Léčba septického šoku

- nové strategie na obzoru?

OA Dr. Stibor B.

ICU, Landesklinikum Baden bei Wien, Austria

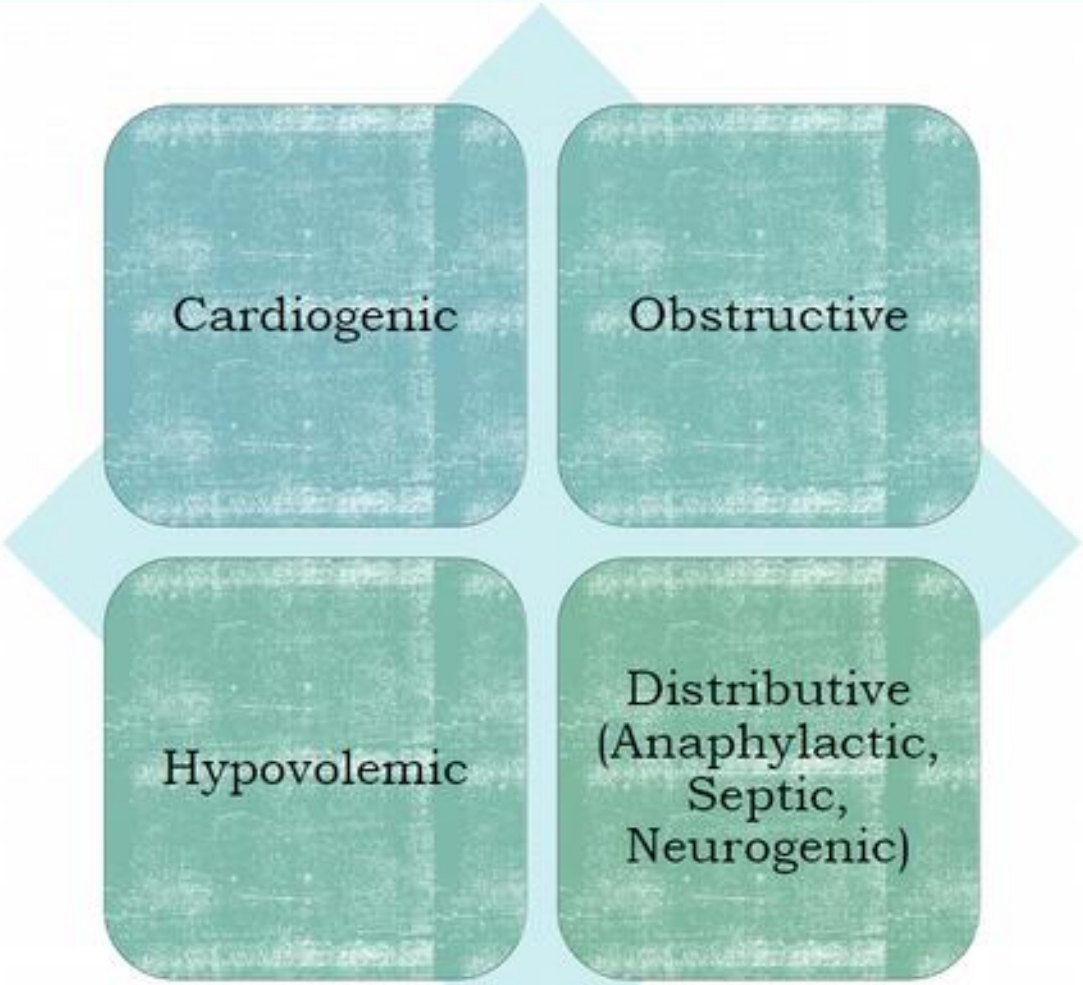
no conflict of interest

OA Dr. Stibor B.

ICU, Landesklinikum Baden bei Wien, Austria

přehled

1. septický šok
2. léčebné strategie
3. selepressin
4. methylene blue
5. angiotensin II
6. cytokine removal



Source: Taeb AM et al. *Nutr Clin Prac* 2017;32(3):296-308.

What is Shock?

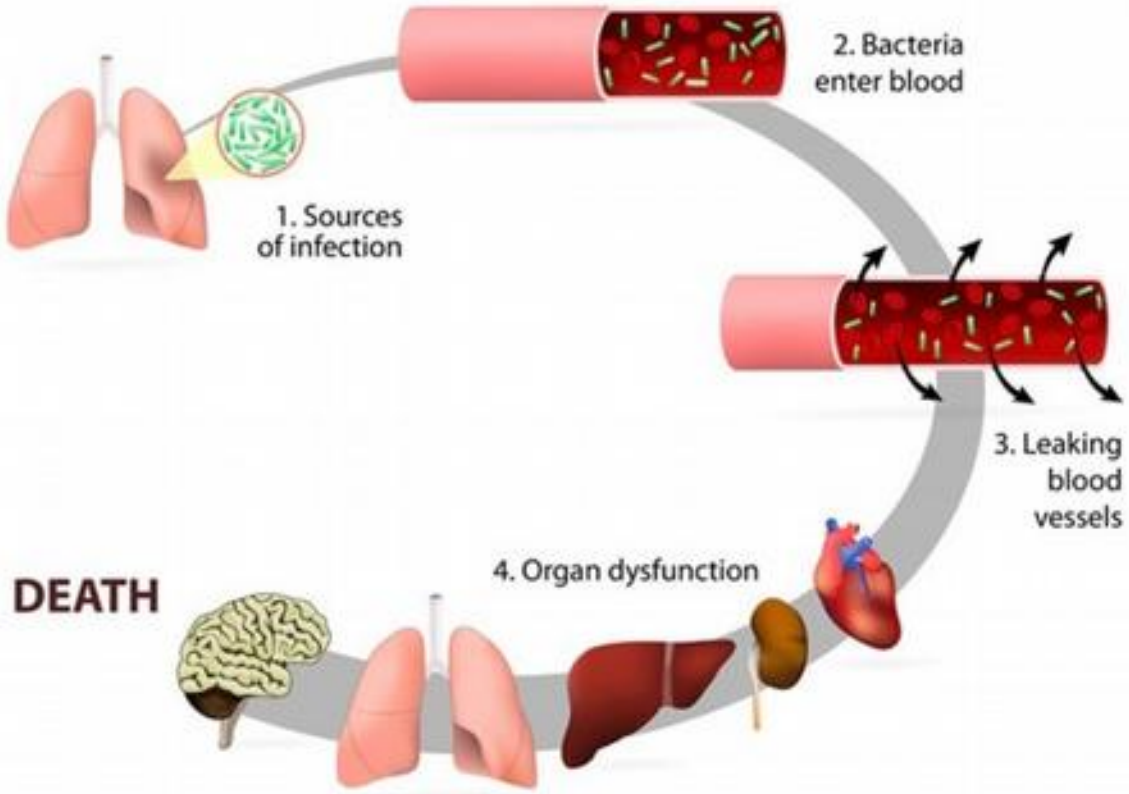
Any state in which oxygen delivery to end organs is insufficient to sustain normal metabolic processes

sepsis

- Mortality rates in the United States are 15 to 25% for patients with sepsis, and about 40% for those who progress to septic shock
- Sepsis represents 30% of ICU admissions globally, and septic shock represents 62% of shock cases that require vasopressor therapy
- The first set of Surviving Sepsis Campaign Guidelines came out in 2004, then were revised in 2008, 2012, and finally 2016

J Crit Care 2017;40:229-42

Septic Shock



Sources: Moranville MP, et al. *J Pharm Pract* 2011;24(1):44-60.
Remick DG. *Am J Pathol* 2007;170(5):1435–1444.

