasoaktive Medikation



31.05.2018 - 02.06.2018		06	08	10	12	14	16	18	20	22	00	02	04	06	08	10	12	14	16	18	20	22	00	02	04	Gesamt		
<b>Medikamenteninfusionen</b>																												
<b>Ziel</b>																												
Empressin 20 i.E. / 50 NaCl 0.4 I.E./ml	2												2 !														2 !	38.4 I.E.
Perfusor																												
NORadrenalin 10mg Perfusor 0.2 mg/ml	5 !						2 !	2 !					5 !	5 !	4.5 !	4 !										2 !	34.8 mg	
Perfusor																												
NORadrenalin 10mg Perfusor 0.2 mg/ml	2												2 !			2 !										3 !	27 mg	
Perfusor																												
Suprarenin 25mg-Perfusor 0.5 mg/ml	1	0.5 !																									4.3 mg	
Perfusor																												
Simdax Glukose 5% 12,5mg/50ml	2																									2 !	2 !	12 mg 47.9 ml [µg/kg/min]
Perfusor	0.05																										0.05	0.05
Solu-Cortef NaCl 0.9 %	4													4 !												4 !	767 mg 192 ml	
Perfusor																												

# efekt terapie

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- stabilizace hemodynamiky
- snížení dávek katecholaminů (60-80%)
- snižování pozitivní bilance
- snížení hladiny laktátu
- pokles zánětlivých parametrů (PCT, CRP, Leu, IL-6)

.....

## K. BLOOD PURIFICATION

1. We make no recommendation regarding the use of blood purification techniques.

*Rationale.* Blood purification includes various techniques, such as high-volume hemofiltration and hemoadsorption (or hemoperfusion), where sorbents, removing either endotoxin or cytokines, are placed in contact with blood; plasma exchange or plasma filtration, through which plasma is separated from whole blood, removed, and replaced with normal saline, albumin, or fresh frozen plasma; and the hybrid system: coupled plasma filtration adsorption (CPFA), which combines plasma filtration and adsorption by a resin cartridge that removes cytokines.

When these modalities of blood purification are considered versus conventional treatment, the available trials are, overall, small, unblinded, and with high risk of bias. Patient selection was unclear and differed with the various techniques. Hemoadsorption is the technique most largely investigated, in



