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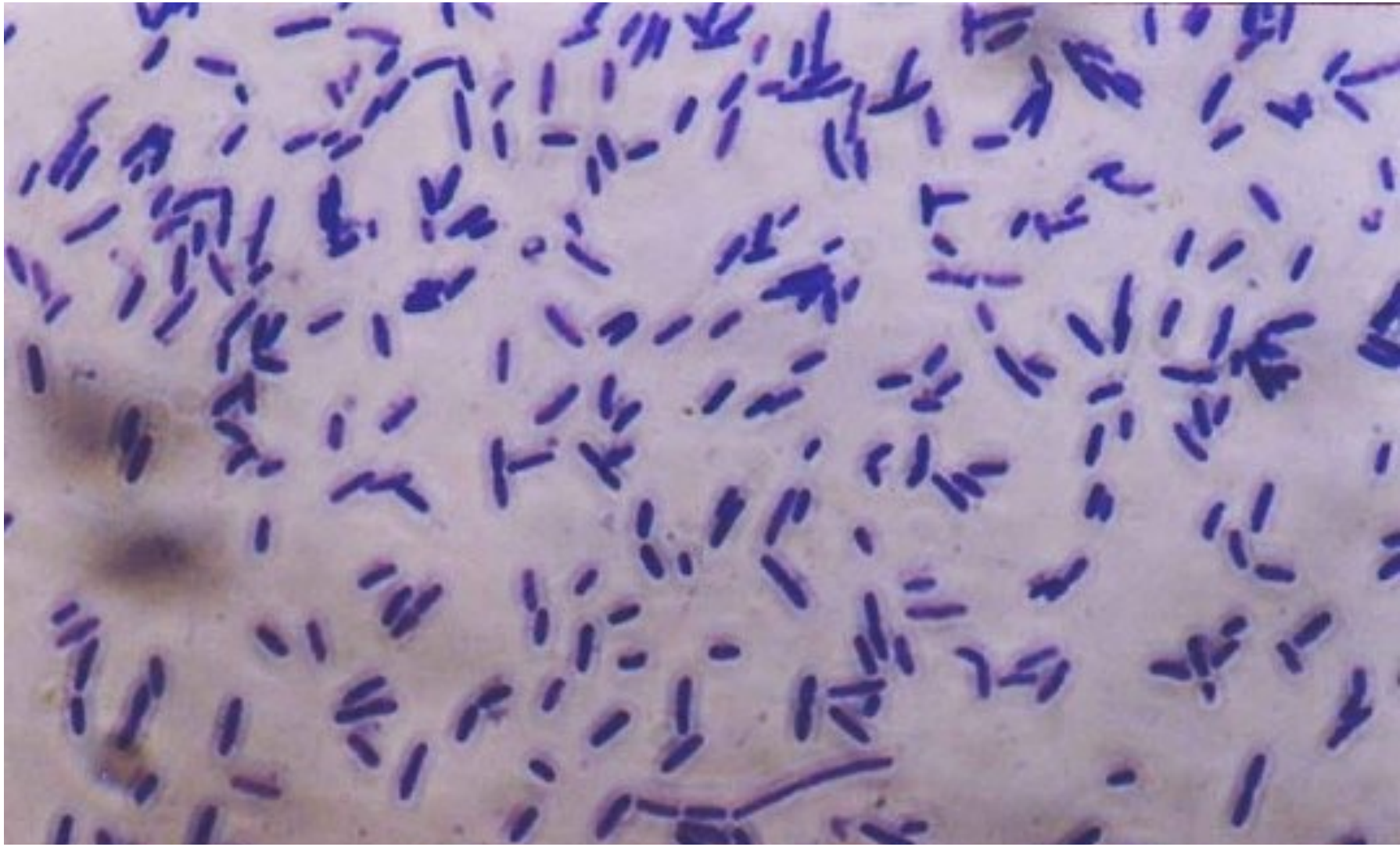
Universität Zürich[UZH]

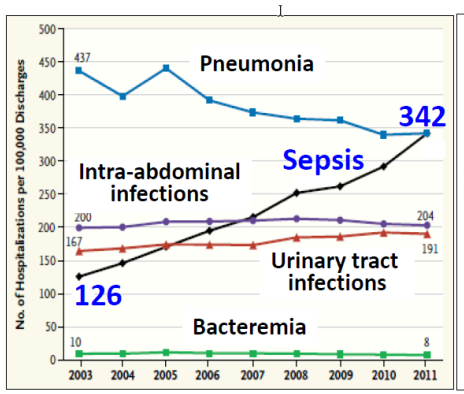
Sepsis

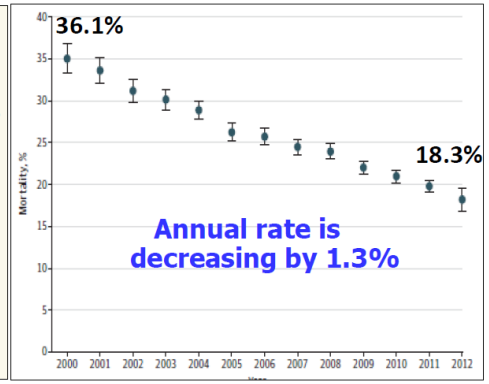


Reto Schüpbach, IFI

08.05.2023

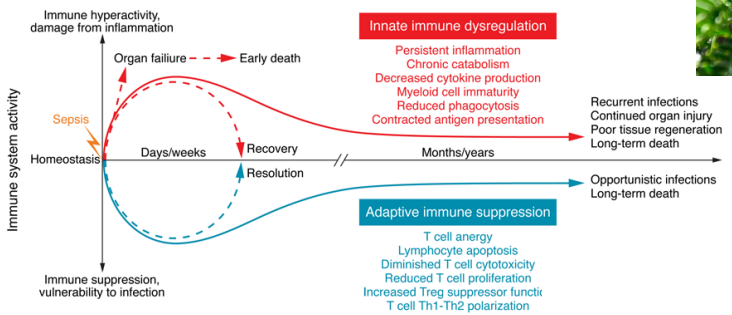
Agenda





1. Epidemiologie
- Inzidenz, Kosten…
- Langzeitfolgen

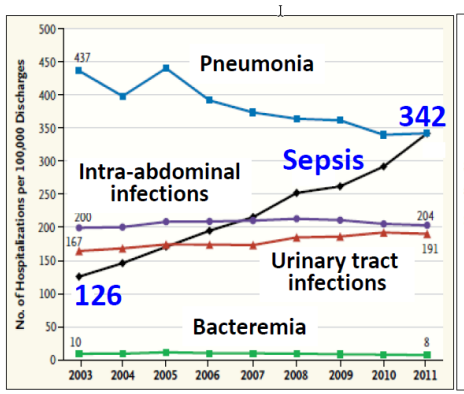
2. Definition
- Sepsis-3
- “Sepsis-4”: Sepsis Typen?

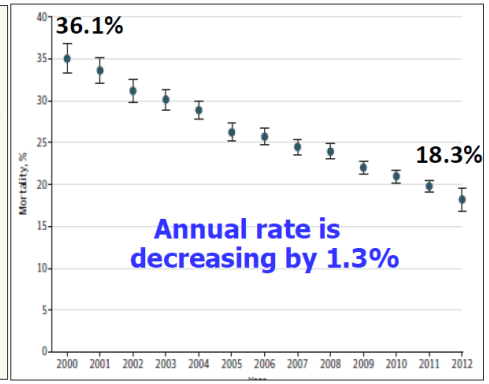


3. Pathophysiologie & Therapeutische Optionen

4. Auftrag an uns?

Agenda





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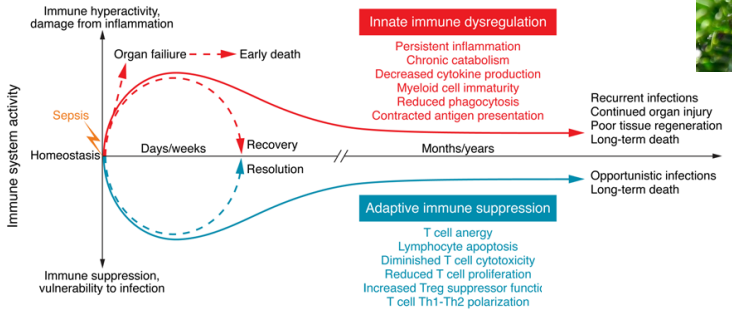
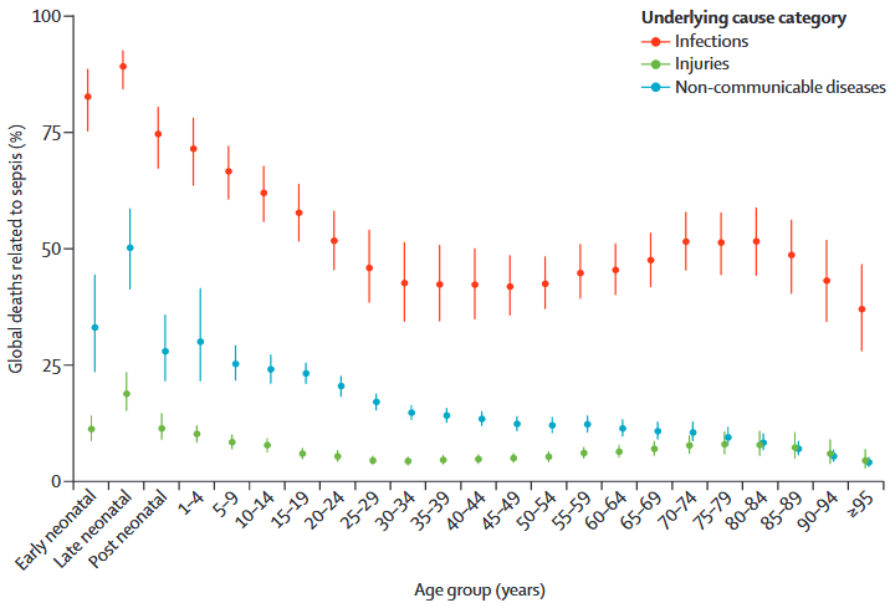


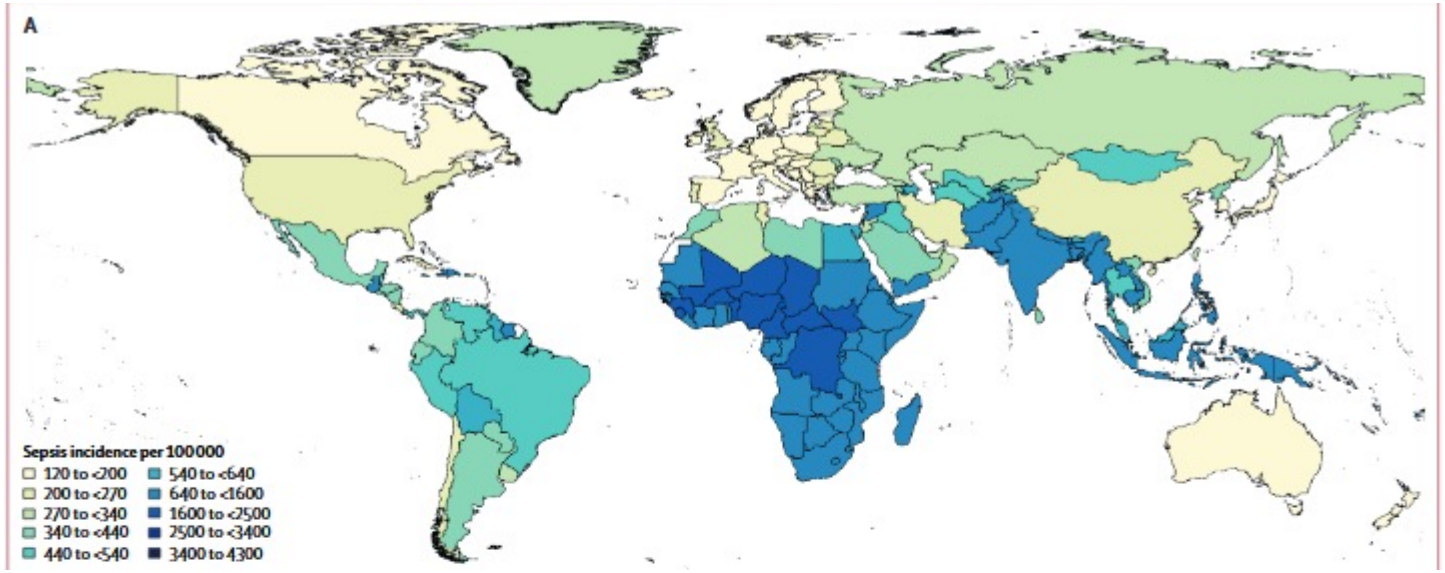
3. Pathophysiologie & Therapeutische Optionen

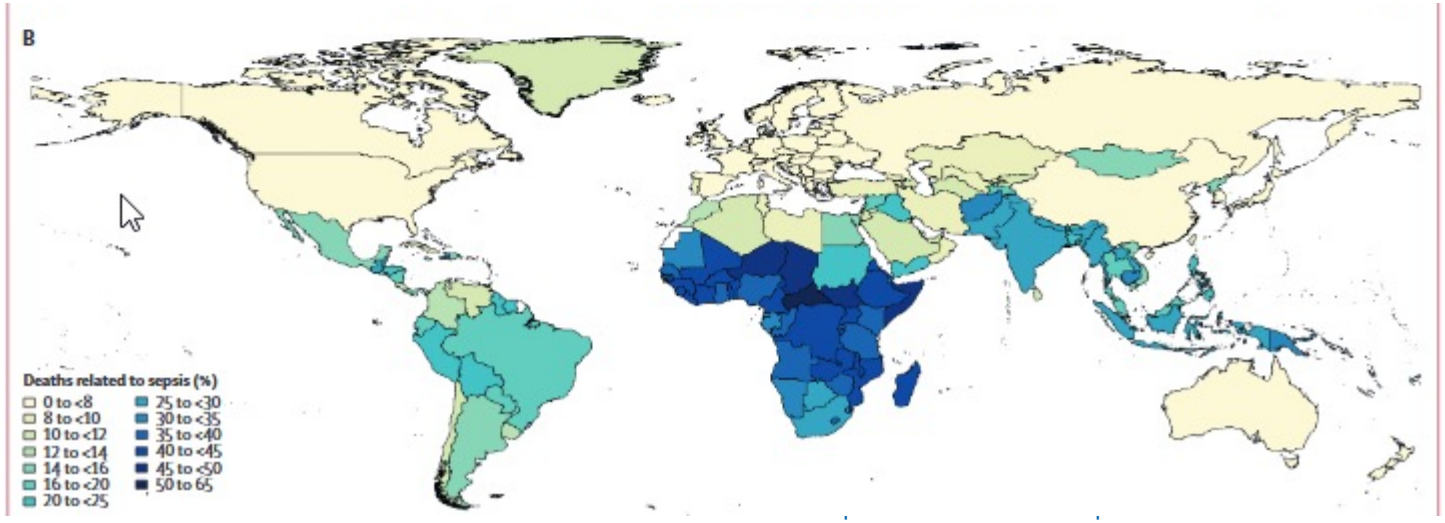
4. Auftrag an uns?

