Sepsis

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Edited by : Haya Khader

Accounting for more than $20 billion
(5.2%) of total US hospital costs in 2011

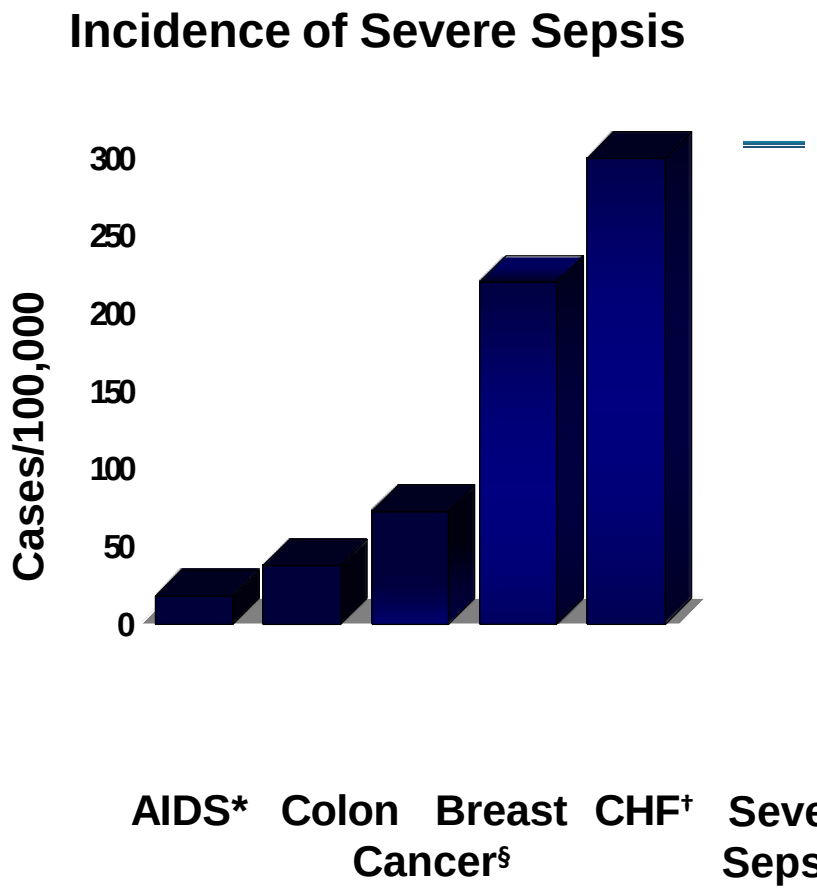
The reported incidence of sepsis is increasing, likely reflecting aging populations with more comorbidities, greater recognition,

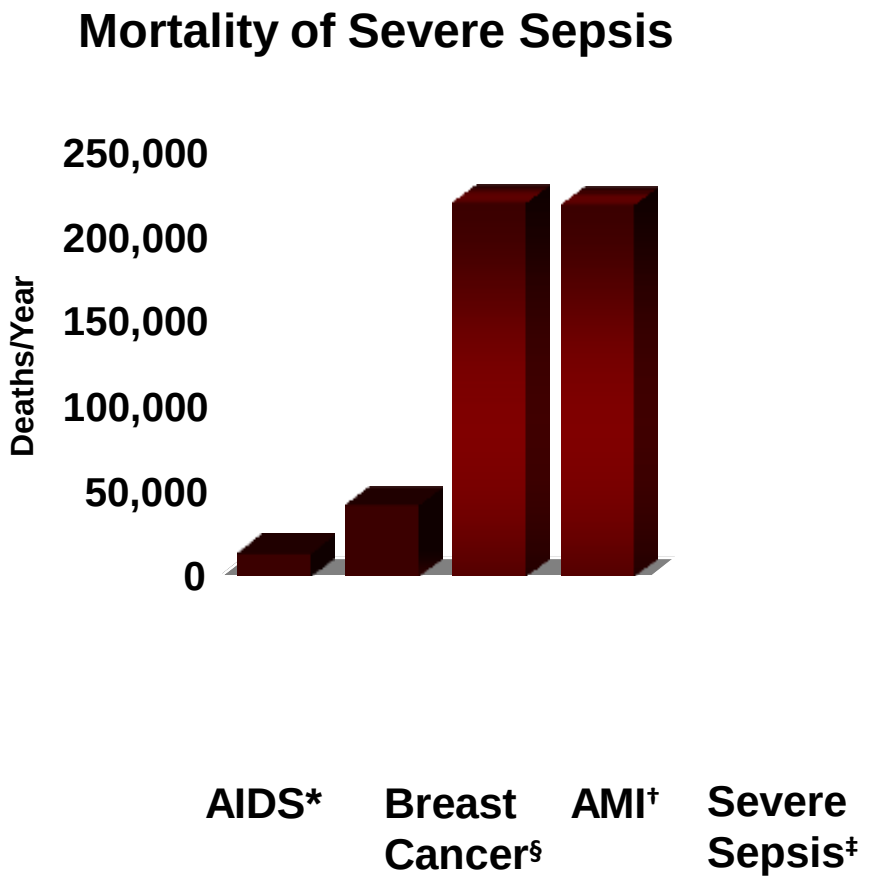
Sepsis is a leading cause of mortality and critical illness worldwide.