Pathophysiology

- Alterations to the endothelium occur
  - Increased leukocyte adhesion
  - Shift to a hypercoagulable state
  - Vasodilation
  - Loss of barrier function


Beatmung
19.05.2018 06:00 - 02.06.2018 06:00
120 100 10 600 40
111 90 9 540 36
102 80 8 480 32
93 70 7 420 28
84 60 6 360 24
75 50 5 300 20
66 40 4 240 16
57 30 3 180 12
48 20 2 120 8
39 10 1 60 4
30 0 0 0 0
06:00
BN Resp. Messung 3 (Archiv)
cmH2O
Ppeak(m)
#PCO2I-A
OxInd
PEEP(m)
#LAKiI-A
29.05
30.05
31.05
01.06
06:00
06:00
06:00
06:00

Infektionsparameter

23.05.2018 06:00 - 02.06.2018 06:00

Variablen \ Zeit	29.05.18 15:17	30.05.18 05:38	31.05.18 05:51	01.06.18 05:26	02.06.18 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

therapeutic strategy

Lactate

- Measure lactate level
- Remeasure if initial lactate is > 2 mmol/L

Cultures

- Obtain blood cultures prior to administration of antibiotics

Antibiotics

- Administer broad spectrum antibiotics

Fluids

- Begin rapid administration of 30 mL/kg crystalloid for hypotension or lactate $\geq$ 4 mmol/L

Pressors

- Apply vasopressors if patient is hypotensive during or after fluid resuscitation to maintain MAP $\geq$ 65 mmHg

Treatment: Sepsis Bundles

- Previous 3-hour and 6-hour bundles were combined into the hour-1 bundle

Source: Levy M, et al. *Crit Care Med* 2018;46(6):997-1000.

Surviving Sepsis Campaign

Fluid Therapy

- **We recommend crystalloids as the fluid of choice for initial resuscitation and subsequent intravascular volume replacement in patients with sepsis and septic shock**

(Strong recommendation, moderate quality of evidence).

- **We suggest using albumin in addition to crystalloids when patients require substantial amounts of crystalloids**

(weak recommendation, low quality of evidence).

Cave!

Krystaloidy

	Na	Cl	K	Ca	Mg	Acetat	Laktat	Malat
NaCl	154	154	--	--	--	--	--	--
Ringer-Lactat	131	112	5,4	1,8	--	--	28	--
Ringer-Lösung	147	156	4,0	2,2	--	--	--	--
Elomel OP	**100**	90	**18**	2,0	3,0	38	--	--
Elomel Isoton	140	108	5,0	2,5	1,5	45	--	--
Elomel Basis	**45**	**65**	**25**	--	2,5	--	--	--
KADC	**90**	**65**	**25**	1,0	1,5	--	--	23
Aqua	--	--	--	--	--	--	--	--

Surviving Sepsis Campaign

Vasoactive agents

- **We recommend norepinephrine as the first choice vasopressor**

(strong recommendation, moderate quality of evidence).

- **We suggest adding either vasopressin (up to 0.03 U/min) or epinephrine to norepinephrine with the intent of raising MAP to target, or adding vasopressin (up to 0.03 U/min) to decrease norepinephrine dosage.**

(weak recommendation, low quality of evidence)

Vasopressors

Advantages

- Support during early resuscitation
- Assist therapeutically for those failing early resuscitation

Disadvantages

- Worsen already inadequate organ perfusion and perfusion in the periphery
- Increase left ventricular work to an unsustainable degree, worsening cardiac output and end-organ perfusion

Sources: Overgaard CB, et al. *Circulation* 2008;118:1047-1056.
Bissell BD, et al. *Ann Pharmacother* 2018;52(9):920-7.

new

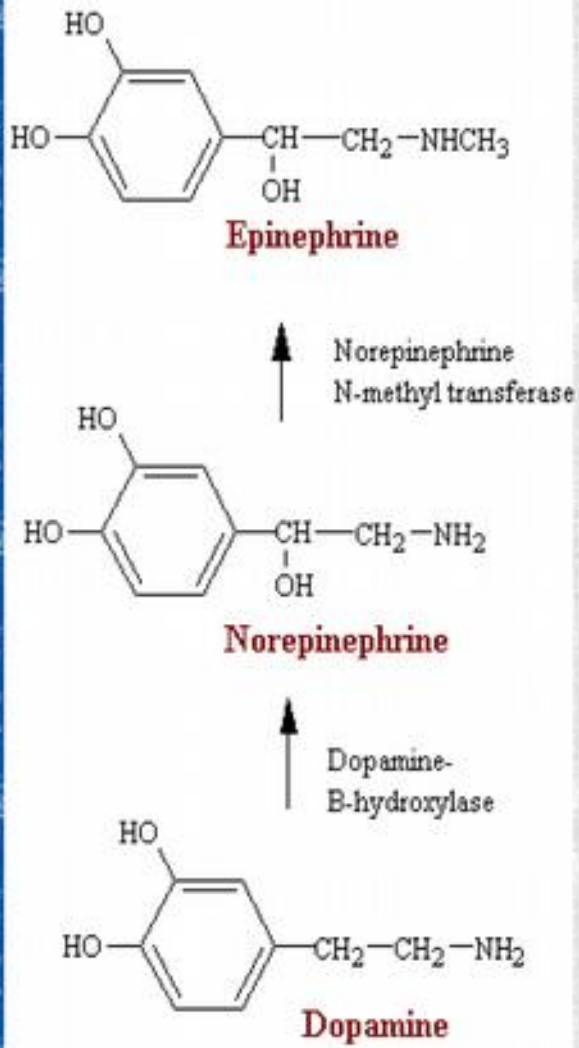
strategies?

new strategies in septic schock

- selepressin
- α_2-agonists
- angiotensin II
- methylene blue
- cytokine removal
- ...
- ...
- ...

???

WHY DO WE NEED ANOTHER VASOPRESSOR?



- Human body has three endogenous vasopressors
  - Catecholamines
  - Non-Catecholamines
    - Vasopressin
    - Angiotensin II
- Importance of combination therapy, different mechanisms
  - Epinephrine to norepinephrine → same receptors

Source: Aafar P, et al. *Crit Care Med* (2014) 42(8):1961-63.

selepressin

selepressin

- high selective vasopressin **V1a** receptor agonist
- potentially mitigating sepsis-induced vasodilatation, vascular leakage, and tissue edema
- no V1b or V2 mediated effects
  - increased procoagulant factors
  - salt and water retention
  - nitric oxide release
  - corticosteroid stimulation

Research

JAMA October 2,2019

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Effect of Selepressin vs Placebo on Ventilator- and Vasopressor-Free Days in Patients With Septic Shock
The SEPSIS-ACT Randomized Clinical Trial

Pierre-Francois Laterre, MD; Scott M. Berry, PhD; Allan Blemings, MS; Jan E. Carlsen, MD; Bruno François, MD; Todd Graves, PhD; Karsten Jacobsen, MD; Roger J. Lewis, MD, PhD; Steven M. Opal, MD; Anders Perner, MD, PhD; Peter Pickkers, MD, PhD; James A. Russell, MD; Nis A. Windeløv, MD, PhD; Donald M. Yealy, MD; Pierre Asfar, MD; Morten H. Bestle, MD, PhD; Grégoire Muller, MD; Cédric Bruel, MD; Noëlle Brulé, MD; Johan Decruyenaere, MD; Alain-Michel Dive, MD, PhD; Thierry Dugernier, MD, PhD; Kenneth Krell, MD; Jean-Yves Lefrant, MD; Bruno Megarbane, MD, PhD; Emmanuelle Mercier, MD; Jean-Paul Mira, MD, PhD; Jean-Pierre Quenot, MD; Bodil Steen Rasmussen, MD, PhD; Hans-Christian Thorsen-Meyer, MD; Margot Vander Laenen, MD; Marianne Lauridsen Vang, MD; Philippe Vignon, MD, PhD; Isabelle Vinatier, MD; Sine Wichmann, MD, PhD; Xavier Wittebole, MD; Anne Louise Kjølbye, MS, PhD; Derek C. Angus, MD, MPH; for the SEPSIS-ACT Investigators

- **>800 pts** in 63 hospitals
  (Belgium, Denmark, France, US, Netherlands)
- July 2015 to August 2017
  (follow-up completed by May **2018**)

Research

JAMA October 2,2019

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Effect of Selepressin vs Placebo on Ventilator- and Vasopressor-Free Days in Patients With Septic Shock

The SEPSIS-ACT Randomized Clinical Trial

- **primary** endpoints:
  ventilator- and vasopressor-free days within 30 days
- key **secondary** endpoints:
  90-day mortality
  kidney replacement therapy-free days
  ICU-free days

Research

JAMA October 2,2019

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Effect of Selepressin vs Placebo on Ventilator- and Vasopressor-Free Days in Patients With Septic Shock