Sepsis: Globale Inzidenz

- 50 Mio erkrankte, 11 Mio Tote
- Abhängigkeit von Alter
- Geographische Unterschiede
- Nationale Unterschiede







Rudd K, Lancet, 2020

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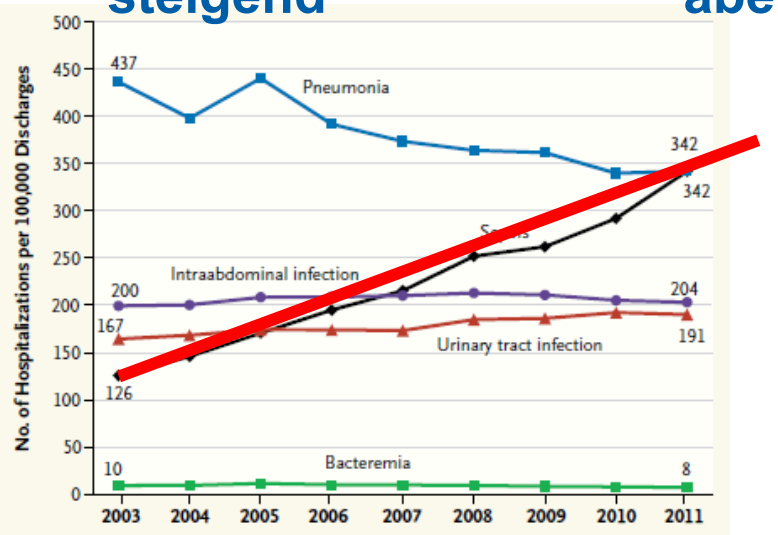
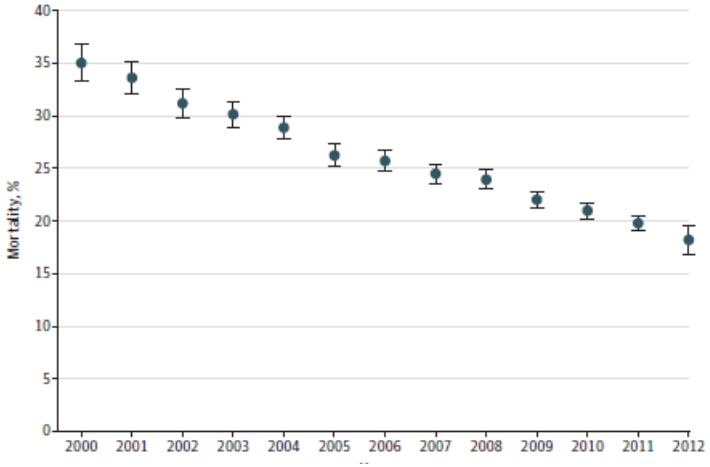
Veränderungen über die Zeit

Inzidenz: steigend aber **Mortalität sinkend**





Rhee C et al.
N Engl J Med 2014;370:1673-5

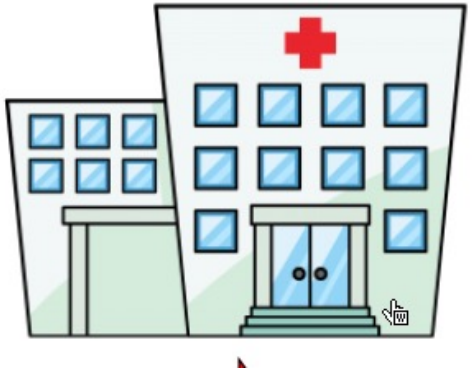
Kaukonen KM et al.
JAMA 2014; 311:1308-16

Kosten in CHF (Schweiz; vor der Pandemie)

- 35K CHF (fatale Fälle 46K CHF) / Fall
- 150-360 Millionen CHF (ICU Kosten
- Indirekte Kosten geschätzt 347 - 844 Millionen CHF

A. Schmid et al. smw 2004

Die eingeschränkte ICU Sicht auf die Sepsis



ICU

Sepsis hits

Sepsis erkannt

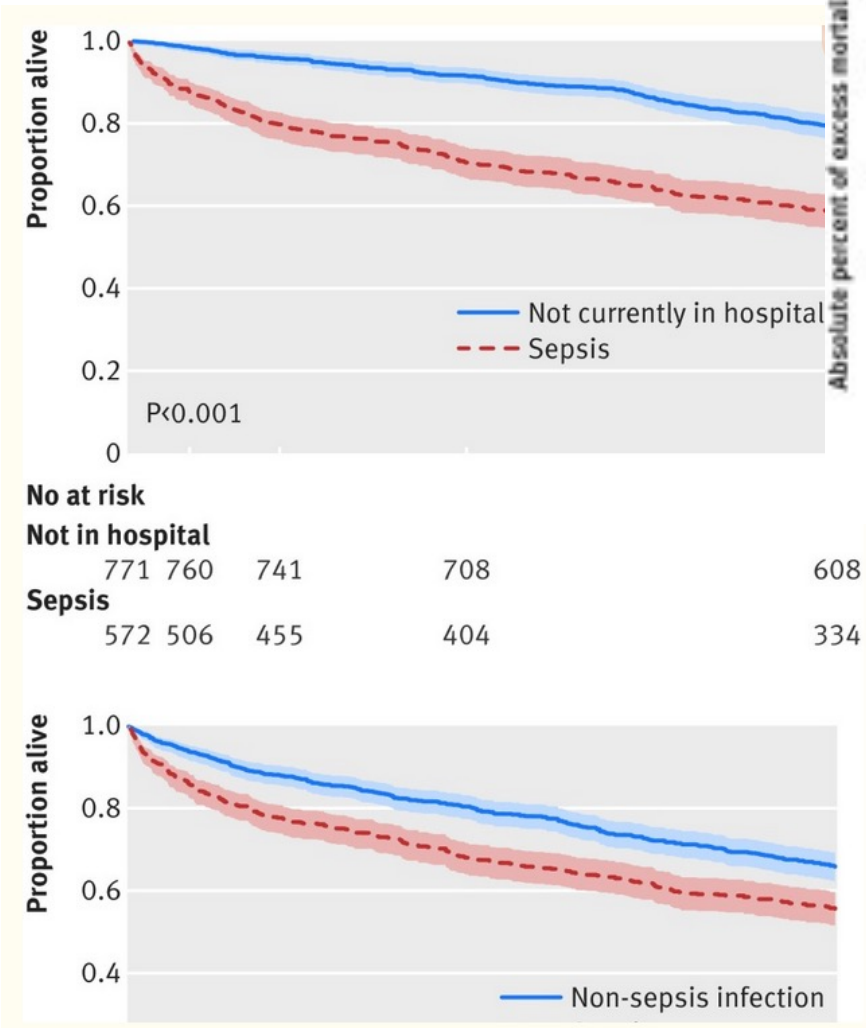
Behandlung

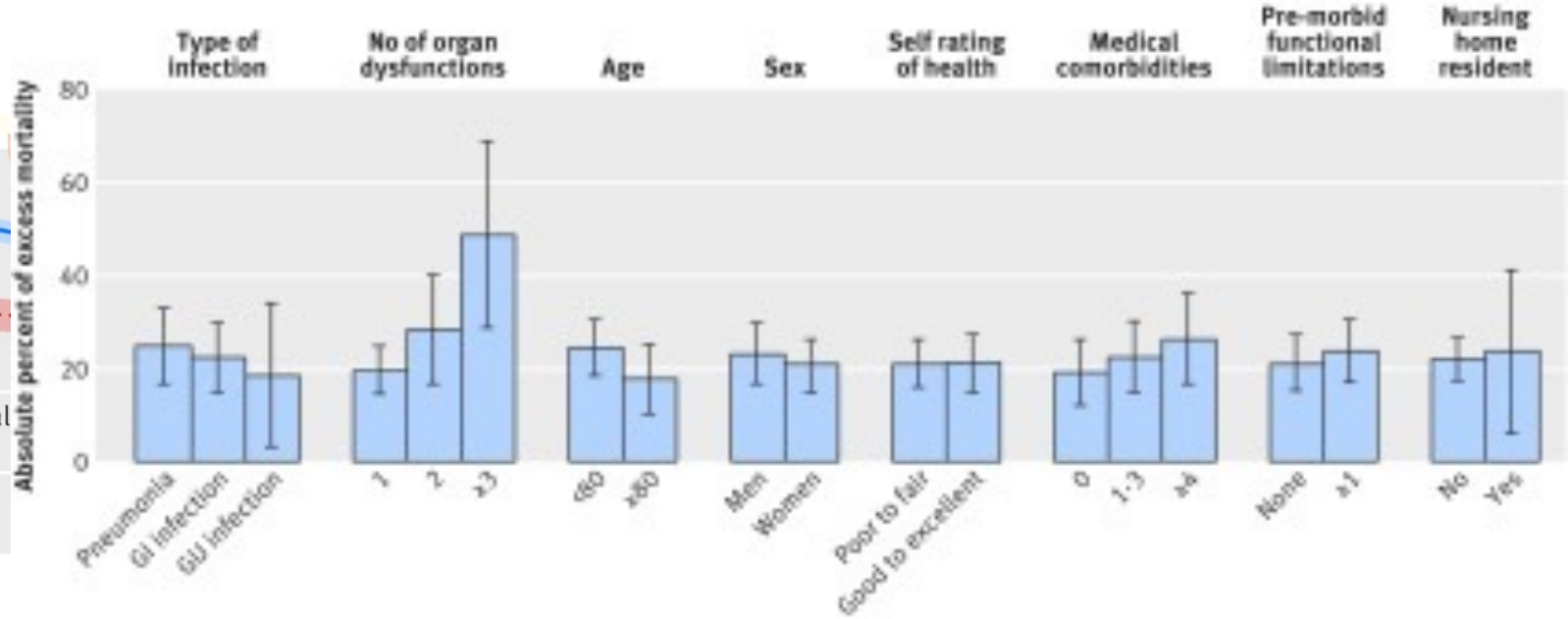
Rehabilitation

Langzeitfolgen

ER ⟷ ward

Mortalität nach der ICU

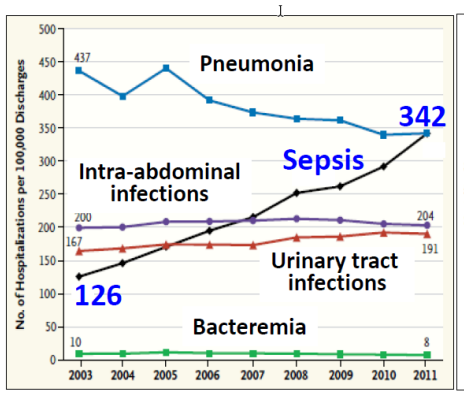


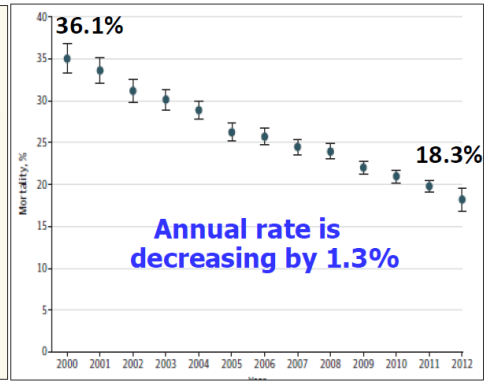


- Übersterblichkeit, selbst 2 Jahre nach Sepsis
- Jeder 5. Sepsis Überlebende stirbt an Spätfolgen
- # der ausgefallenen Organe korreliert mit später Mortalität

Prescott HC et al. BMJ 2016; 353:2375

Agenda





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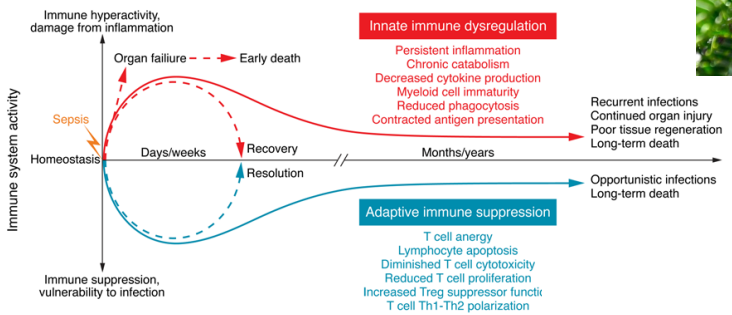

3. Pathophysiologie & Therapeutische Optionen

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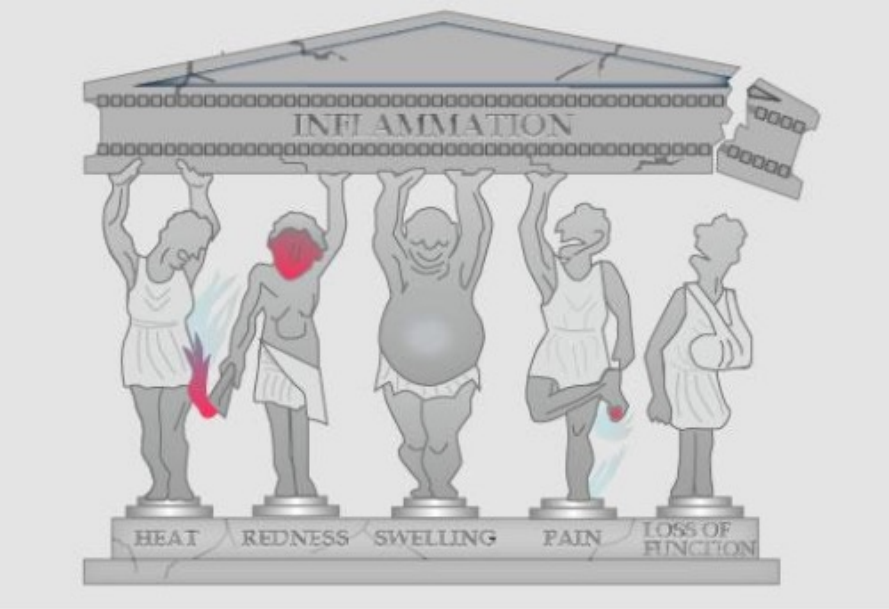
Definition

$$1 + 1 = 2$$

Sepsis =

- Bis 1992: Positive Blutkulturen (Definition von Hugo Schottmüller 1914)