***intoxikace***



Adsorptionsspektrum  
CytoSorb® 300

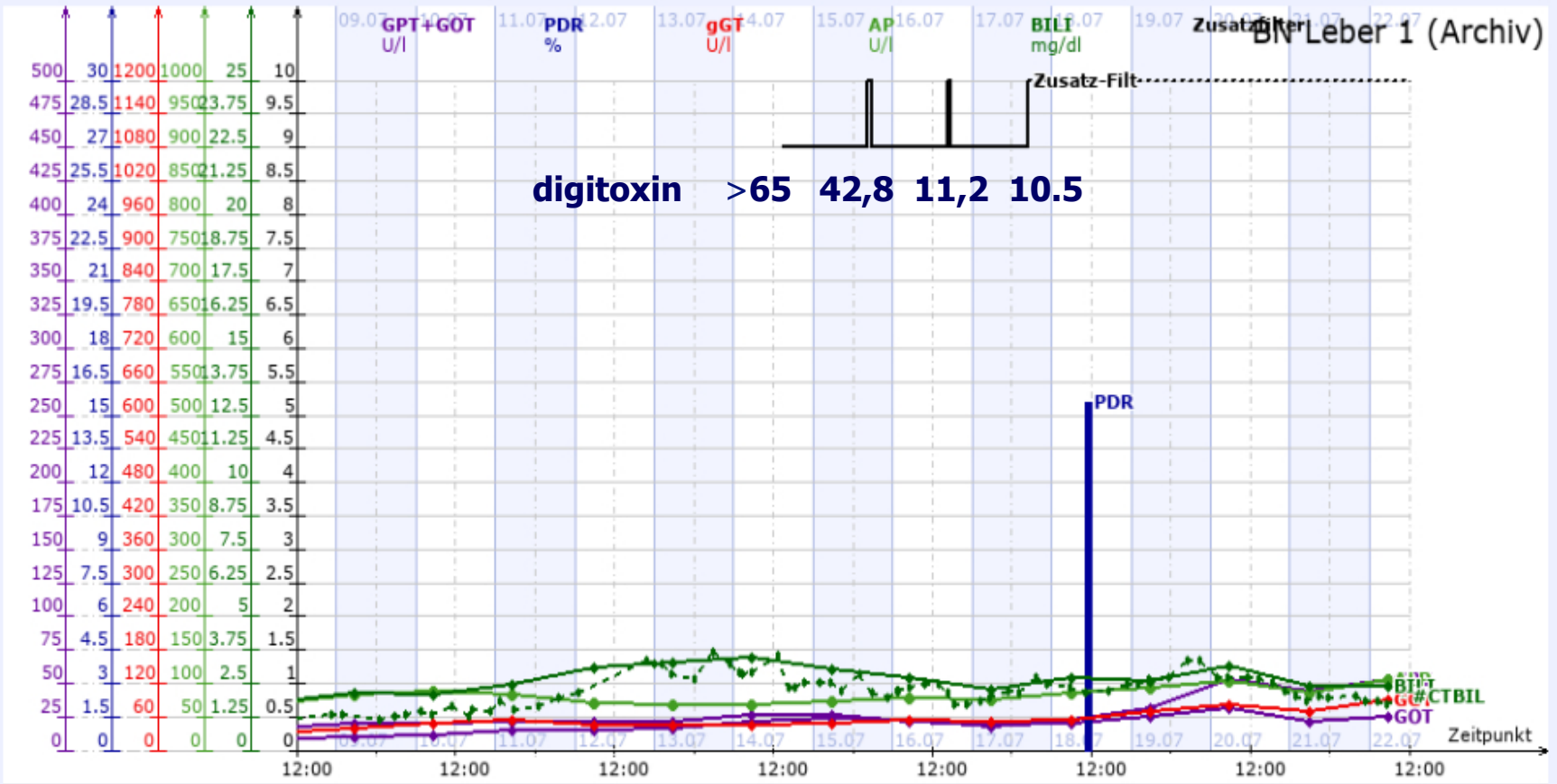
Substanz	Molekulargewicht [kDa]	Klinisch relevante Entfernung erhöhter [%]	Bemerkungen [F, V, D]
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Medikamente			
Amiodaron	Nein		Antiarrhythmikum [D]
Digoxin	Ja		Herzglykosid [D]
Amlodipin	Ja		Calciumkanalblocker [D, V]
Verapamil	Ja		Calciumkanalblocker [D]
Diazepam	Ja		Benzodiazepin [D]
Amitriptylin	Ja		Antidepressivum [D]
Quetiapin	Ja		Atypisches Neuroleptikum [V, D]
Venlafaxin	Ja		Antidepressivum [F, V]
Heparin	Nein		Antikoagulanzen [V]
Ticagrelor	Ja		Thrombozytenaggregationshemmer [D]
Rivaroxaban	Ja		Antikoagulanzen (direkter Faktor Xa Inhibitor) [D]
Dabigatran	Ja		Antikoagulanzen (direkter Thrombin Inhibitor) [D]

Heparin	Nein		Antikoagulanzen [V]
Ticagrelor	Ja		Thrombozytenaggregationshemmer [D]
Rivaroxaban	Ja		Antikoagulanzen (direkter Faktor Xa Inhibitor) [D]
Dabigatran	Ja		Antikoagulanzen (direkter Thrombin Inhibitor) [D]