The SEPSIS-ACT Randomized Clinical Trial

- stopped for **futility** at the end of part 1
- **no** significant **differences**
  in the primary endpoint or key secondary endpoints

methylene blue

methylene blue

- $C_{16}H_{18}N_3SCl$ *(methylthioninium chloride)*
- first prepared in 1876 by Heinrich Caro
- is on the WHO's List of **Essential Medicines** *(the most effective and safe medicines needed in a health system)*

methylene blue

1 Medical uses
- 1.1 Methemoglobinemia
- 1.2 Combined with light
- 1.3 Urinary tract infection
- 1.4 Cyanide poisoning
- 1.5 Dye or stain
- 1.6 Placebo
- 1.7 Ifosfamide toxicity
- 1.8 Shock

methylene blue

- ✓ působí intracelulárně
- ✓ inhibuje inducibilní NO syntetázu
  přímo inhibuje NO
  inhibuje guanylátcyklázu
- ✓ zmírňuje vasodilataci vyvolanou NO

CME

CARDIOTHORACIC ANESTHESIOLOGY:

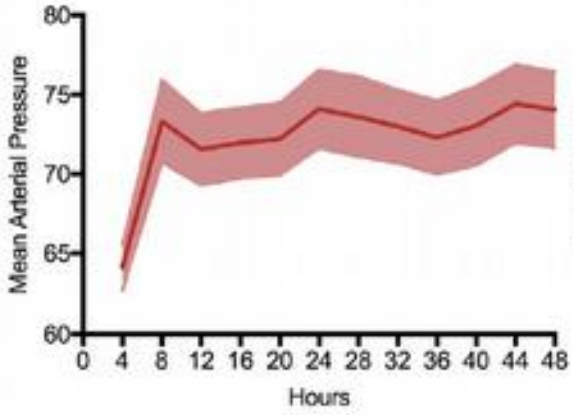
The Annals of Thoracic Surgery CME Program is located online at http://www.annalsthoracicsurgery.org/cme/home. To take the CME activity related to this article, you must have either an STS member or an individual non-member subscription to the journal.

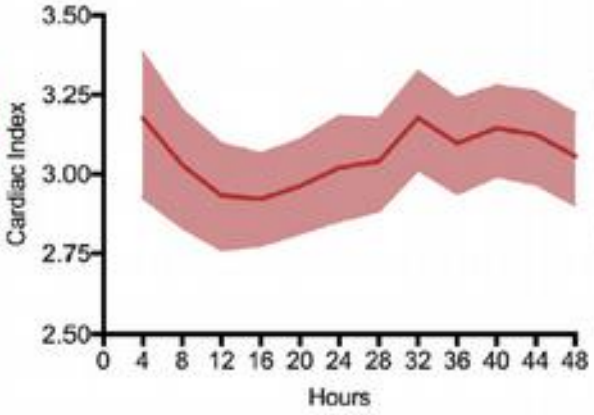
Methylene Blue for Vasoplegic Syndrome After Cardiac Operation: Early Administration Improves Survival

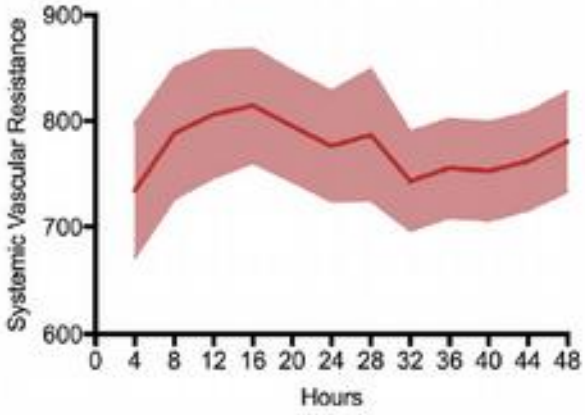
J. Hunter Mehaffey, MD, Lily E. Johnston, MD, MPH, Robert B. Hawkins, MD, Eric J. Charles, MD, Leora Yarboro, MD, John A. Kern, MD, Gorav Ailawadi, MD, Irving L. Kron, MD, and Ravi K. Ghanta, MD

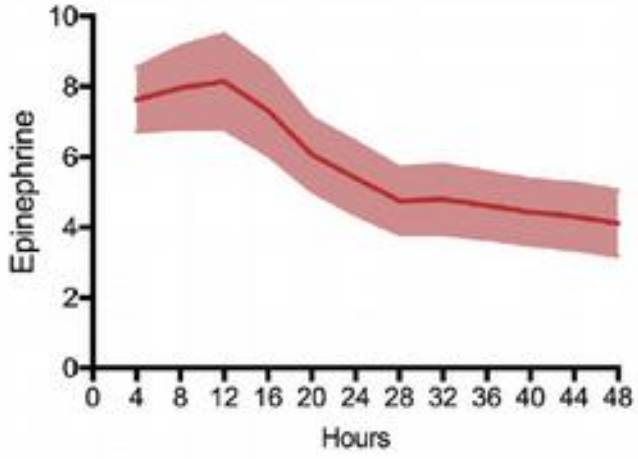
Division of Thoracic and Cardiovascular Surgery, Department of Surgery, University of Virginia, Charlottesville, Virginia

- ✓ Jan 1, 2011 to Jun 30, 2016
- ✓ in 118 patients with vasoplegic syndrome after CPB (3,3% of all)
- ✓ bolus dose of 2 mg/kg intravenous MB followed by 12-hour infusion at 0.5 mg/kg/h









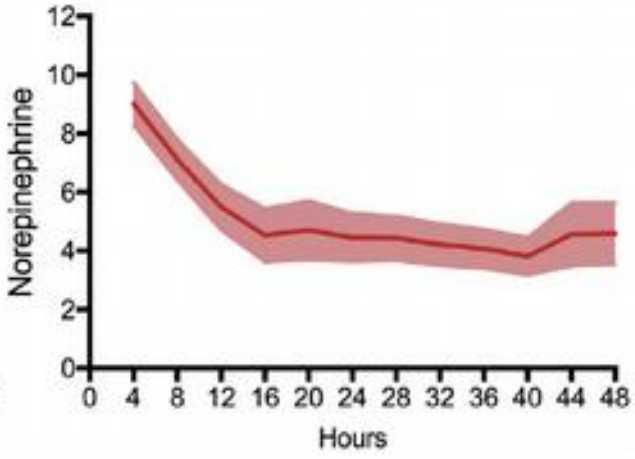


Fig 2. Vasopressor requirements (epinephrine and norepinephrine) after methylene blue administration. Graphs are means and 95% confidence intervals.

CME

CARDIOTHORACIC ANESTHESIOLOGY:

The Annals of Thoracic Surgery CME Program is located online at http://www.annalsthoracicsurgery.org/cme/home. To take the CME activity related to this article, you must have either an STS member or an individual non-member subscription to the journal.

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Division of Thoracic and Cardiovascular Surgery, Department of Surgery, University of Virginia, Charlottesville, Virginia

Coclusions:

Early (OR, 40.7%) versus late (ICU, 59.3%) administration of MB was associated with **significantly reduced** operative **mortality** rate (**10.4%** versus **28.6%**, p=0.018) and risk-adjusted major adverse events (odd ratio 0.35, p=0.037).

Methylene blue in the treatment of vasodilatory shock: a Meta–analysis

Wang Yi, Li Wenzhe, Yu Xiangyou

RESULTS:

- totally 269 relative articles were collected
- finally 6 RCTs with 214 patients were enrolled (108 in methylene blue group, and 106 in control group)
- methylene blue could significantly improve MAP ($P < 0.0001$)
- reduce the serum Lac levels ($P = 0.02$)
- mortality was decreased without statistical difference

CONCLUSIONS:

Methylene blue could significantly increase MAP in the patients with refractory hypotension caused by vascular paralysis during the course of vasodilatory shock, decrease the Lac levels, and does not increase the risk of death.