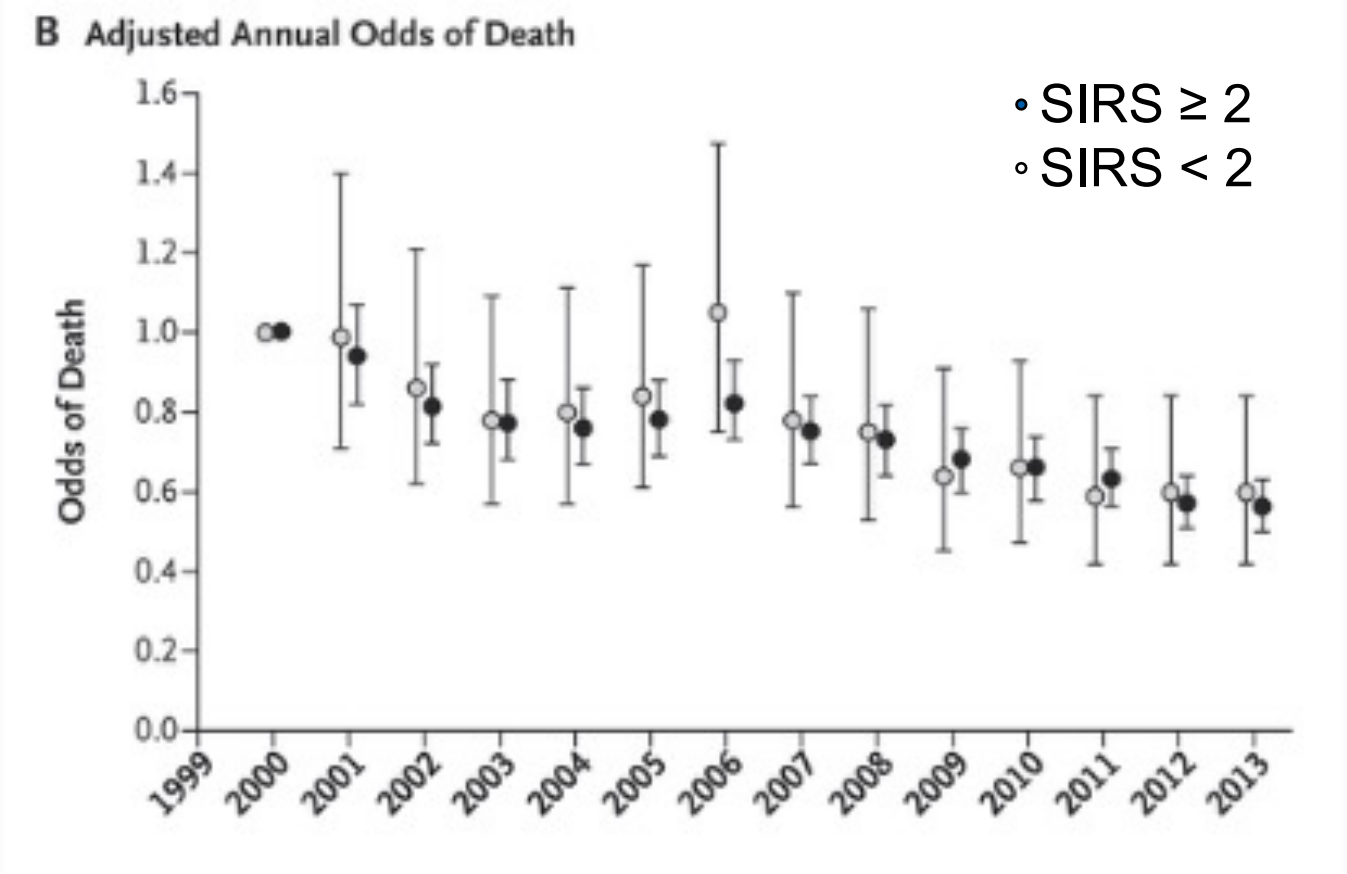
- 1992 Einführung der SIRS Kriterien
  - Fieber (oder Hypothermie)
  - Tachykardie
  - Tachypnoe
  - Leukozytose / Leukopenie
  - **Vermutete Infektion + SIRS = Sepsis**



http://twicsy.com/i/jXwxMh

Problempatienten bei Verwendung der SIRS-Kriterien

SIRS/Sepsis Definition verfehlt Erkennung von vitaler Gefährdung



Kaukonen K et al. N Engl J Med 2015;372:1629-1638.

… Sepsis-3 wurde kreiert

Clinical Review & Education

Special Communication | CARING FOR THE CRITICALLY ILL PATIENT

The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)

Mervyn Singer, MD, FRCP; Clifford S. Deutschman, MD, MS; Christopher Warren Seymour, MD, MSc; Manu Shankar-Hari, MSc, MD, FFICM; Djillali Annane, MD, PhD; Michael Bauer, MD; Rinaldo Bellomo, MD; Gordon R. Bernard, MD; Jean-Daniel Chiche, MD, PhD; Craig M. Coopersmith, MD; Richard S. Hotchkiss, MD; Mitchell M. Levy, MD; John C. Marshall, MD; Greg S. Martin, MD, MSc; Steven M. Opal, MD; Gordon D. Rubenfeld, MD, MS; Tom van der Poll, MD, PhD; Jean-Louis Vincent, MD, PhD; Derek C. Angus, MD, MPH

IMPORTANCE Definitions of sepsis and septic shock were last revised in 2001. Considerable advances have since been made into the pathobiology (changes in organ function, morphology, cell biology, biochemistry, immunology, and circulation), management, and epidemiology of sepsis, suggesting the need for reexamination.

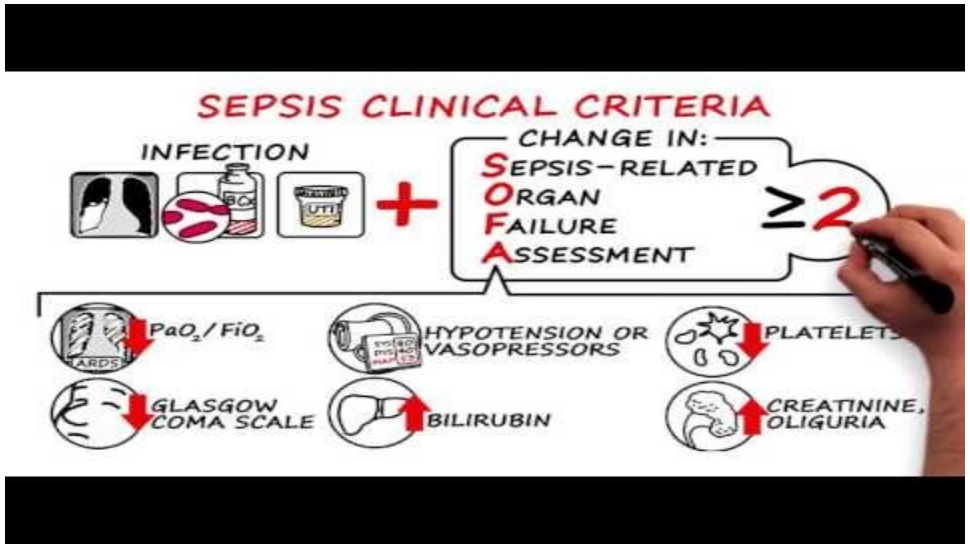
OBJECTIVE To evaluate and, as needed, update definitions for sepsis and septic shock.

Editorial page 757

Author Video Interview, Author Audio Interview, and JAMA Report Video at jama.com

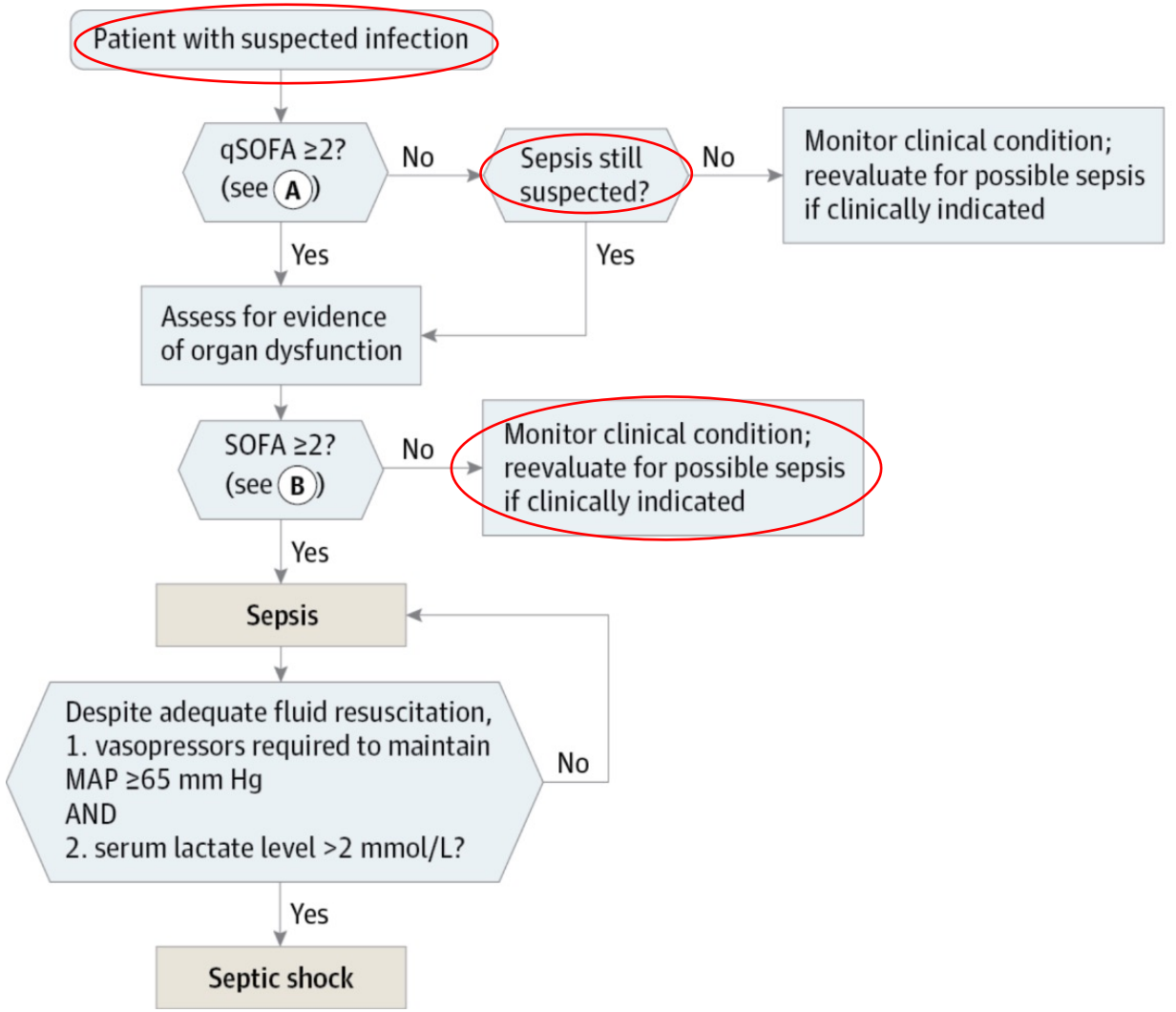
Related articles pages 762 and 775

Sepsis-3; Video



https://www.youtube.com/watch?v=L5xKW--drRg

Diagnostisches Vorgehen



A qSOFA Variables

- Respiratory rate
- Mental status
- Systolic blood pressure

B SOFA Variables

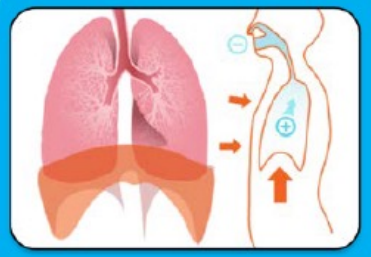
- PaO_2/FiO_2 ratio
- Glasgow Coma Scale score
- Mean arterial pressure
- Administration of vasopressors with type and dose rate of infusion
- Serum creatinine or urine output
- Bilirubin
- Platelet count

JAMA. 2016;315(8):801-810. doi:10.1001/jama.2016.0287

qSOFA

Quick SOFA (qSOFA)

C Seymour et al. JAMA 2016;315:762-774



Atemfrequenz ≥ 22/min

Verändertes Bewusstsein (GCS < 15)

Systolischer Blutdruck ≤ 100 mmHg

DGIIN
Deutsche Gesellschaft für Internistische Intensivmedizin und Notfallmedizin

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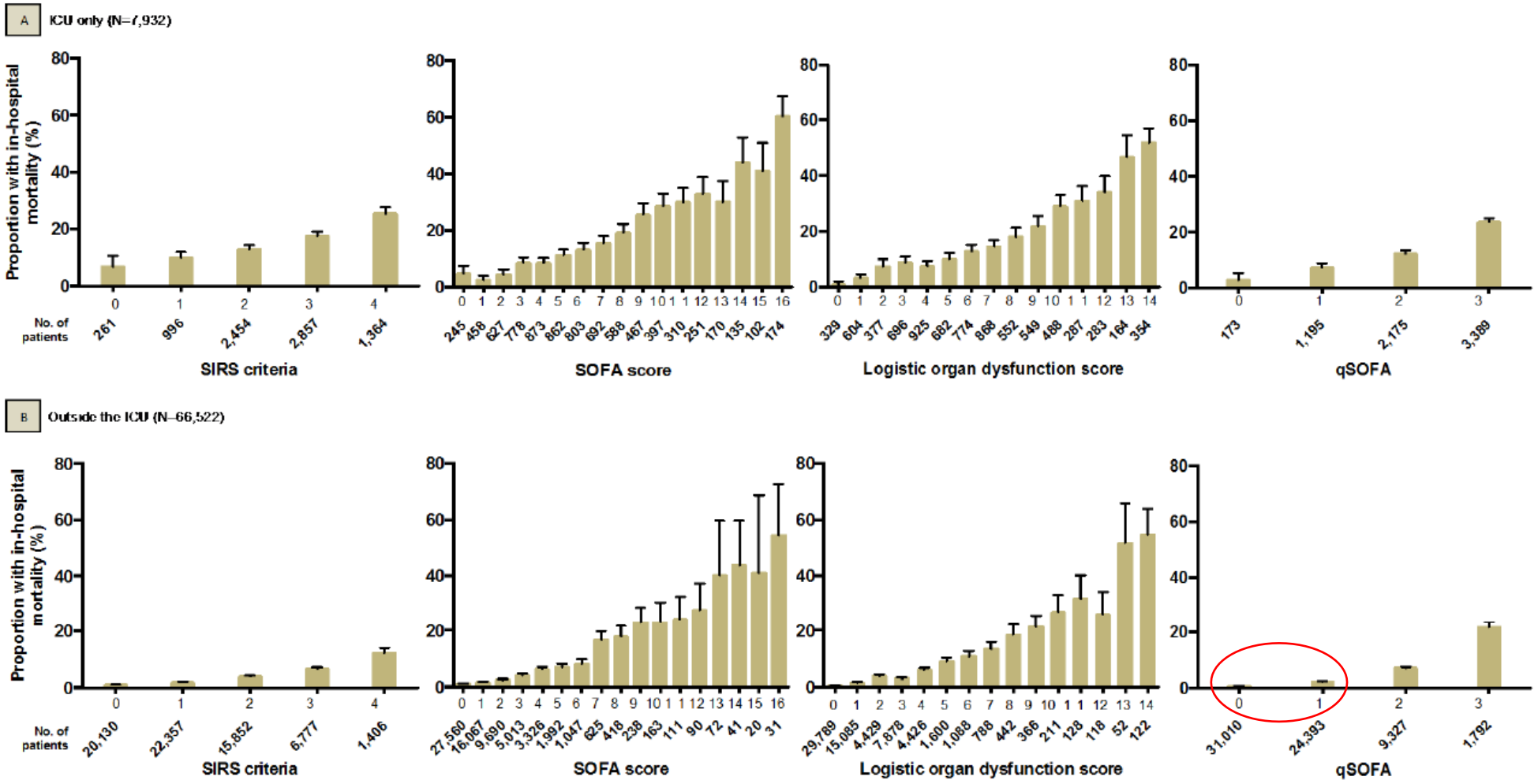
qSOFA ≥ 2 prädiktiv?!?



