



# Sepse

„The difficulty lies, not in the new ideas, but in escaping from the old ones, which ramify, for those brought up as most of us have been, into every corner of our minds.“

*John Maynard Keynes*



Hele Hippokrate, všichni říkají,  
že choroby jsou způsobené  
zlými duchy, co si myslíš ty?

Nesmysl Galene, nějaký toxin  
musí být příčinou chorob!



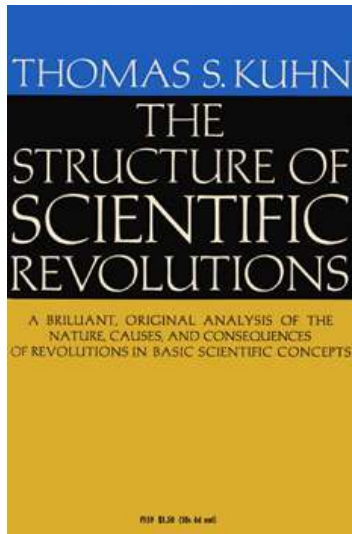
ca. 460-370 př.n.l.



## HUGO SCHOTTMULLER (1867-1936)



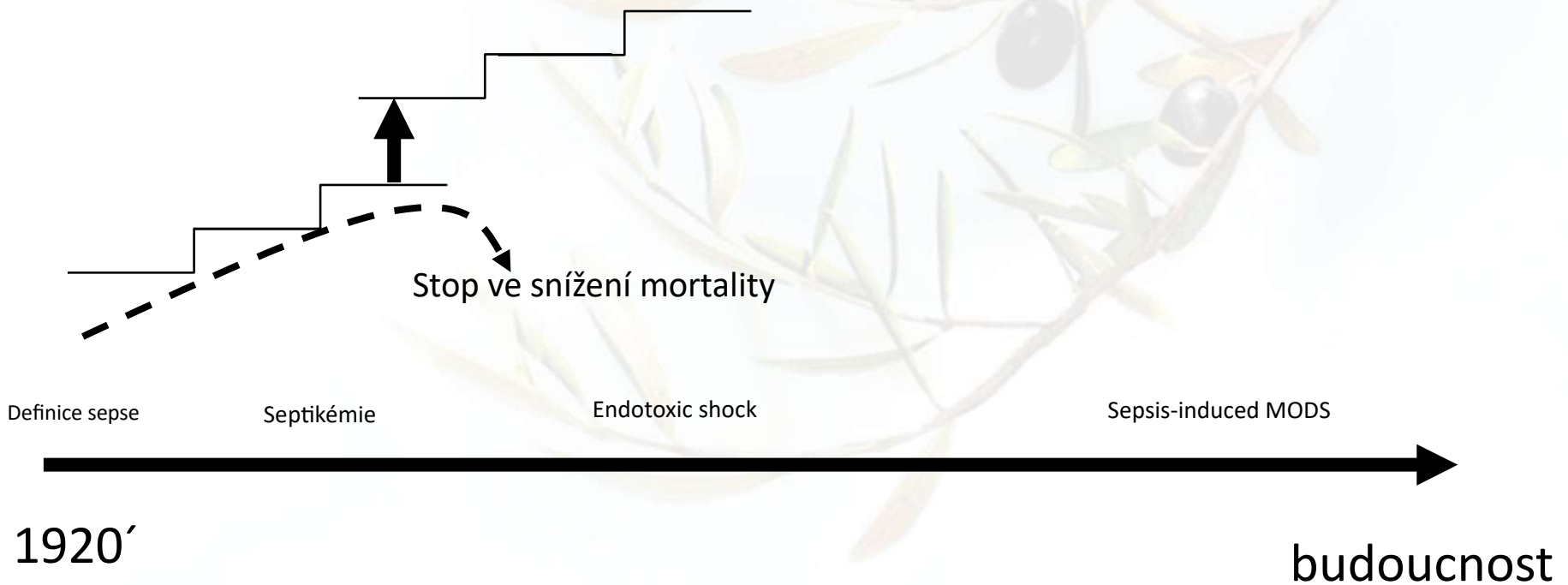
- *Modern definition of sepsis(1914):* "Sepsis is present if a focus has developed from which pathogenic bacteria, constantly or periodically, invade the blood stream in such a way that this causes subjective and objective symptoms."
- "Therapy should not be directed against bacteria in the blood but against the released bacterial toxins"

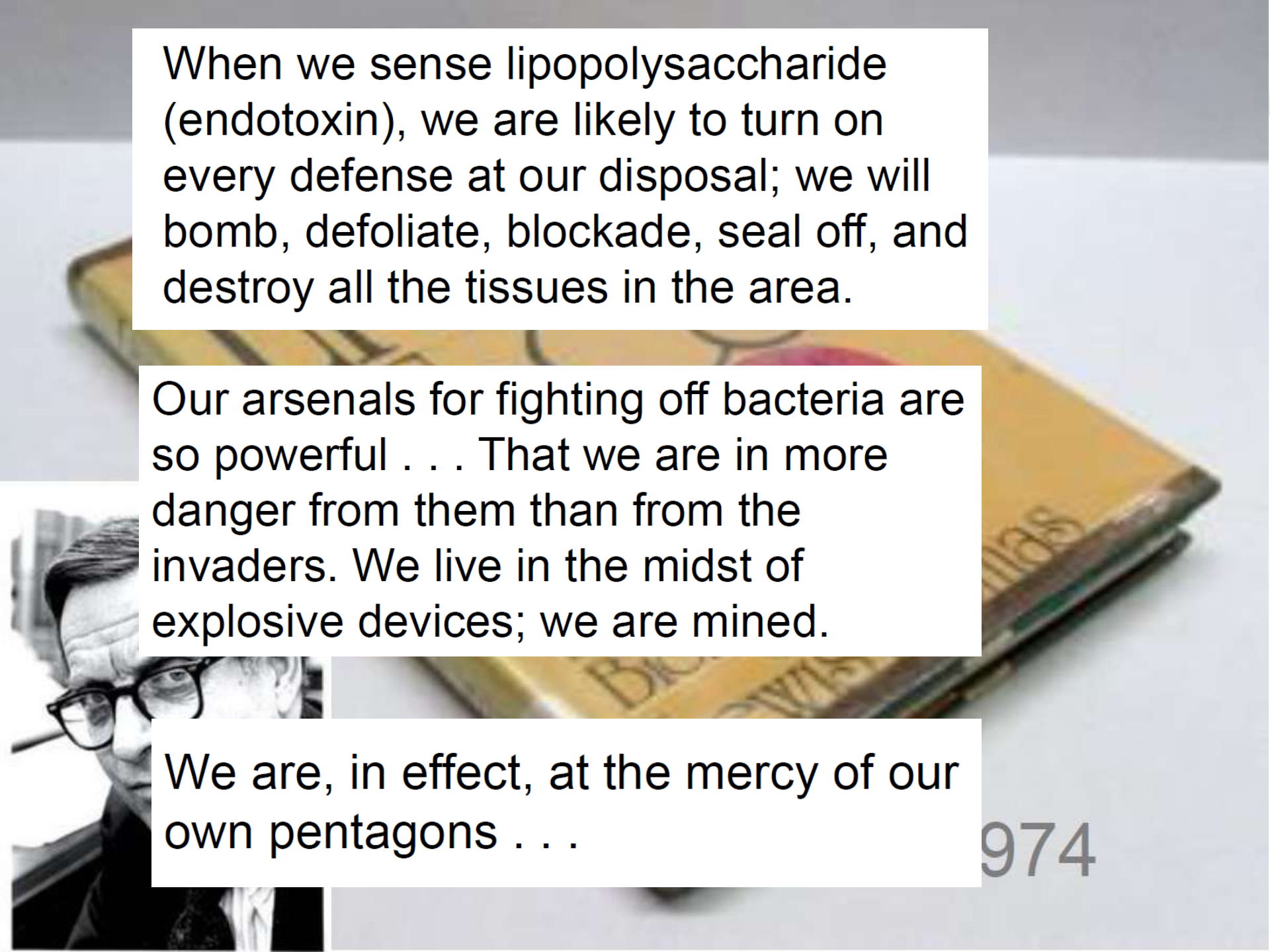


## the man who changed the way the world looked at science

One of "The Hundred Most Influential Books"

sales **at 1.4 million copies**. For a cerebral work of this calibre, these are Harry Potter-scale numbers.



A stack of books is visible in the background, with a man's face wearing glasses partially visible on the left side. The text is overlaid on a white rectangular background.

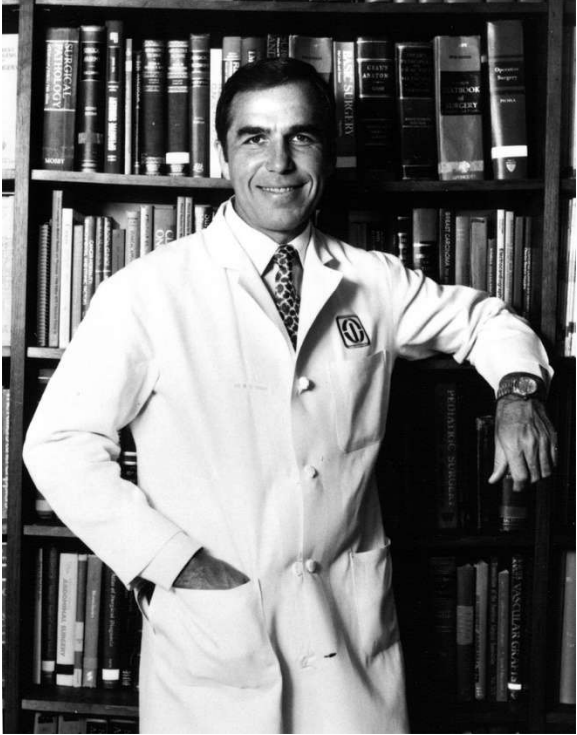
When we sense lipopolysaccharide (endotoxin), we are likely to turn on every defense at our disposal; we will bomb, defoliate, blockade, seal off, and destroy all the tissues in the area.

Our arsenals for fighting off bacteria are so powerful . . . That we are in more danger from them than from the invaders. We live in the midst of explosive devices; we are mined.

We are, in effect, at the mercy of our own pentagons . . .



# Roger C. Bone (1941-1997)



## A Piece of My Mind

### Another 'Taste of Lemonade'

Ten months ago on this page, I recounted my experience of being diagnosed with renal cancer. After recovering from my operation in which my right kidney and adrenal gland were removed, I became more appreciative and reflective toward the world around me. At the Medical College of Ohio School of Medicine Convocation some months later, I shared lemonade and cookies with new medical students.

Later, in my formal talk to the students, I advised them to balance the scientific with the humanistic. Students, like many of us, are caught up in the pressures of daily life and do not take time to savor the present. I told them that they must devote time to be with family and friends and to enjoy a Beethoven symphony or a good novel or a fine dinner.

Recently I learned that I have metastasis to both lungs and a positive bone scan. As a cancer survivor, I have seen the last two years with the threat of this possibility. The reality is not easy to accept. There is denial, anger, and a sense of great loss.

However, I have come to realize that the observations I wrote on this page are still true:

1. Good health is often taken for granted; however, it is the most precious commodity one possesses.
2. One's spouse, children, family, and friends are the essential ingredients that allow one to endure an experience such as a serious and unexpected illness.
3. When faced with death, one realizes the importance of God and one's relationship to God.
4. The things one does throughout one's life that seem so urgent are, most of the time, not so important.

Those observations have become a way of life for me. In my previous essay, I quoted American writers Thornton Wilder and Henry David Thoreau, who both noted that most men and women lead frantic and desperate lives, seldom pausing to reflect on their activities. I am glad that the initial diagnosis of cancer prepared me for the most feared of its complications, metastatic disease. However, I am most happy that the initial diagnosis made me think anew about life and therefore consider the contemplative philosophies of both Wilder and Thoreau. One activity that brought me peace after the initial diagnosis was quiet times where I just enjoyed being alone surrounded by nature, similar to, I imagine, Thoreau contemplating Walden Pond.

The day that my metastasis was confirmed was, of course, very traumatic: the shock of the findings and an initial flurry about what should be done and how soon. Finally, I politely called a halt to all activity for the day. I told my staff and friends at work that I was simply going home to be with my family and to sit and look at the river.

Which is what I did. Our house sits on a rather steep bluff and the Maumee River curves around a very wide bend below it. Our yard slopes gently to the edge of the bluff, then descends through grasses and wildflowers and bushes to the edge of the river. Birds and squirrels and chipmunks populate this slope. If you stand above the slope on a quiet day gazing over the river, you can hear the rustling of the animals in the brush. Occasionally, a bird sings sweetly.

It was a perfect October day, sunny, 70 degrees breeze. The wide, blue river sparkled when stirred by the wind. On both sides of the river trees grew down to the water. They were still mostly green, with only a hint of yellow.

The river's course flows in such a way that every year the sun seems to set exactly into the valley, being extinguished by the cool water.

I sat on a lawn chair, my suit coat and hat beside me. At that moment, time stopped. The present, and future—was compressed into one moment.

Thoreau went to Walden Pond to be in communion with nature, he found it. He recognized and recorded for us the closeness to the unity between nature and man.

Thornton Wilder, nearly a half century later, emphasized that the everyday wonders of our world end quickly and without warning. Life is short; be certain you are enjoying it.

Time slipped past, and I was surprised to find myself next to my chair. My daughter had just returned from the drink. The sun had set. My dog had chipped. Far down the upstream.

I look my wife in the eye and say, "Life has been good." I smile and say, "Life has been good."

### A Piece of My Mind The Taste of Lemonade on a Summer Afternoon

Every once in a while, you appreciate just being someone. The location need not be exotic. The event need not be elaborate. It is just a place. At a certain time, it is important to you. I experienced this sensation recently on a Friday afternoon. It was on a boat, before the fall convocation for first-year medical students at the Medical College of Ohio where I serve as president and chief executive officer.