Therefore, methylene blue should be a potential and safe vasoconstrictor

Review

A systematic analysis of methylene blue for drug-induced shock

Brandon J. Warrick, Anita Paula Tataru & Susan Smolinske

Pages 547-555 | Received 02 Dec 2015, Accepted 14 Apr 2016, Published online: 19 May 2016

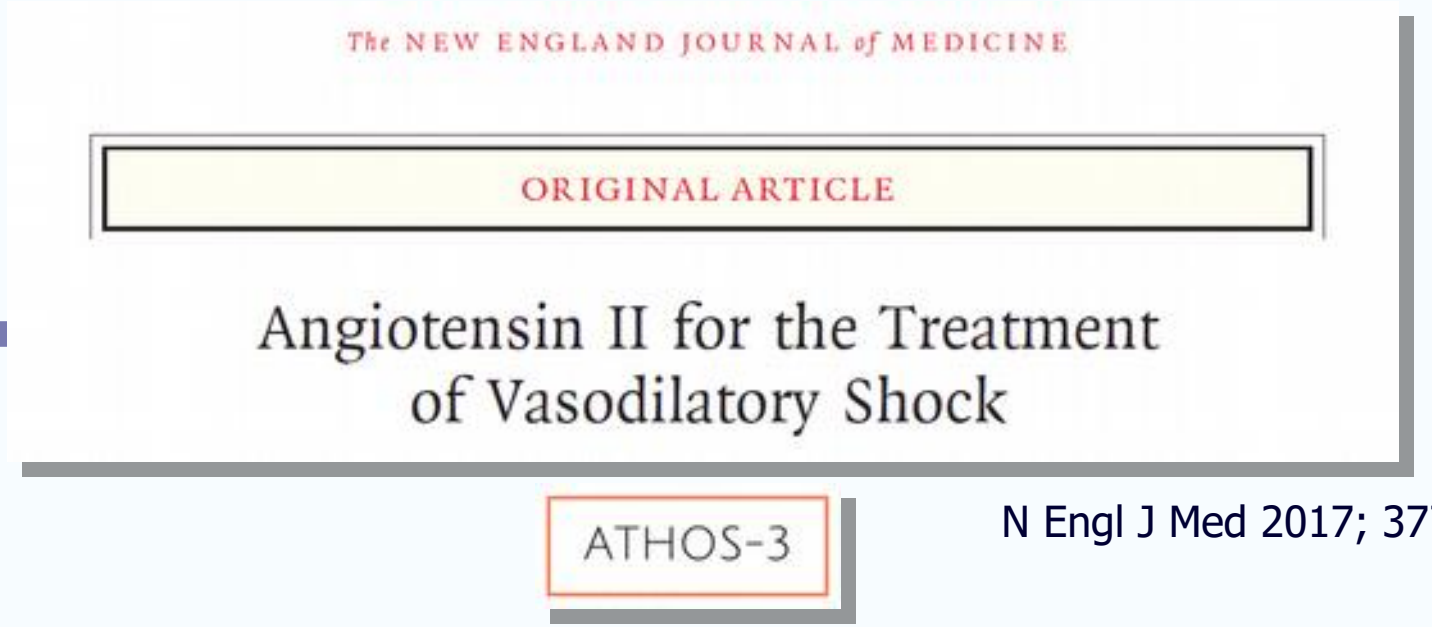
Clin Toxic 2016;54:547-55

CONCLUSIONS:

While there are compelling cases describing an improved hemodynamic status following MB, there are also several cases without observed change.

Currently, there is not enough evidence available to recommend the routine administration of MB in refractory pharmacologically induced shock.

angiotensin II



N Engl J Med 2017; 377:419-430

- multinational, double-blind, randomized, controlled trial
- 321 patients
- primary end points:
  - response of MAP at hour 3*
  - changes in the cardiovascular and the total SOFA score

* with response defined as a MAP of **75 mmHg** or higher or an increase in MAP from baseline of at least **10 mmHg**, without an increase in the dose of background vasopressors

The NEW ENGLAND JOURNAL of MEDICINE

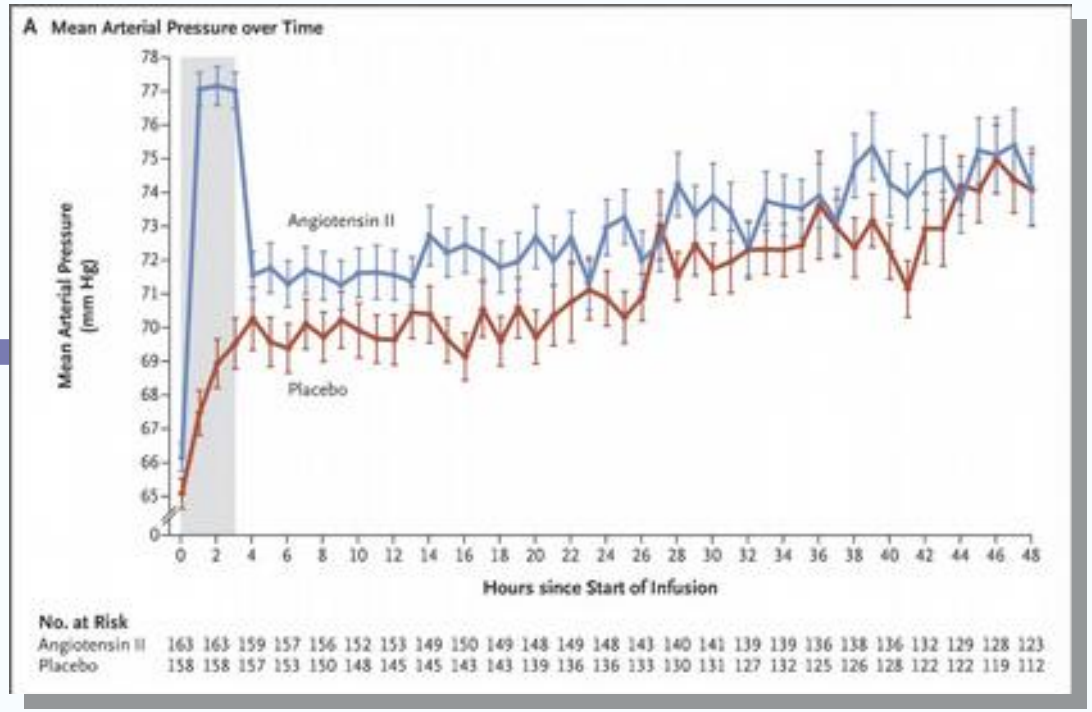
ORIGINAL ARTICLE

Angiotensin II for the Treatment of Vasodilatory Shock

N Engl J Med 2017; 377:419-430

METHODS

We randomly assigned patients with vasodilatory shock who were receiving more than 0.2 μg of norepinephrine per kilogram of body weight per minute or the equivalent dose of another vasopressor to receive infusions of either angiotensin II or placebo. The primary end point was a response with respect to mean arterial pressure at hour 3 after the start of infusion, with response defined as an increase from baseline of at least 10 mm Hg or an increase to at least 75 mm Hg, without an increase in the dose of background vasopressors.