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qSOFA:

Quick SOFA (qSOFA)

C Seymour et al. JAMA 2016;315:762-774

Einsatz als einfaches Screening Werkzeug (prähospital, Notaufnahme, Normalstation, ***nicht*** ICU)

Positiv wenn 2 von 3 Kriterien erfüllt

qSOFA score = 2 Punkte: 3fach höhere Sterblichkeit

qSOFA = 3 Punkte: 14fach höhere Sterblichkeit

Weitere Suche nach Organdysfunktion

Therapie beginnen oder eskalieren

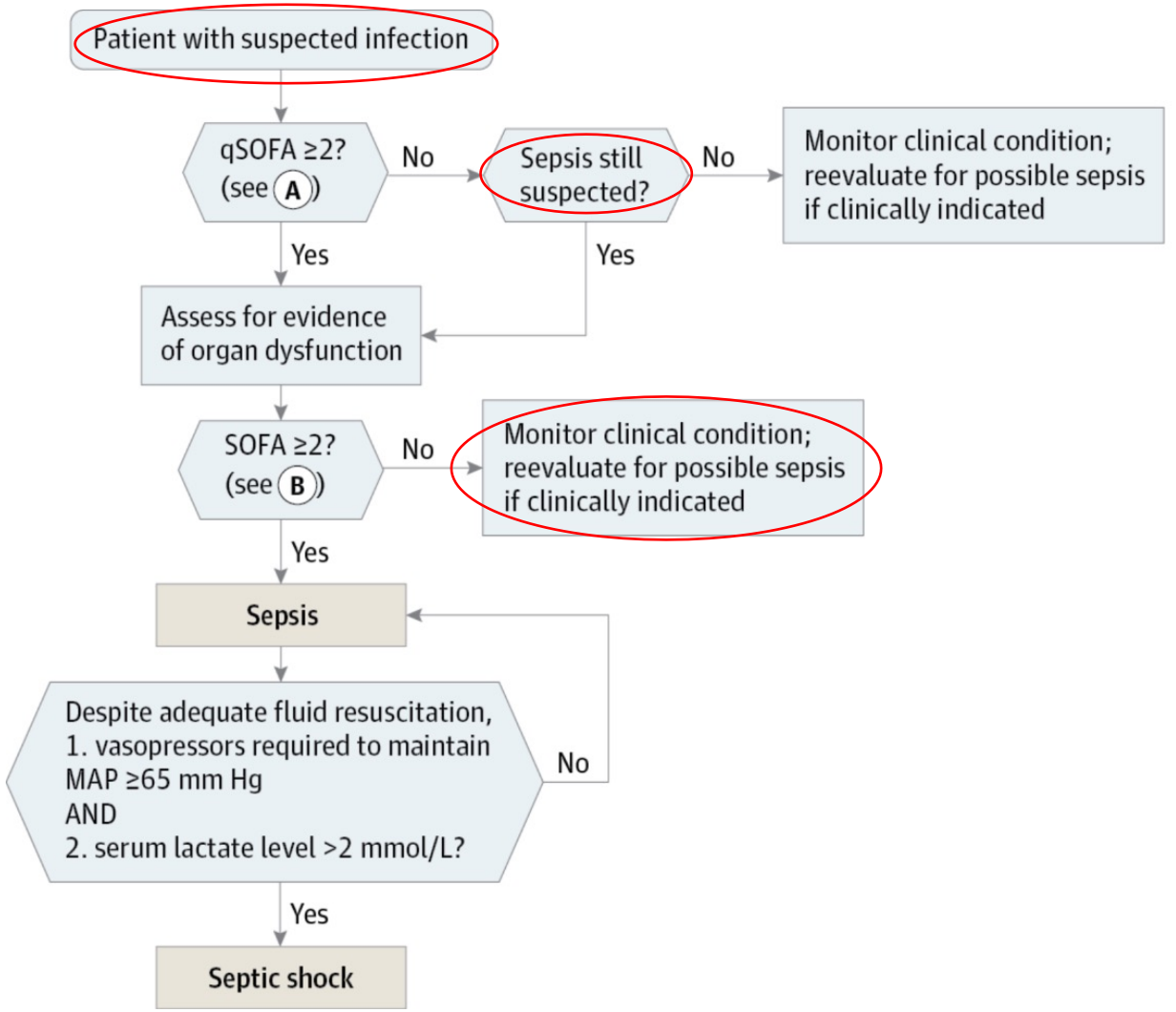
Monitoring intensivieren

DGIIN Deutsche Gesellschaft für Internistische Intensivmedizin und Notfallmedizin

qSOFA verpasst jede 4. Bakteriämie!

Sensitivity analysis or subgroup		No. patients	AUC (95% CI) for qSOFA above baseline
UPMC	Validation cohort, primary model	74,454	0.83 (0.82, 0.83)
	Multiple imputation ^	74,454	0.83 (0.82, 0.84)
	Altered mentation defined as GCS<15	74,454	0.83 (0.81, 0.84)
	Restricted: presumed infection	56,511	0.80 (0.79, 0.80)
	Restricted: confirmed bacteremia	3,449	0.76 (0.74, 0.78)
	Excluded: DNR/DNI/CMO at time of infection	72,819	0.83 (0.81, 0.85)
	Excluded: antibiotics administered ≥24 hrs after culture	67,014	0.84 (0.83, 0.86)
	Added: serum lactate ≥2.0 mmol/L	74,454	0.84 (0.83, 0.85)
	Time window: 24 hrs after time of infection	74,454	0.83 (0.83, 0.84)

Diagnostisches Vorgehen



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Sepsis-3

1. Geeignet, um infektionsbedingte Mortalität vorauszusagen

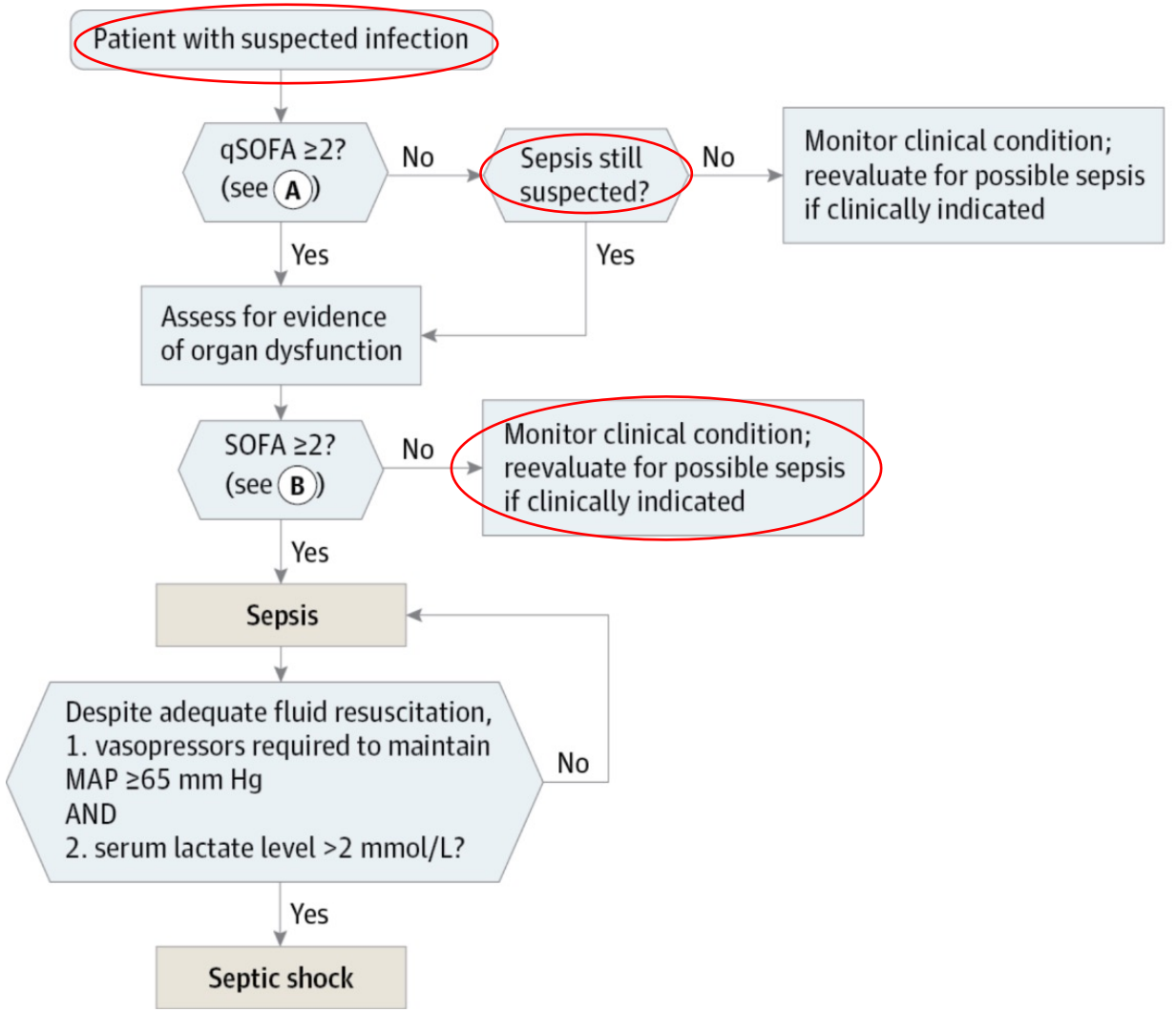
2. Unbrauchbar beim Entscheid für/gegen Antibiotikagabe

3. 25% aller Patienten mit Bakteriämie haben einen qSOFA < 2!

- “Sepsis sine sepsis”

4. Ungeeignet für ICU Patienten

Diagnostisches Vorgehen



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Definitionen

Sepsis-2:

- $\text{Sepsis} = \text{f}[(\text{Infection}) + (\text{SIRS})]$

Sepsis-3:

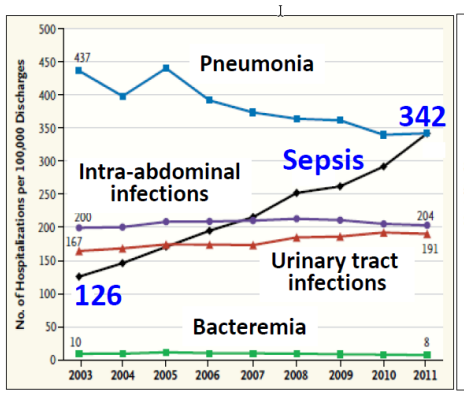
- $\text{Sepsis} = \text{f}[(\text{Infection}) + (\text{q}SOFA) + (SOFA)]$

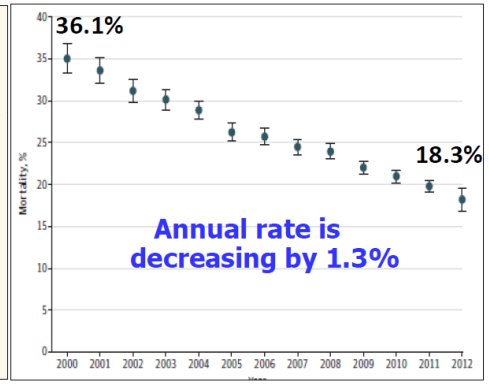
Sepsis SwissDRG:

- $\text{Sepsis} = \text{f}[(\text{Infection}) + (\Delta \geq 2\ SOFA\ (72h^{-1})]$

Zukunft: Sepsis mit Aufgliederung nach Typen?

Agenda





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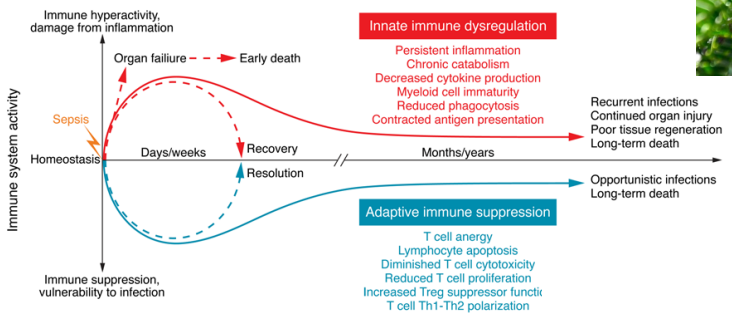

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Was können wir für Sepsis-Patienten tun?