long-term physical, psychological, and cognitive disabilities with significant health care and social implications

high incidence and mortality rate for sepsis

Comparison With Other Major Diseases



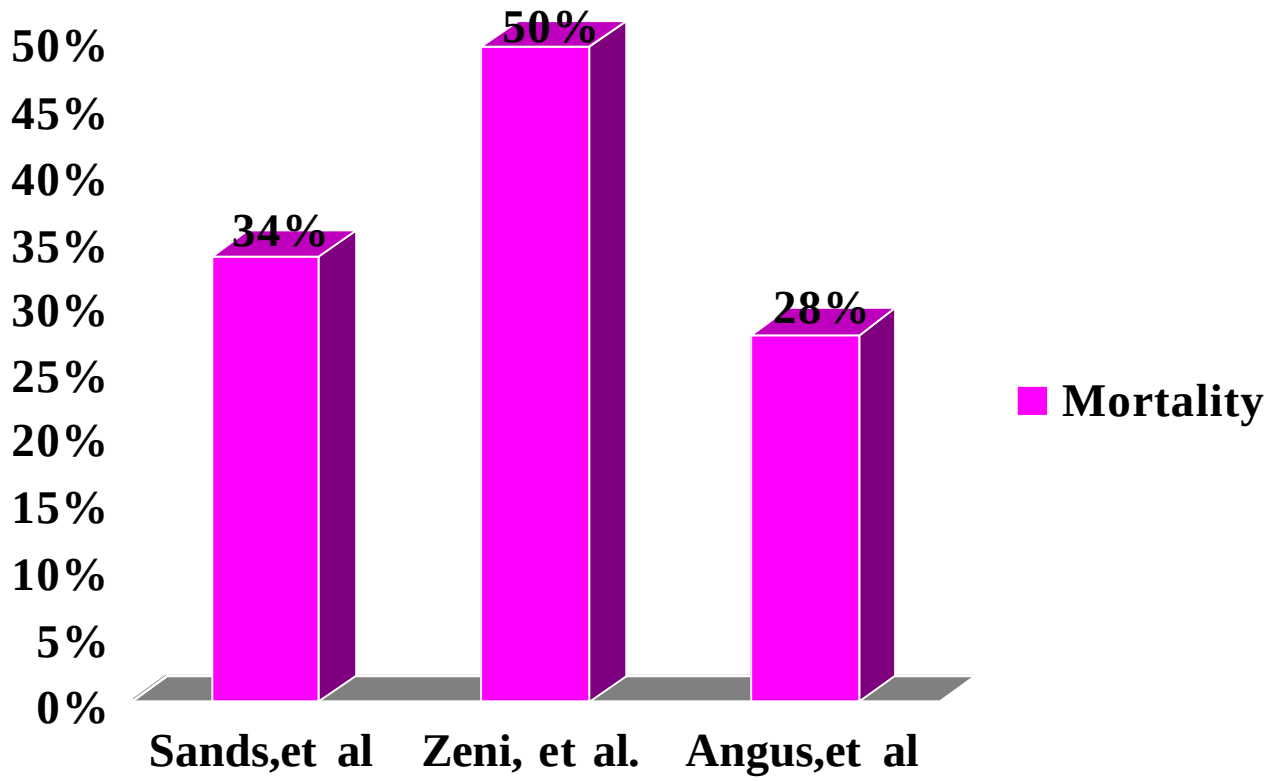


†National Center for Health Statistics, 2001. §American Cancer Society, 2001. *American Heart Association. 2000. ‡Angus DC et al. *Crit Care Med.* 2001;29(7):1303-1310.

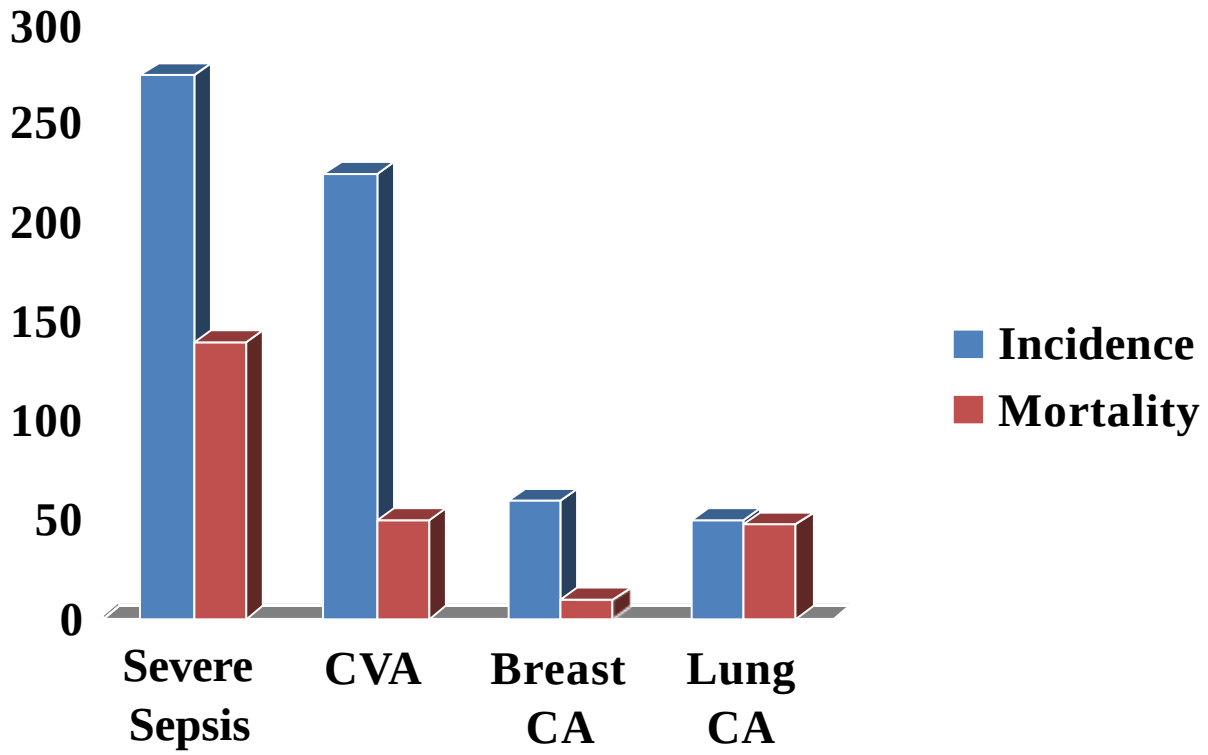
Sepsis, Mortality Rates

- **Overall = 30% - 50%**
- **By syndrome definition:**
  - **Sepsis = 16%**
  - **Septic shock = 46%**