My staff had arranged for me to meet informally with the The Convocation was great and full of life. A faint breeze splashing water was the only sound. There was a light breeze and the sun was just setting. There was a sense of peace. The sun was just setting. There was a sense of peace. The sun was just setting. There was a sense of peace.

1. Good health is often taken for granted; however, it is the most precious commodity one possesses. 2. One's spouse, children, family, and friends are the essential ingredients that allow one to endure an experience such as a serious and unexpected illness.

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My recovery was uneventful save for parentheses of my own recollection from that overnight. I was disappointed after a quick stay as the week passed. My life returned to normal. But I found that things were not quite what they were before. I found that I had more time to be contemplative. Some of the things that I had more time to be contemplative. Some of the things that I had more time to be contemplative.

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© by Roseanne K. Young, Associate Editor  
JAMA, December 6, 1995—Vol 274, No. 21

• "Sepsis is defined as an invasion of microorganisms and/or their toxins into the bloodstream, along with the organism's reaction against this invasion." (1989)

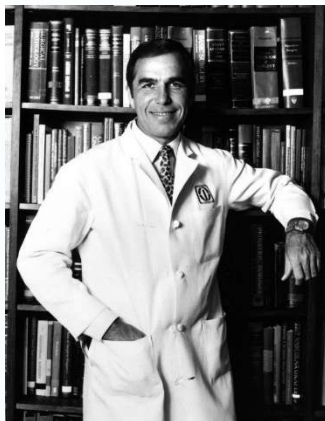
We should

JAMA February 15, 1996—Vol 275, No. 7

A Piece of My Mind



Biotech éra



éra antibiotik  
i.v. tekutiny

Stop ve snížení mortality

Definice sepsie

Septikémie

Endotoxic shock

Sepsis-induced MODS

1920'

budoucnost

A wooden door with a stone archway, featuring a central text box. The door is made of vertical wooden planks and has two horizontal metal bars across it. The archway is made of dark grey stone blocks. The text "Biotech éra" is written in a bold, black font inside a white rounded rectangle with a black border.

**Biotech éra**



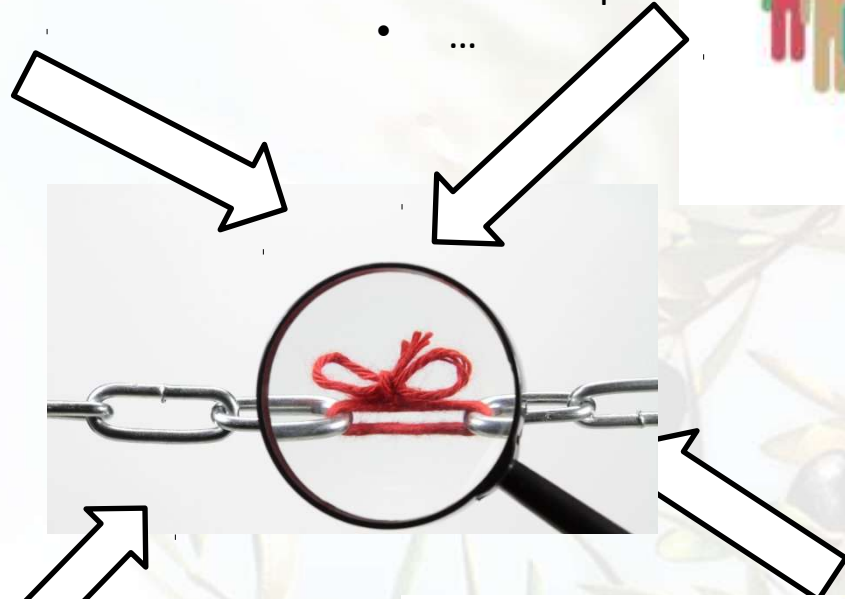
REMEMBER THE DEAD

@SETUVORA



SIRS - vše nebo nic  
Max 10% úmrtí

- Věk
- Komorbidity
- Křehkost/fitnes
- Genetický make-up
- Microbiota
- Imunosuprese
- ...



- Antibiotika
- Katecholaminy
- Transfúze
- Výživa
- Sedace
- Tekutiny
- CRRT, UPV, ECMO
- ....

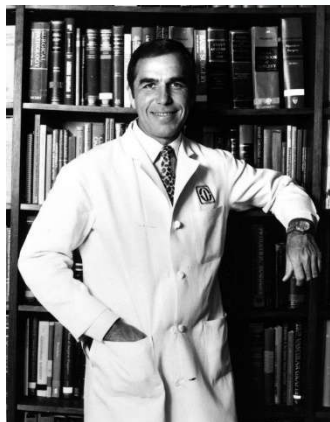


- Pneumonie
- Urosepse
- Peritonotis
- Fasciitis
- Cholangitis
- Meningitis
- ...



**Surviving  
Sepsis  
Campaign**

Biotech éra



éra antibiotik  
i.v. tekutiny

Selhání anti-sepsis  
pokusů

Stop ve snížení mortality

1. definice sepse

Septikémie

Endotoxic shock

Sepsis-induced MODS

1920'

budoucnost



## 2001 Intenzivisté v říši divů





# The New England Journal of Medicine

*Owned, published, and © copyrighted, 2001, by the MASSACHUSETTS MEDICAL SOCIETY*

Volume 345(19)

8 November 2001

pp 1368-1377

## Early Goal-Directed Therapy in the Treatment of Severe Sepsis and Septic Shock



Notice: Because of its possible clinical implications, this article is being released before its publication date. The report will be published on March 8.

### EFFICACY AND SAFETY OF RECOMBINANT HUMAN ACTIVATED PROTEIN C FOR SEVERE SEPSIS

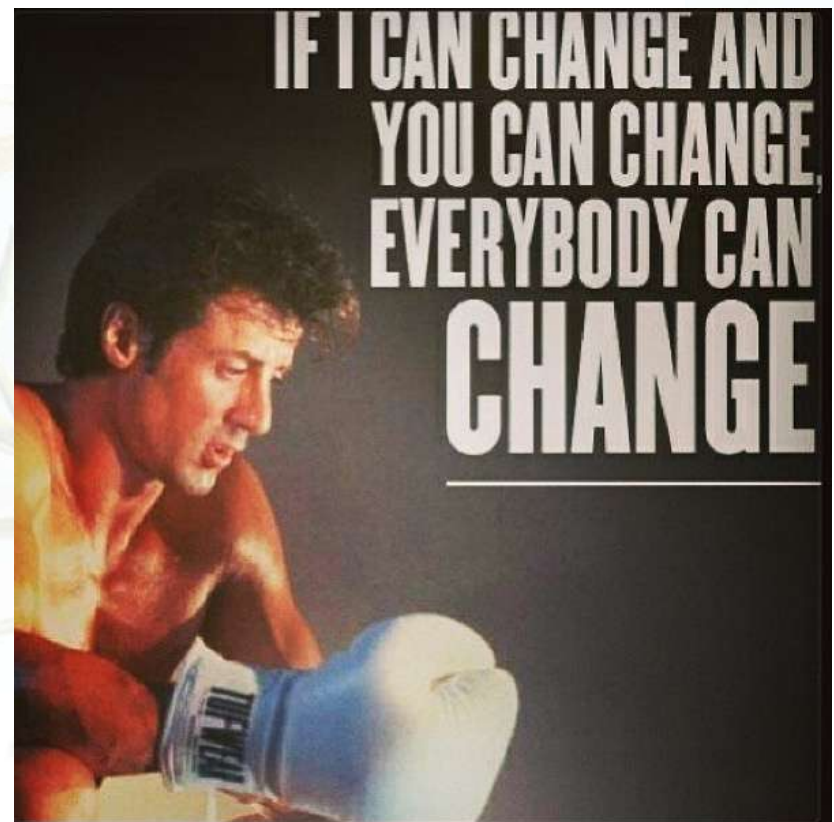
GORDON R. BERNARD, M.D., JEAN-LOUIS VINCENT, M.D., PH.D., PIERRE-FRANCOIS LATERRE, M.D., STEVEN P. LAROSA, M.D., JEAN-FRANCOIS DHAINAUT, M.D., PH.D., ANGEL LOPEZ-RODRIGUEZ, M.D., JAY S. STEINGRUB, M.D., GARY E. GARBER, M.D., JEFFREY D. HELTERBRAND, PH.D., E. WESLEY ELY, M.D., M.P.H., AND CHARLES J. FISHER, JR., M.D.,  
FOR THE RECOMBINANT HUMAN ACTIVATED PROTEIN C WORLDWIDE EVALUATION IN SEVERE SEPSIS  
(PROWESS) STUDY GROUP\*

### INTENSIVE INSULIN THERAPY IN CRITICALLY ILL PATIENTS

GREET VAN DEN BERGHE, M.D., PH.D., PIETER WOUTERS, M.Sc., FRANK WEEKERS, M.D., CHARLES VERWAEST, M.D., FRANS BRUYNINCKX, M.D., MIET SCHETZ, M.D., PH.D., DIRK VLASSELAERS, M.D., PATRICK FERDINANDE, M.D., PH.D., PETER LAUWERS, M.D., AND ROGER BOUILLON, M.D., PH.D.



# Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock



**Jak se vařila SSC...  
aneb  
o čem se mluví méně**

Surviving Sepsis  
Campaign





# United States Patent and Trademark Office

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## An Agency of the Department of Commerce



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United States Patent  
Rivers

5,673,694  
October 7, 1997

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Method and apparatus for continuous measurement of central venous oxygen saturation

### Abstract

An apparatus (10) and method for measurement of oxygen saturation of venous blood for use with a *central venous catheter* (60) are described. The apparatus (10) includes a fiber optic bundle (12) having a distal end (14) and a proximal end (16). The fiber optic bundle (12) further includes afferent and efferent light-conducting fibers (18) for sending signals and receiving signals for generating oxygen saturation measurements. A sheath (28) is disposed about the fiber optic bundle (12) for encapsulating and protecting the fiber optic bundle (12) and exposing the distal end (14) of the fiber optic bundle (12). The apparatus (10) includes a locking device (30) for locking the fiber optic bundle (12) relative to a catheter (11) into which the fiber optic bundle (12) is inserted to fix the relative relationship between the fiber optic bundle (12) and the catheter (11) when disposed in situ during an oxygen saturation measurement procedure.

---

**Inventors:** Rivers; Emanuel Phillip (Franklin, MI)



**PAGE ONE**

# New Therapy for Sepsis Infections Raises Hope but Many Questions

By **THOMAS M. BURTON**  
*August 14, 2008; Page A1*



**Emanuel P. Rivers**

Hospital statisticians who worked on it had concerns about the data and recalculated the results with all 288 patients, according to people familiar with the events. When they did, these people say, the death-rate gap wasn't statistically significant.

The Lilly logo is written in a red, cursive script font.

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## Lilly Receives FDA Approval to Market Xigris™

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Wednesday, November 21, 2001

Eli Lilly and Company (NYSE: LLY) announced today that the U.S. Food and Drug Administration (FDA) has approved Xigris™