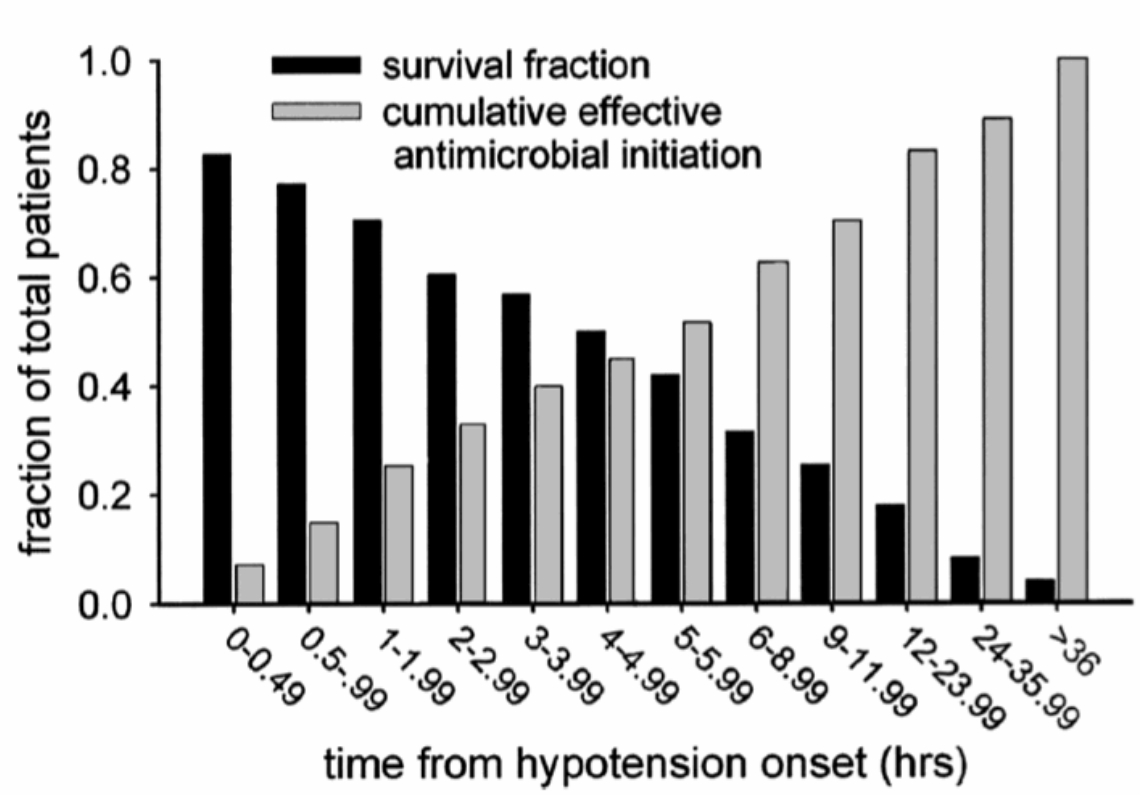
$$\text{Sepsis} = f[(\text{Infection}) + (qSOFA) + (SOFA)]$$

Diagnosis

Infektion:
- Erkennen
- Behandeln
  - Antibiotika
  - Chirurgie

Wirtsreaktion:
- überbrücken
- spez. Therapie

Therapieverzug ist tödlich!

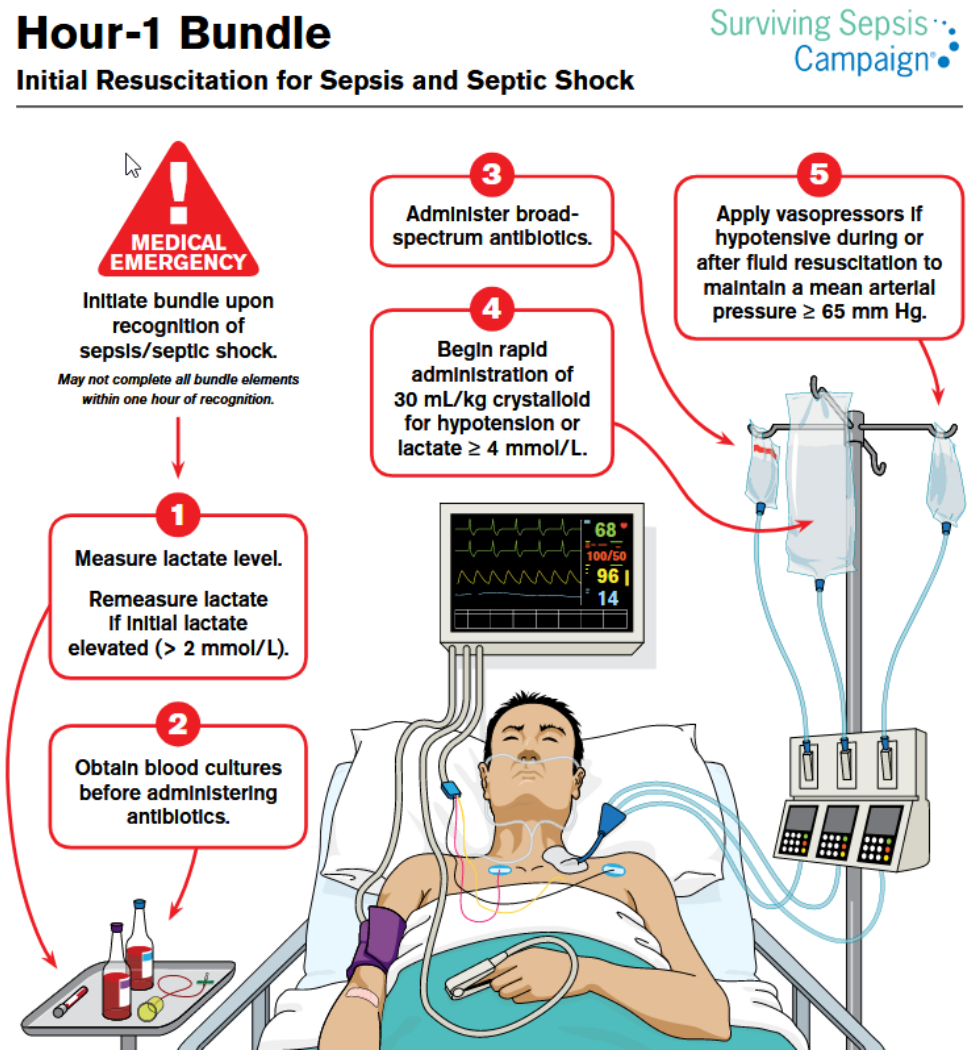


Der Kardiologe:
«Zeit ist (Herz-)-Muskel

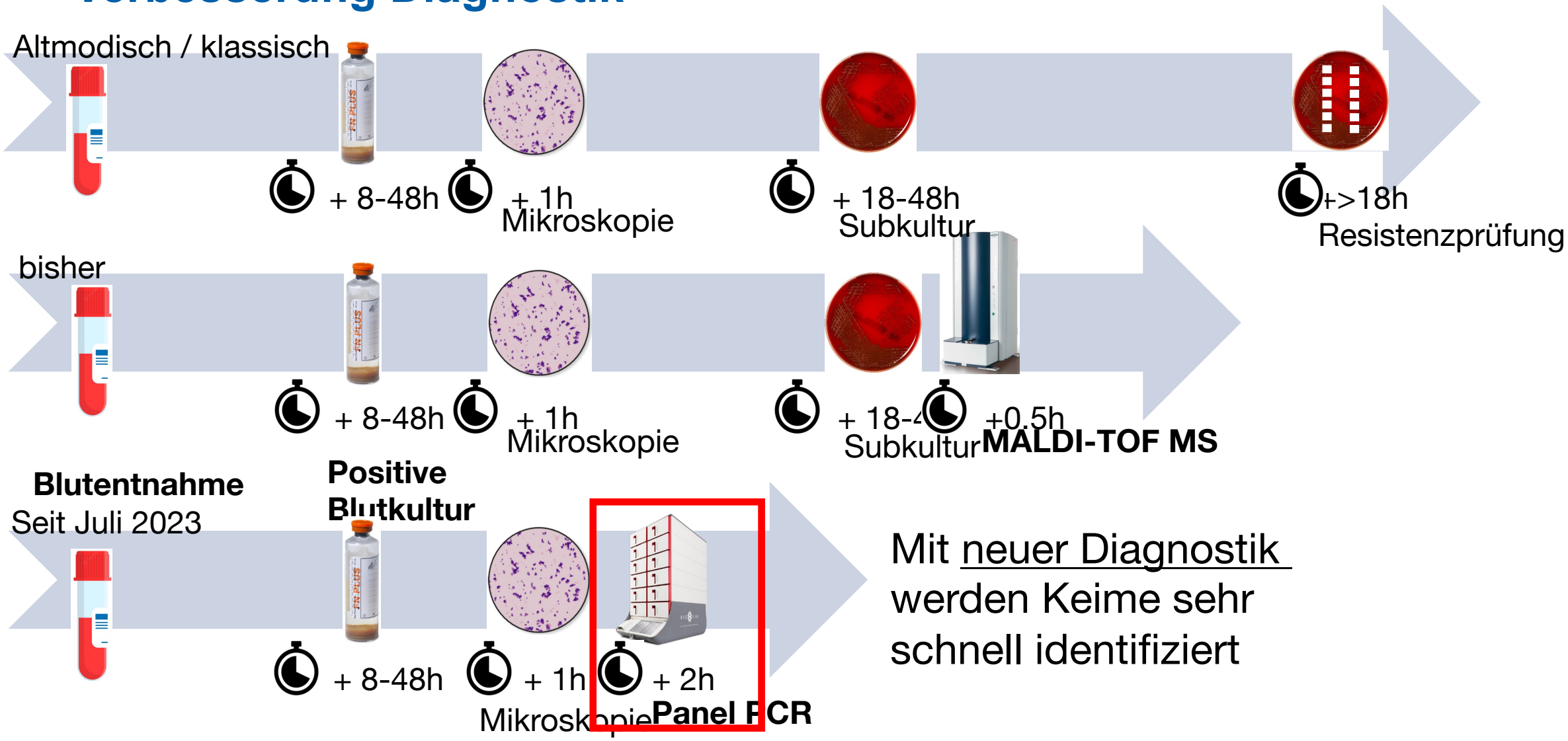
Der intensivist:
«Zeit ist Ihr Leben!»

[1] Kumar A et al. Crit Care Med 2006;

Verbesserung Prozesse



Verbesserung Diagnostik



Mit <u>neuer Diagnostik</u> werden Keime sehr schnell identifiziert

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Noli: ubi pus ibi-penem (ubi pus, ibi evacua!)

Bildgebung:
- US
- CT
- MR (Fasziitis !!!!!)

Was können wir für Sepsis-Patienten tun?

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Prozesse

Wirtsreaktion:
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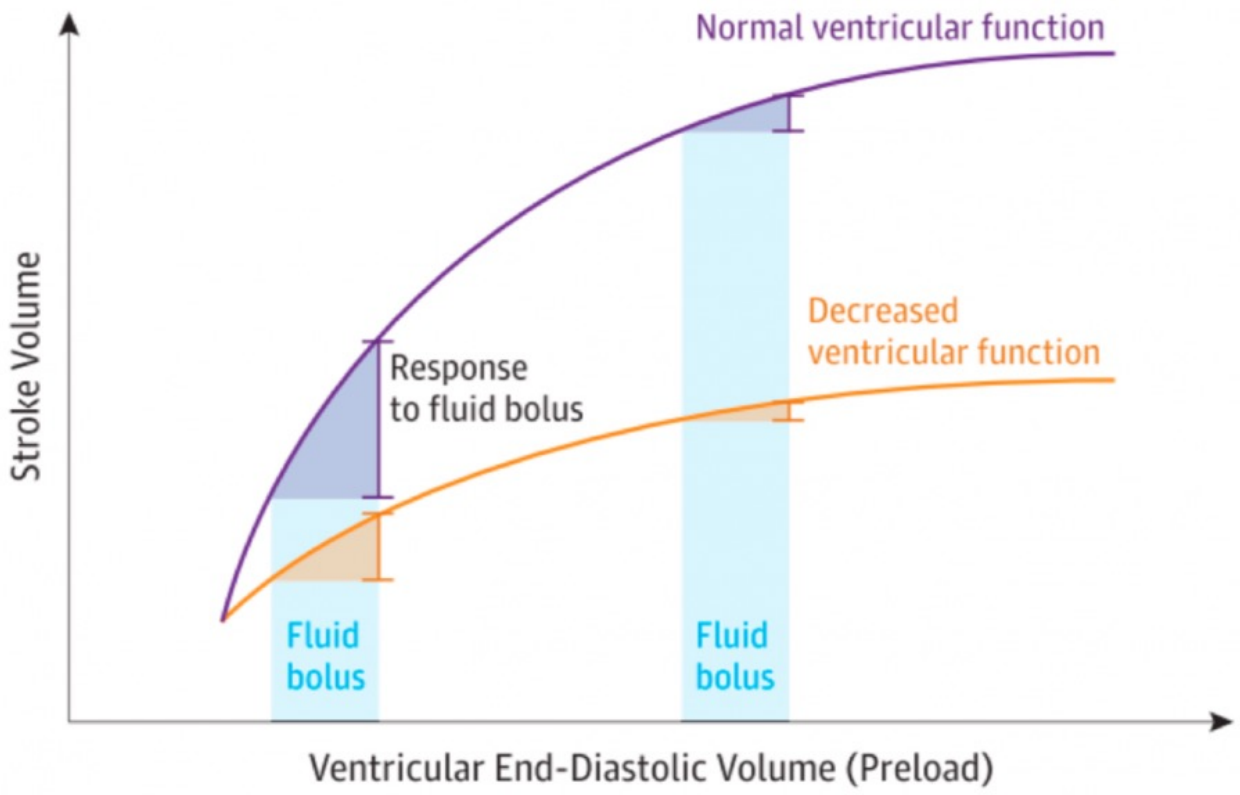
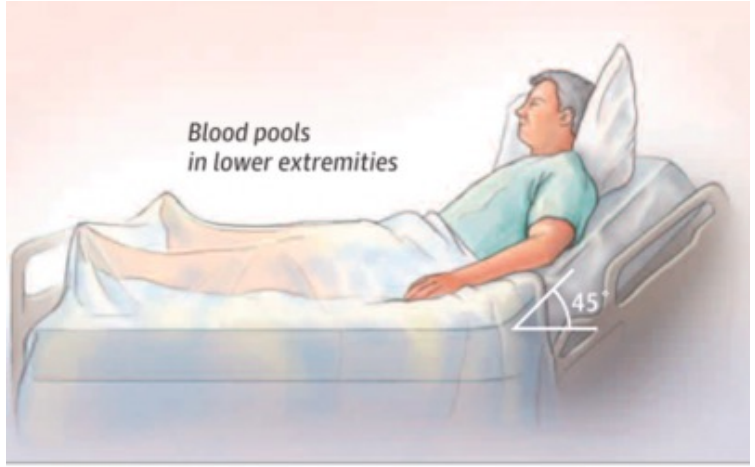
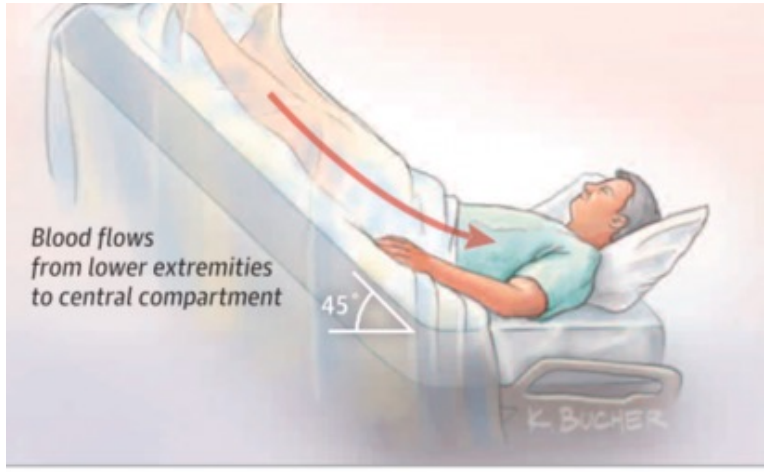
- spez. Therapie