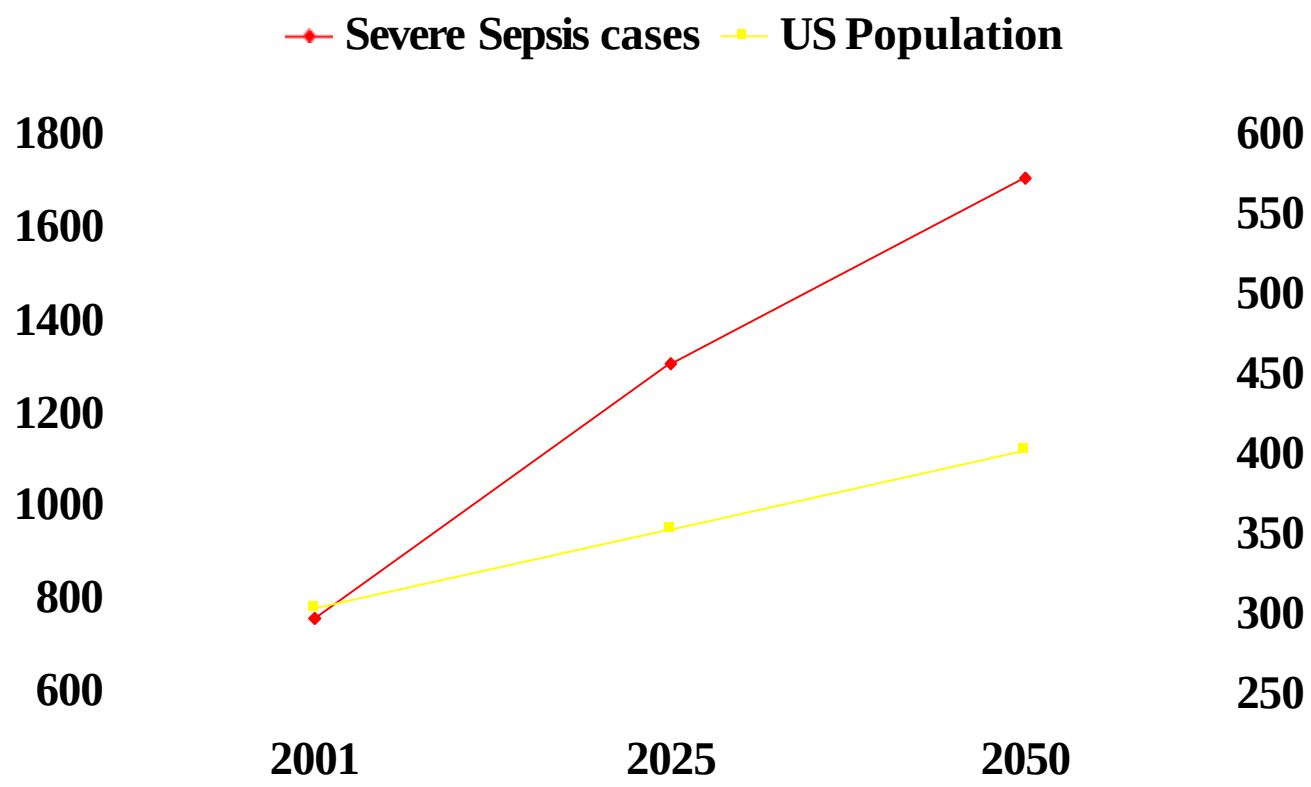
Sepsis is deadly



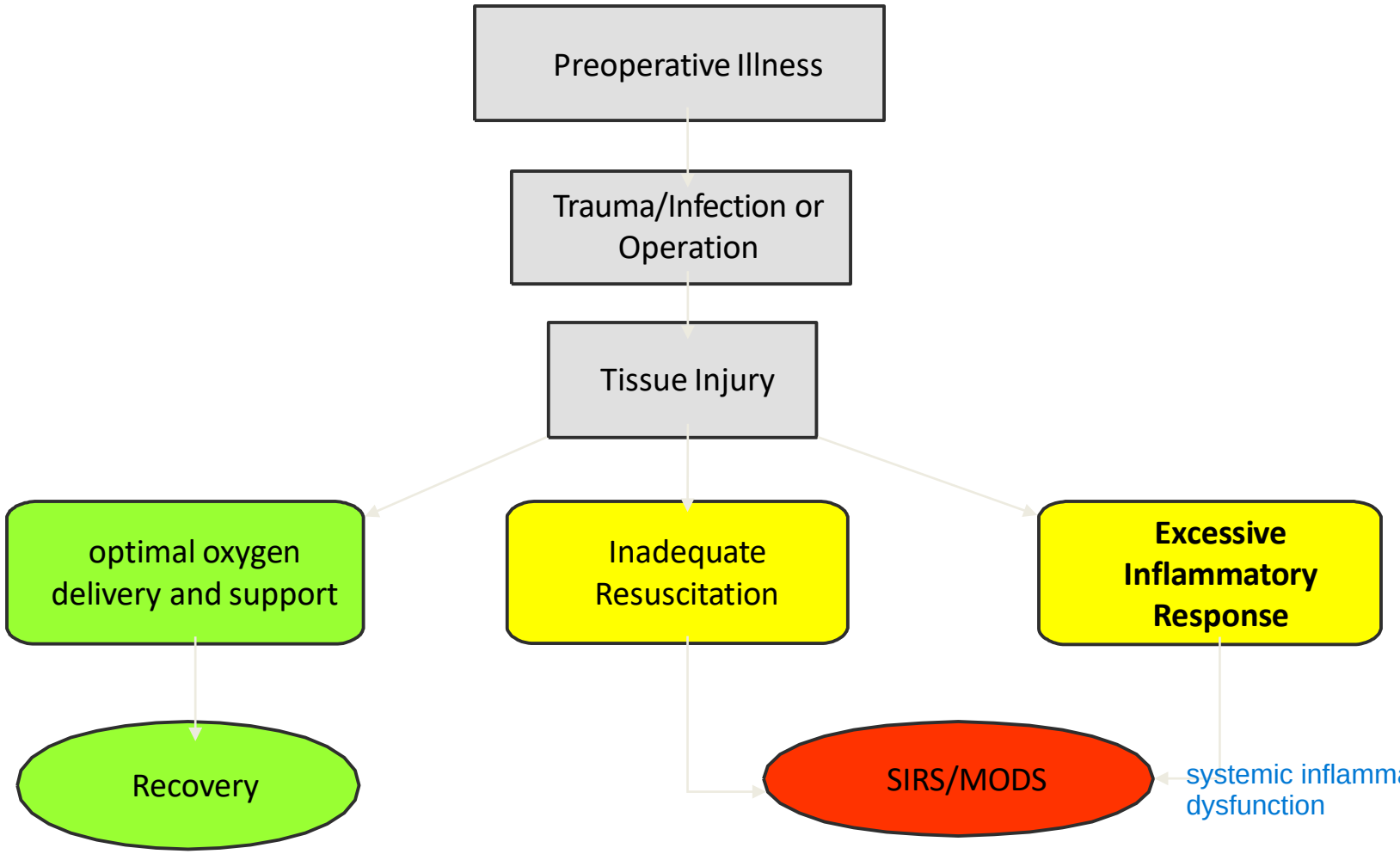
Sepsis is Common



Sepsis is increasing in incidence

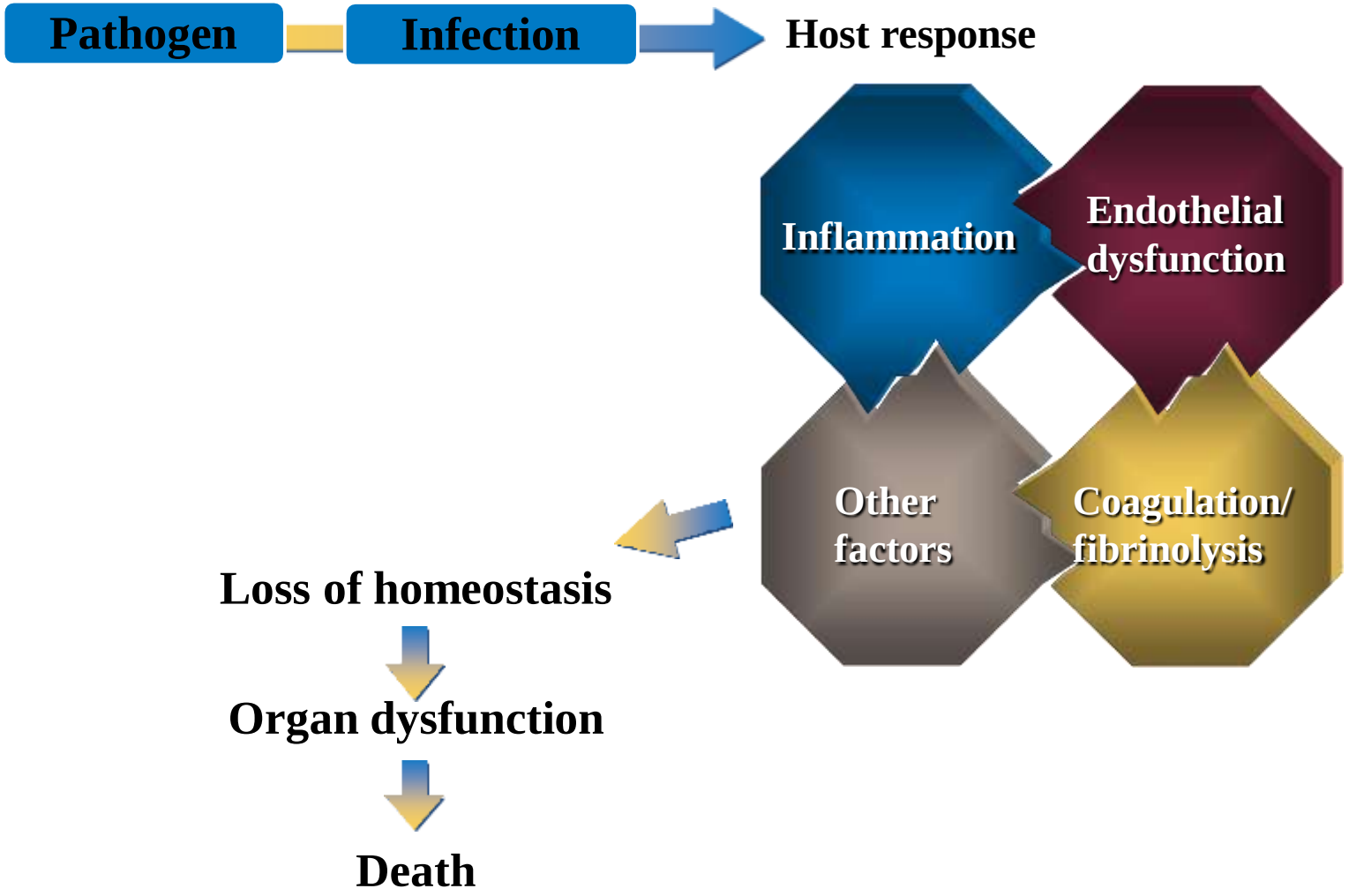


Pathogenesis of SIRS/MODS



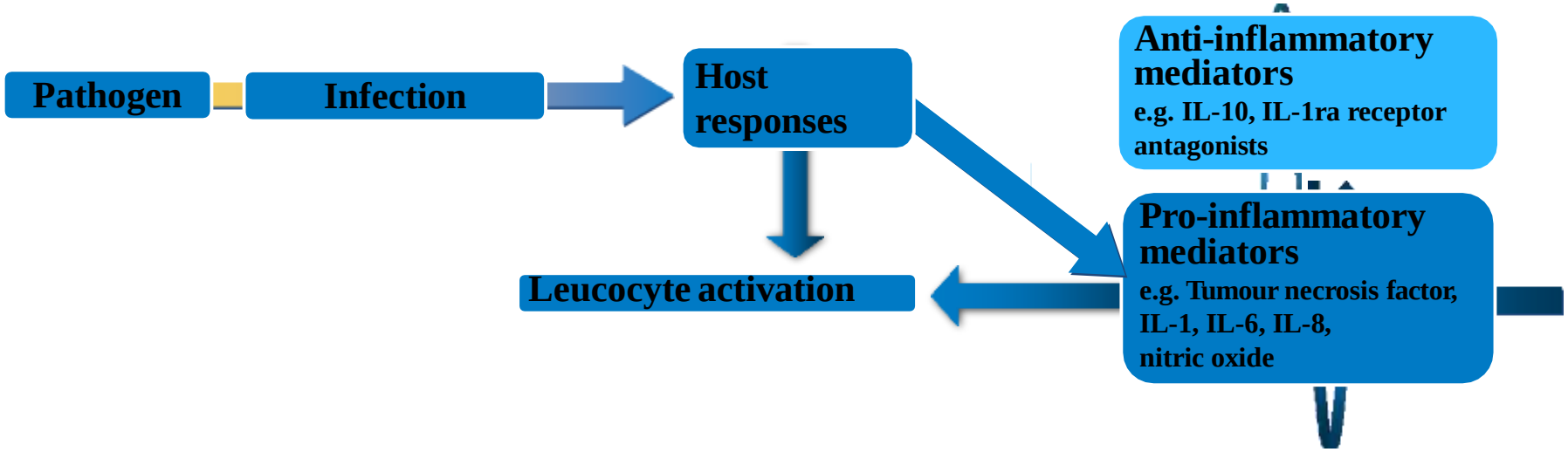
Pathogenesis of sepsis

An overview



Pathogenesis of sepsis

An overview

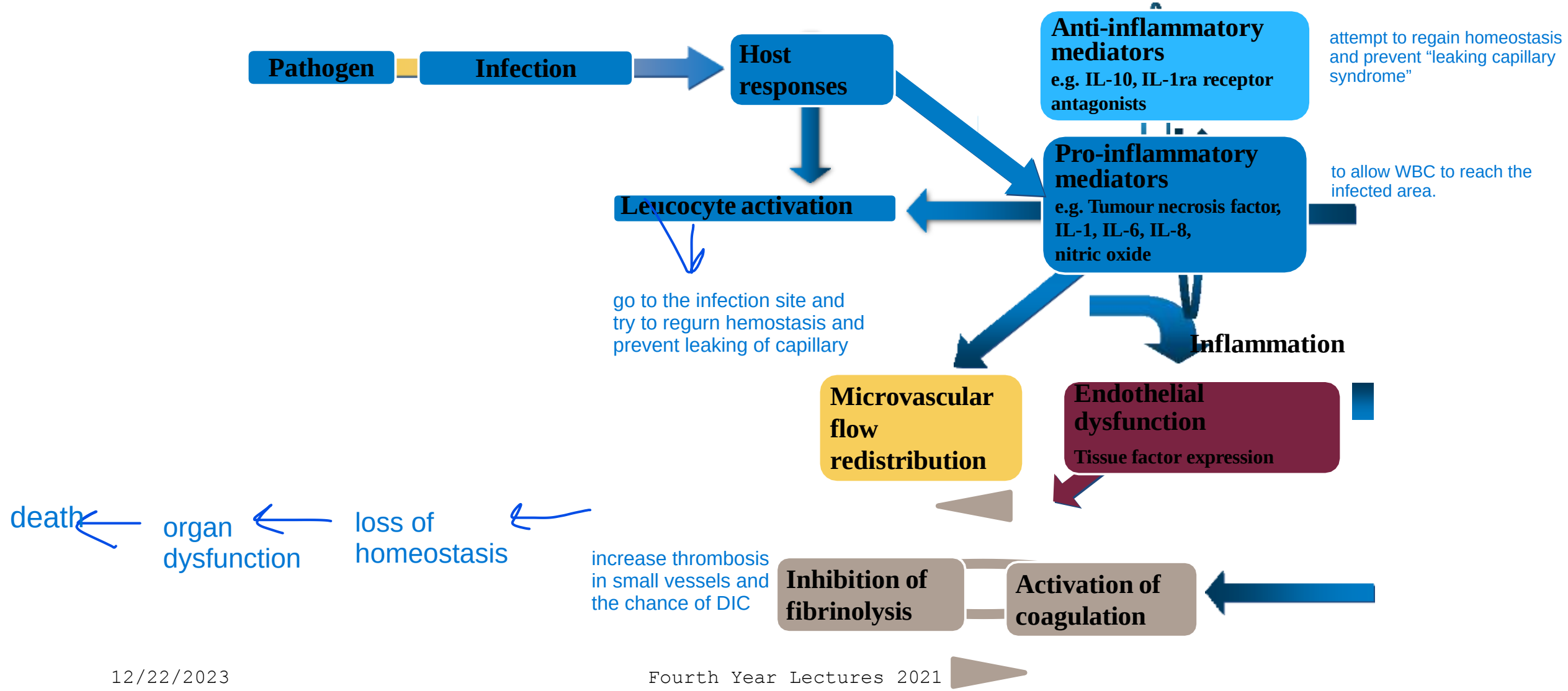


Inflammation

