



# SEPSIS

from the intensivist point of view

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ARK, FN u svaté Anny v Brně

# structure of the lecture

- Difference in the terms
- Sepsis definition – past and present
- Epidemiology/Economics
- DG (clinics, lab, scores: qSOFA, SOFA)
- Th (ATB, resuscitation protocol, Th acc. pathophysiology). Personalised/presicion medicine

# TERMS

- **Infection** – presence of the alien microorganism eliciting counteraction (local/systemic)
- **Bacteriemia** – presence of the bacteria in the blood (viremia/fungemia/parasitemia)
- **Inflammation** – defence mechanism against the infection (local/systemic; short-longterm; +/- (immunodepression))
- **Sepsis**



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

Andrew Rhodes<sup>1\*</sup>, Laura E. Evans<sup>2</sup>, Waleed Alhazzani<sup>3</sup>, Mitchell M. Levy<sup>4</sup>, Massimo Antonelli<sup>5</sup>, Ricard Ferrer<sup>6</sup>, Anand Kumar<sup>7</sup>, Jonathan E. Sevransky<sup>8</sup>, Charles L. Sprung<sup>9</sup>, Mark E. Nunnally<sup>2</sup>, Bram Rochweg<sup>3</sup>, Gordon D. Rubenfeld<sup>10</sup>, Derek C. Angus<sup>11</sup>, Djillali Annane<sup>12</sup>, Richard J. Beale<sup>13</sup>, Geoffrey J. Bellinghan<sup>14</sup>, Gordon R. Bernard<sup>15</sup>, Jean-Daniel Chiche<sup>16</sup>, Craig Coopersmith<sup>8</sup>, Daniel P. De Backer<sup>17</sup>, Craig J. French<sup>18</sup>, Seitaro Fujishima<sup>19</sup>, Herwig Gerlach<sup>20</sup>, Jorge Luis Hidalgo<sup>21</sup>, Steven M. Hollenberg<sup>22</sup>, Alan E. Jones<sup>23</sup>, Dilip R. Karnad<sup>24</sup>, Ruth M. Kleinpell<sup>25</sup>, Younsuk Koh<sup>26</sup>, Thiago Costa Lisboa<sup>27</sup>, Flavia R. Machado<sup>28</sup>, John J. Marini<sup>29</sup>, John C. Marshall<sup>30</sup>, John E. Mazuski<sup>31</sup>, Lauralyn A. McIntyre<sup>32</sup>, Anthony S. McLean<sup>33</sup>, Sangeeta Mehta<sup>34</sup>, Rui P. Moreno<sup>35</sup>, John Myburgh<sup>36</sup>, Paolo Navalesi<sup>37</sup>, Osamu Nishida<sup>38</sup>, Tiffany M. Osborn<sup>31</sup>, Anders Perner<sup>39</sup>, Colleen M. Plunkett<sup>25</sup>, Marco Ranieri<sup>40</sup>, Christa A. Schorr<sup>22</sup>, Maureen A. Seckel<sup>41</sup>, Christopher W. Seymour<sup>42</sup>, Lisa Shieh<sup>43</sup>, Khalid A. Shukri<sup>44</sup>, Steven Q. Simpson<sup>45</sup>, Mervyn Singer<sup>46</sup>, B. Taylor Thompson<sup>47</sup>, Sean R. Townsend<sup>48</sup>, Thomas Van der Poll<sup>49</sup>, Jean-Louis Vincent<sup>50</sup>, W. Joost Wiersinga<sup>49</sup>, Janice L. Zimmerman<sup>51</sup> and R. Phillip Dellinger<sup>22</sup>

# SEPSIS definition

- Consensual conference ACCP/SCCM, held in 1991, defined sepsis as activation of the systemic inflammatory reaction (SIRS) as a reaction on presence of the alien (micro)organism and stratified its clinical course (sepsis → severe sepsis → septic shock) (1).

Bone RC, Balk RA, Cerra FB, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. Chest 1992 Jun;101(6):1644-55.

## **SIRS (at least 2 out of 4 marks)**

Temperature  $\geq 38^{\circ}\text{C}$ , or  $\leq 36^{\circ}\text{C}$

HR  $\geq 90$  beats/min

Respirations  $\geq 20$ /min

WBC count  $\geq 12,000/\text{mm}^3$ , or  $\leq 4,000/\text{mm}^3$ , or  $>10\%$  immature Neu

**SIRS elicited by microorganism = SEPSIS**

SEPSIS + 1 organ dysfunction (e.g. Hypotension corrected by fluids) =

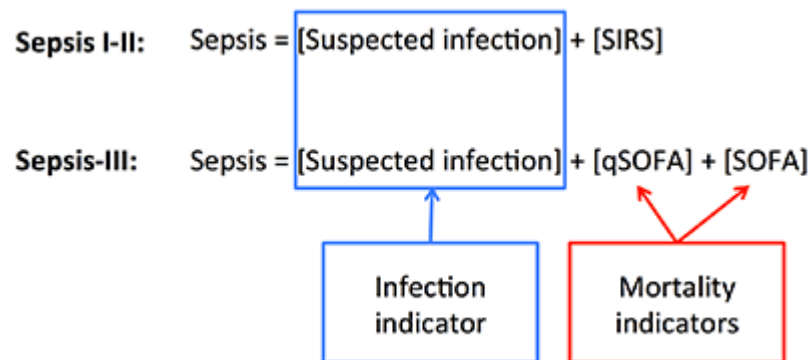
**SEVERE SEPSIS**

SEVERE SEPSIS + shock (vasopressors) = **SEPTIC SHOCK**

# DG sepsis (Sepsis-3)

3rd Sepsis conference, held by SCCM/ESICM in 2015 suggested fundamental reclassification: no SIRS and newly to define sepsis in the ICU as a change in organ function ICU (defined as dSOFA  $\geq 2$ ) which is caused by (suspected) infection. Septic shock is newly defined as hypotension (MAP  $> 65$  mmHg) reacting only on vasopressors and simultaneously signs of tissue hypoperfusion (lactate  $> 2$  mmol/l).

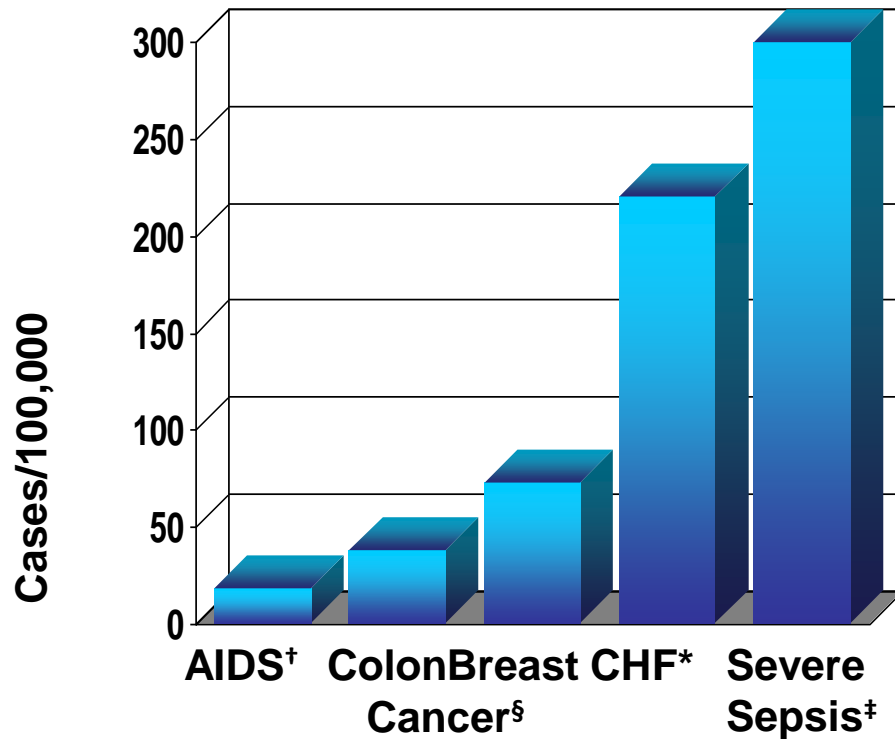
Singer M, Deutschman CS, Seymour CW et al (2016) The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 315(8):801–810