IPS-Therapie

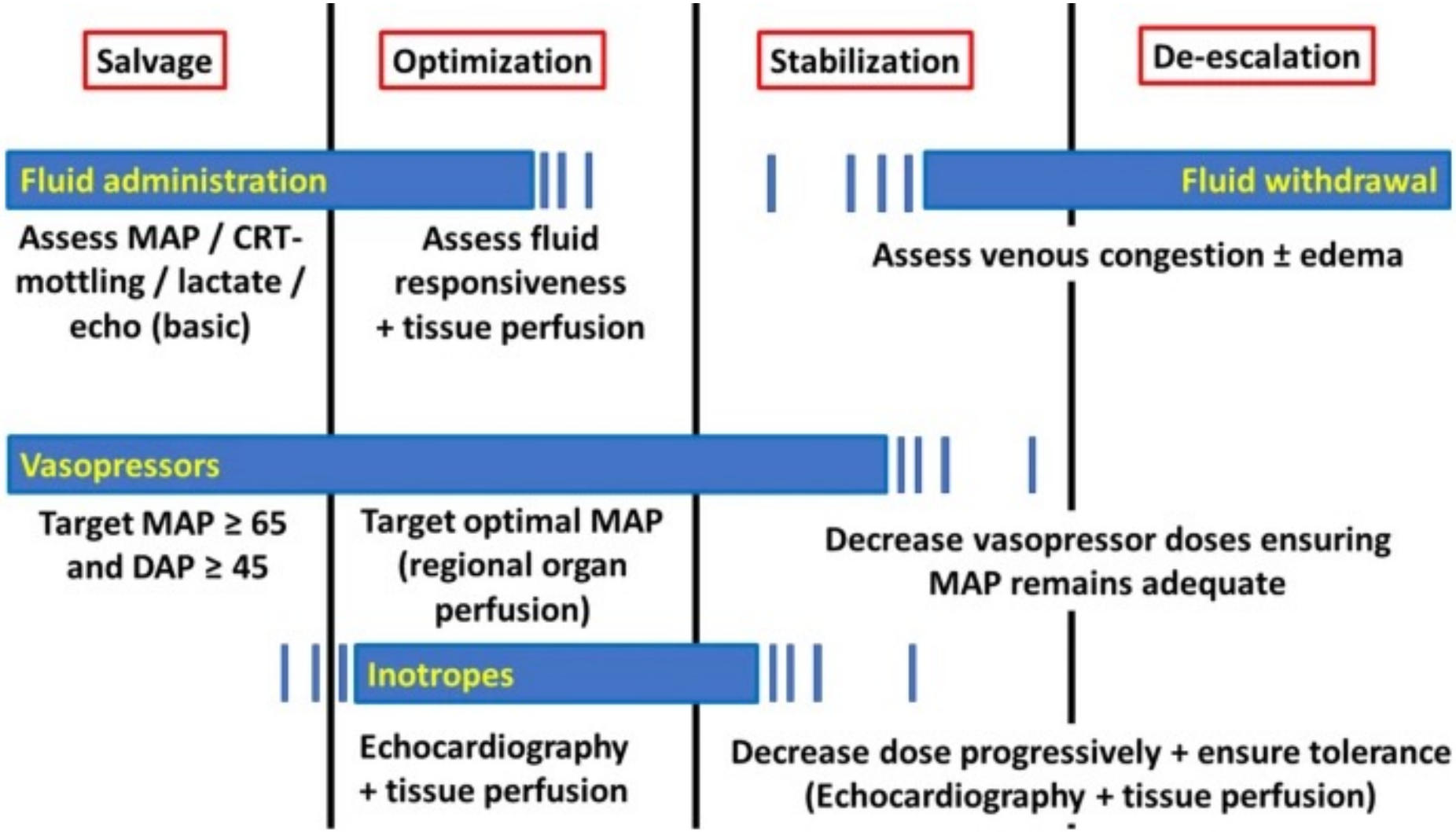




Passive leg raise, from Bentzer et al JAMA 2016

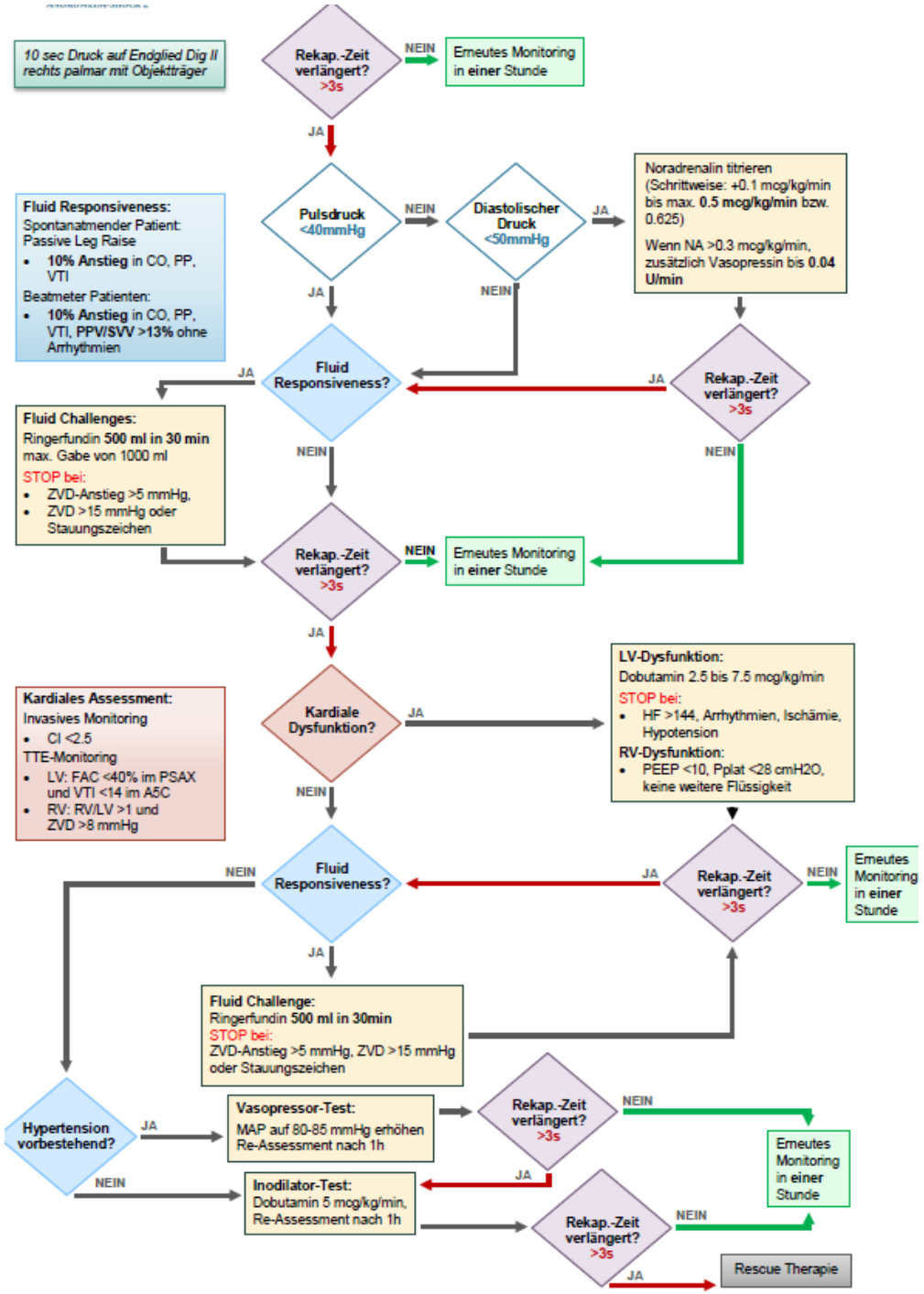


Volume tolerance



De Backer, Crit. Care 2022

Targeting novel goals?



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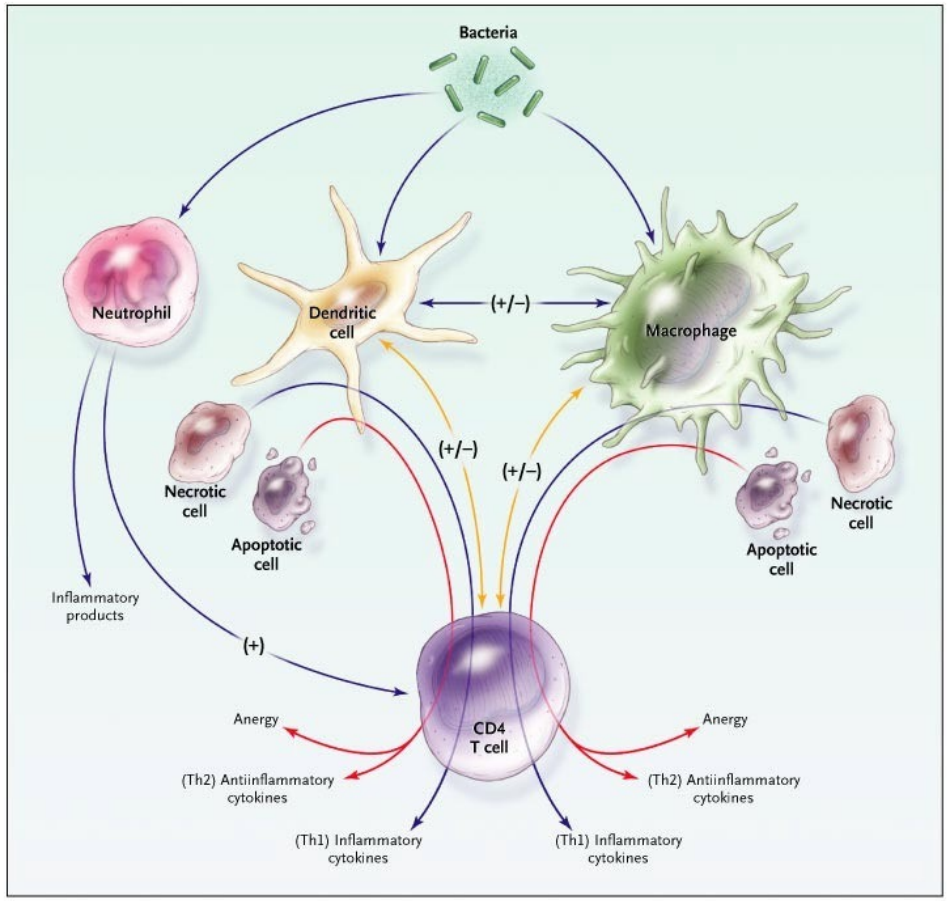
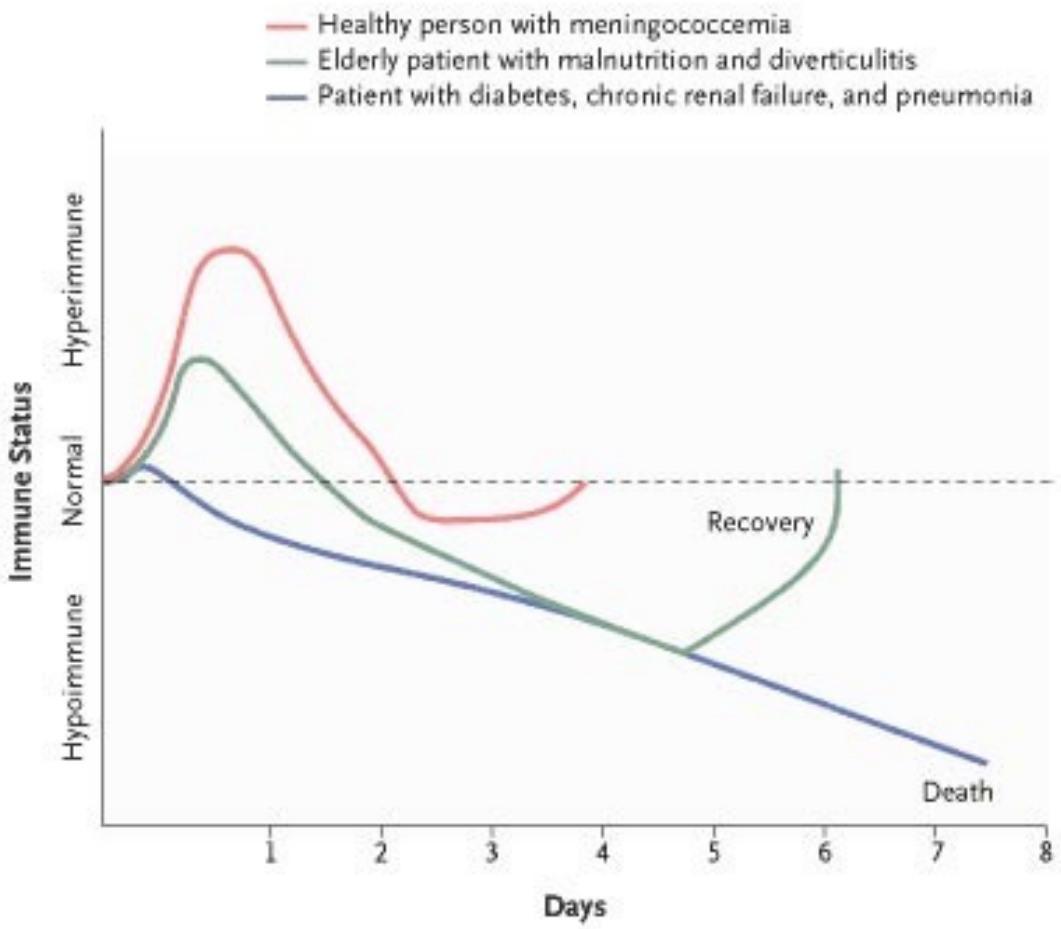
Therapie der fehlgeleiteten Immunantwort

1. High dose steroids
2. E.coli J5 antisera
3. Anti-lipid A E5
4. Anti-lipid A HA1A
5. BPI
6. TNF mAb
7. Chimeric TNF mAb
8. Humanized TNF mAb
9. TNF-Fab
10. sTNFR1:Fc
11. sTNFR2:Fc
12. IL-1ra
13. Heparin
14. Antithrombin
15. C1H inhibitor
16. TFPI
17. APC
18. NAPc2
20. PMX-B conjugants
21. PMX-B columns
22. Anti-CD14 Mab
23. G-CSF
24. Interferon γ
25. PAF inhibitors
26. PAF-AH
27. IVIG
28. Ibuprofen
29. Anti-β2 integrin
30. Albumin hemoperfusion
30. NO synthase inhibitors
31. Growth hormone
32. rHDL
33. Lipid emulsions
34. Stress dose steroids
35. Tight insulin control
36. TLR4 antagonists (E5564; TAK 242)
37. Bradykinin inhibitors
38. Thrombomodulin
39. Alkaline phosphatase
40. Talactoferrin
41. Interferon β
42. ....