- Initial response to any pathogens is the release of pro-inflammatory mediators
  - *to allow WBC to reach the infected area.*
- Subsequently, an anti-inflammatory response
  - *attempt to regain homeostasis and prevent "leaking capillary syndrome".*
- The ability to activate and then eventually downregulate the inflammatory response to infection is a vital immune process and it is this ability that is lost in sepsis and severe sepsis.

Pathogenesis of sepsis

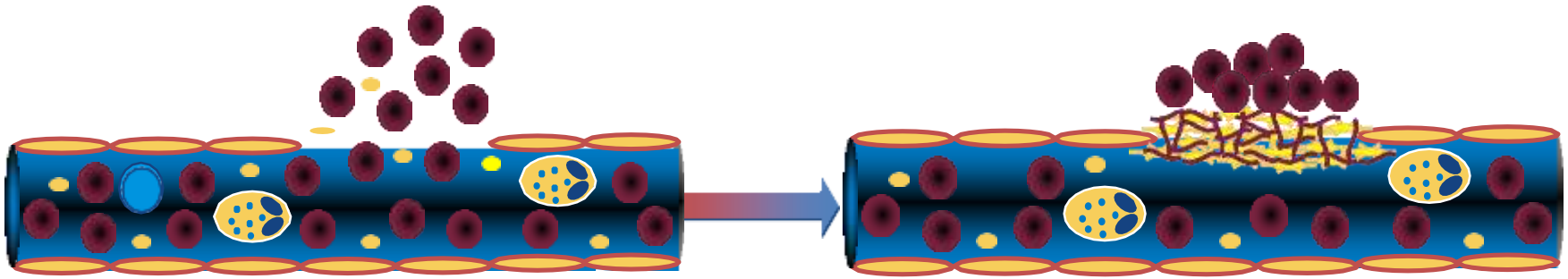
An overview



The role of the endothelium

Release of mediators of vasodilatation and/or vasoconstriction regulate vasomotor activity

- Release of cytokines and inflammatory mediators
- Allows leucocytes to access infection sites
- Plays an important role in the coagulation cascade, maintaining the physiological equilibrium between coagulation and fibrinolysis