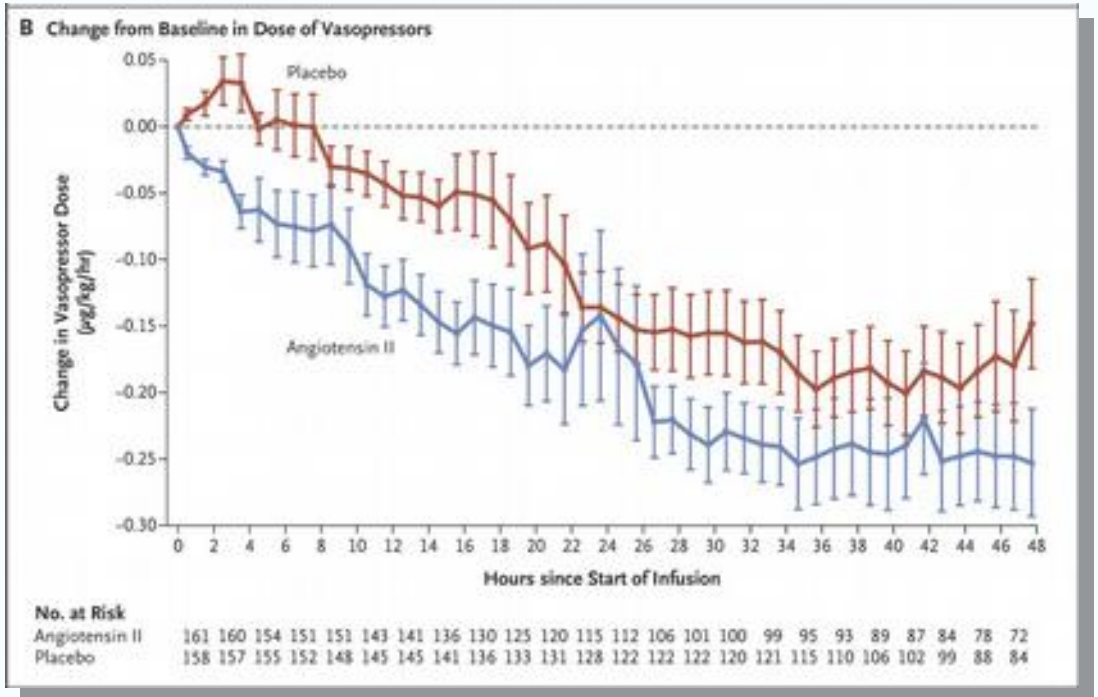
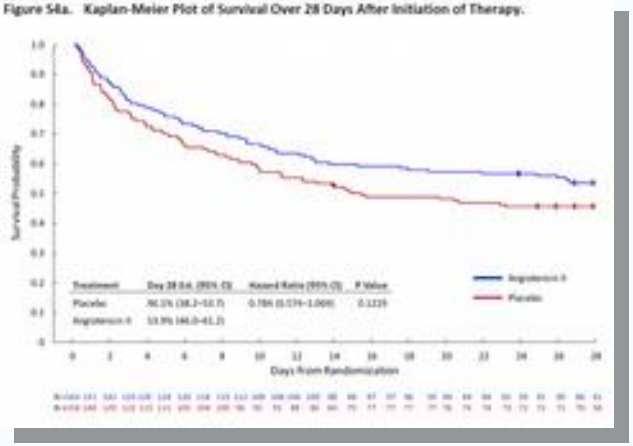
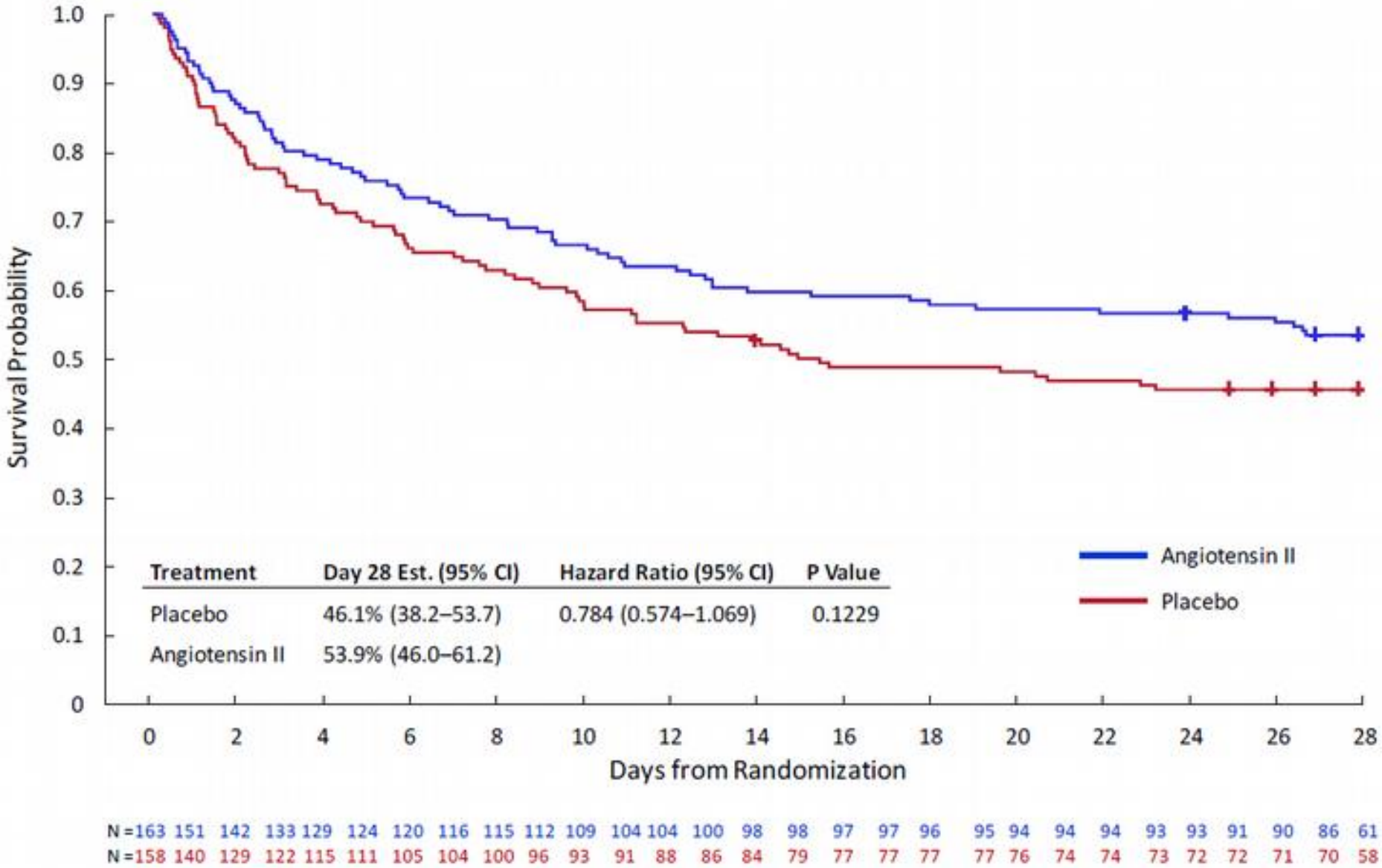


Figure 5Ba. Kaplan-Meier Plot of Survival Over 28 Days After Initiation of Therapy.

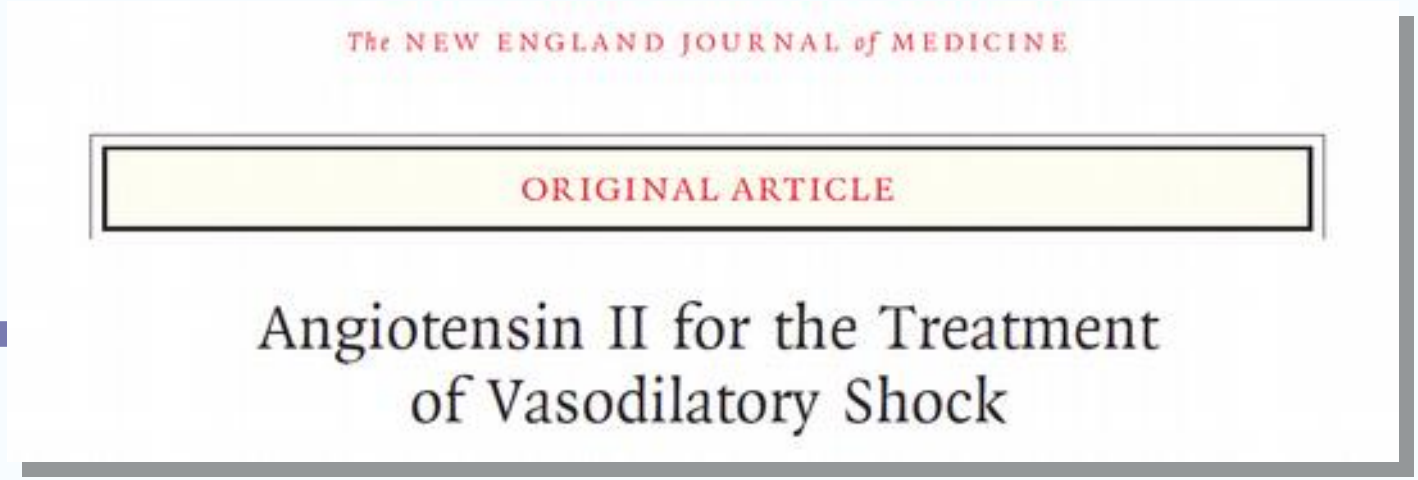


A Mean Arterial Pressure over Time

Figure S4a. Kaplan-Meier Plot of Survival Over 28 Days After Initiation of Therapy.



Placebo 158 157 155 152 148 145 145 141 136 133 131 128 122 122 122 120 121 115 110 106 102 99 88 84



N Engl J Med 2017; 377:419-430

In patients with refractory vasodilatory shock does the addition of angiotensin II improve blood pressure?