Leber2

08.07.2017 12:00 - 22.07.2017 12:00



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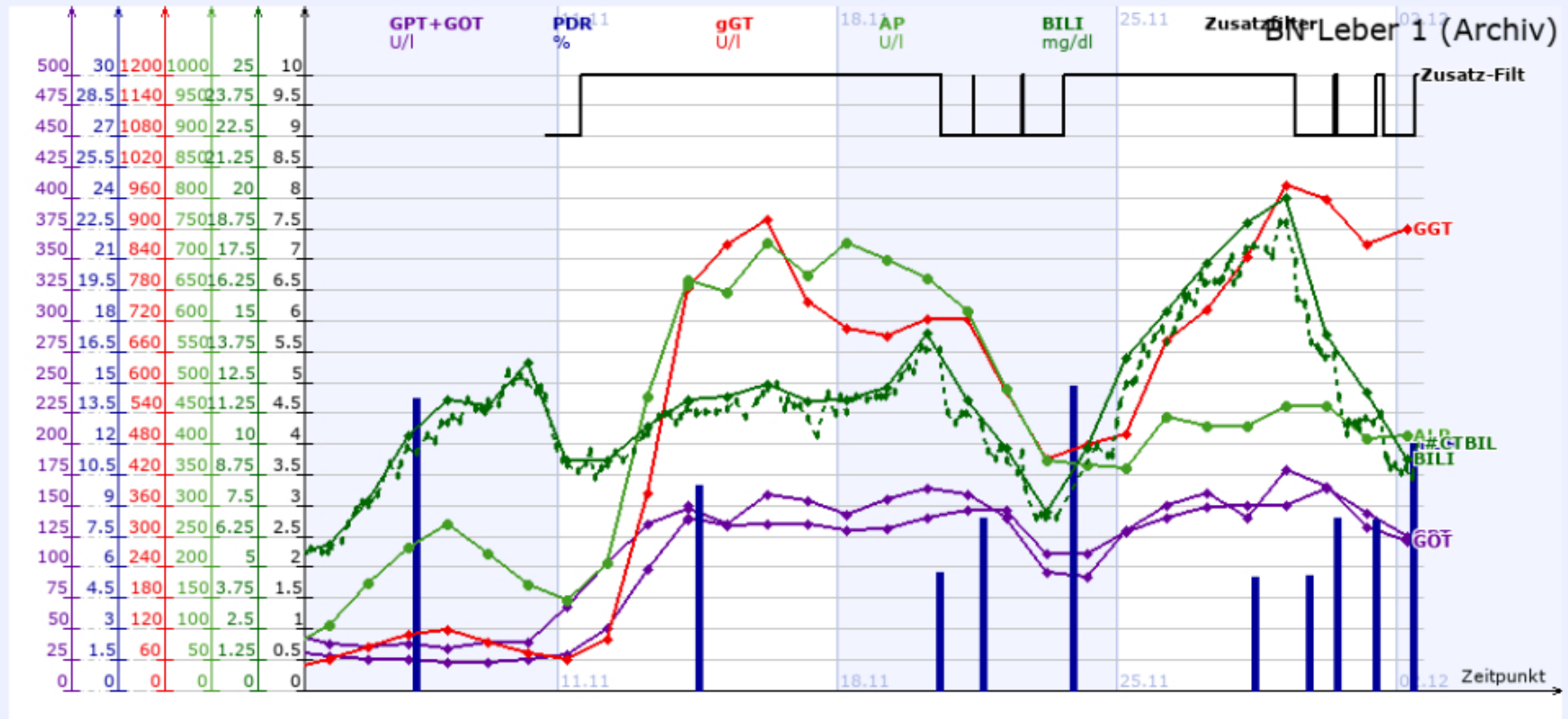
***jaterní  
selhání***