"The approval of Xigris breaks new ground," says Mitchell Levy, M.D., F.C.C.M.,



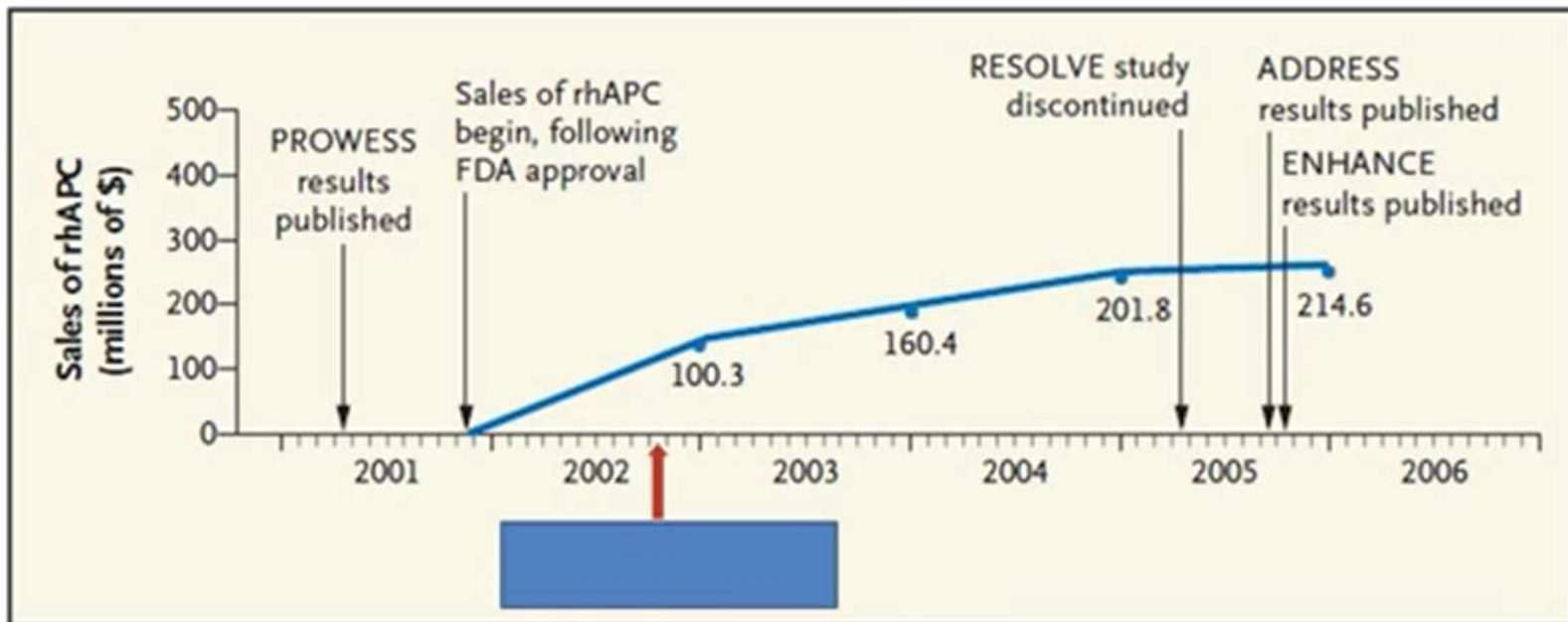


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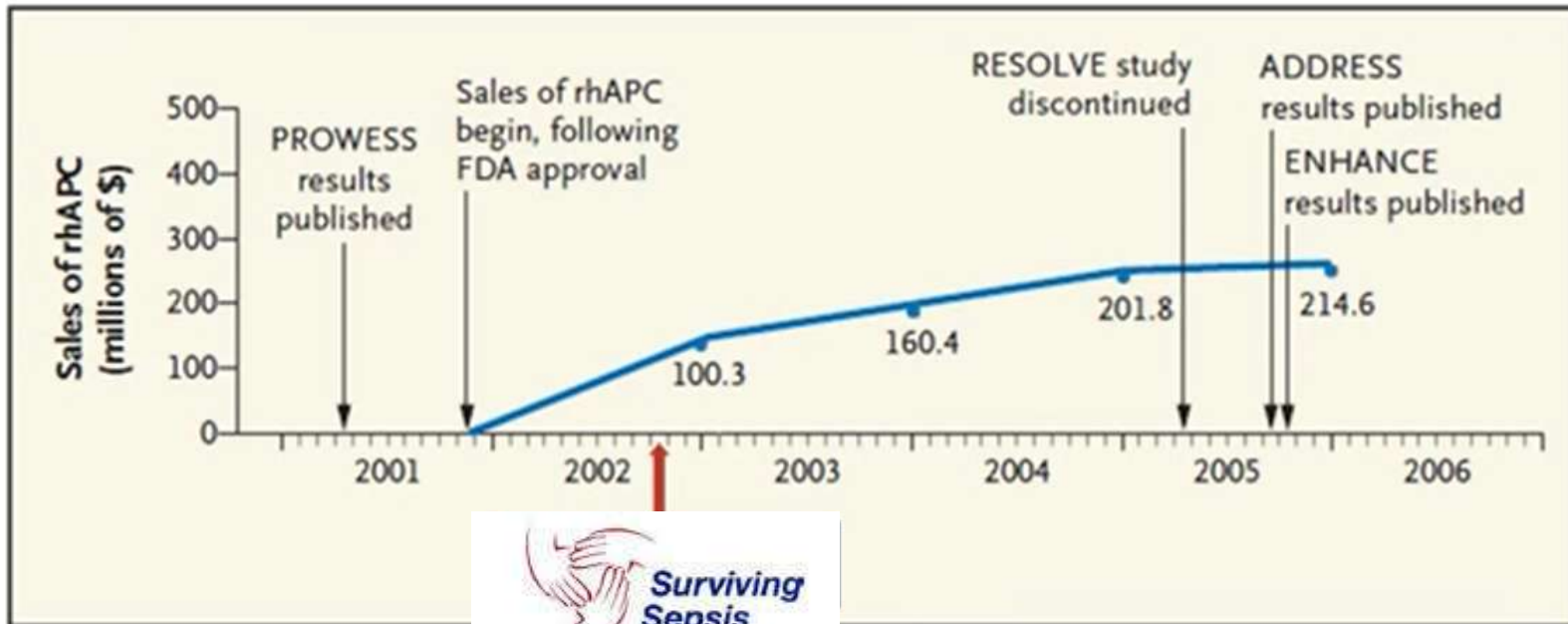


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## Surviving Sepsis — Practice Guidelines, Marketing Campaigns, and Eli Lilly

Peter Q. Eichacker, M.D., Charles Natanson, M.D., and Robert L. Danner, M.D.

"To improve sales of rhAPC, in 2002, Lilly hired *Belsito and Company*, a public relations firm, to develop and help implement a marketing strategy. The Surviving Sepsis Campaign was established, in theory to raise awareness of severe sepsis and generate momentum toward the development of treatment guidelines."



## Surviving Sepsis — Practice Guidelines, Marketing Campaigns, and Eli Lilly

Peter Q. Eichacker, M.D., Charles Natanson, M.D., and Robert L. Danner, M.D.

"..... Lilly provided 90% of the funding and almost all participants had financial or other relationships with the company

The remaining 10% was provided by American Edwards, manufacturer of the PreSep catheter used to treat sepsis."

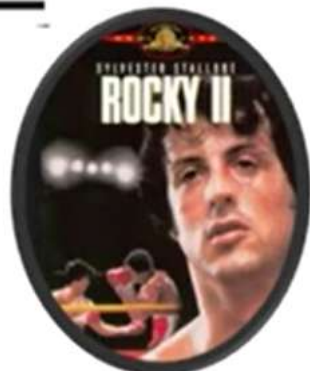


PreSep Central Venous Oximetry

Special Article

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Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock: 2008



Special Article

---

**Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: 2012**



Special Article

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



Andrew Rhodes, MB BS, MD(Res) (Co-chair)<sup>1</sup>; Laura E. Evans, MD, MSc, FCCM (Co-chair)<sup>2</sup>;  
Waleed Alhazzani, MD, MSc, FRCPC (methodology chair)<sup>3</sup>; Mitchell M. Levy, MD, MCCM<sup>4</sup>;



**Pride Comes  
Before The  
Fall**

2013

2014

The NEW ENGLAND JOURNAL of MEDICINE

# A Randomized Trial of Protocol-Based Care for Early Septic Shock

The ProCESS Investigators\*

## Goal-Directed Resuscitation for Patients with Early Septic Shock

The ARISE Investigators and the ANZICS Clinical Trials Group\*

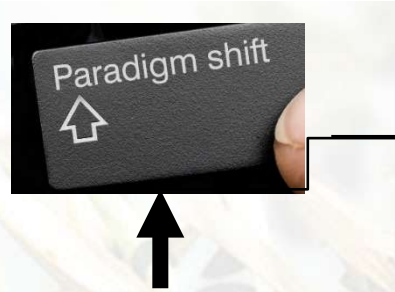
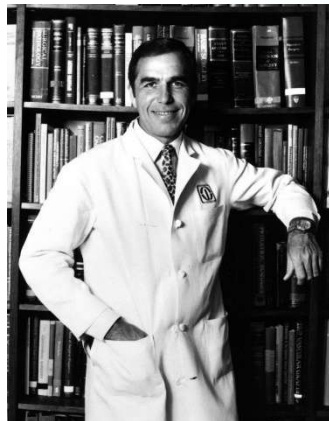
## Trial of Early, Goal-Directed Resuscitation for Septic Shock

Paul R. Mouncey, M.Sc., Tiffany M. Osborn, M.D., G. Sarah Power, M.Sc.,  
David A. Harrison, Ph.D., M. Zia Sadique, Ph.D., Richard D. Grieve, Ph.D.,  
Rahi Jahan, B.A., Sheila E. Harvey, Ph.D., Derek Bell, M.D., Julian F. Bion, M.D.,  
Timothy J. Coats, M.D., Mervyn Singer, M.D., J. Duncan Young, D.M.,  
and Kathryn M. Rowan, Ph.D., for the ProMISe Trial Investigators\*

# *P.E.Marik, myth-buster, status quo destabilizer*



Biotech éra



éra antibiotik  
i.v. tekutiny

Selhání anti-sepsis  
pokusů

Stop ve snížení mortality

1. definice sepse

Septikémie

Endotoxic shock

Sepsis-induced MODS

1920'

budoucnost



# Sepsis care: pre-2001 éra:

1. Rozpoznej sepsi včas
2. Dej ATBs, tekutiny a vazopresory, pokud třeba
3. Sleduj pozorně



# Post EGDT éra:

1. viz 1-3 výše
2. „do it better“



Fix what is  
broken



# Někdy nedělejte nic (wait and watch)



Analýzy prokazují, že brankář má větší šanci chytit penaltu, pokud zůstane stát na místě.

Přesto většina brankářů nepřijme tento fakt.

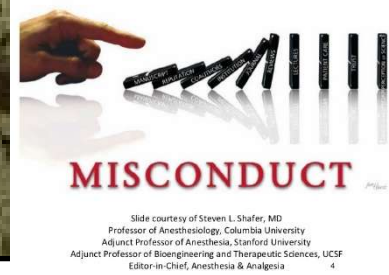
Vysvětlení: zůstat stát navozuje dojem “hloupého, pasivního” naopak, jakákoliv akce je vnímána jako dobrá snaha, byť neúspěšná



$DO_2 / VO_2$  paradigma  
SvO<sub>2</sub>, lactate  
targets...

Tekutinová resuscitace  
Bolusy tekutin  
Bilance tekutin  
Umělé koloidy

A kurva...



Blood purification

Nálož vazopresorů

Nálož ATB

...UPV, sedace, transfúze, výživa...

Dokonce i samotná intenzivní péče.....

# Effect of Systematic Intensive Care Unit Triage on Long-term Mortality Among Critically Ill Elderly Patients in France

## A Randomized Clinical Trial

Bertrand Guidet, MD; Guillaume Leblanc, MD; Tabassome Simon, MD, PhD; Maguy Woimant, MD; Jean-Pierre Quenot, MD; Olivier Ganansia, MD; Maxime Maignan, MD; Youri Yordanov, MD; Samuel Delerme, MD; Benoit Doumenc, MD; Muriel Fartoukh, MD; Pierre Charestan, MD; Pauline Trognon, MD; Bertrand Galichon, MD; Nicolas Javaud, MD; Anabela Patzak, MD; Maité Garrouste-Orgeas, MD; Caroline Thomas, MD; Sylvie Azerad, PharmD; Dominique Pateron, MD; Ariane Boumendil, PhD; for the ICE-CUB 2 Study Network

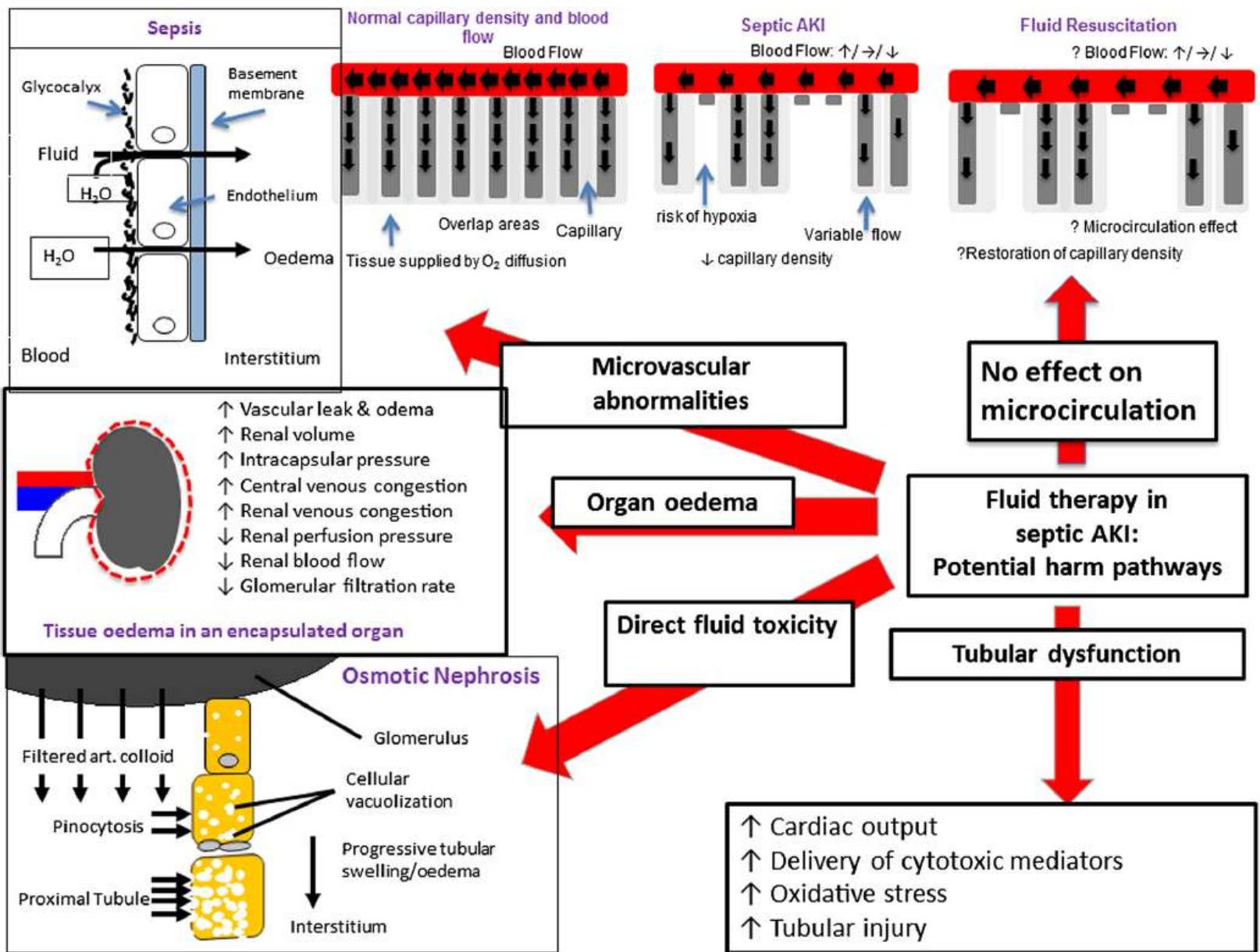
### Key Points

**Question** Does a program to increase intensive care unit (ICU) admission rates among critically ill elderly patients have a

1.66-1.95). After adjustments for baseline characteristics, patients in the systematic strategy group were more likely to be admitted to an ICU (RR, 1.68; 95% CI, 1.54-1.82) and had a higher risk of in-hospital death (RR, 1.18; 95% CI, 1.03-1.33) but had no significant increase in risk of death at 6 months (RR, 1.05; 95% CI, 0.96-1.14). Functional status and physical quality of life at 6 months were not significantly different between groups.

6 months vs standard practice (adjusted relative risk, 1.05).

**Meaning** A program to promote systematic ICU admission among critically ill elderly patients increased ICU use but did not reduce 6-month mortality.