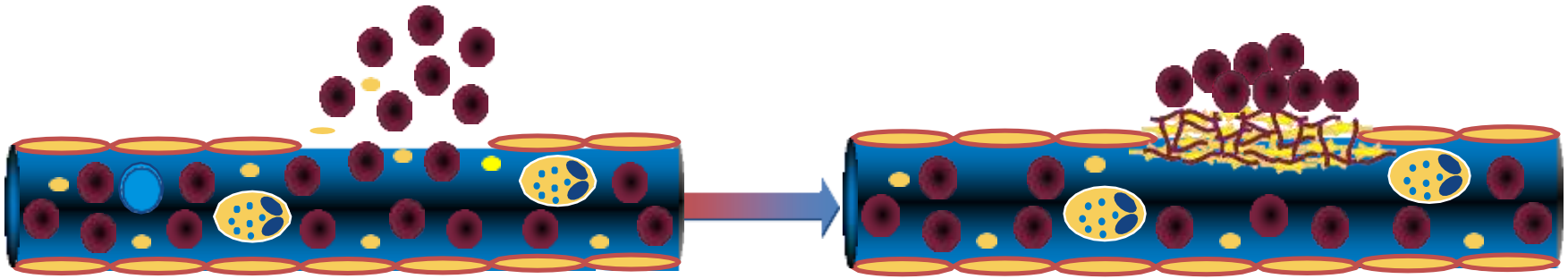


Tissue injury **Formation of fibrin clot**

The role of the endothelium

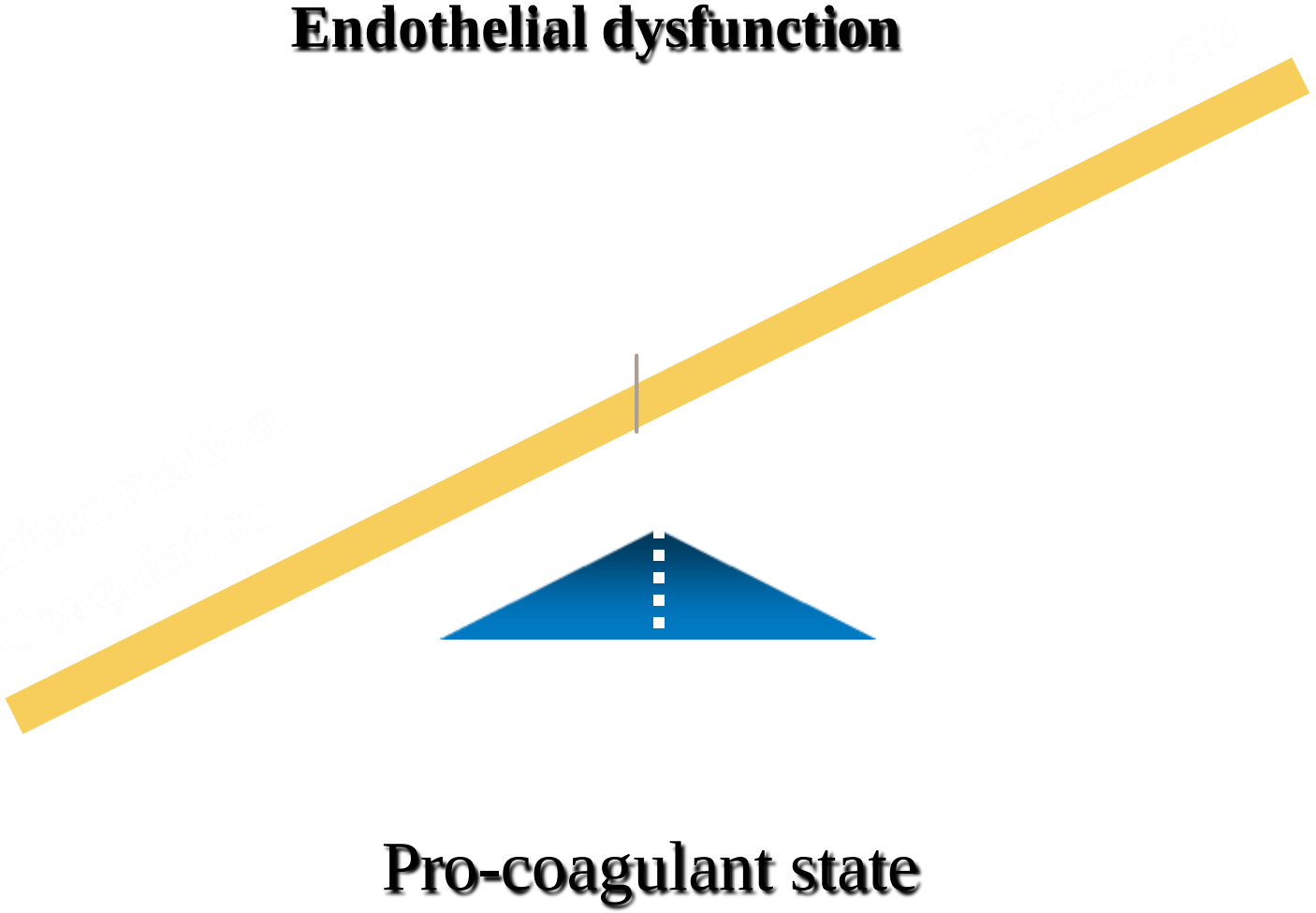
In sepsis, the regulatory function of the endothelium fails, leading to:

- Excessive vasodilation and relative hypovolaemia
- Leaking capillaries and generalised tissue damage (due to open the junction)
- Tissue factor (TF) release initiates **procoagulant state**
- Micro-thrombus formation compromising blood supply and leading to tissue necrosis