Hintergrund: Komplexe Interaktion zwischen PAMS und Immunsystem





Hotchkiss, NEJM 2003

Sepsis: Ein Syndrom, viele Phänotypen, vielfältige Pathophysiologie

© Thierry Calandra, CHUV

Ein grosser Schritt: Sepsis Phenotypen

Table 1. Characteristics of Cohorts and Clinical Trials

	Sepsis Endotyping in Emergency Care (SENECA)[a]		Genetic and Inflammatory Markers of Sepsis (GenIMS)[9]	A Controlled Comparison of Eritoran in Severe Sepsis (ACCESS)[6]	Activated Protein C Worldwide Evaluation in Severe Sepsis (PROWESS)[8]	Protocol-Based Care for Early Septic Shock (ProCESS)[7]
	Derivation Cohort	Validation Cohort				
No. of patients	20 189	43 086	583	1706[b]	1690	1341
No. of sites	12	12	28	197	164	31
Enrollment period	2010-2012	2013-2014	2001-2003	2006-2010	1998-2000	2008-2013
Location of enrollment	ED	ED	ED	ED, medical ward, ICU	ED, medical ward, ICU	ED
Primary intervention	None	None	None	Eritoran (toll-like receptor 4 antagonist) vs placebo	Drotrecogin alfa (activated protein C) vs placebo	EGDT as standard care vs usual care
Primary outcome	28-d mortality[c]	28-d mortality[c]	28-d mortality	28-d mortality	28-d mortality	60-d mortality
Inclusion criteria	Sepsis-3 criteria (defined as both a body fluid culture and administration of antibiotics plus ≥2 SOFA points within first 6 h after ED arrival)	Sepsis-3 criteria (defined as both a body fluid culture and administration of antibiotics plus ≥2 SOFA points within first 6 h after ED arrival)	Community-acquired pneumonia with severe sepsis (defined by Sepsis-2 criteria and ≥3 SOFA points)	Severe sepsis and septic shock (defined as meeting ≥3 SIRS criteria, dysfunction in ≥1 organ, and APACHE II score of 21-37)	Severe sepsis and septic shock (defined as meeting ≥3 SIRS criteria and dysfunction in ≥1 organ)	Severe sepsis or septic shock (defined as meeting ≥2 SIRS criteria and either serum lactate level ≥4 mmol/L or refractory hypotension)

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; ED, emergency department; EGDT, early goal-directed therapy; ICU, intensive care unit; SIRS, systemic inflammatory response syndrome; SOFA, Sequential Organ Failure Assessment.

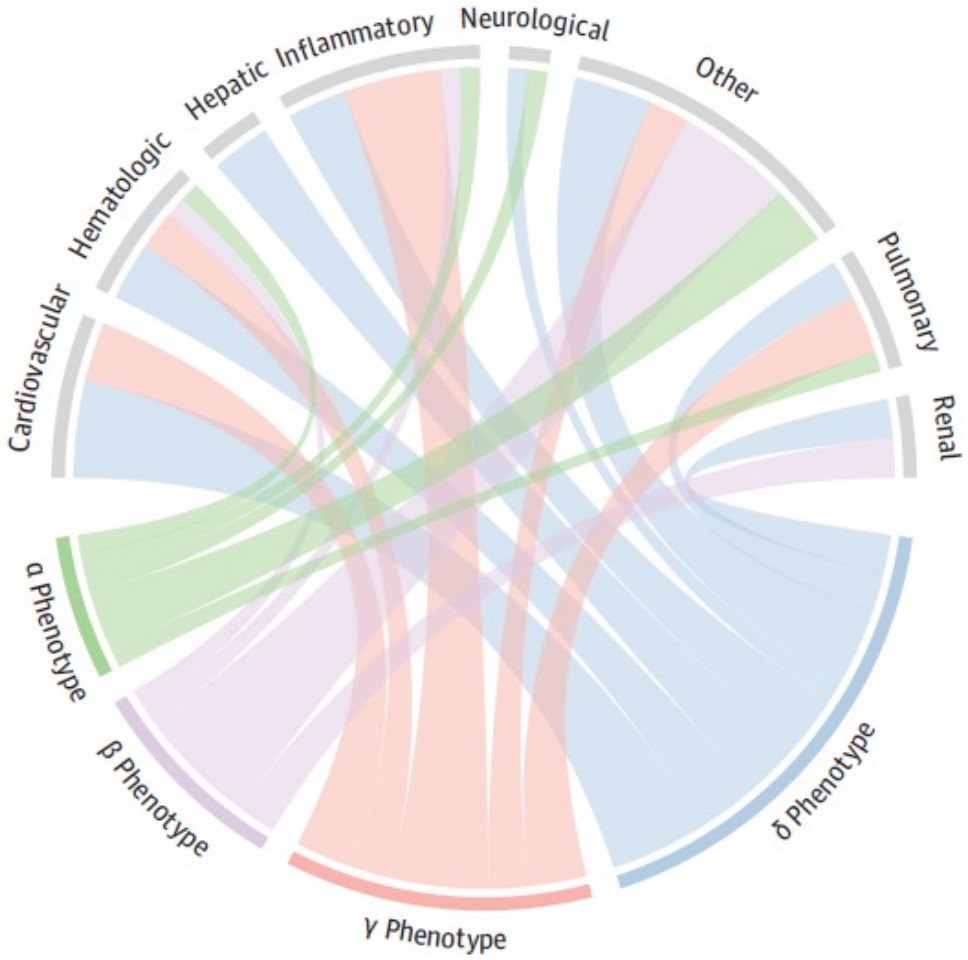
[a] There were 16 552 unique patients among 20 189 total patients in the derivation cohort and 31 160 unique patients among 43 086 total patients in the validation cohort.

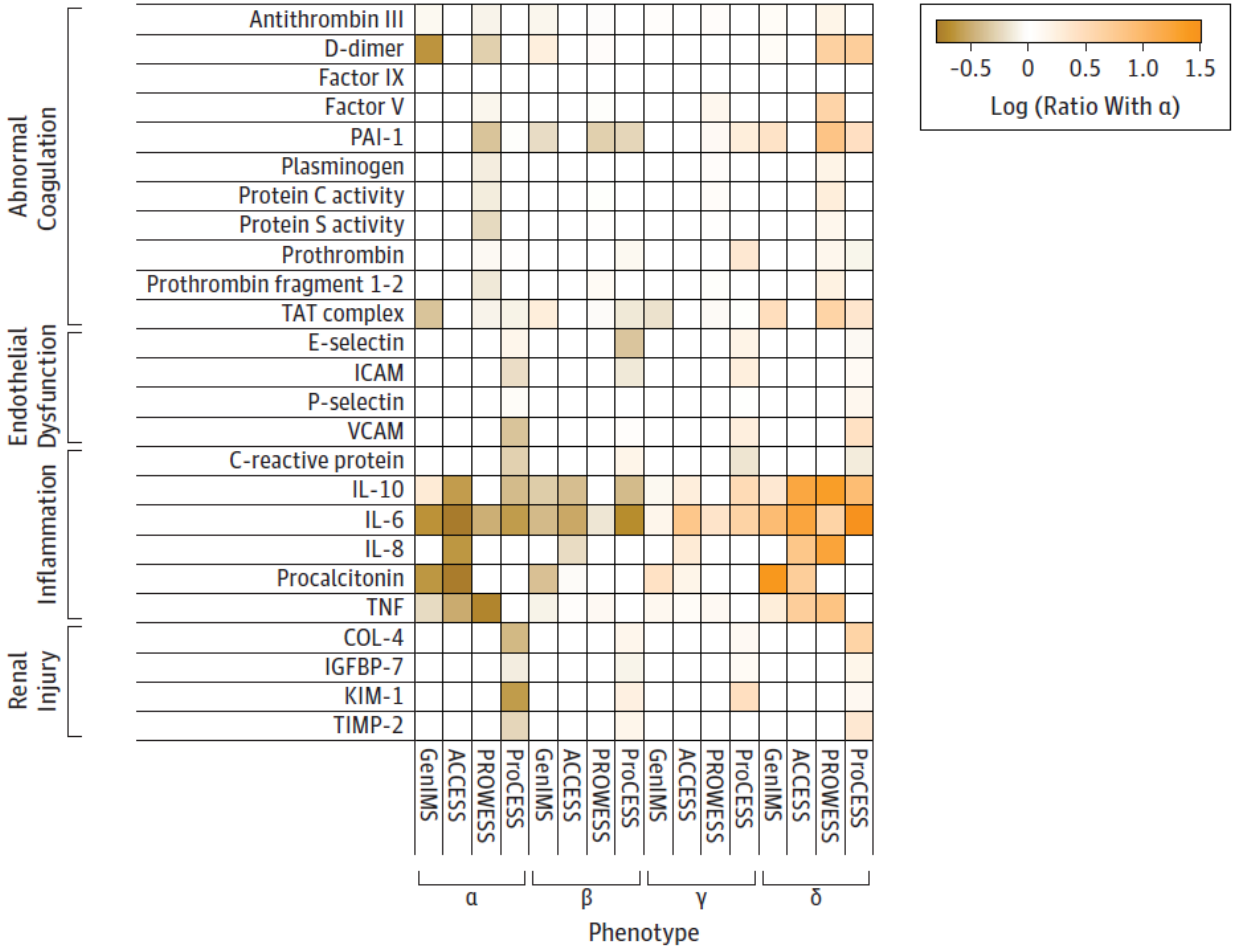
[b] Indicates total with available data.

[c] Measured among unique patients in each cohort.