# **SEPSIS epidemiology**

- **problem for the whole society**

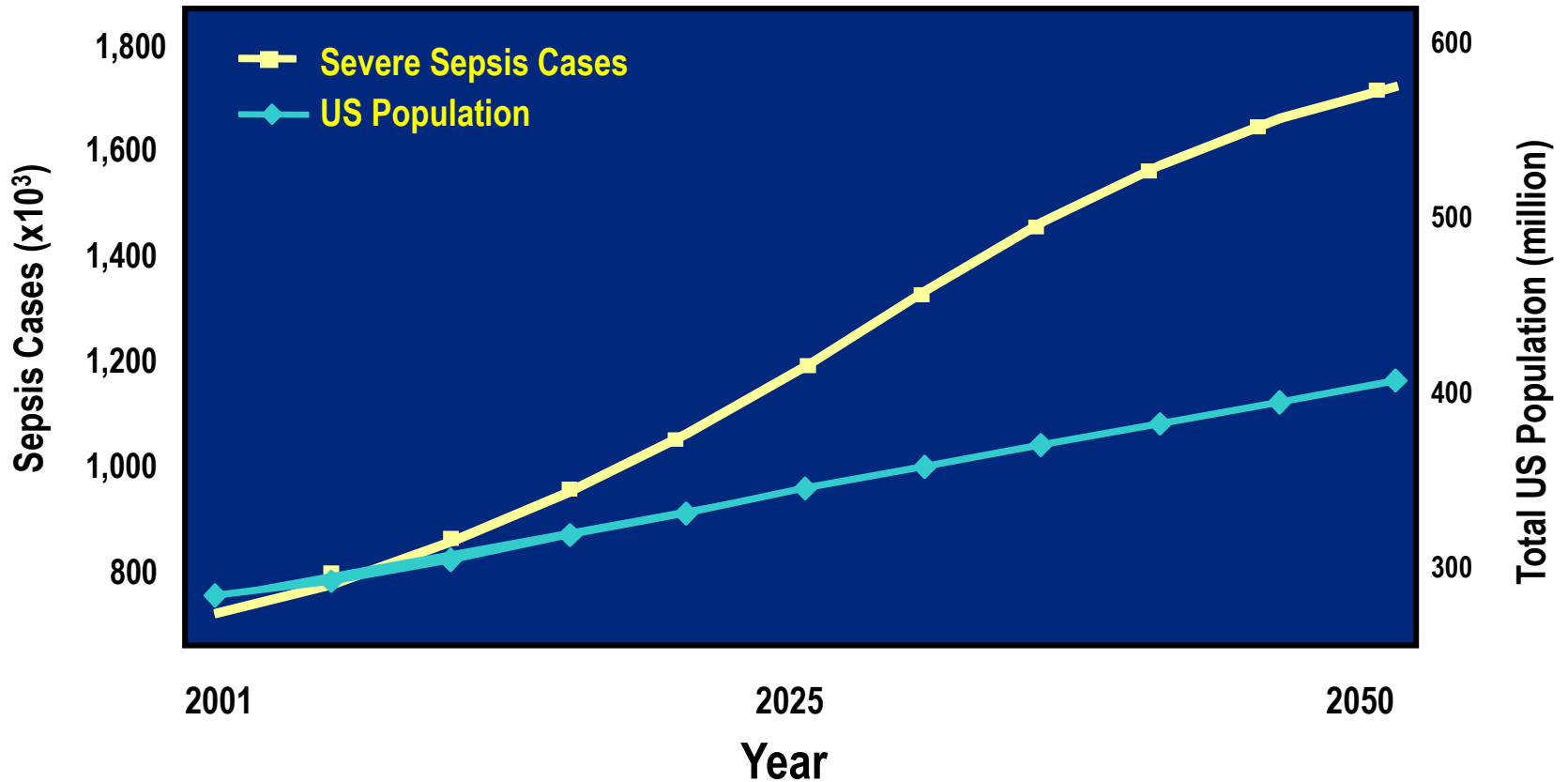
# incidence of Severe Sepsis



<sup>†</sup>National Center for Health Statistics, 2001. <sup>§</sup>American Cancer Society, 2001. \*American Heart Association, 2000. <sup>‡</sup>Angus DC et al. *Crit Care Med.* 2001.



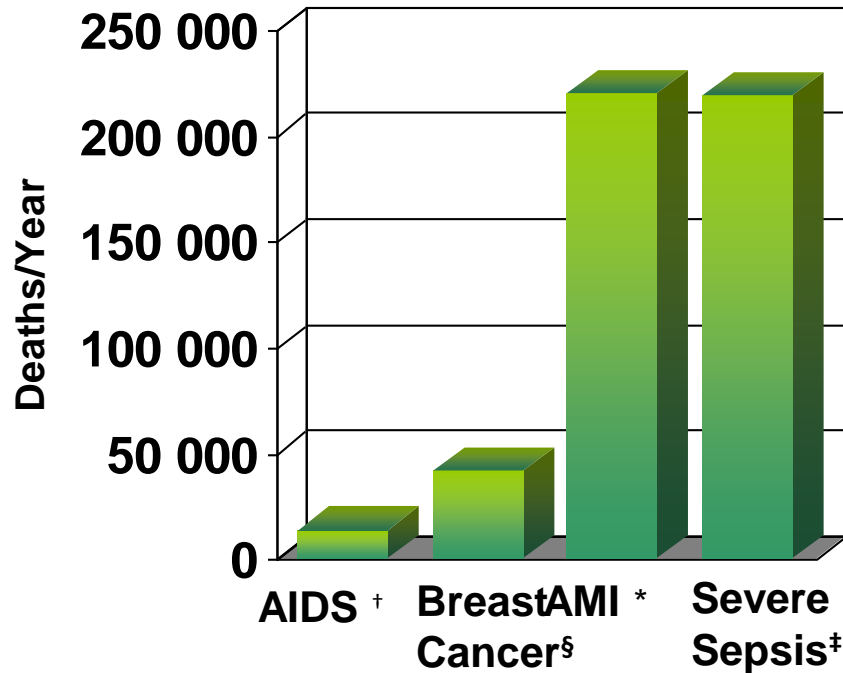
# Severe Sepsis - incidence rising



Angus DC, et al. *JAMA* 2000;284:2762-70.

Angus DC, et al. *Crit Care Med* 2001;29:1303-10.

# mortality Severe Sepsis



†National Center for Health Statistics, 2001. §American Cancer Society, 2001. \*American Heart Association. 2000. ‡Angus DC et al. *Crit Care Med.* 2001.