**Fig. 3** Illustration of possible injury pathways that might be associated with overzealous fluid resuscitation in patients at risk of or developing septic AKI (interpretation of data from references [29–32])

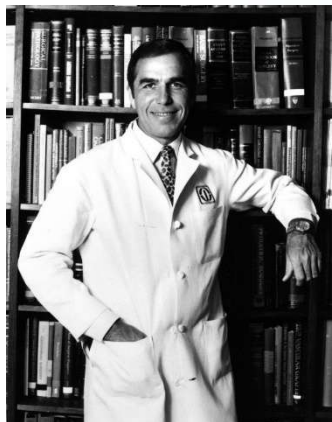
# AXIOM moderní (intenzivní) medicíny

**spokojený lékař  $\neq$  spokojený pacient**



Normalizace fyziologie, cílená na čísla, může být škodlivá

Biotech éra



less iatrogenic harm



Limity SSC

éra antibiotik  
i.v. tekutiny

Selhání anti-sepsis  
pokusů

Stop ve snížení mortality

1. definice sepse

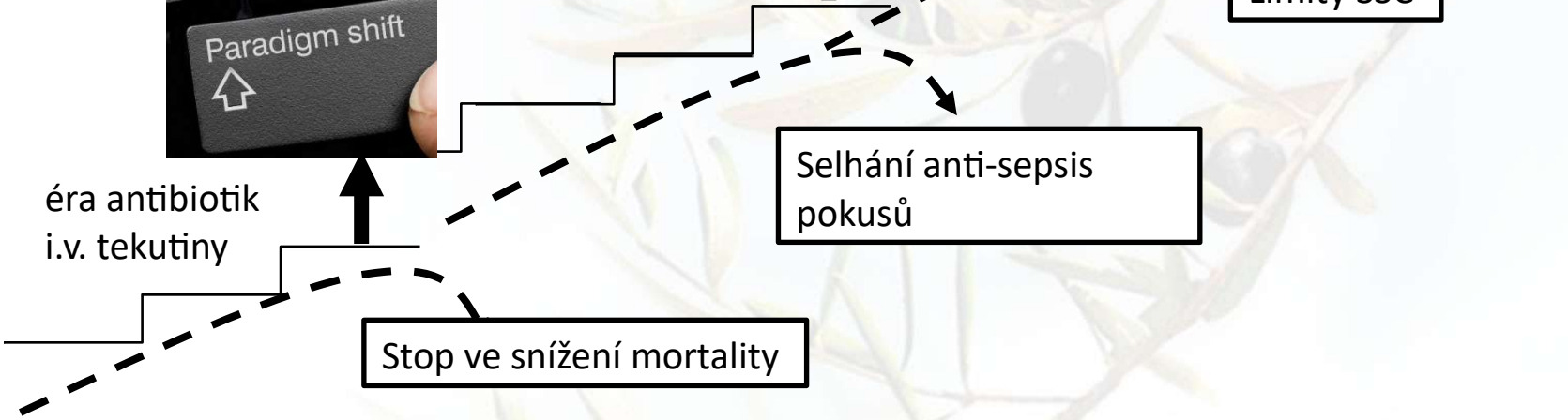
Septikémie

Endotoxic shock

Sepsis-induced MODS

1920'

budoucnost





Omyly „těžkých  
vah“

# I „těžké váhy“ se mohou mýlit



## Reviews

### The Hemodynamic Derangements in Sepsis\*

#### Implications for Treatment Strategies

*Paul E. Marik, MD, FCCP; and Joseph Varon, MD, FCCP*

*CHEST 1998; 114:854-860*

„Aggressive volume resuscitation is considered the best initial therapy for the cardiovascular instability of sepsis. Hypotension can often be reversed with fluid administration alone. Fluid requirements for the initial resuscitation of patients with septic shock are frequently large, with up to 10 L of crystalloid or 4 L of colloid being required in the first 24 hours“.

„charisma-based medicine“



# I „těžké váhy“ se mohou mýlit



CHEST 1998; 114:854–860

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## A rational approach to fluid therapy in sepsis

P. Marik<sup>1,\*</sup> and R. Bellomo<sup>2</sup> *British Journal of Anaesthesia*, 116 (3): 339–49 (2016)

*Great myth in the management of sepsis:  
„sepsis is primarily a volume-depleted state“*



CHEST

Postgraduate Education Corner

CONTEMPORARY REVIEWS IN CRITICAL CARE MEDICINE

## Hemodynamic Evaluation and Monitoring in the ICU\*

*Michael R. Pinsky, MD, FCCP*

### *Hemodynamic Monitoring Truths*

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Tachycardia is never a good thing.

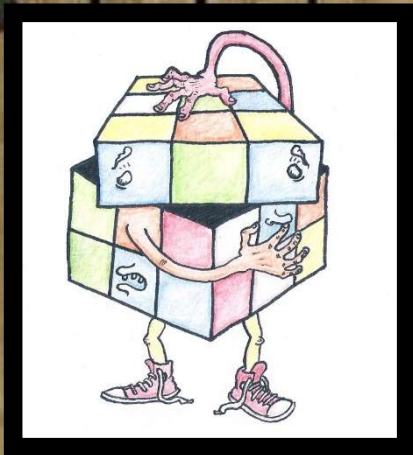
Hypotension is always pathologic.

There is no such thing as normal cardiac output.

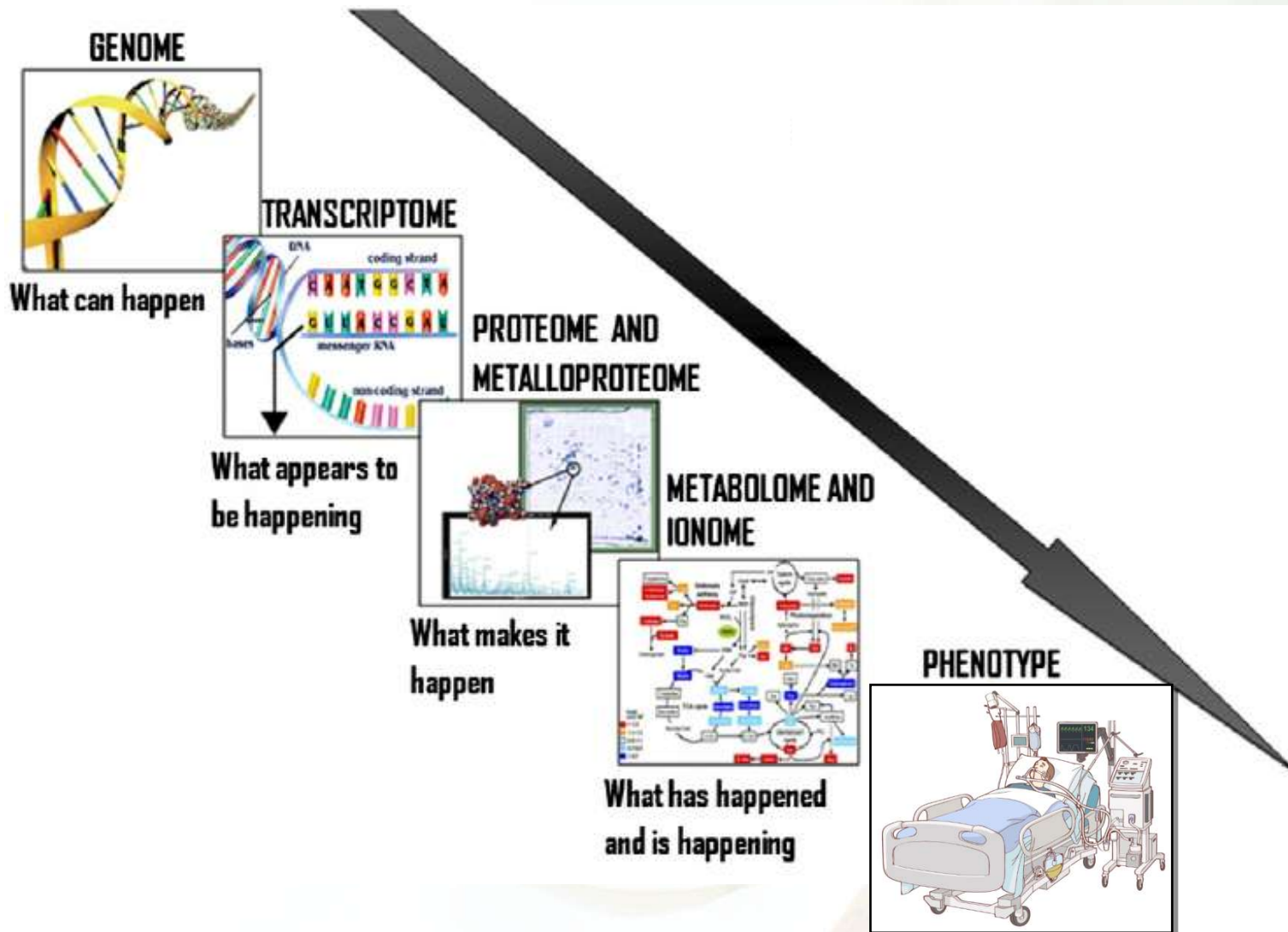
Central venous pressure is only elevated in disease.

Peripheral edema is of cosmetic concern.

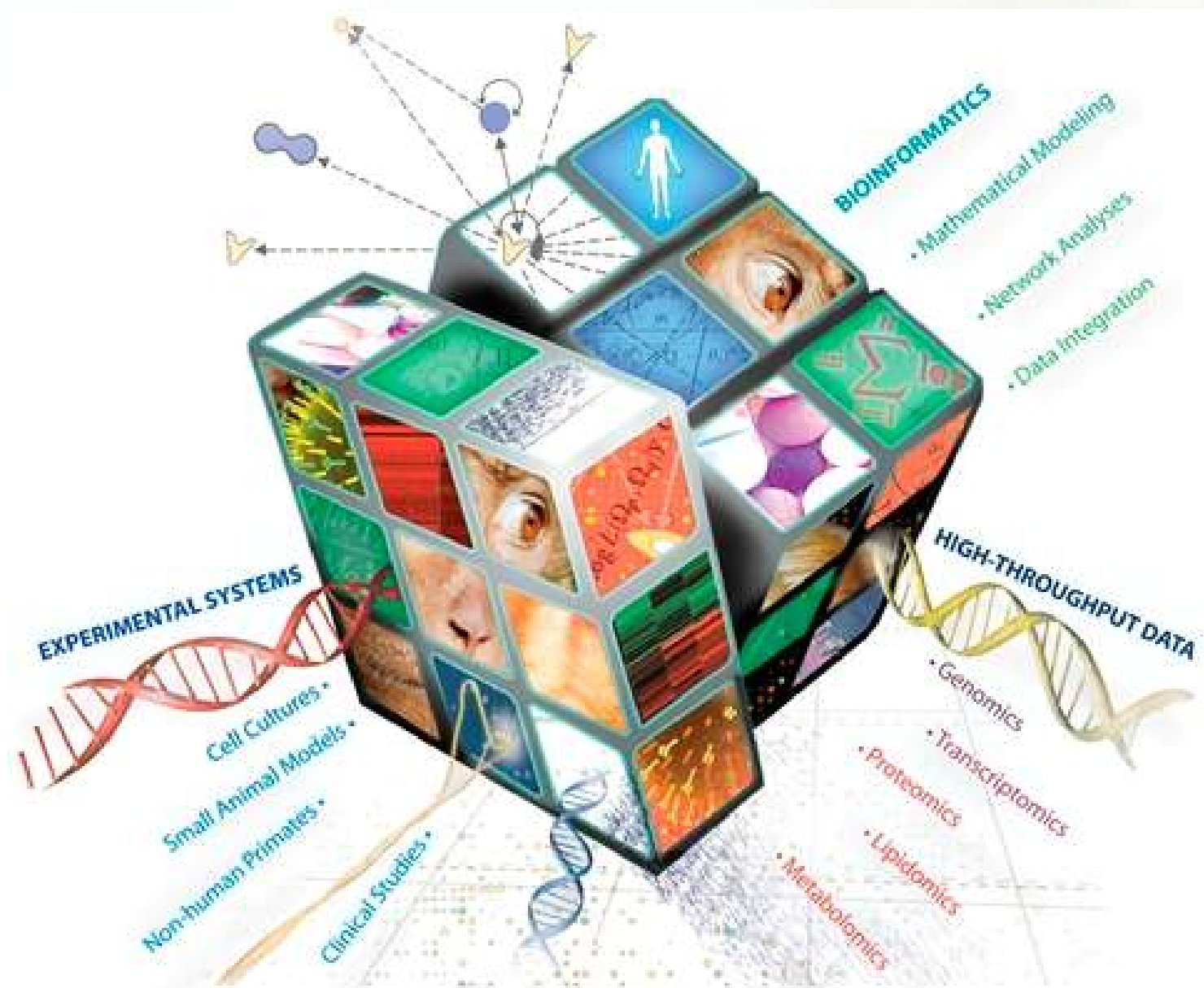
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# Podobná klinická prezentace (klinický fenotyp)