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# LIVER

Leber2

04.11.2017 15:00 - 02.12.2017 15:00



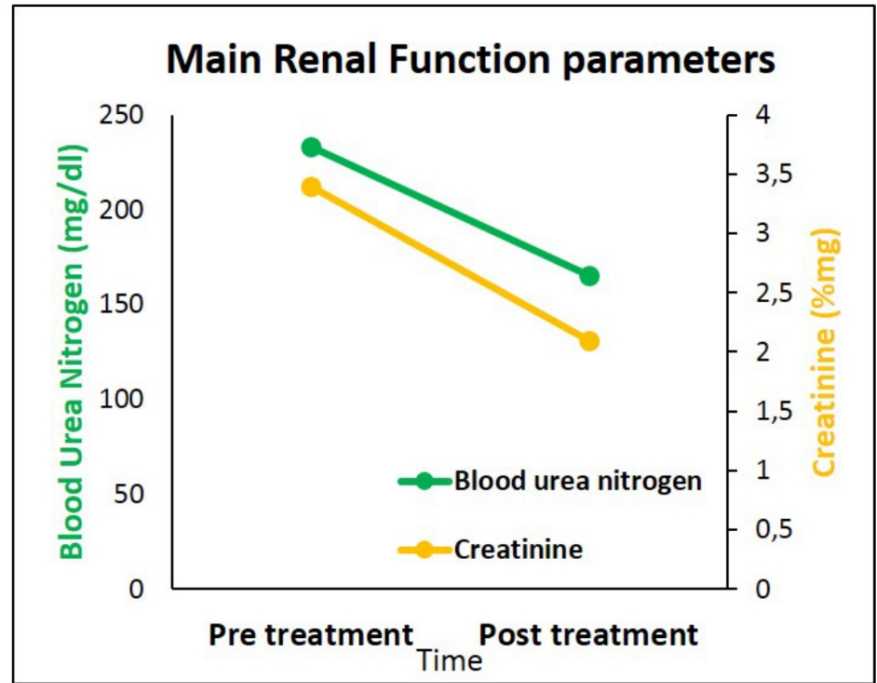
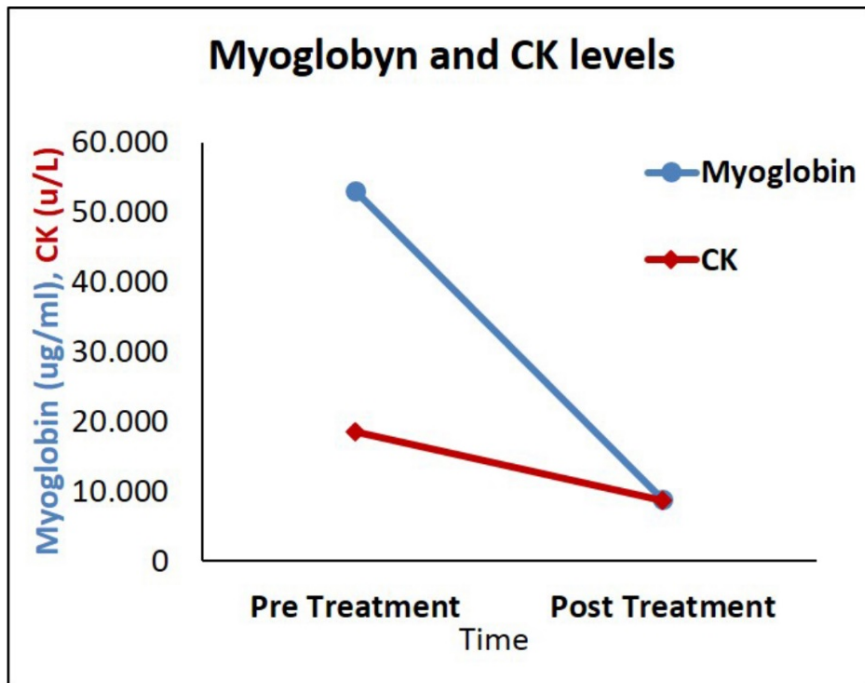