# Treating seniors, severely ill, males ...

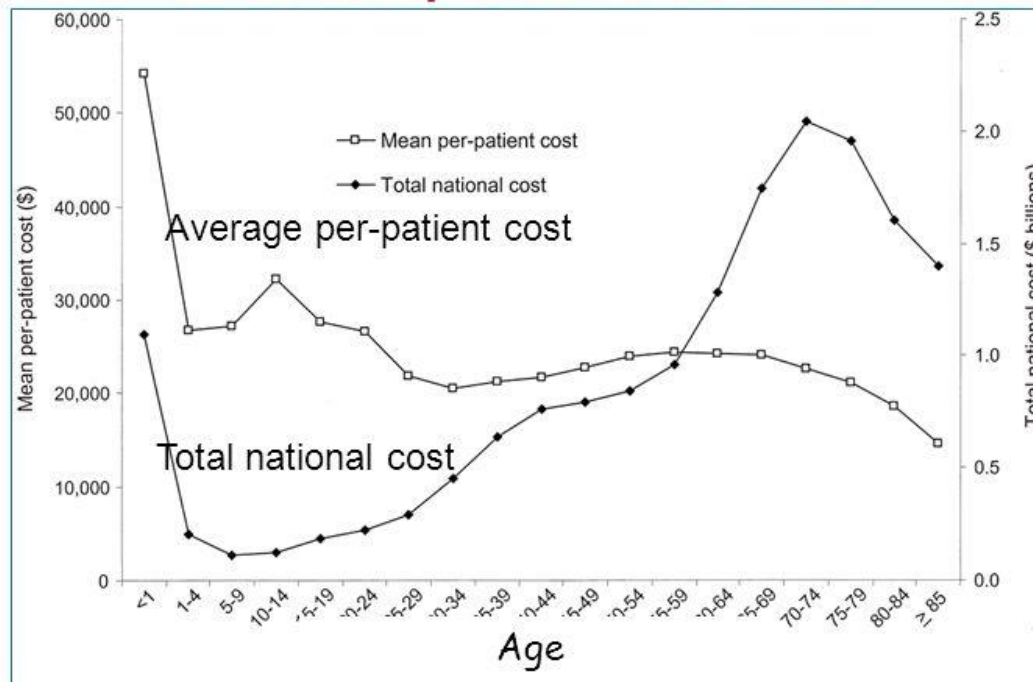
## Severe sepsis incidence and mortality increase with age



Angus Crit Care Med 29:1301, 2001

... extreme costs...

## Severe Sepsis Costs a Lot



- Average LOS 19.6 days
- Average cost \$22,100/case
- Total national hospital cost was **\$16.7 BILLION**
  - 52.3% of costs in those >64 years
  - 30.8% total costs in those >74 years



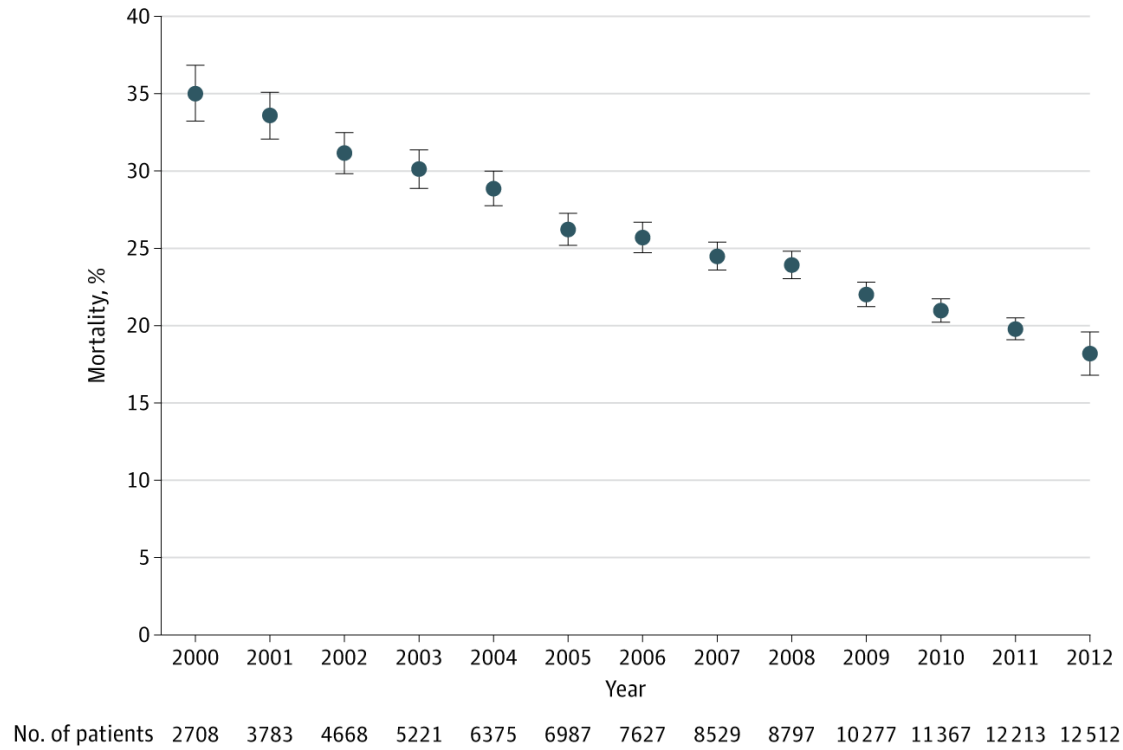
Angus et al, Crit Care Med 2001; 29: 1303-10



## Mortality related to severe sepsis and septic shock among critically ill patients in Australia and New Zealand, 2000-2012.

Kaukonen KM1, Bailey M2, Suzuki S3, Pilcher D4, Bellomo R5.

JAMA. 2014;311(13):1308-1316. doi:10.1001/jama.2014.2637



# diagnostics SEPSIS I

- **clinics**

# triage of the patients

## Questions:

**Is he/she ill at all?**

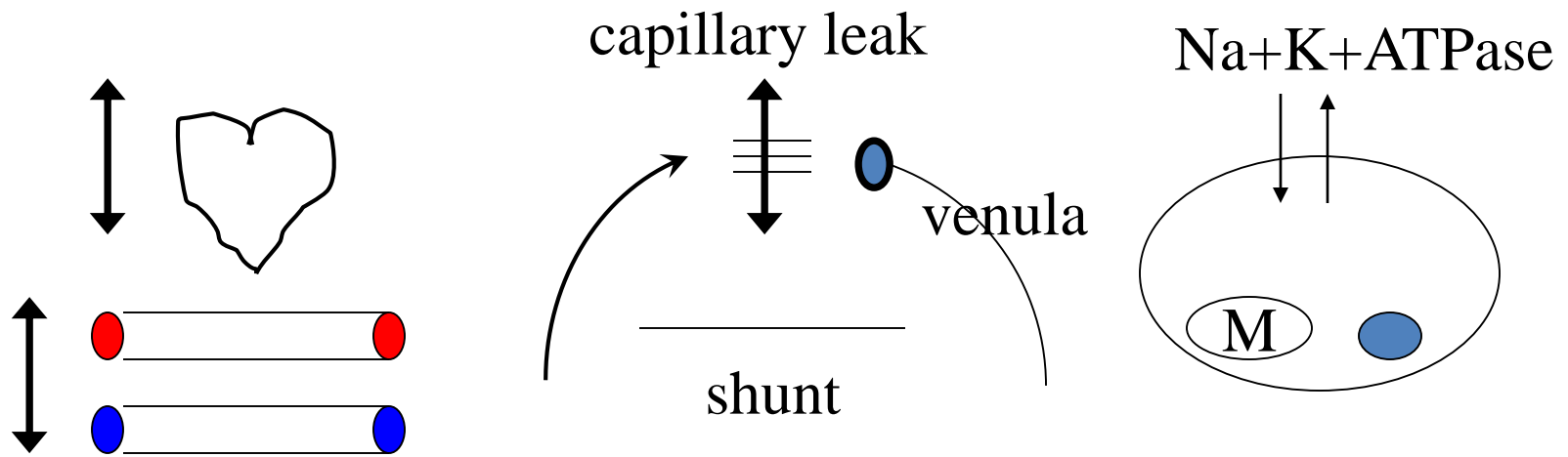
**Can be treated as an out-patient?**

**Stay in the hospital?**

**Stable/unstable? Admitted to a monitored bed?**

# SHOCK – term definition

Situation when CV system is not capable to deliver nutrients (O<sub>2</sub>) to the peripheral tissues. This leads to **energetic** ⇒ **functional** ⇒ **morphological** cell failure. Failure of **micro** (macro)circulation



**HEMODYNAMIC compromise**

**inbalance of OXYGEN (O<sub>2</sub>) consumption (V<sub>O2</sub>) and delivery (D<sub>O2</sub>)**

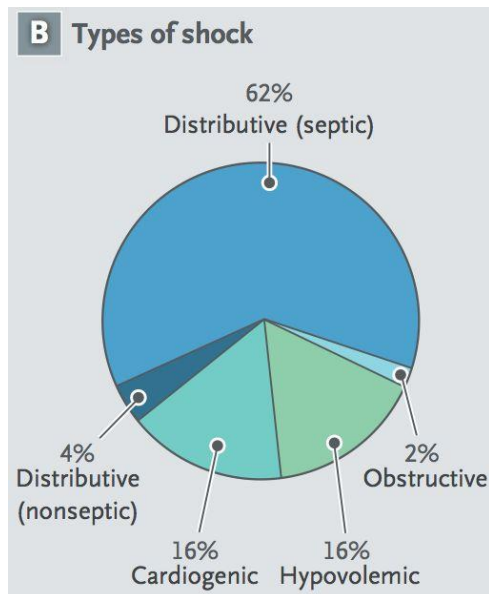


# shock state

## - 3 gates to the body

### JL Vincent:

- CNS – qualitative/quantitative
- Skin
- Kidney



The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

CRITICAL CARE MEDICINE

Simon R. Finfer, M.D., and Jean-Louis Vincent, M.D., Ph.D., Editors

## Circulatory Shock

Jean-Louis Vincent, M.D., Ph.D., and Daniel De Backer, M.D., Ph.D.