Odlišná buněčná a molekulární odpověď



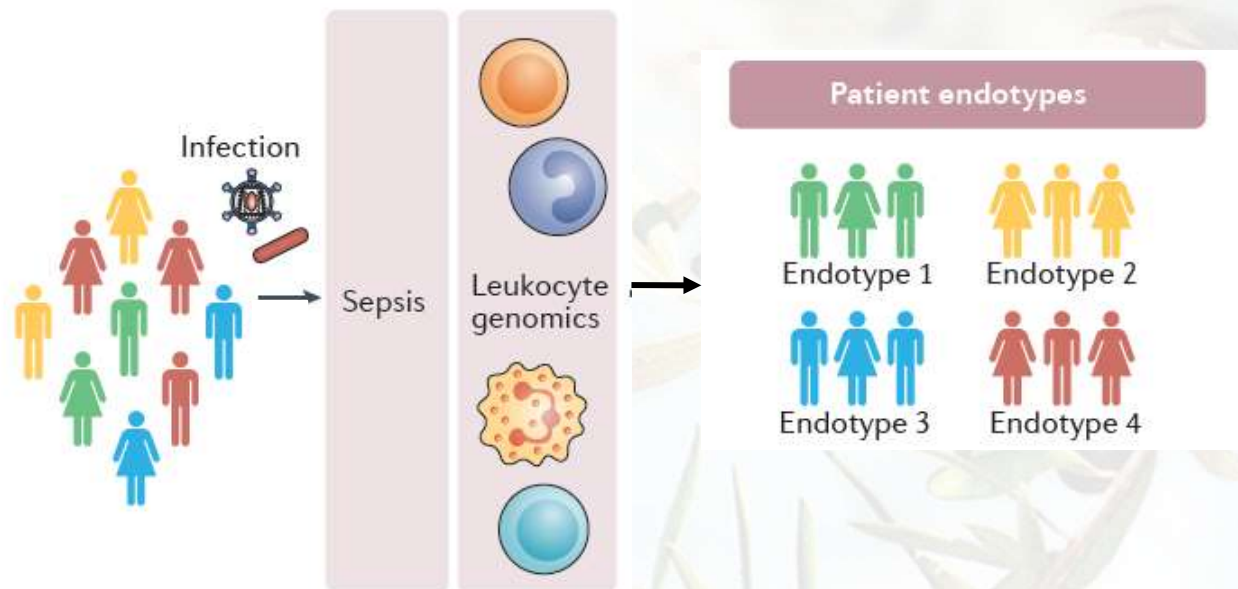
# Classification of patients with sepsis according to blood genomic endotype: a prospective cohort study



THE LANCET

Brendon P Scicluna, Lonneke A van Vught, Aeilko H Zwinderman, Maryse A Wiewel, Emma E Davenport, Katie L Burnham, Peter Nürnberg, Marcus J Schultz, Janneke Horn, Olaf L Cremer, Marc J Bonten, Charles J Hinds, Hector R Wong, Julian C Knight, Tom van der Poll, on behalf of the MARS consortium\*

2017



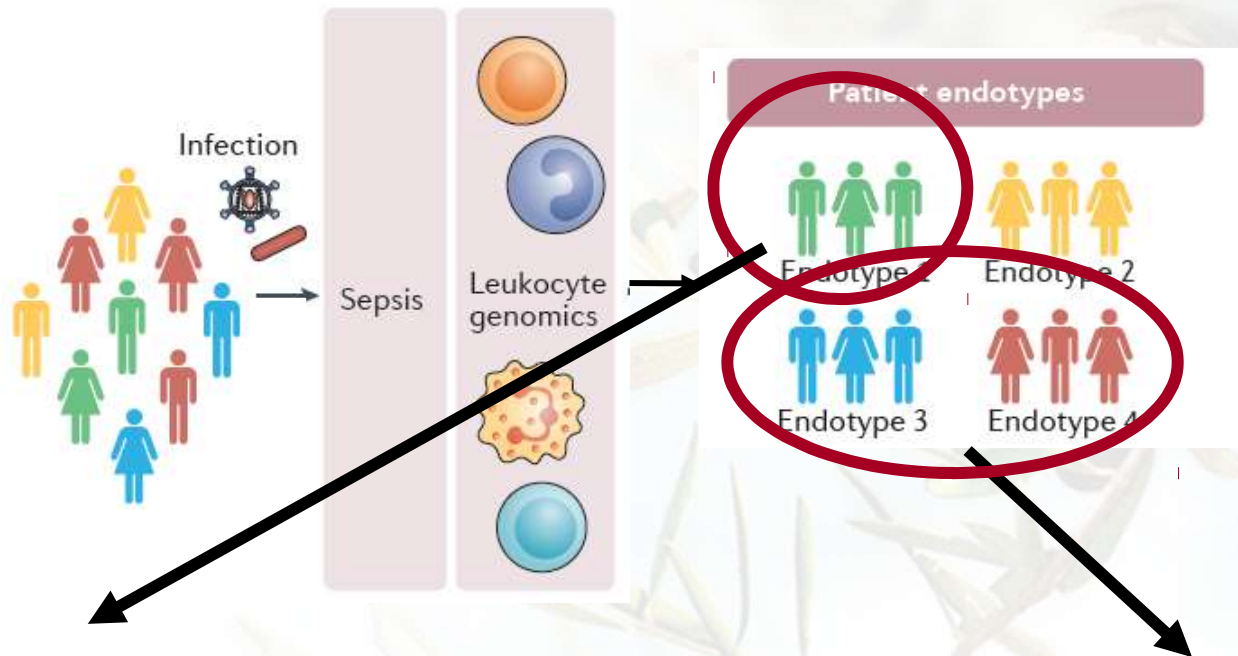
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2017



Typ 1 - Sepsis response signature

40%

2x vyšší mortalita

Imunoparalytický fenotyp

Typ 3,4 - Sepsis response signature

Proinflammatorní fenotyp

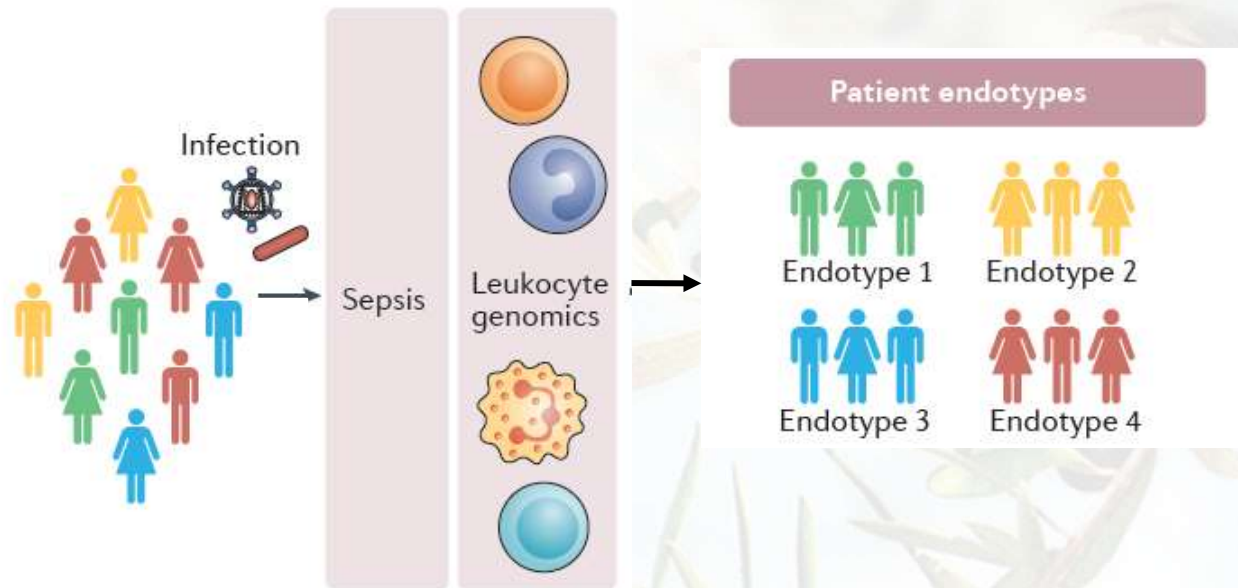
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2017



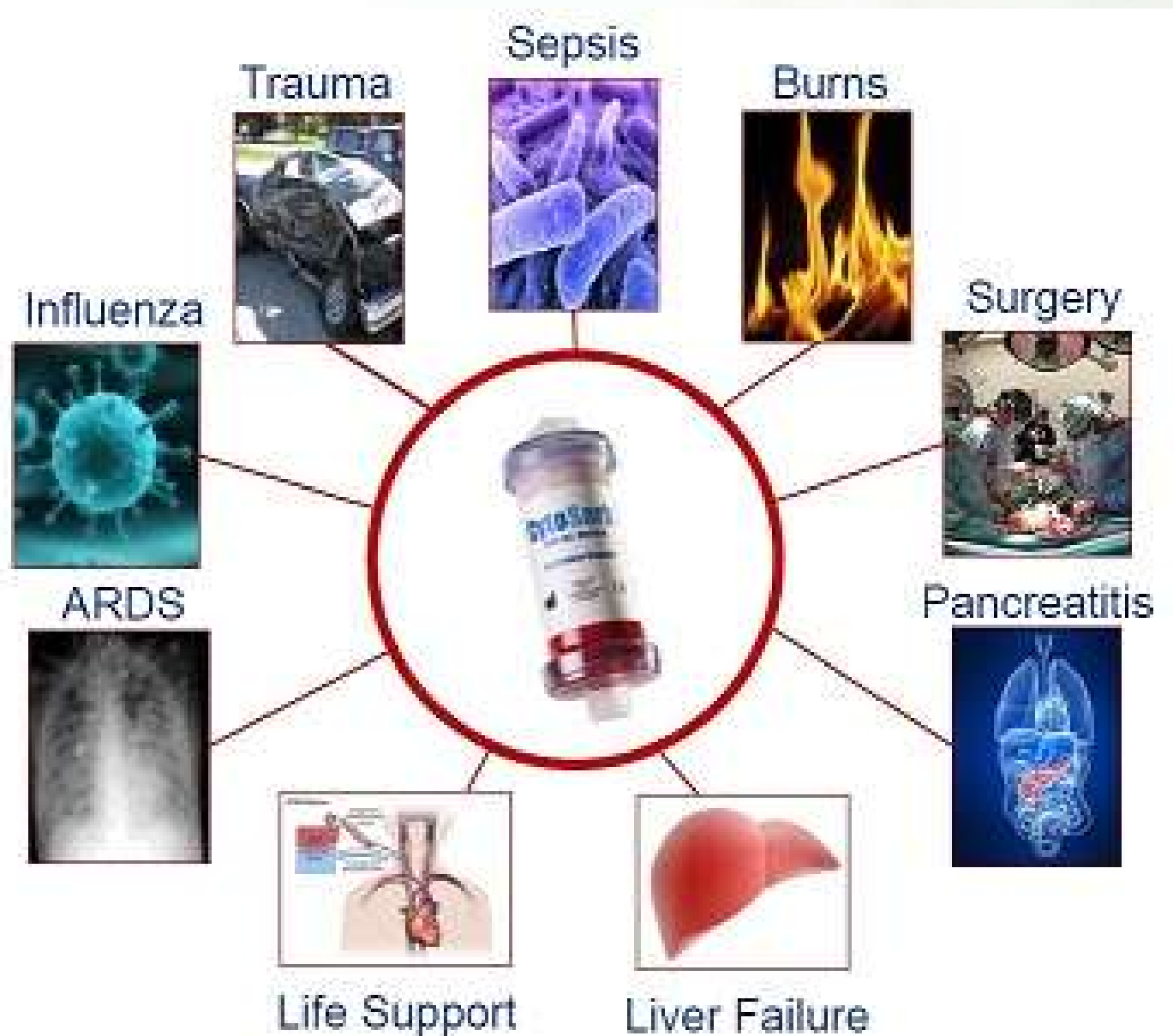
- Imunoparalýza je u řady pacientů přítomna velmi časně
- Jednotlivé SRS nelze rozpoznat klinicky!



# Hemopurifikační metody



# CytoSorb aneb dvakrát do stejné řeky...

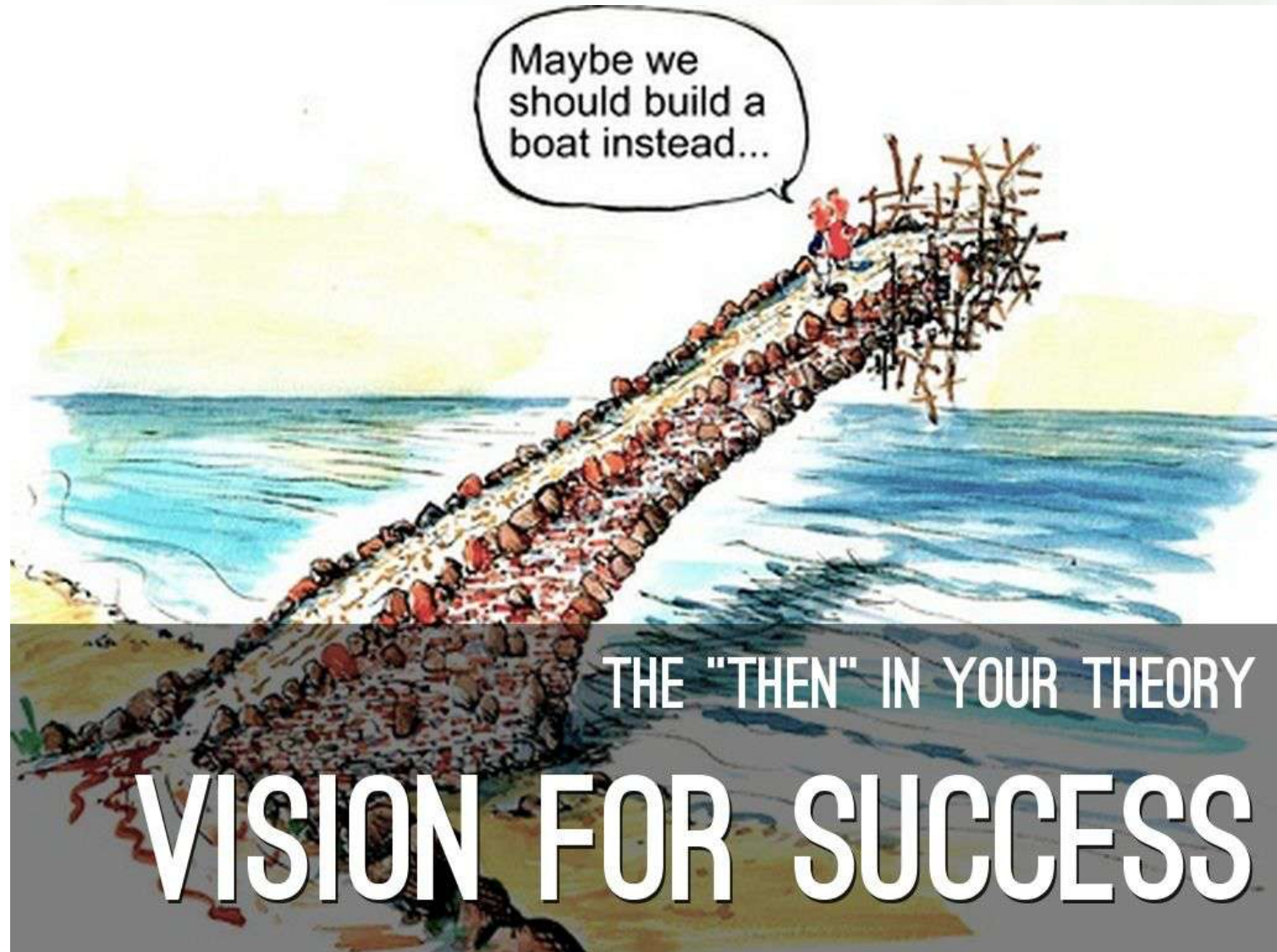


největší ryze elektronický burzovní trh v USA



Zastavte cytokiny dříve, než  
oni zastaví vás<sup>®</sup> (M. Matějovič)