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***crush  
syndrom***

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# Rhabdomyolysis

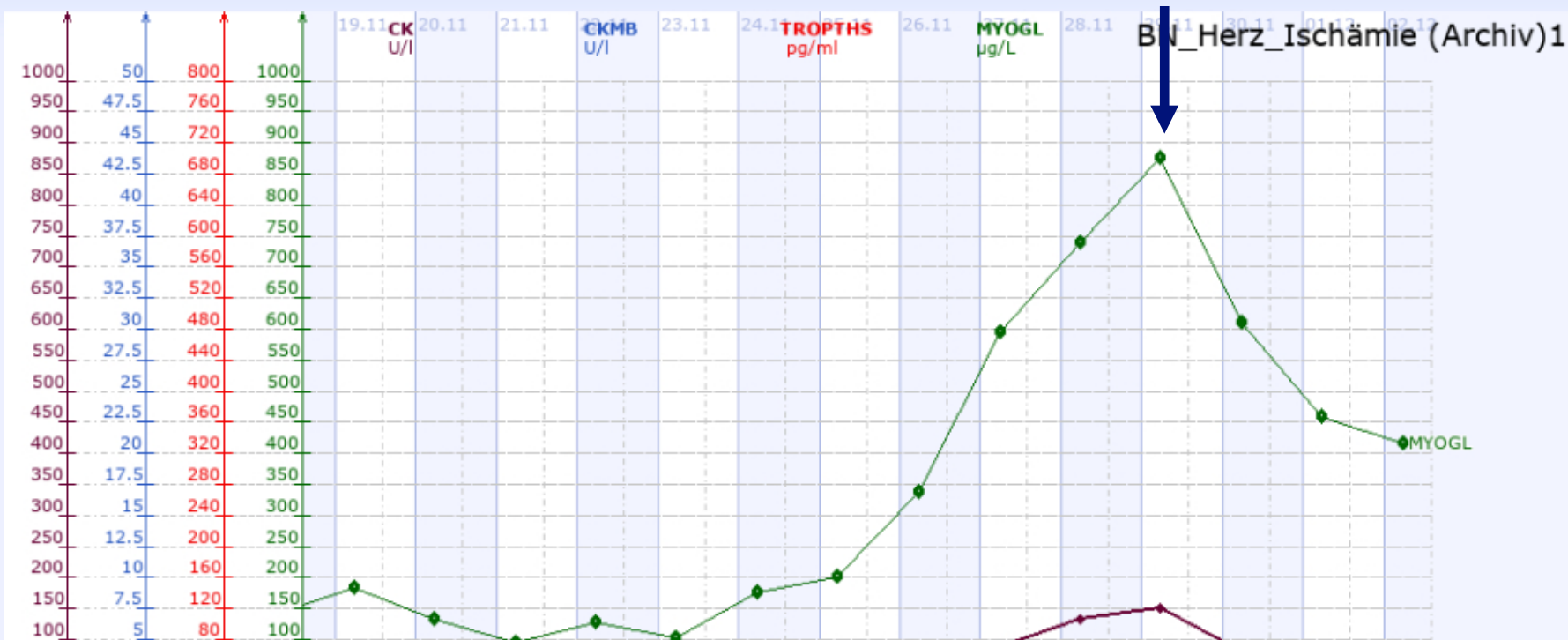


- Improvement in renal function
- High Reduction of circulating myoglobin and CK from the blood in 24H
- ***Discharge from hospital in good conditions after 38 post-surgery.***

Herz\_Ischämie

18.11.2017 14:00 - 02.12.2017 14:00

# Cytosorb



Herz Ischämie

25.11.2017 13:16 - 02.12.2017 13:16

Variablen	Zeit	26.11.17	27.11.2017	28.11.17	29.11.17	30.11.17	01.12.17	02.12.17	
		05:35	05:43	05:56	05:44	05:36	05:32	05:47	
TROPHS[pg/ml]		31.4	29.4	28.2	32.5	33.7	21.5	20.9	22.1
LDH[U/l]		423	508		538				391
CK[U/l]		31	88		132	151	80	37	21
NTproBNP[ng/L]		2720!			6495	5493!	1946	1006!	630!
Myoglobin[µg/L]		336.9	595.7		739.4	875.7	609.3	457.7	415.3

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***probíhající  
studie***

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**Table 1.** Literature summary of clinical reports relating to CytoSorb therapy in peer-reviewed and indexed medical journals