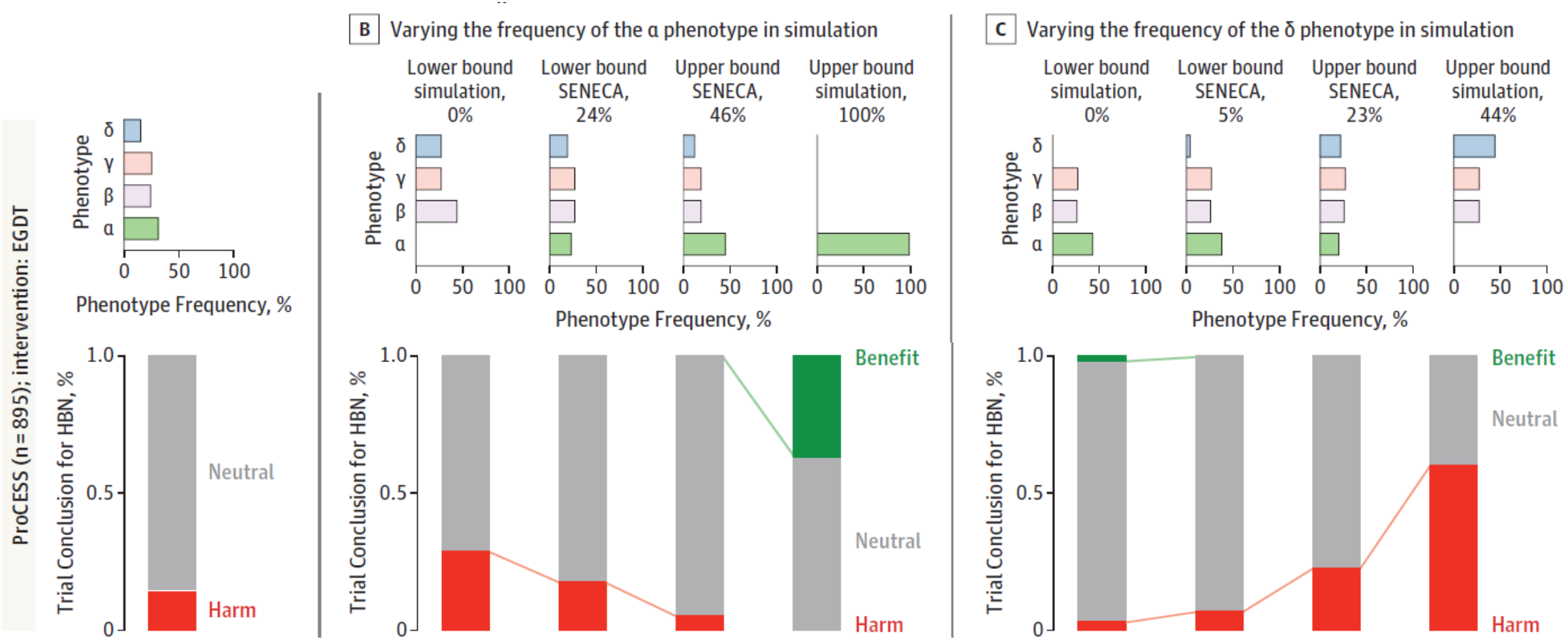
Seymour Ch. JAMA 2019

Phenotypen α - δ





Einfluss von Phänotyp auf Einzeltherapiemassname



Personalized Swiss Sepsis Study: CH Effort für Patienten mit Sepsis

BioMedIT

SIB Swiss Institute of Bioinformatics

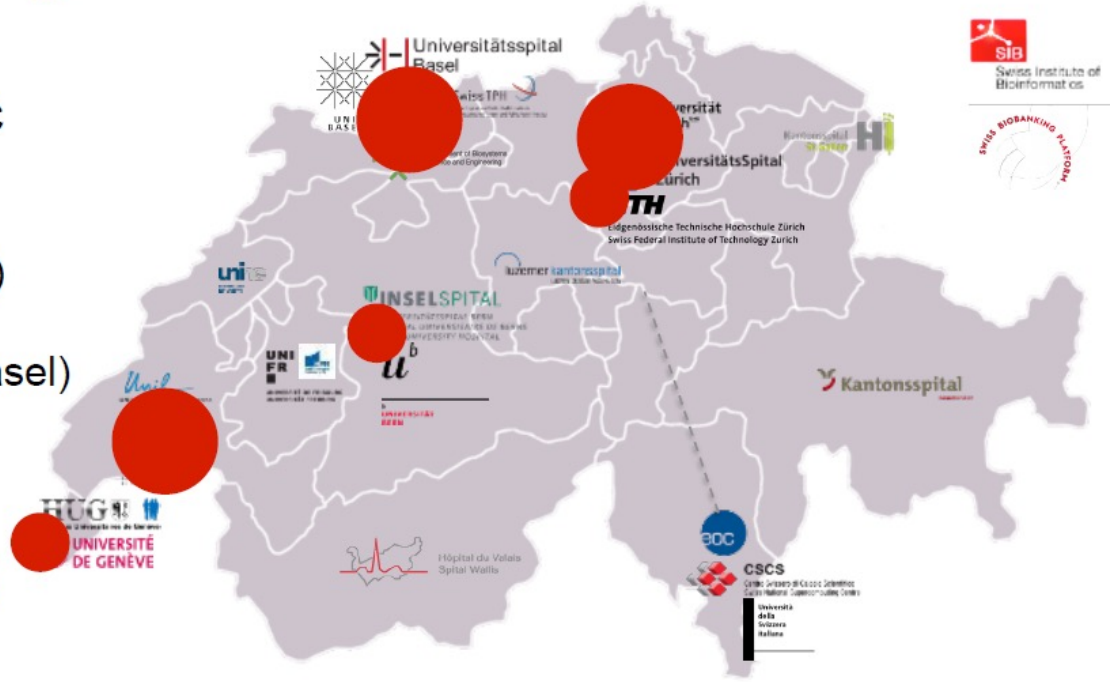
SPHN Swiss Personalized Health Network

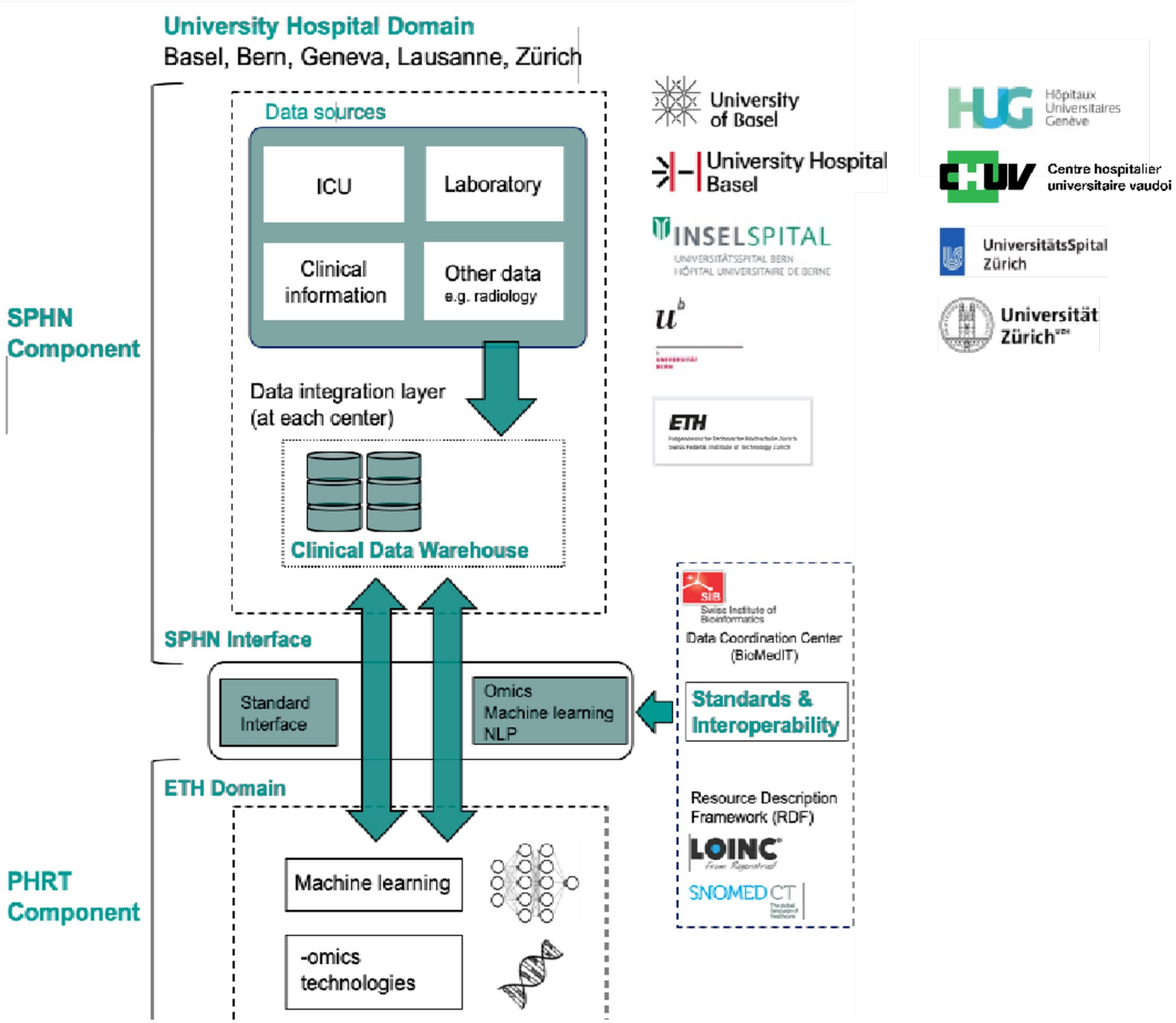
Create an IT infrastructure for research with biomedical data in academia

Make clinical care data available for research

BioMedIT nodes coordinated by SPHN DCC
Torsten Schwede

- **Vital-IT** (SIB, Lausanne)
  Ioannis Xenarios
- **sciCORE** (University Basel)
  Thierry Sengstag
- **SIS** (ETHZ)
  Bernd Rinn
- **S3IT** (University Zurich)
  Marcel Riedi

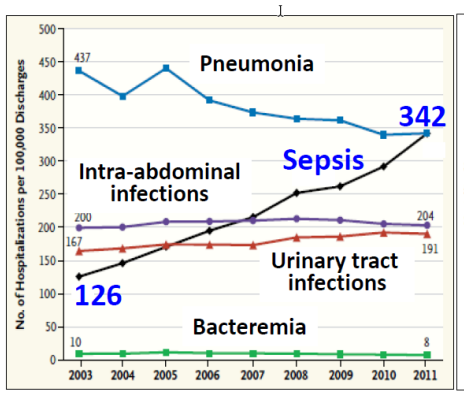


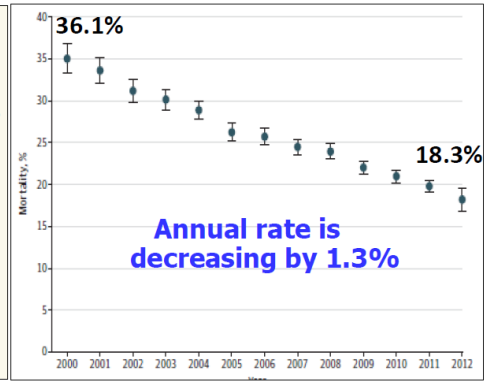


Datenaustausch zwischen Spitälern

- Daten werden über sichere Verbindung ausgetauscht.
- Zentralisierte Lagerung an ETH (Leonhard Med)
- Bisher 18000+ Patientinnen und Patienten auf Intensivstationen eingeschlossen.
- Datenmuster und künstliche Intelligenz sollen helfen, Sepsis früher zu erkennen.

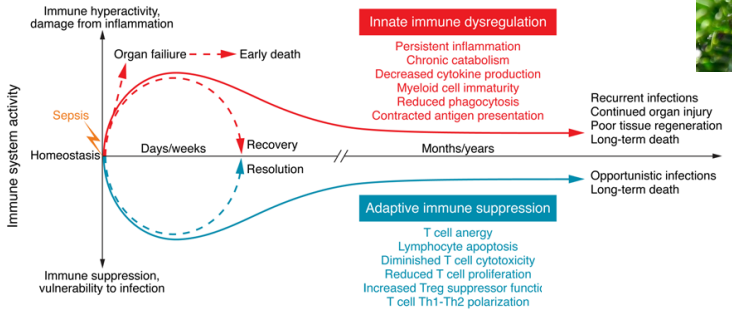
Agenda





1. Epidemiologie
   - Inzidenz, Kosten…
   - Langzeitfolgen

2. Definition
   - Sepsis-3
   - “Sepsis-4”: Sepsis Typen?



3. Pathophysiologie & Therapeutische Optionen

4. Auftrag an uns?

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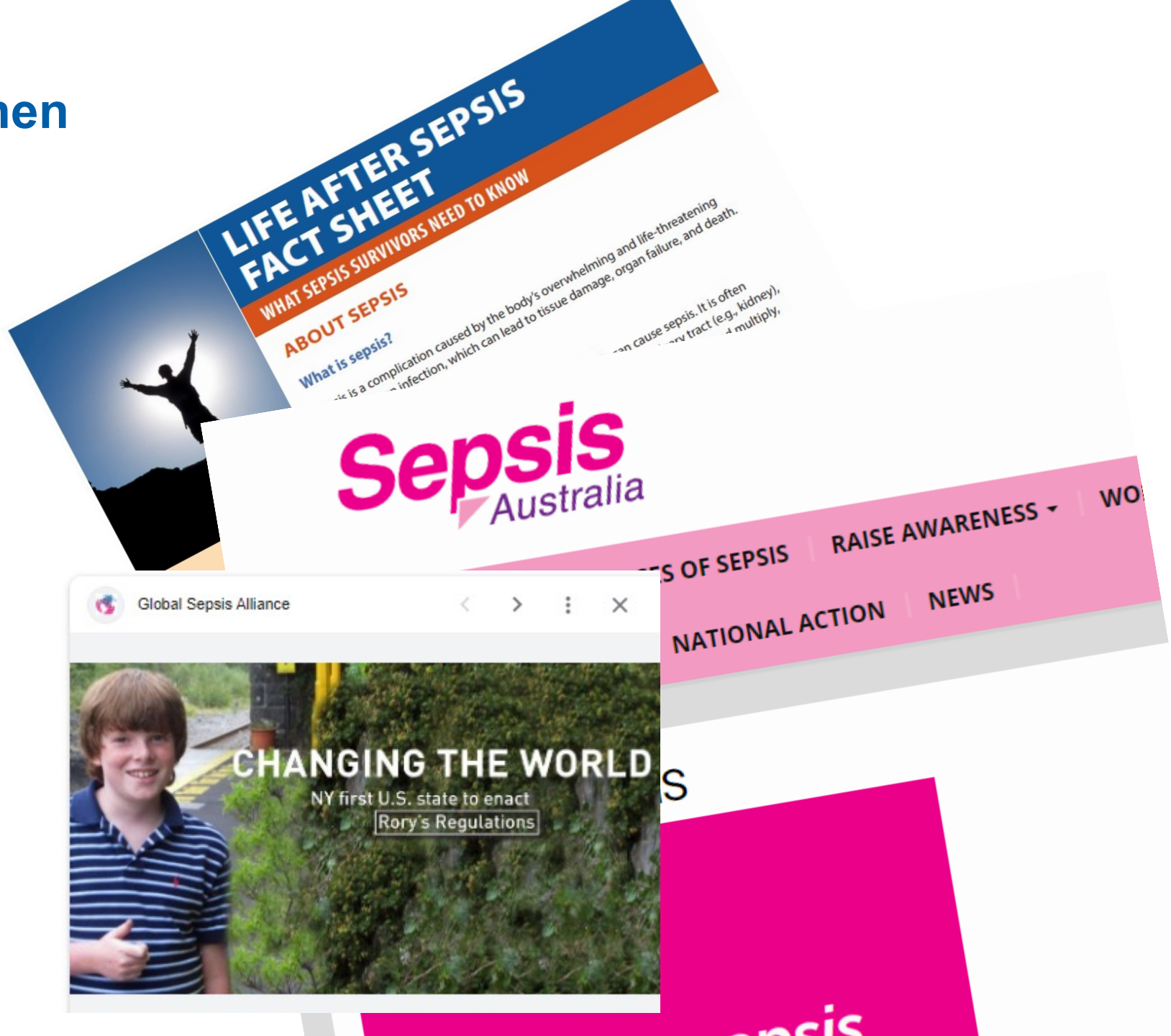
Nationale Kampagnen



Sepsis Prävention Schweiz

Swiss Sepsis National Action Plan: A coordinated national action plan to stop sepsis-related preventable deaths and to improve the support of people affected by sepsis in Switzerland

Luregn J. Schlapbach[1,2†], Elisa A. Zimmermann[1*†], Sylvain Meylan[3], Martin Stocker[4], Peter M. Suter[5] and Stephan M. Jakob[6] on behalf of the Swiss Sepsis National Action Plan Working Group

[1]Department of Intensive Care and Neonatology, and Children's Research Center, University Children's Hospital Zurich, Zurich, Switzerland, [2]Child Health Research Centre, The University of Queensland, and Paediatric Intensive Care Unit, Queensland Children's Hospital, Brisbane, QL, Australia, [3]Infectious Diseases Service, Department of Medicine, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland, [4]Department of Pediatrics, Children's Hospital Lucerne, Lucerne, Switzerland, [5]University of Geneva, Geneva, Switzerland, [6]Department of Intensive Care Medicine, Bern University Hospital, University of Bern, Bern, Switzerland

Take home message

- Sepsis ist ein Syndrom, schwierig zu fassen und definieren
- Die aktuelle Definition (Sepsis-3) ist ein Mortalitäts-Prädiktor
- Erkennen von Sepsis-”Typen” könnte ein weiterführender Behandlungsansatz werden
- Aktuelle Therapie umfasst:
  - Rasche Kulturabnahme und empirische antibiotische Therapie
  - Evaluation des Bedarfes einer Herd-Kontrolle (Chirurgie; Bildgebung!)
  - Optimierung der Homöostase (Korrektur eines potentielle Volumenmangels, kein Überfüllen!, erhalten des Kreislaufes etc.)
  - “Best standard of care”
- Bedarf einer nationalen Kampagne insbesondre zur Verbesserung der post-Sepsis care