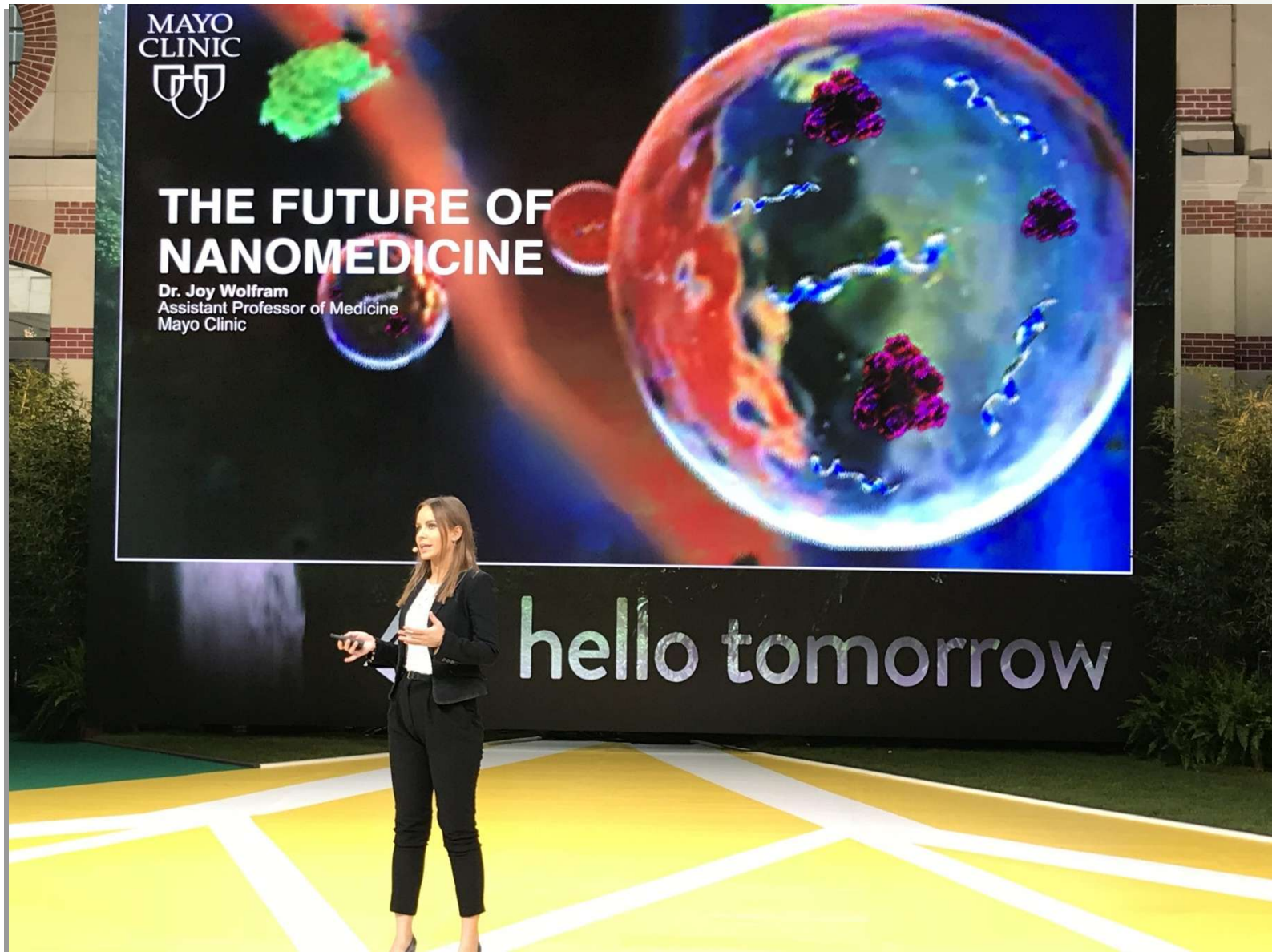
# Bridge over troubled water?



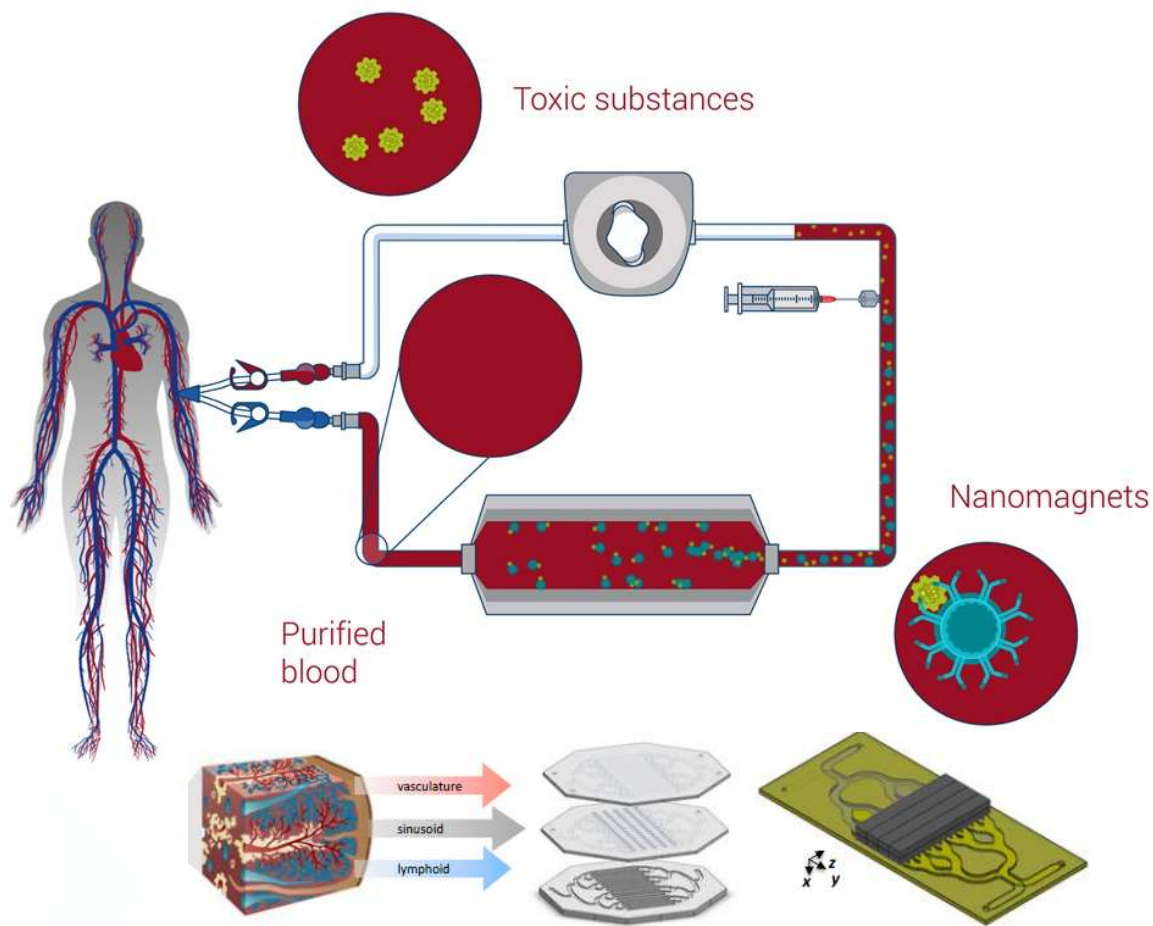
THE "THEN" IN YOUR THEORY

VISION FOR SUCCESS

# Real big deal



# „Inspirováno slezinou“ aneb skutečně nový koncept - bioslezina

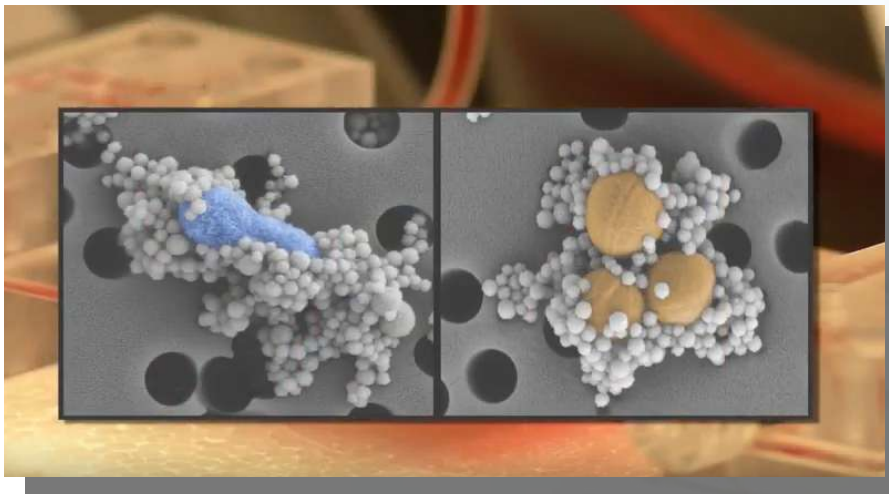


Magnetické nanoperličky s lidskými opsoniny (MBL)  
Bez aktivace komplementu, koagulace, inflamace

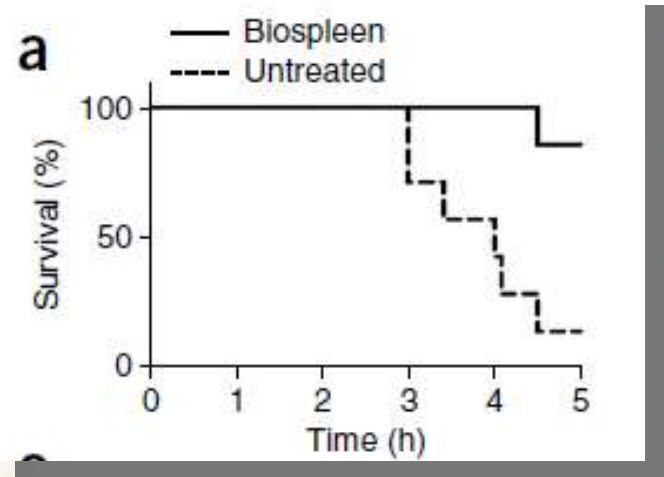


nature  
medicine

published online 14 September 2014;



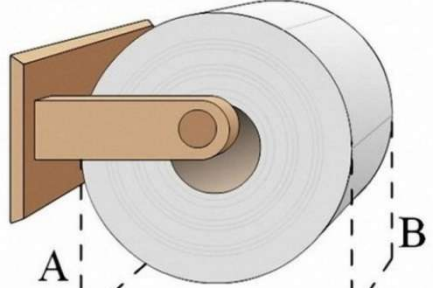
90% cirkulujících bakterií



Wyss Institute for Biologically Inspired Engineering, Boston, Massachusetts, USA.  
Harvard School of Engineering and Applied Sciences, Cambridge, Massachusetts, USA