Authors' Conclusions:

- Angiotensin II effectively increased blood pressure in patients with vasodilatory shock that did not respond to high doses of conventional vasopressors

Reality:

- trial is likely to make angiotensin II available (the trial was conducted in consultation with the FDA)
- Angiotensin II is coming to an ICU near you

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Angiotensin II for the Treatment of Vasodilatory Shock

- Giapreza®
- **2017** (December) approved from FDA
- **2019** (August) approved from EMA
- 3.500 €/day

cytokine removal therapy

synonyma

- cytokine adsorption therapy
- cytokine reduction
- extracorporeal cytokine adsorption
- haemoadsorption
- cytokine removal therapy

Cytosorb

> 31.000 použití celosvětově (cca 5.000 kardiochirurgie)

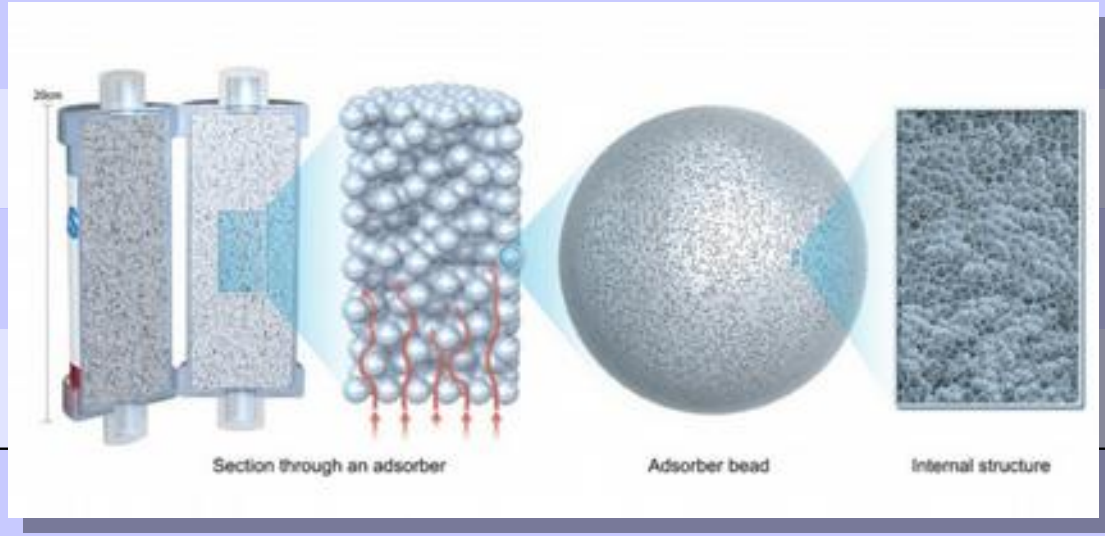
> 600 ICUs ve více jak 43 zemích

Landesklinikum Baden: > 400 použití (od roku 2015)

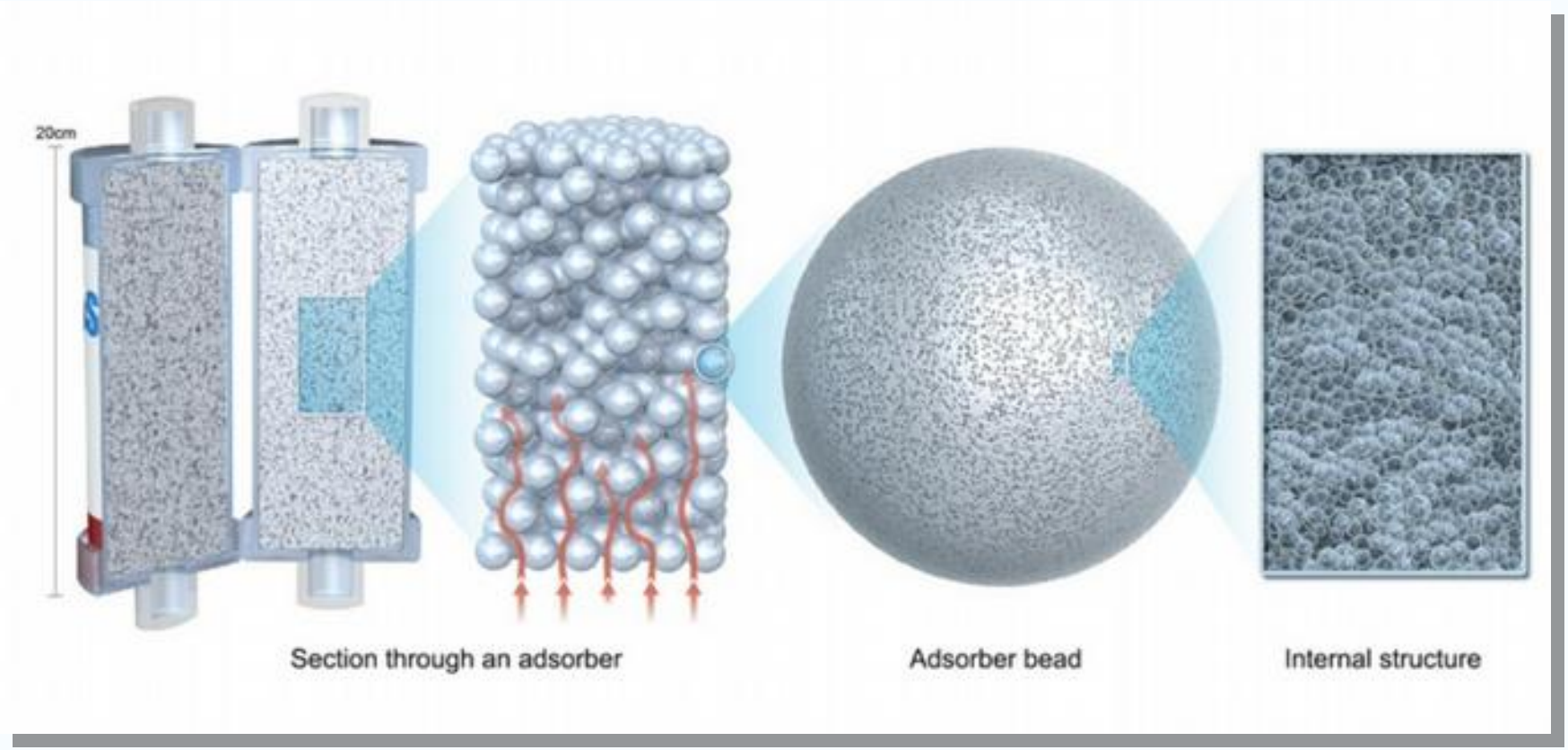
mimotělní oběh (hemodialýza, kardiochirurgie)

indikace

- kardiochirurgie
- septický šok
- rhabdomyolýza
- hepatální selhání
- digitoxin intoxikace



Cytosorb filtr



povrch >40.000 m2 (cca 5 fotbalových hřišť)


post haemofilter
CytoSorb


toSorb

indikace

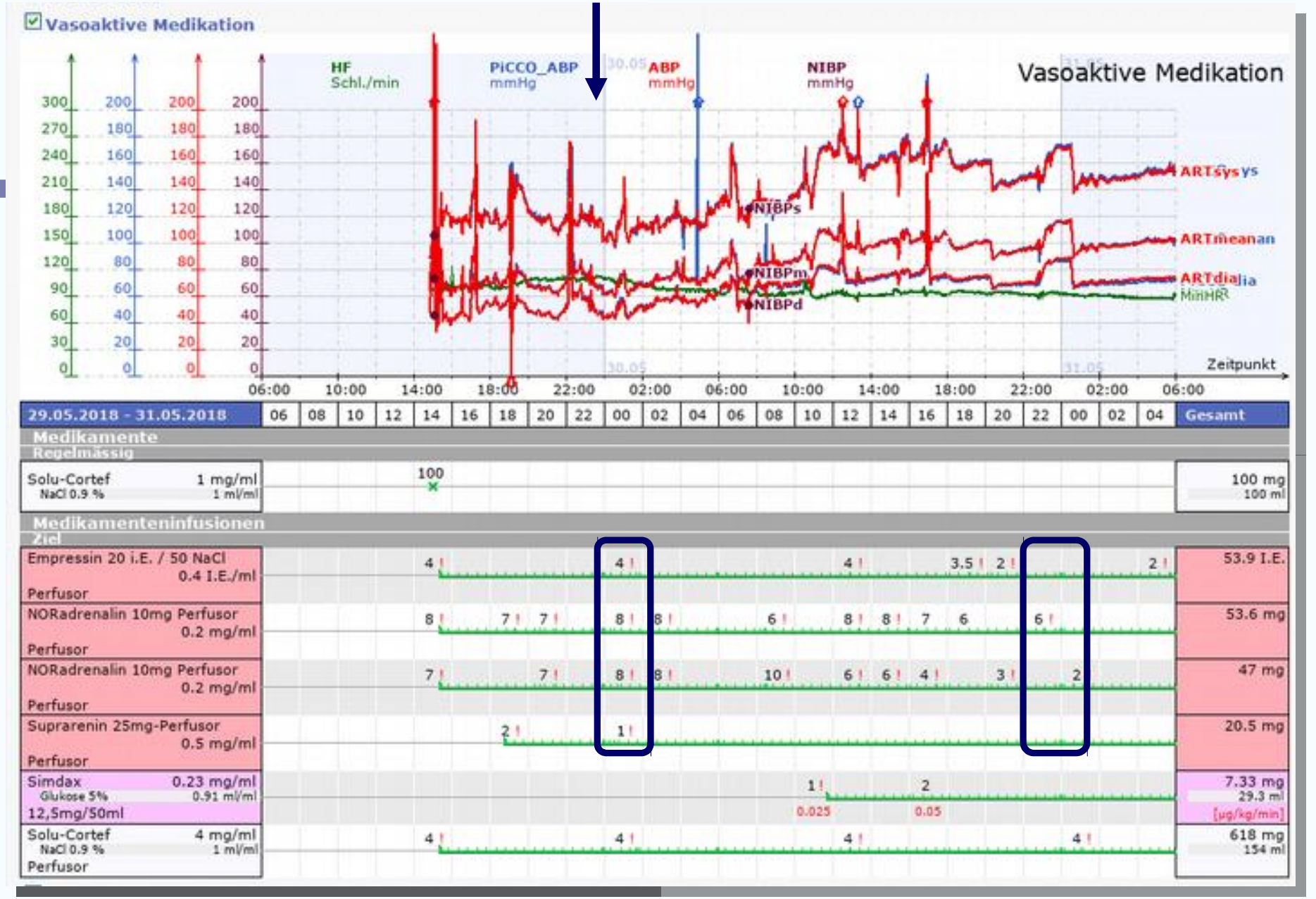
- sepse a septický šok
- kardiochirurgické operace (odpojení od MO)
- rhabdomyolýza *(crush syndrom)*
- SIRS (st.p. CPR, akutní pankreatitida)
- intoxikace (lékové či jiné)
- *many others …*