N ENGL J MED 369:18 NEJM.ORG OCTOBER 31, 2013

# quick SOFA

(2 out of 3 criteria)

Quick SOFA( q SOFA) *Seymour et al*

Parameters	Criteria
Respiratory rate	$\geq 22/\text{min}$
Altered mentation	GCS $< 13$
Systolic blood pressure	$\leq 100\text{mmHg}$

Early Screening for Performance Improvement

# Sequential [Sepsis-Related] Organ Failure Assessment (SOFA) Score

System	0	1	2	3	4
Respiration PaO <sub>2</sub> /FiO <sub>2</sub> , mmHg (kPa)	≥400 (53.3)	<400 (53.3)	<300 (40)	<200 (26.7) with respiratory support	<100 (13.3) with respiratory support
Coagulation Platelets, x10 <sup>3</sup> /uL	≥150	<150	<100	<50	<20
Liver Bilirubin, mg/dL (umol/L)	<1.2 (20)	1.2 - 1.9 (20 - 32)	2.0 - 5.9 (33 - 101)	6.0 - 11.9 (102 - 204)	>12.0 (204)
Cardiovascular	MAP ≥70mmHg	MAP <70mmHg	Dopamine <5 or Dobutamine (any dose)	Dopamine 5.1 - 15 or Epinephrine ≤0.1 or Norepinephrine ≤0.1	Dopamine >15 or Epinephrine >0.1 or Norepinephrine >0.1
CNS GCS Score	15	13 - 14	10 - 12	6 - 9	<6
Renal Creatinine, mg/dL (umol/L) Urine Output, mL/d	<1.2 (110)	1.2 - 1.9 (110 - 170)	2.0 - 3.4 (171 - 299)	3.5 - 4.9 (300 - 440)	>5.0 (440)  <200

\*Catecholamine Doses = ug/kg/min for at least 1hr

# CardioVascular (CV) signs of instability

## MACROsigns (macrohemodynamics):

### A) Hypotension:

- a) systolic arterial pressure (SAP) < 90 mm Hg or its sudden drop of 30-40 mmHg or
- b) mean arterial pressure (MAP) < 60 mm Hg.
- **CAVE:** shock state can be present without hypotension (so called hidden/compensated shock) – mortality is high

### B) Tachycardia – heart beats > 100/min.

- **CAVE:** tachycardia not present in patients on beta-blockers.

## MICROsigns (microcirculation and tissue metabolism):

- **Whenever supply (DO<sub>2</sub>) does not meet demand (VO<sub>2</sub>) – hypoperfusion—anaerobic metabolism**

# hypotension

$$\text{MAP} = \text{SV} \times \text{SVR}$$

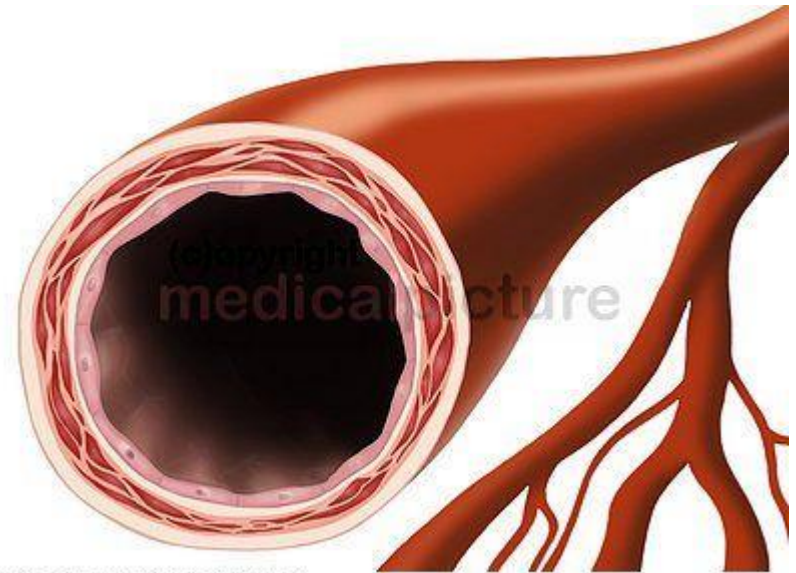


Problem?

**ECHO**

(tamponade, tension PNO)

MAP



© medicalpicture no: 59580

Problem?

**CRT**

# Skin

- **Spots on the skin**  
(mottled skin)
- **Nail bed perfusion**  
(capillary refill time)
- **Cold periphery**  
( $T_{\text{cent}} - T_{\text{toe}}$ ;  $T_{\text{forearm}} - T_{\text{thumb}}$ )