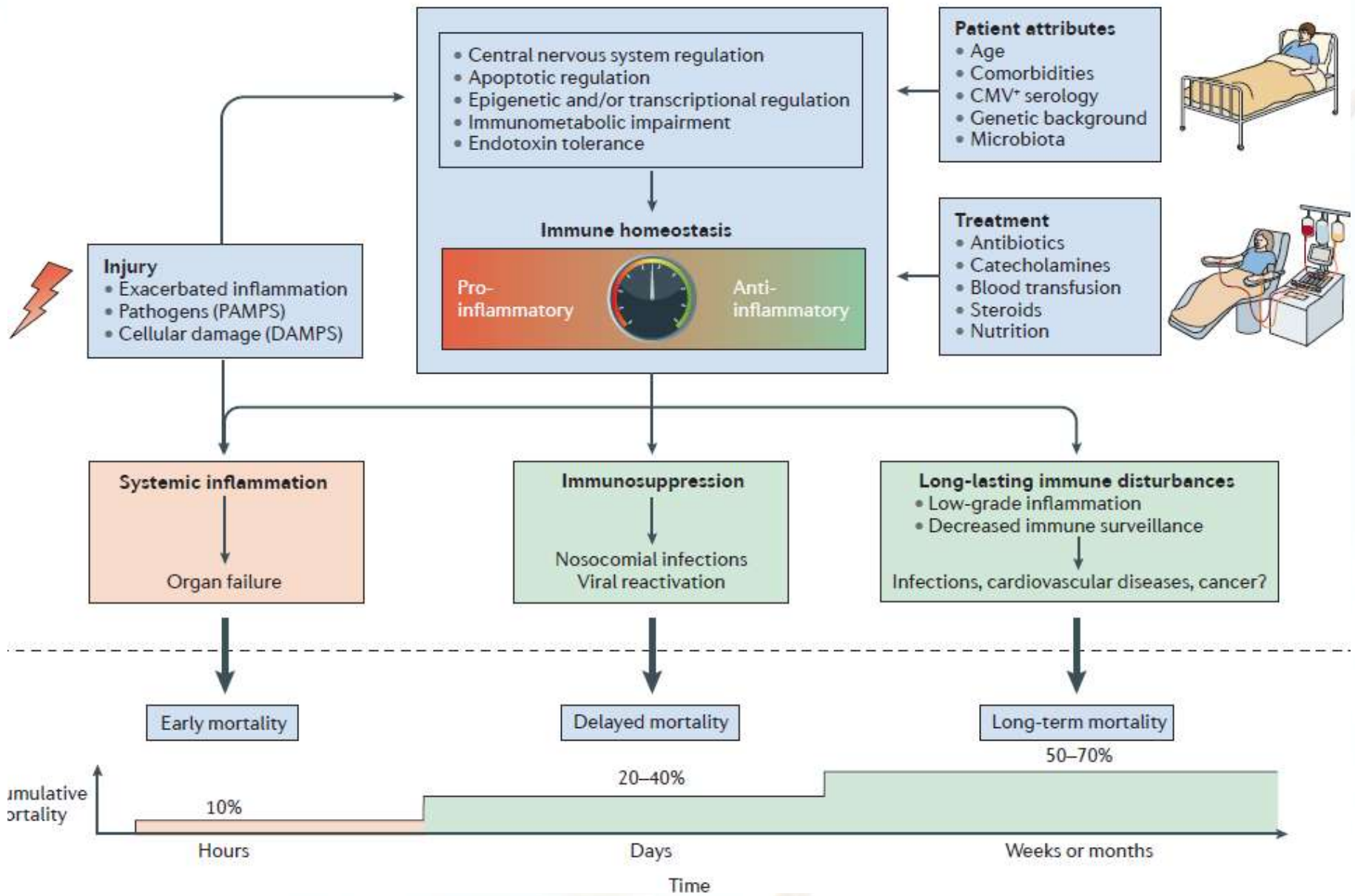


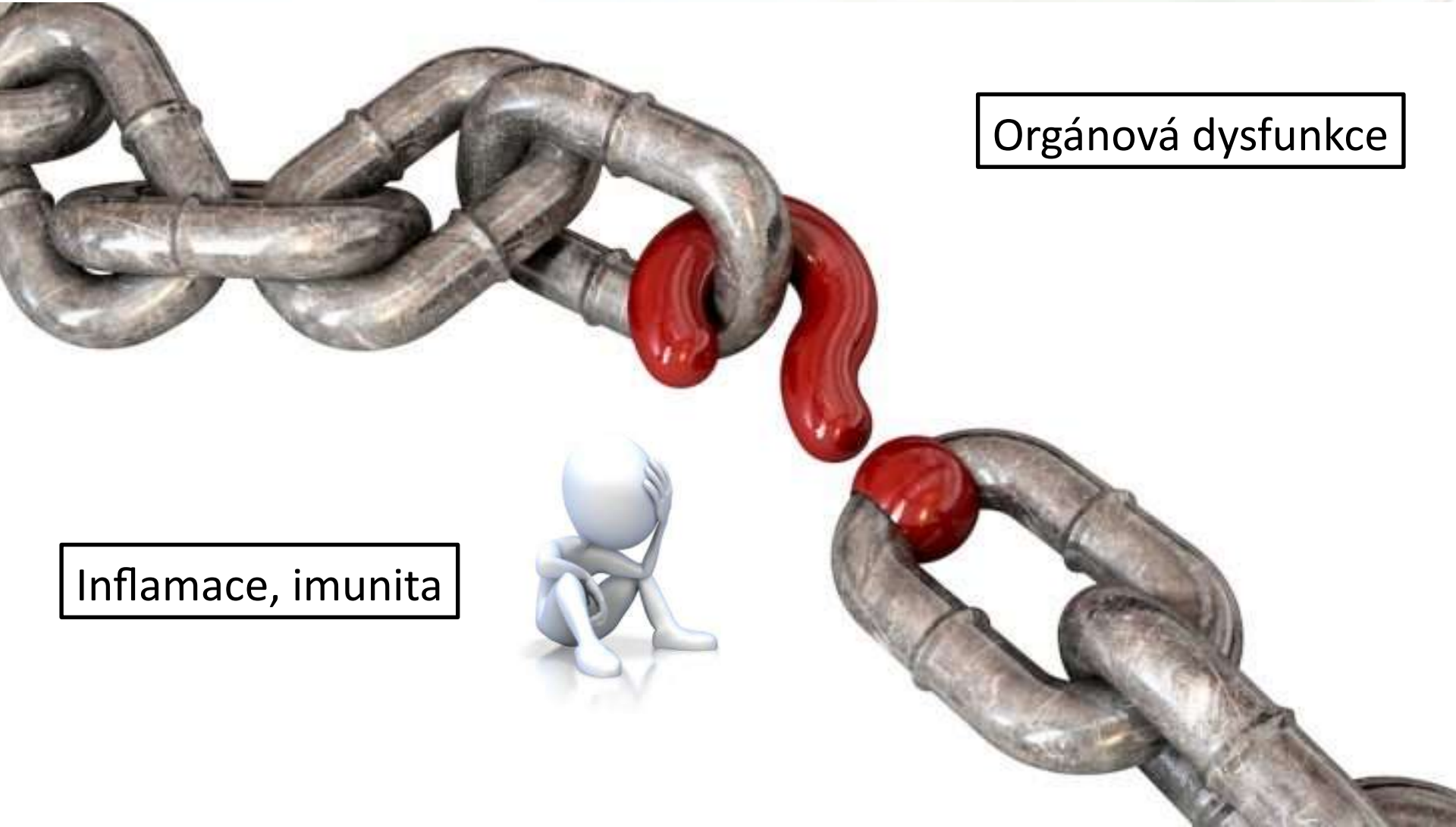
THE GREAT



DEBATE







Orgánová dysfunkce

Inflamace, imunita



## Concepts in Emergency and Critical Care

Roger C. Bone, MD, Section Editor


# Reevaluation of the Role of Cellular Hypoxia and Bioenergetic Failure in Sepsis

Richard S. Hotchkiss, MD, Irene E. Karl, PhD

JAMA 1992;267:1503



A TIME WHEN THERE WAS NO LAW AND  
MAN...WOMAN... AND BEAST ROAMED THE EARTH-UNTAMED!



Now on the Giant Screen  
in breathtaking PanaMation  
and vivid Color—  
the dawn of civilization  
recreated as never before  
...with all its realism,  
savagery and scenic  
splendors!

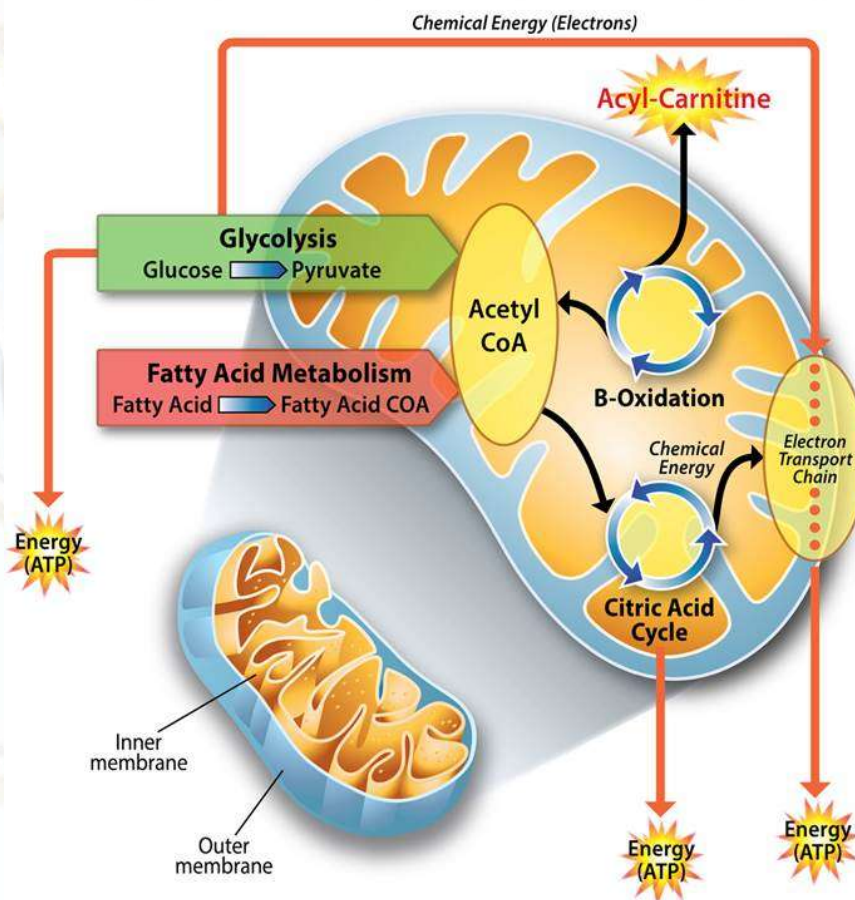
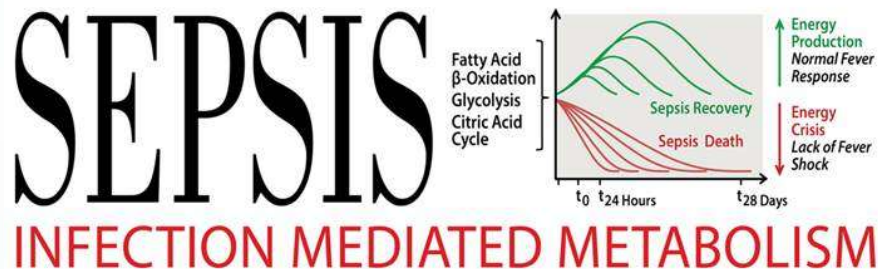
# THE MYSTERY OF MODS

by Mervyn Singer

# Metabolicko-bioenergetický re-programming



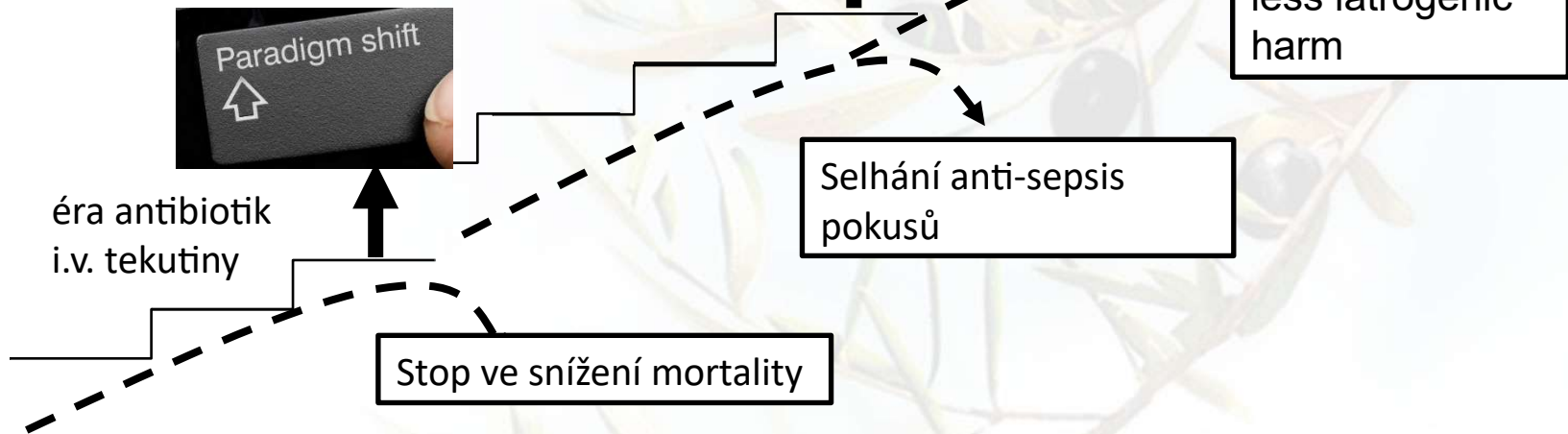
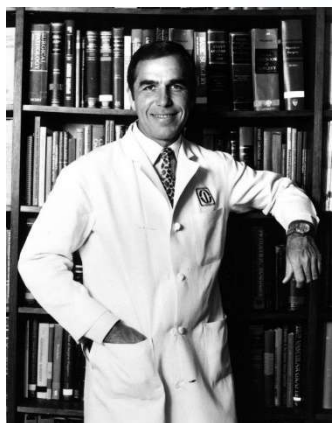
Úsporný režim