obecně přijímané indikace neexistují

efekt terapie

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

Cytosorb


Vasoaktive Medikation
HF
Schl./min
PiCCO_ABP
mmHg
ABP
mmHg
NIBP
mmHg
Vasoaktive Medikation
ARTsys
NIBPs
ARTmean
NIBPm
ARTdia
NIBPd
MinHR
Zeitpunkt
06:00 10:00 14:00 18:00 22:00 02:00 06:00 10:00 14:00 18:00 22:00 02:00 06:00
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
Medikamente
Regelmässig
Solu-Cortef 1 mg/ml
NaCl 0.9 % 1 ml/ml
100 mg
100 ml
Medikamenteninfusionen
Ziel
Empressin 20 i.E. / 50 NaCl
0.4 I.E./ml
Perfusor
53.9 I.E.
NORadrenalin 10mg Perfusor
0.2 mg/ml
Perfusor
53.6 mg
NORadrenalin 10mg Perfusor
0.2 mg/ml
Perfusor
47 mg
Suprarenin 25mg-Perfusor
0.5 mg/ml
Perfusor
20.5 mg
Simdax 0.23 mg/ml
Glukose 5% 0.91 ml/ml
12,5mg/50ml
0.025
0.05
7.33 mg
29.3 ml
[µg/kg/min]
Solu-Cortef 4 mg/ml
NaCl 0.9 % 1 ml/ml
Perfusor
618 mg
154 ml

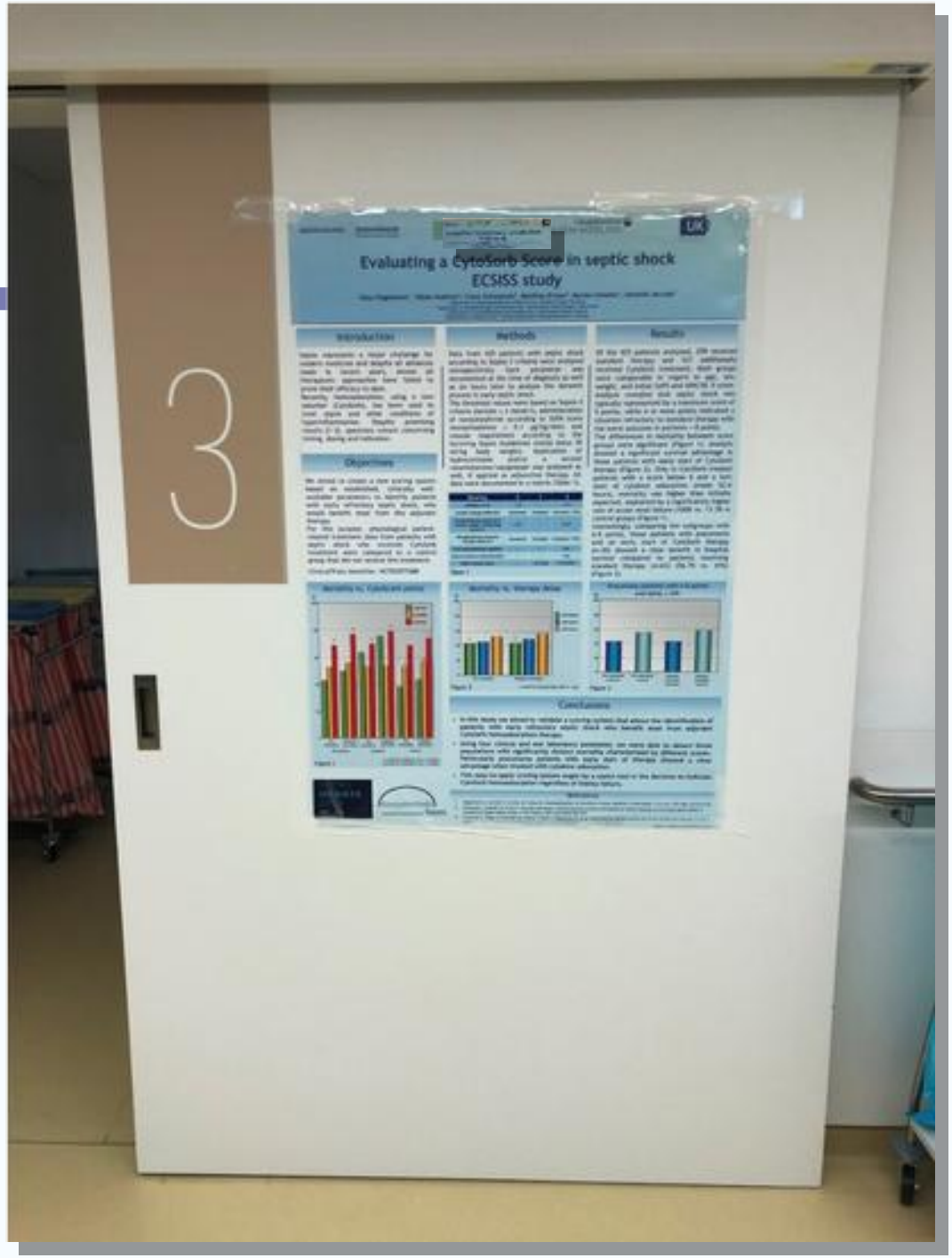

Vasoaktive Medikation
HF
Schl./min
PiCCO_ABP
mmHg
ABP
mmHg
NIBP
mmHg
Vasoaktive Medikation
NIBPs
NIBPm
NIBPd
ARTsys
ARTmean
ARTdia
MinHR
Zeitpunkt
06:00 10:00 14:00 18:00 22:00 02:00 06:00 10:00 14:00 18:00 22:00 02:00 06:00
31.05.2018 - 02.06.2018
06 08 10 12 14 16 18 20 22 00 02 04 06 08 10 12 14 16 18 20 22 00 02 04
Gesamt
Medikamenteninfusionen
Ziel
Empressin 20 i.E. / 50 NaCl
0.4 I.E./ml
Perfusor
38.4 I.E.
NORadrenalin 10mg Perfusor
0.2 mg/ml
Perfusor
34.8 mg
NORadrenalin 10mg Perfusor
0.2 mg/ml
Perfusor
27 mg
Suprarenin 25mg-Perfusor
0.5 mg/ml
Perfusor
4.3 mg
Simdax
0.23 mg/ml
Glukose 5%
0.91 ml/ml
12,5mg/50ml
12 mg
47.9 ml
[µg/kg/min]
Solu-Cortef
4 mg/ml
NaCl 0.9 %
1 ml/ml
Perfusor
767 mg
192 ml