Authors	Disease or surgery	Number of Patients	Study type	Outcome		Control group (yes/no)	Comments
				primary	secondary		
Kogelmann et al. [83]	Sepsis with need for renal replacement therapy	26	Case series	Vasopressor requirement	Hospital mortality and blood lactate levels	No	Decreased catecholamine demand, predicted mortality (APACHE II), and lactate levels. No increased adverse effects
Friesecke et al. [104]	Refractory septic shock	20	Prospective single-center cohort	NE requirement after 6 and 12 h of CytoSorb	SOFA score, resolution of shock, and lactate clearance	No	Decrease in NE requirement and serum lactate. Improved mortality compared to predicted
Schadler et al. [107]	Sepsis or septic shock with ARDS	97	Randomized, controlled multicenter trial	Plasma IL-6 levels	Multiple organ dysfunction score, entilation time, time course of oxygenation	Yes	No significant difference in primary and secondary outcomes
Nemeth et al. [134]	Orthotopic heart transplant	84	Prospective, observational	Hemodynamic stability, vasopressor demand (48 h post-operatively), and post-operative inflammatory response (CRP and PCT)	Volume of postoperative bleeding, rate or reoperation, need for blood products (first 24 h post-operatively), need for postoperative RRT	Yes	Significantly decreased vasopressor demand and less frequent RRT with CytoSorb. No difference in inflammatory response. No increased adverse events
Bernardi et al. [106]	CPB surgery	37	Randomized, single-center controlled trial	Serum IL-1 $\beta$ , IL-6, IL-18, TNF- $\alpha$ , and IL-10 levels during first 5 days post-operatively	Measurement of other inflammatory markers, 30-day mortality	Yes	No reduction in proinflammatory response or mortality following treatment. Strong inter-individual response to CytoSorb, suggesting some patients may have exaggerated inflammatory responses
Träger et al. [136]	CPB surgery complicated by infective endocarditis	39	Case series	Serum IL-6 and IL-8, vasopressor dose, MAP, lactate levels, and need for post-operative support	Postoperative and 24-h post-operative APACHE II score, and intensive care and hospital length of stay	Yes	Reduction in serum IL-6, IL-8, and lactate levels. Improvement in hemodynamic stability following CytoSorb compared to control.
Träger et al. [105]	CPB surgery complicated by SIRS	16	Case series	Not applicable	Not applicable	No	Overall reduction in cytokine levels and improvement in hemodynamic stability and organ function. No increased adverse effects

MAP, mean arterial pressure; NE, norepinephrine; PCT, procalcitonin; CPB, cardiopulmonary bypass.

The International CytoSorb Registry [132] has been established to collect and analyze treatment data from all over the world, and is being independently managed by the Center of Clinical Studies at the University of Jena, Germany. Its goal is to track patient mortality (primary endpoint) and secondary outcomes such as hospital- and intensive care unit-length of stay, vasopressor use, renal replacement therapy, and end-organ function. Multi-center data from 198 patients (68% of whom had sepsis with a mean APACHE II score of 33.1) were analyzed in the registry's third interim analysis and reported in 2017 [133].

Se  
markedly  
therapy  
APACHE  
patients  
Given th  
thus far,  
reporting increases in the future.

**CytoSorb®**

The CytoSorb registry

therapy were  
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none of the  
side effects.  
technology  
cian self-re-

## Adsorbption of Cytokines Early in Septic Shock: the ACCESS Study

### Study Design

<a href="#">Study Type</a> ⓘ:	Observational
<a href="#">Actual Enrollment</a> ⓘ:	20 participants
Observational Model:	Case-Control
Time Perspective:	Prospective
<a href="#">Study Start Date</a> ⓘ:	October 2014
<a href="#">Actual Primary Completion Date</a> ⓘ:	December 2017
<a href="#">Actual Study Completion Date</a> ⓘ:	December 2017