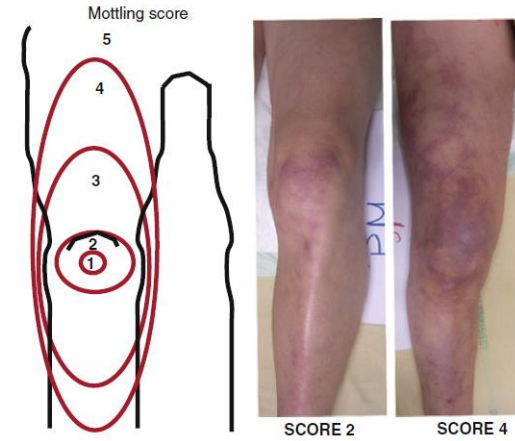


# INTENSIVE CARE MEDICINE

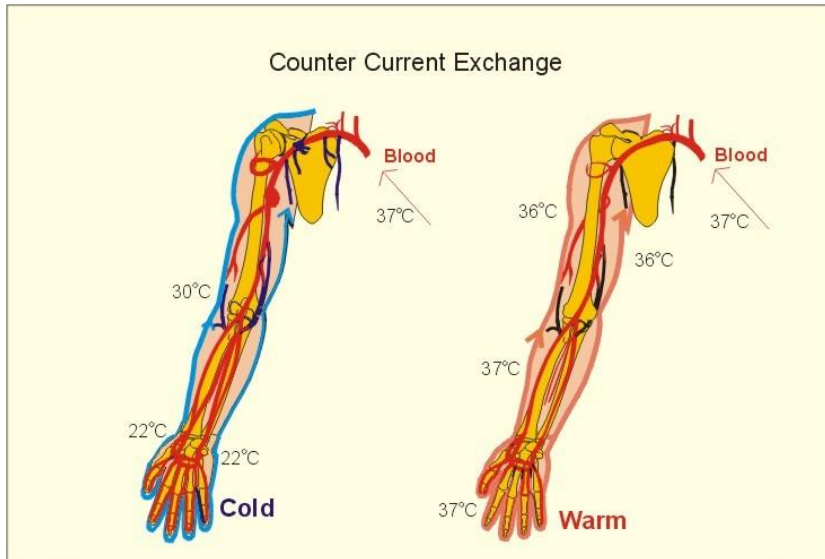
**Articles**

**184** **185** **186** **187** **188** **189** **190** **191** **192** **193** **194** **195** **196** **197** **198** **199** **200** **201** **202** **203** **204** **205** **206** **207** **208** **209** **210** **211** **212** **213** **214** **215** **216** **217** **218** **219** **220** **221** **222** **223** **224** **225** **226** **227** **228** **229** **230** **231** **232** **233** **234** **235** **236** **237** **238** **239** **240** **241** **242** **243** **244** **245** **246** **247** **248** **249** **250** **251** **252** **253** **254** **255** **256** **257** **258** **259** **260** **261** **262** **263** **264** **265** **266** **267** **268** **269** **270** **271** **272** **273** **274** **275** **276** **277** **278** **279** **280** **281** **282** **283** **284** **285** **286** **287** **288** **289** **290** **291** **292** **293** **294** **295** **296** **297** **298** **299** **300** **301** **302** **303** **304** **305** **306** **307** **308** **309** **310** **311** **312** **313** **314** **315** **316** **317** **318** **319** **320** **321** **322** **323** **324** **325** **326** **327** **328** **329** **330** **331** **332** **333** **334** **335** **336** **337** **338** **339** **340** **341** **342** **343** **344** **345** **346** **347** **348** **349** **350** **351** **352** **353** **354** **355** **356** **357** **358** **359** **360** **361** **362** **363** **364** **365** **366** **367** **368** **369** **370** **371** **372** **373** **374** **375** **376** **377** **378** **379** **380** **381** **382** **383** **384** **385** **386** **387** **388** **389** **390** **391** **392** **393** **394** **395** **396** **397** **398** **399** **400** **401** **402** **403** **404** **405** **406** **407** **408** **409** **410** **411** **412** **413** **414** **415** **416** **417** **418** **419** **420** **421** **422** **423** **424** **425** **426** **427** **428** **429** **430** **431** **432** **433** **434** **435** **436** **437** **438** **439** **440** **441** **442** **443** **444** **445** **446** **447** **448** **449** **450** **451** **452** **453** **454** **455** **456** **457** **458** **459** **460** **461** **462** **463** **464** **465** **466** **467** **468** **469** **470** **471** **472** **473** **474** **475** **476** **477** **478** **479** **480** **481** **482** **483** **484** **485** **486** **487** **488** **489** **490** **491** **492** **493** **494** **495** **496** **497** **498** **499** **500**

**Springer**



**Fig. 1** *Left*: the mottling score is based on a mottling area extension on the legs. Score 0 indicates no mottling; score 1, a modest mottling area (coin size) localized to the center of the knee; score 2, a moderate mottling area that does not exceed the superior edge of the kneecap; score 3, a mild mottling area that does not exceed the middle thigh; score 4, a severe mottling area that does not go beyond the fold of the groin; score 5, an extremely severe mottling area that goes beyond the fold of the groin. *Right*: Examples of the mottling score



Ulf C. Schneider  
Peter Vajkoczy

**“The beach position”:  
crossed legs as a marker  
for a favourable clinical course  
in neurological intensive care  
unit patients**

Accepted: 19 November 2011  
Published online: 8 December 2011  
© Copyright jointly held by Springer and  
ESICM 2011





# diagnostics SEPSIS II

- lab

# availability of acute biochemistry/haematology results



**POC analysators:**  
3 in St. Anna

**Central lab**  
- Building D

# lab

## Severity of the case:

- PaO<sub>2</sub> (> 13 kPa, > 8 kPA)
- SaO<sub>2</sub> (comparion with SpO<sub>2</sub>)
- PaCO<sub>2</sub> (> 6...8 kPa, simultaneously with pH)
- pH (7,36 – 7,44; logaritmic scale)
- BE (only MAc has neg BE, degrees of + in RAc – ability to compensate (kindney), chronicity)

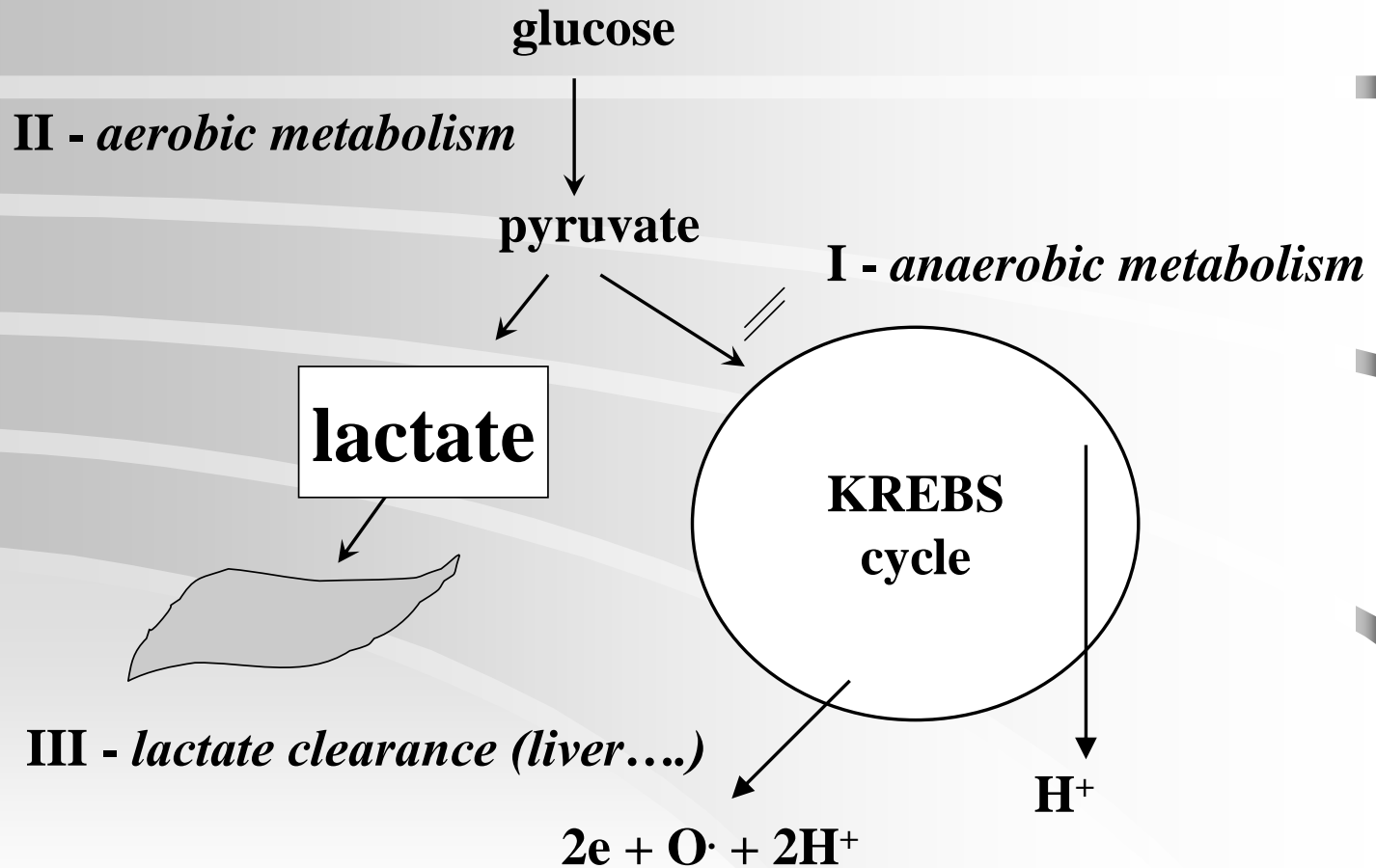
## Sepsis (sensitivity > specificity)

- Leu, CRP, PCT....