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


3
Evaluating a CytoSorb Score in septic shock
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Introduction
Objectives
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Evaluating a CytoSorb Score in septic shock
ECSISS study

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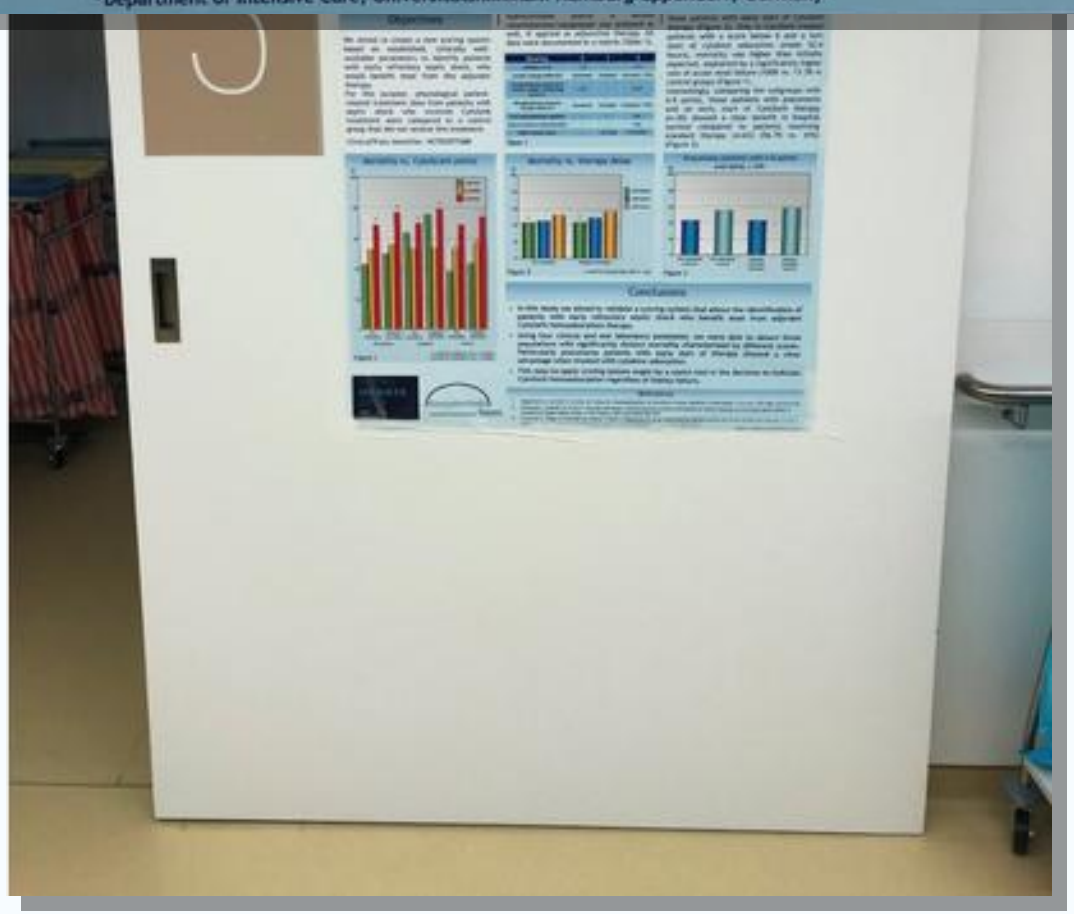
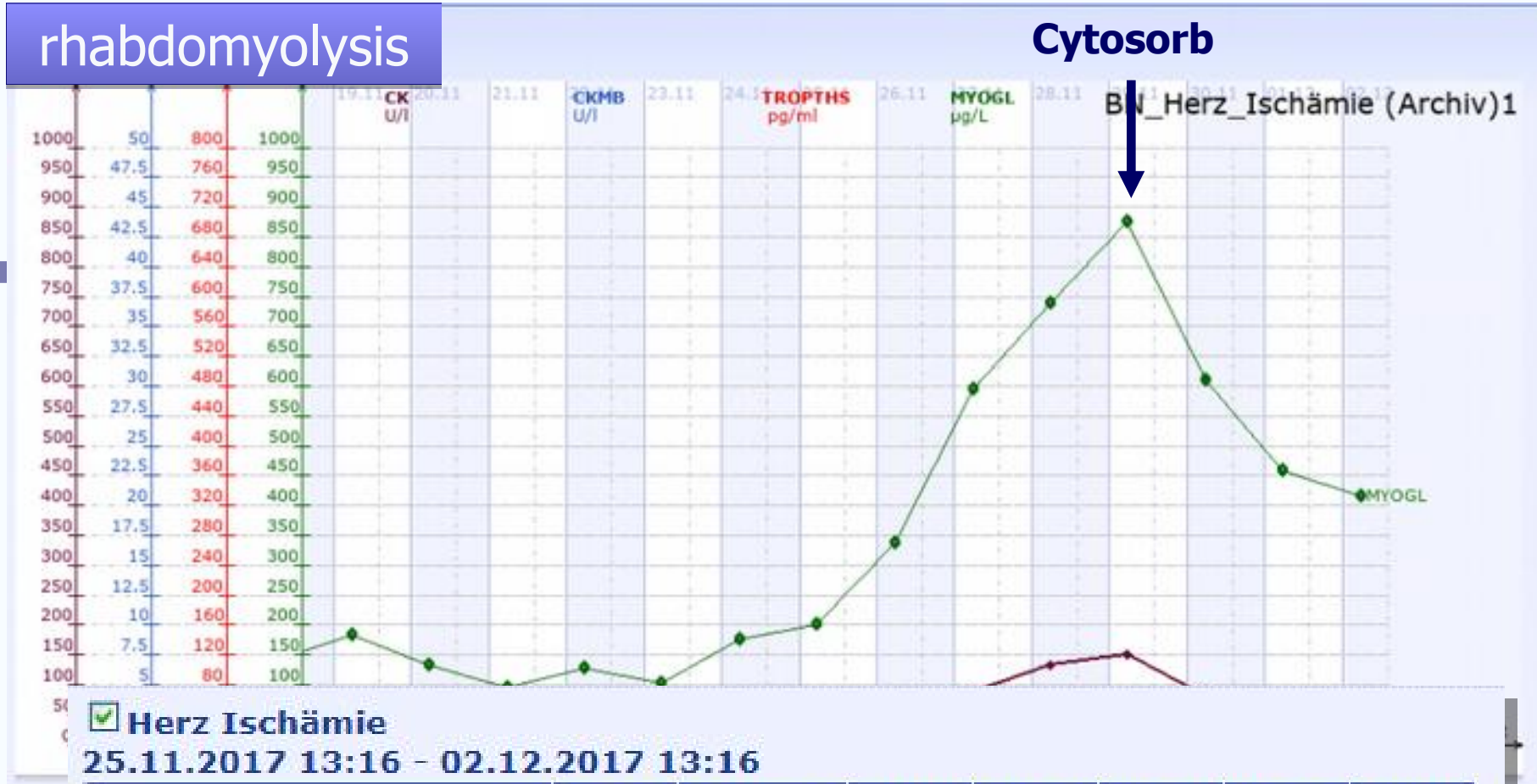


intoxication

hepatic failure

bridging

rhabdomyolysis



Herz Ischämie

25.11.2017 13:16 - 02.12.2017 13:16

Variablen \ Zeit	26.11.17 05:35	27.11.2017 05:43	27.11.2017 05:56	28.11.17 05:44	29.11.17 05:36	30.11.17 05:32	01.12.17 05:31	02.12.17 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

Lactate

- Measure lactate level
- Remeasure if initial lactate is > 2 mmol/L

Cultures

- Obtain blood cultures prior to administration of antibiotics

Antibiotics

- Administer broad spectrum antibiotics

Fluids

- Begin rapid administration of 30 mL/kg crystalloid for hypotension or lactate $\geq$ 4 mmol/L

Pressors

- Apply vasopressors if patient is hypotensive during or after fluid resuscitation to maintain MAP $\geq$ 65 mmHg

Treatment: Sepsis Bundles

- Previous 3-hour and 6-hour bundles were combined into the hour-1 bundle

Source: Levy M, et al. *Crit Care Med* 2018;46(6):997-1000.

« Critical care is not hard. It is just about doing the simple things really well - and not doing anything stupid »

Dr Dan Mullany 2002

selský rozum	common sense	sentido común
Hausverstand	buo senso	здра́вый смысл


…děkuji Vám za pozornost