#### Sponsor:

Zsolt Molnár, MD, PhD, DEAA



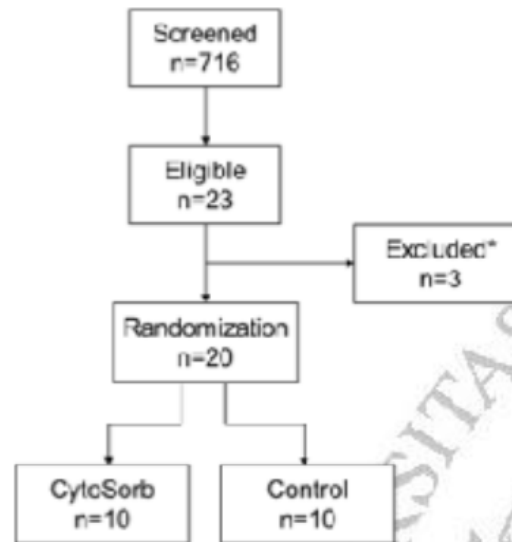


# The ACCESS trial

## Adsorption of Cytokines Early in Septic Shock

Hachwar F et al, *Paper submitted for publication*

**Fig. 1** Flowchart of patient screening and involvement



\*Three were excluded because they died before the randomization

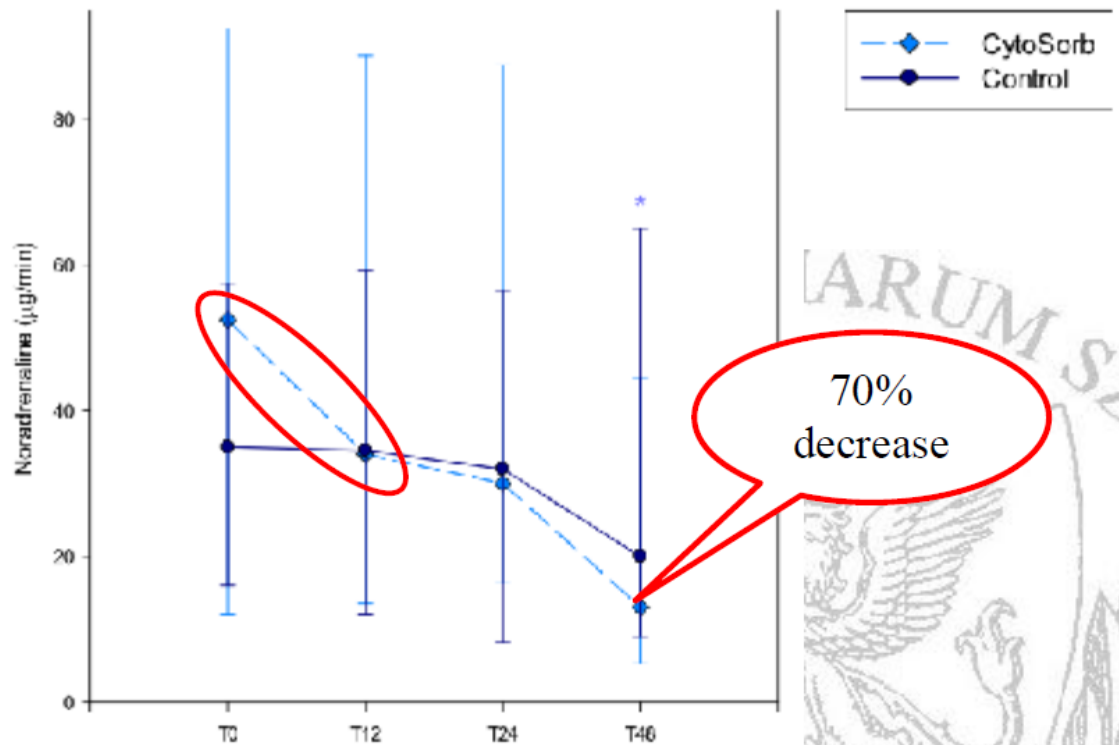


# The ACCESS trial

## Adsorption of Cytokines Early in Septic Shock

Hachwar F et al, Paper submitted for publication

Vasopressor



Data are shown as median and interquartile ranges

\*p<0.05 vs. T<sub>0</sub>



# Multicentre PRCTs

- Homogeneous population, < 24h, after standard resuscitation - **OK**
- IPPV - **OK**
- PCT >3 ng/ml - **higher (~ 15-20)**
- NA  $\geq$  10  $\mu\text{g}/\text{min}$  - **higher (~ 40-50 $\mu\text{g}/\text{min}$ )**
- P
- S
- N

Please join the **CRISS**-trial!  
(**Cytokine Removal In Septic Shock**)  
Protocol will be out shortly

No



***otázky***



# otázky

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- ✓ adsorpce pro- i antiinflamatorních mediátorů
- ✓ validita hodnot zánětlivých parametrů
- ✓ farmakokinetika léků (ATB, ...)?
- ✓ vliv na *outcome* pacientů