# Lab – lactate

marker „anaerobic metabolism“

## BLOOD LACTATE LEVEL



# therapy SEPSIS

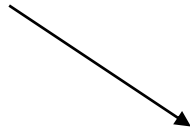
- **ATB**
- **Supportive care**  
(gas exchange (lungs) + perfusion (CV system) + failing organ replacement/support)
- **Acc. to pathophysiology**

# To treat??? (interaction microb – organism)

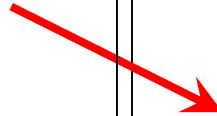
**ACQUISITION**



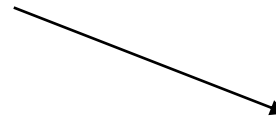
**CARRIAGE**



**OVERGROWTH**



**COLONIZATION**



**INFECTION**



**SURVEILLANCE SAMPLES**  
(throat, rectum)



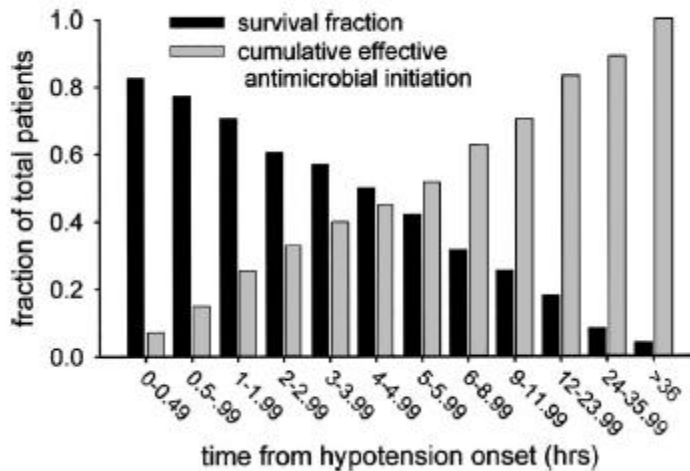
**DIAGNOSTIC SAMPLES**  
LOWER AIRWAY, BLOOD, BLADDER

# 1 (golden) hour in Septic Shock

Duration of hypotension before initiation of **effective** antimicrobial therapy is the critical determinant of survival in human septic shock\*

Anand Kumar, MD; Daniel Roberts, MD; Kenneth E. Wood, DO; Bruce Light, MD; Joseph E. Parrillo, MD;

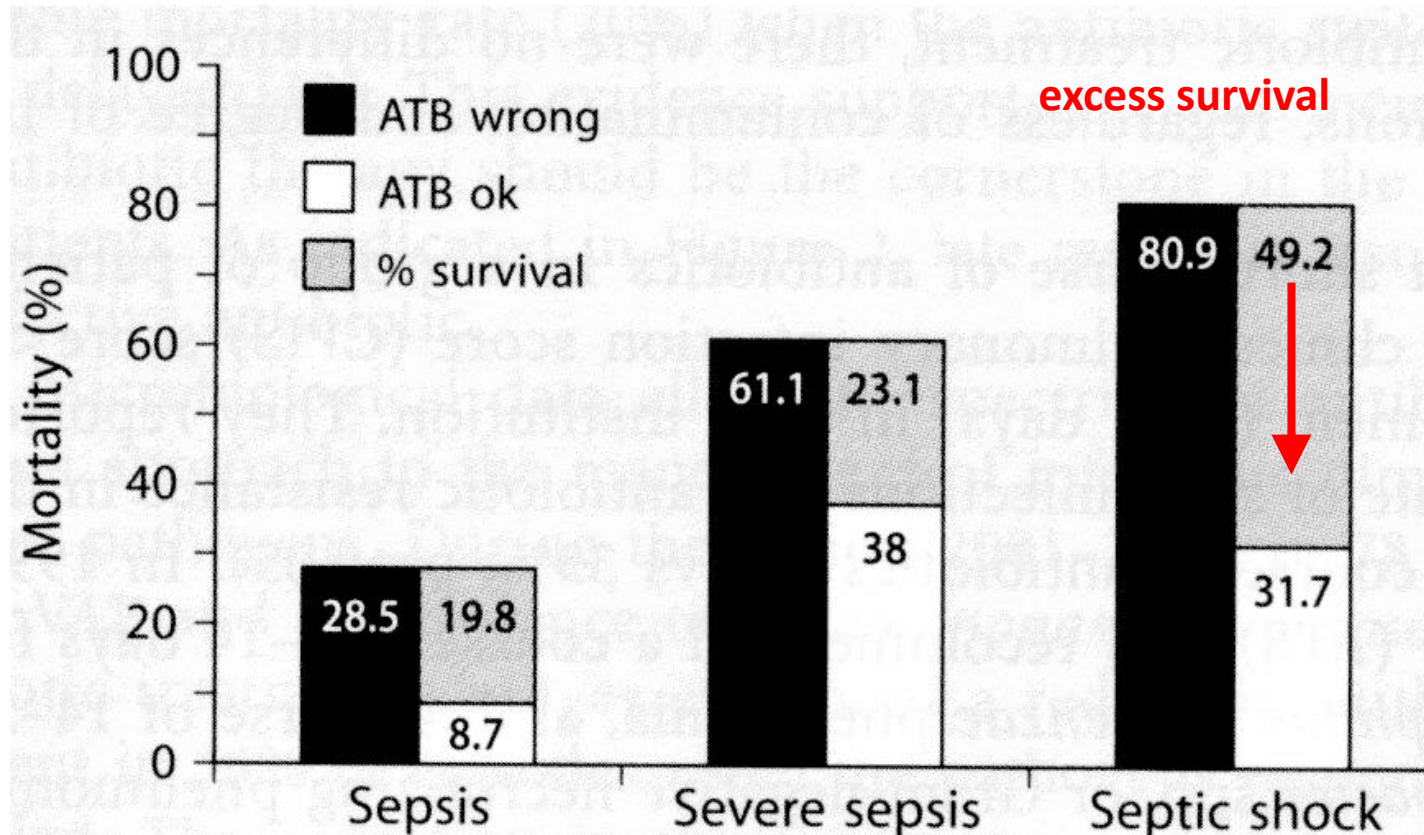
(Crit Care Med 2006; 34:1589–1596)



## Effective:

- a) ATB acc. microbiology results within 48 hrs
- b) ATB empirically acc. given clinical syndrome

# adequate ATB – Septic Shock



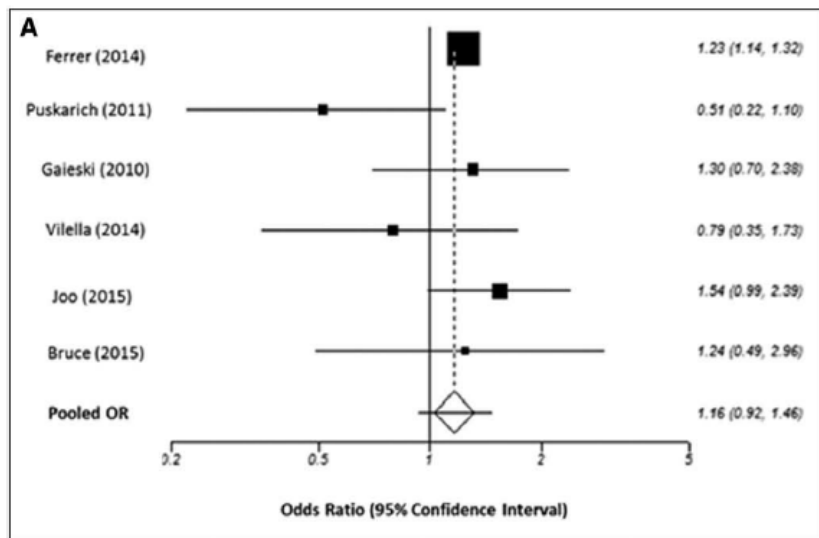


# 1 hour ???

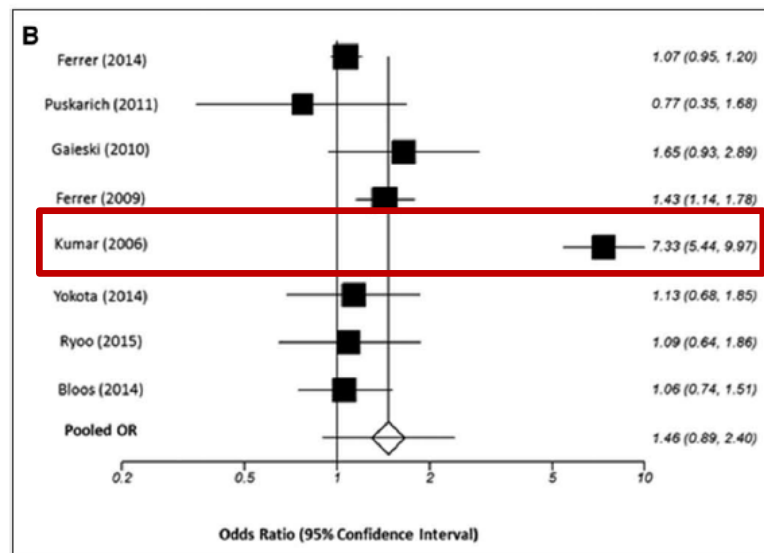
## The Impact of Timing of Antibiotics on Outcomes in Severe Sepsis and Septic Shock: A Systematic Review and Meta-Analysis\*