13  
komnata

Biotech éra



1. definice sepsie

Septikémie

Endotoxic shock

Sepsis-induced MODS

1920'

budoucnost

# Co mají společného?

Meningokoková infekce

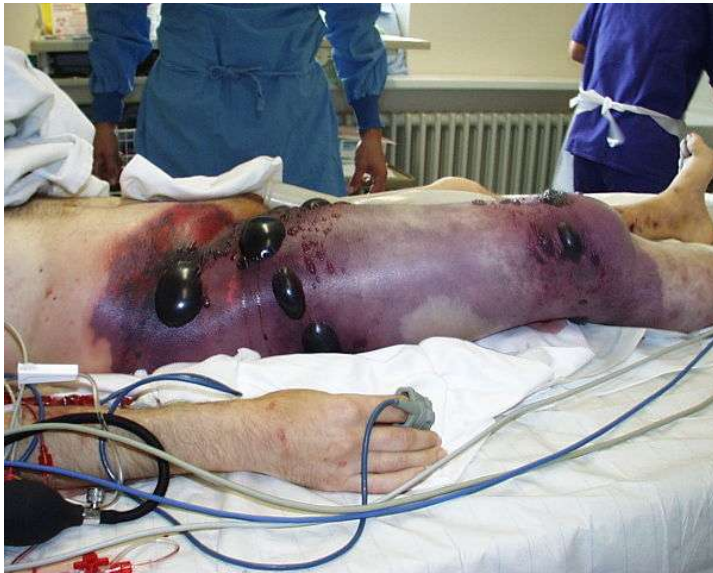


Pooperační pneumonie



# Co mají společného?

STSS



Ebola virus

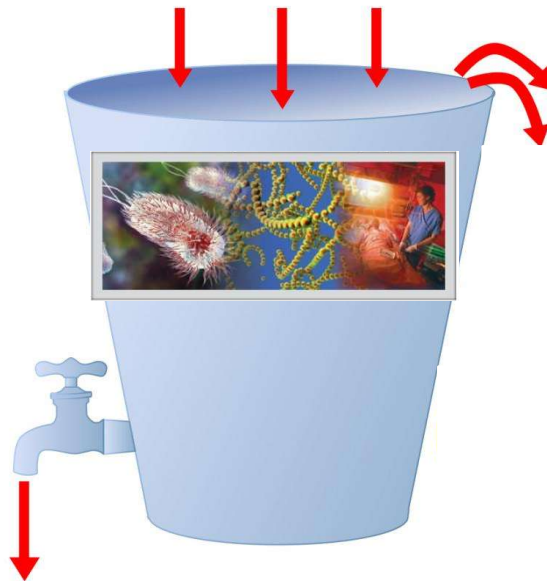


**Vysoké riziko úmrtí**  
**Život ohrožující orgánová dysfunkce**



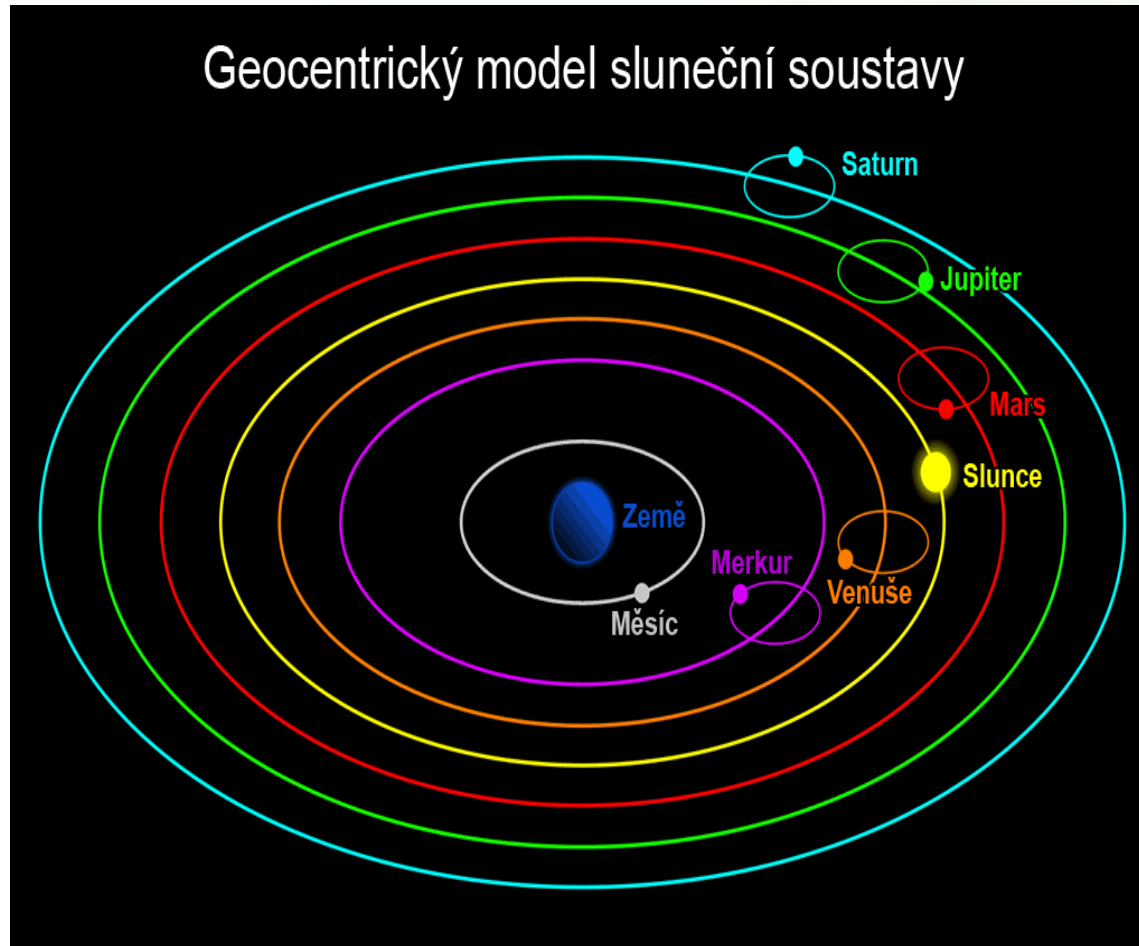
# Sepse jako kognitivní koš všech druhů predátorů (patogenů), druhů kořisti (pacienta) a zásahů medicíny

predátor – oběť – lékař/léčba



sepsis

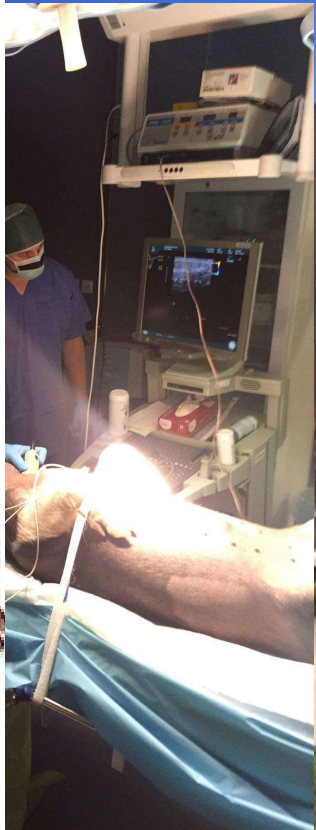
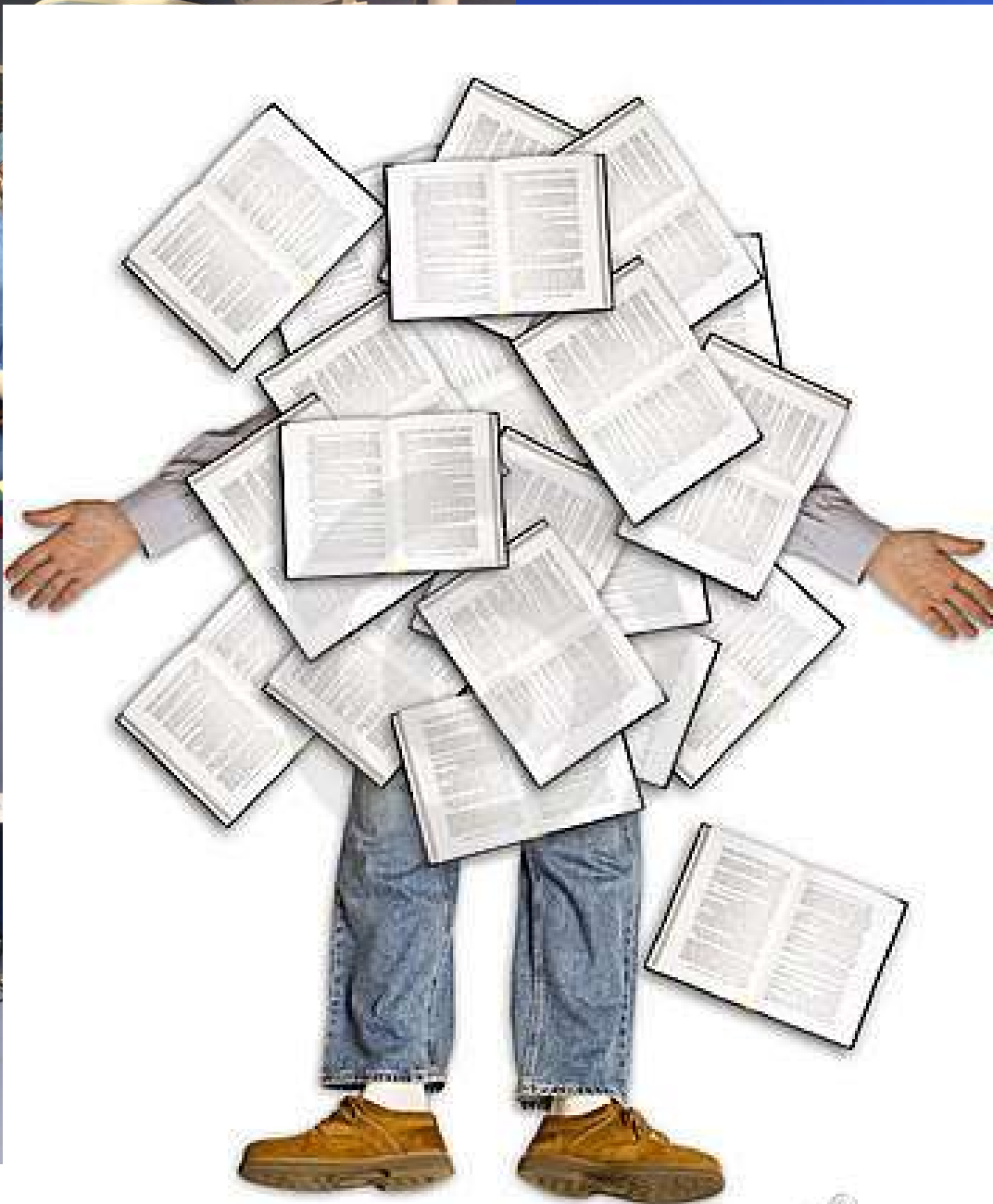
# Geocentrický model sepsy 80-90.let

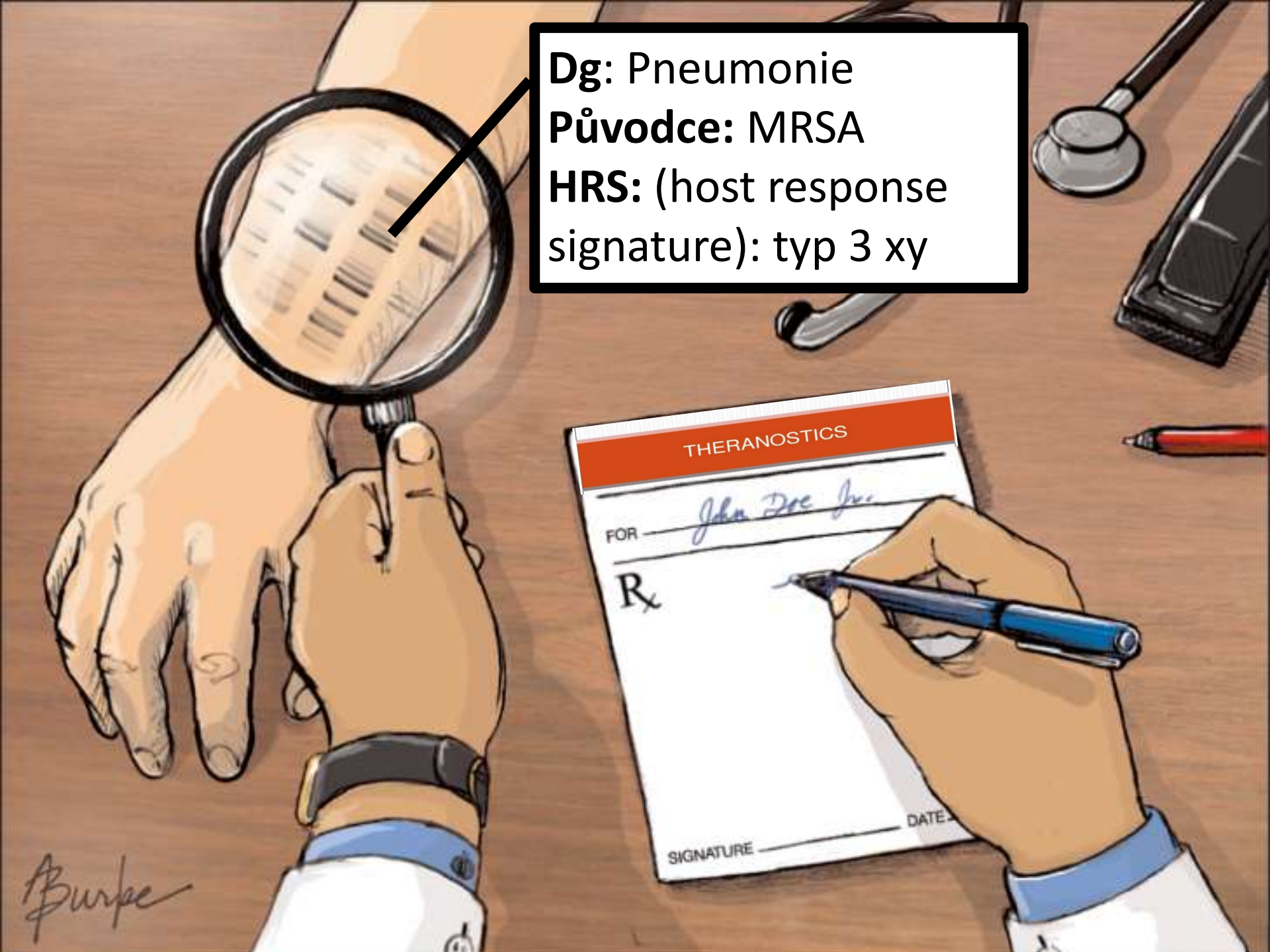


...přinesl téměř 30 let nereprodukovatelných RCT



**Milá sepse, ve skutečnosti neexistuješ!**





**Dg:** Pneumonie  
**Původce:** MRSA  
**HRS:** (host response signature): typ 3 xy

THERANOSTICS

FOR

*John Doe Jr.*

R<sub>x</sub>

SIGNATURE

DATE

Burke

**WAIT**



**WHAT?!**

# The Biggest Key to Happiness: Growing from adversity



- In studies of people facing trauma, many describe their experience as a catalyst for profound change and transformation, leading to a phenomenon known as "post-traumatic growth".