selekce cílové skupiny pacientů

# PREDICTING STEROID RESPONSE IN SEPTIC SHOCK

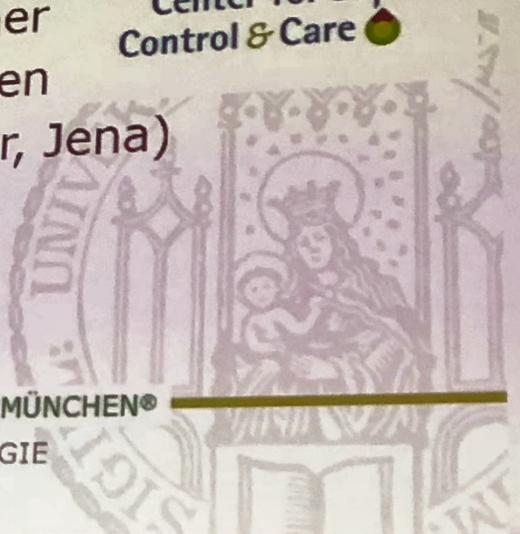


- Berlin cohort of CORTICUS (Didier Keh, Berlin)
  - 83 patients (60 survivors, 23 non-survivors)
  - 120 variables at baseline including clinical measures, organ failure scores, leukocyte counts and circulating cytokine levels: Interleukin-(IL)-6, 8, 10, 12 p70, IFN- $\gamma$ , TNF- $\alpha$ , TNF-receptor I (sTNF-RI), FAS (all BD), and E-selectin (R&D)



- Decision trees were applied to those treated with either hydrocortisone (HC) or placebo to discriminate between 28-day-survivors and non-survivors (R König, M Bauer, Jena)

Center for Sepsis  
Control & Care

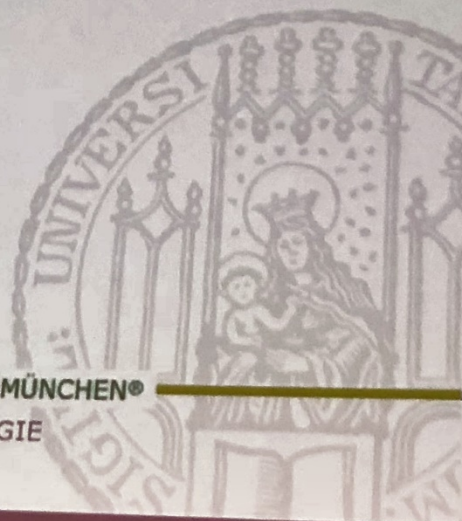
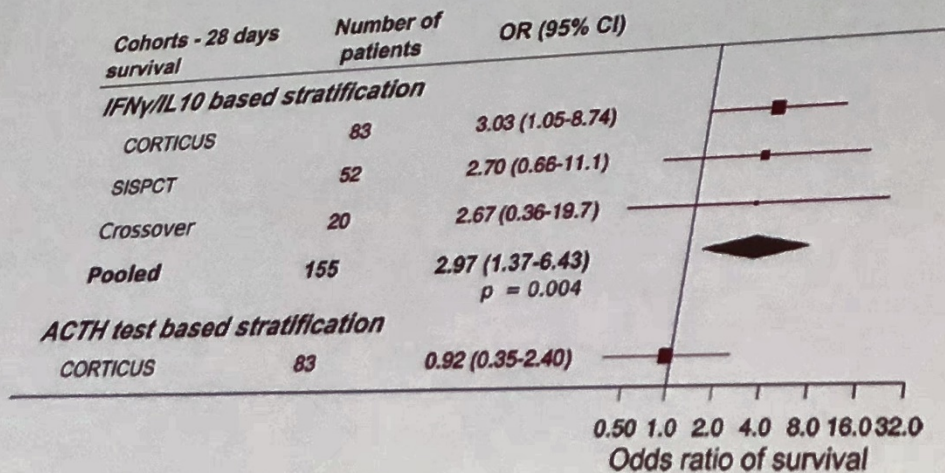


all or some?

Steroids for all or some? Josef Briegel

## VALIDATION IN SUBGROUP OF SISPECT

- Munich cohort of SISPECT (Josef Briegel, Munich)
  - 112 patients (selenium: n=59, placebo: n=53)
  - 52 patients of placebo group (35 steroid, 17 no steroids)



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 KLINIK FÜR ANÄSTHESIOLOGIE  
 MUNICH GERMANY

some?

Steroids for all or some? Josef Briegel

## SUMMARY AND HYPOTHESIS

- Preliminary data from the CORTICUS-subgroup of Berlin (D. Keh) suggest that the response to hydrocortisone in septic shock can be predicted by IFN $\gamma$ /IL10 ratio at baseline
- High IFN $\gamma$ /IL10 was predictive for better survival in patients not treated with hydrocortisone (R. König, M. Bauer)
- Stratification of steroid treatment by assessment of the immune status may increase survival of patients with septic shock
- This hypothesis has to be proven in controlled trials







...děkuji Vám za pozornost