Sarah A. Sterling, MD; W. Ryan Miller, MD; Jason Pryor, MD; Michael A. Puskarich, MD; Alan E. Jones, MD

care are not supported by the available evidence. (*Crit Care Med* 2015; 43:1907–1915)



3 hr ED triage



1 hr hypotension

# RIVERS protocol

The NEW ENGLAND  
JOURNAL of MEDICINE

Publication in NEJM in 2001 presented results of „Chicago ED trial“ by Emanuel Rivers (absolute mortality reduction by 16 %), aggressive (CVC, ScvO<sub>2</sub> measurement, RBC, dobutamine) – concept of **EGDT** in ED/ICU conditions was born.

**RIVERS, E., NGUYEN, B., HAVSTAD, S., ET AL.** *Early goal-directed therapy in the treatment of severe sepsis and septic shock.* N Engl J Med, 2001, 345, p. 1368–1377.

**Test: continual monitoring ScvO<sub>2</sub>, protocol: fluid + vasopressor + dobutamine + RBC**

# 2012 RECOMMENDATIONS

## A. INITIAL RESUSCITATION

1. Protocolized, quantitative resuscitation of patients with sepsis-induced tissue hypoperfusion (defined in this document as hypotension persisting after initial fluid challenge or blood lactate concentration  $\geq 4$  mmol/L). Goals during the first 6 hr resuscitation:

- a. Central venous pressure 8–12 mm Hg
- b. Mean arterial pressure  $\geq 65$  mm Hg
- c. Urine output  $\geq 0.5$  mL/kg/hr
- d. Central venous (superior vena cava) or mixed venous oxygen saturation 70% or 65%, respectively (grade 1C).

2. In patients with elevated lactate levels, targeting resuscitation to normalize lactate (grade 2C).

# 2016 RECOMMENDATIONS

## A. INITIAL RESUSCITATION

1. Sepsis and septic shock are medical emergencies, and we recommend that treatment and resuscitation begin immediately (BPS).

2. We recommend that, in the resuscitation from sepsis-induced hypoperfusion, **at least 30 mL/kg of IV** crystalloid fluid be given within the first 3 hours (strong recommendation, low quality of evidence).

3. We recommend that, following initial fluid resuscitation, additional fluids be guided by frequent reassessment of hemodynamic status (BPS).

Remarks: Reassessment should include a thorough clinical examination and evaluation of available physiologic variables (heart rate, blood pressure, arterial oxygen saturation, respiratory rate, temperature, urine output, and others, as available) as well as other noninvasive or invasive monitoring, as available.

4. We recommend further hemodynamic assessment (such as assessing cardiac function) to determine the type of shock if the clinical examination does not lead to a clear diagnosis (BPS).

5. We suggest that dynamic over static variables be used to predict fluid responsiveness, where available (weak recommendation, low quality of evidence).

6. We recommend an initial target **MAP 65 mmHg** in patients with septic shock requiring vasopressors (strong recommendation, moderate quality of evidence).

7. We suggest guiding **resuscitation to normalize lactate** in patients with elevated lactate levels as a marker of tissue hypoperfusion (weak recommendation, low quality of evidence).

# „SEPSIS TRILOGY“ (PROCESS, ARISE, PROMISE)

- **ProCESS** (hospital mortality at D60): n = 1351, 31 centers, mortality 21 % (EGDT), 18.2 % (modified protocol), 18.9 % (standard care).
- **ARISE** (comparison „all cause“ mortality at D90): n = 1600, 51 centers, mortality 18.6 % (EGDT) and 18.8% (standard).
- **ProMISe** (comparison „all cause“ mortality at D90): n = 1260, 56 centers, mortality 29.5 % (EGDT) and 29.2 % (standard).

**Metaanalysis: EGDT not superior, more costly.**

**Investigators TP.** *A randomised trial of protocolised care for early septic shock.*

N Engl J Med, 2014, 370, p. 1683–1693.

**ARISE Investigators.** *Goal-directed resuscitation for patients with early septic shock.* N Engl J Med, 2014, 371, p. 1496–1506. doi: 10.1056/NEJMoa1404380. Epub 2014, Oct 1.

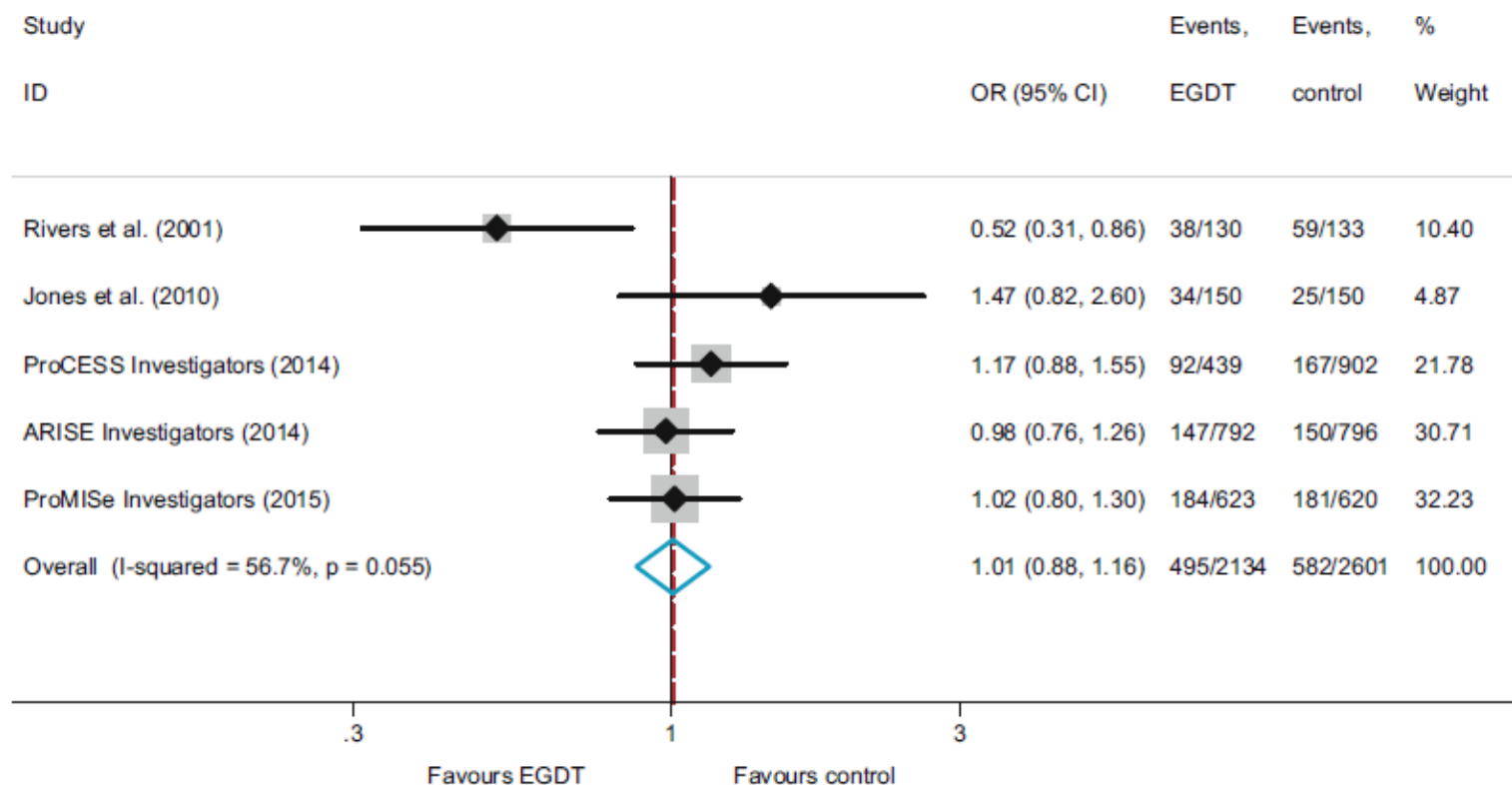
**MOUNCEY, PR., OSBORN, TM., POWER, GS., ET AL.** *Trial of early, goal-directed resuscitation for septic shock.* N Engl J Med, 2015, 372, p. 1301–1311. doi: 10.1056/NEJMoa1500896. Epub 2015, Mar 17.

**ANGUS, DC., BARNATO, AE., BELL, D., ET AL.** *A systematic review and meta-analysis of early goal-directed therapy for septic shock: the ARISE, ProCESS and ProMISe Investigators.* Intensive Care Med, 2015, 41, p. 1549–1560. doi: 10.1007/s00134-015-3822-1. Epub 2015, May 8.



D. C. Angus  
 A. E. Barnato  
 D. Bell  
 R. Bellomo  
 C.-R. Chong

## A systematic review and meta-analysis of early goal-directed therapy for septic shock: the ARISE, ProCESS and ProMISe Investigators



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3. We recommend that, following initial fluid resuscitation, additional fluids be guided by frequent reassessment of hemodynamic status (BPS).

Remarks: Reassessment should include a thorough clinical examination and evaluation of available physiologic variables (heart rate, blood pressure, arterial oxygen saturation, respiratory rate, temperature, urine output, and others, as available) as well as other noninvasive or invasive monitoring, as available.

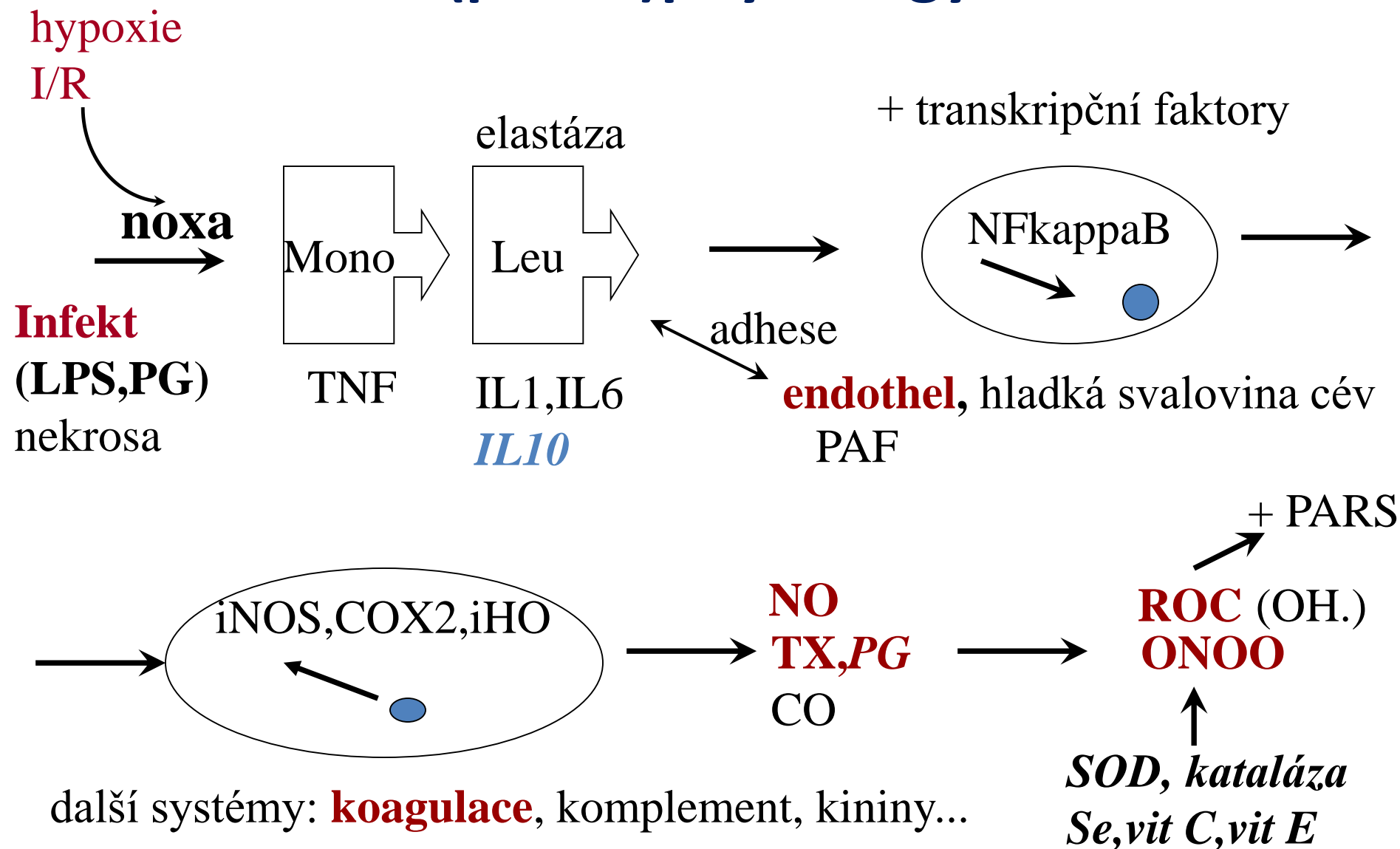
4. We recommend further hemodynamic assessment (such as assessing cardiac function) to determine the type of shock if the clinical examination does not lead to a clear diagnosis (BPS).

5. We suggest that dynamic over static variables be used to predict fluid responsiveness, where available (weak recommendation, low quality of evidence).

6. We recommend an initial target **MAP 65 mmHg** in patients with septic shock requiring vasopressors (strong recommendation, moderate quality of evidence).

7. We suggest guiding **resuscitation to normalize lactate** in patients with elevated lactate levels as a marker of tissue hypoperfusion (weak recommendation, low quality of evidence).

# treatment of septic shock acc. (patho)physiology



# The acc. pathophysiology of septic shock II

anticytokiny (antiTNF-alfa, TNF sol rec, IL-1ra, antiPAF.....)

blokátory NOS (meth. Modř, L-NMMA), iNOS,

COX - ibuprofen, COX 2

antioxidační koktejly (NAC - broncholylin, pentoxyphilyn)

blokátory PARS (nikotinamid)

TXA1 - PgE2

**coagulation: AT III, activated protein C – not on the market**

complement: inhibitor C1 esterase

- **hydrocortisone – most severe forms of SS**
- **vasopresine – YES (less severe SS?)**
- **mimotělní eliminační metody – ne (D.Payen)**
- **angiotensine II (sepsis + ARDS?)**



# therapy SEPSIS conclusion

**Algorithm leading to error elimination:**

- **Time to check the patient**
- **Consult**
- **Repeat/Monitor (clinics, lab)**

# CONCLUSION

- Neurology – „time is brain“
- Cardiology – time is muscle“
- Intensive care (SEPSIS) – **TIME IS LIFE**

**Public: Education (sepsis.....)**

**Hospitals: Active search for unstable patients -  
RRT/METcall**