- Inactivation of Protein C (natural anticoagulant) and suppression of fibrinolysis (breakdown of clots)



Tissue injury **Formation of fibrin clot**

Loss of homeostasis in sepsis



Disseminated Intravascular Coagulation (DIC)

DIC can cause:

- bleeding
- large vessel thrombosis
- haemorrhagic tissue necrosis
- microthrombi leading to organ failure

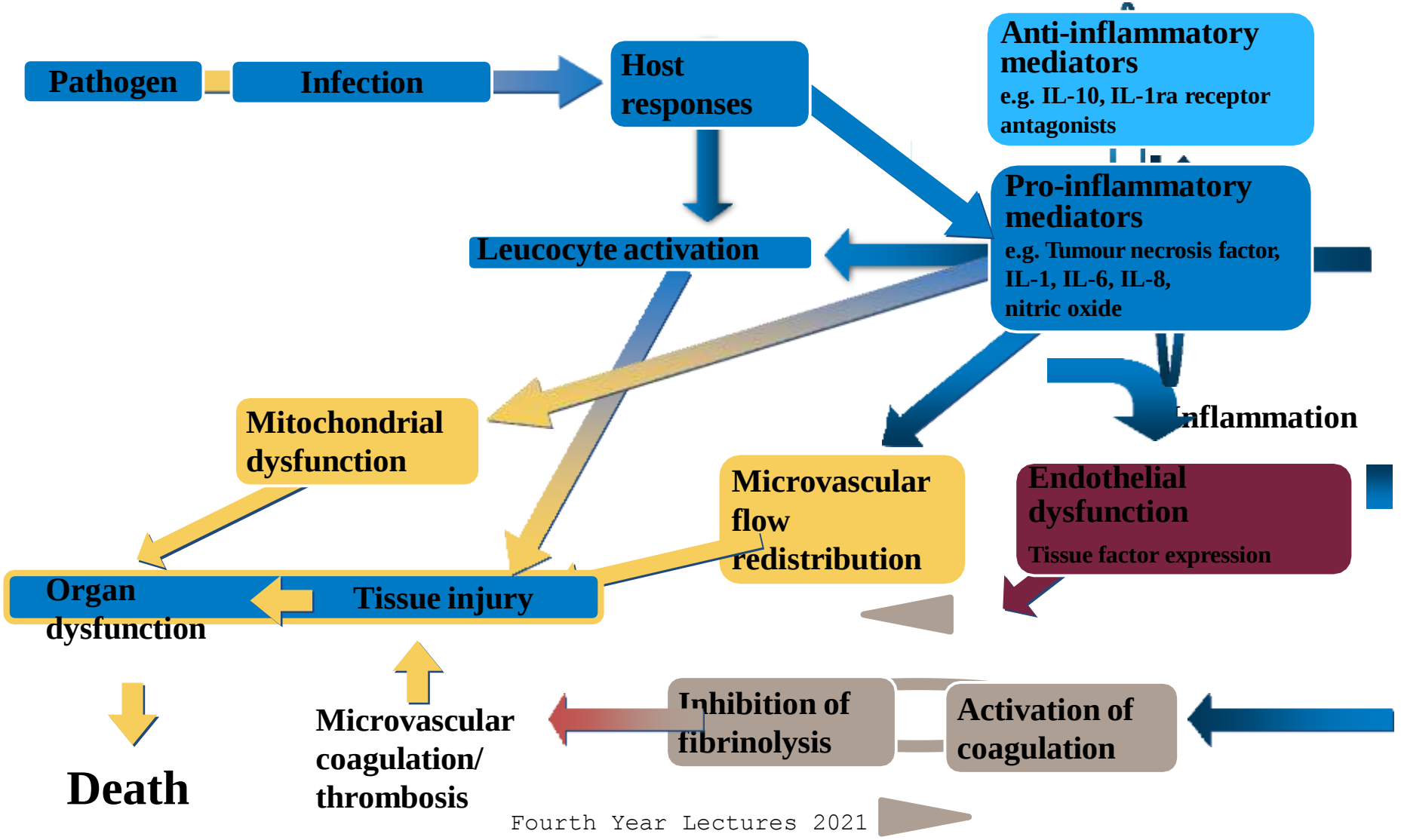
Widespread clotting causes consumption of:

- Low platelets
- clotting factors long clotting time
- fibrinogen

As a result, bleeding risk increases

Pathogenesis of sepsis

An overview



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The Compensatory Anti-inflammatory Response syndrome (CARS) in Critically ill patients

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Molecular Mediators in Pathophys

Systemic Inflammatory Response Syndrome
TNF-alpha / IL-1, IL-6 / Interferon-gamma
procalcitonin / platelet activating factor

Compensatory Anti-inflammatory
Response Syndrome

- Parallel to SIRS is CARS
  - Compensatory Anti-inflammatory Response System
    - Attempts to down regulate the SIRS response
    - IL-4, IL-10, transforming growth factor beta, CSF, soluble receptors to TNF, antagonists to TNF-alpha and IL-1
    - If CARS reaction is severe it will manifest as anergy and infection susceptibility

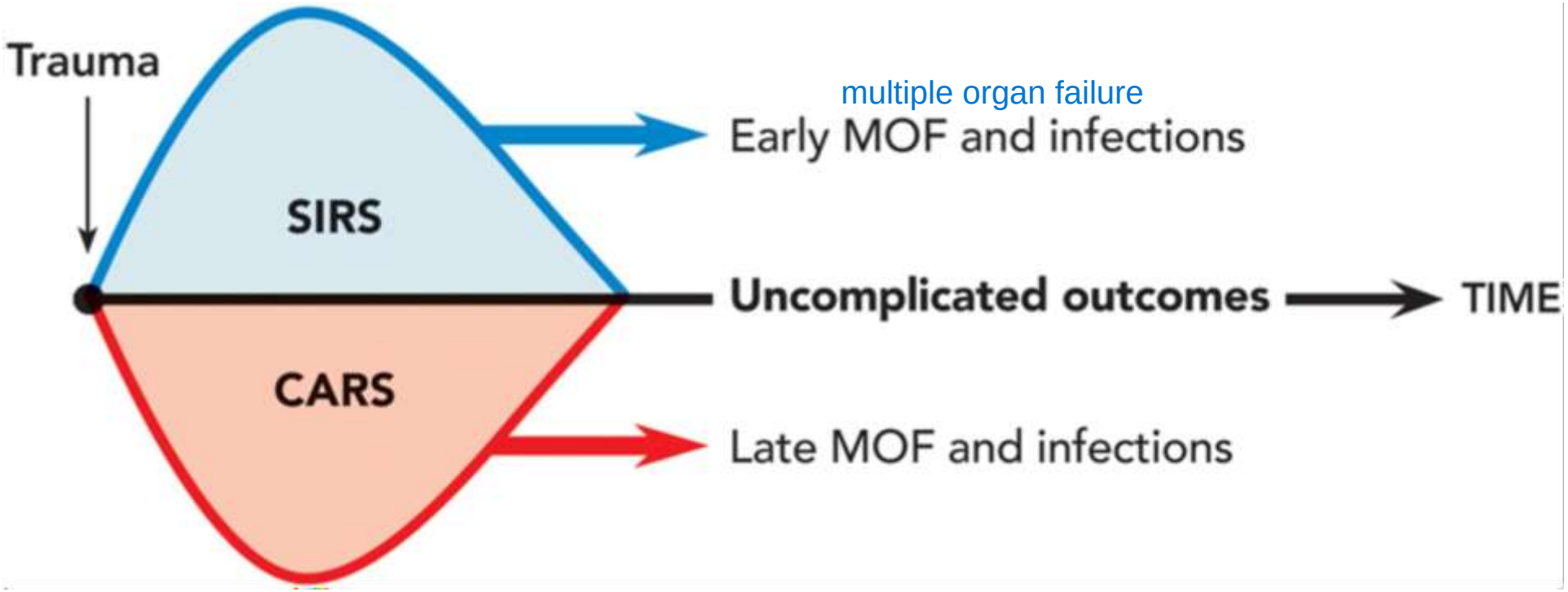
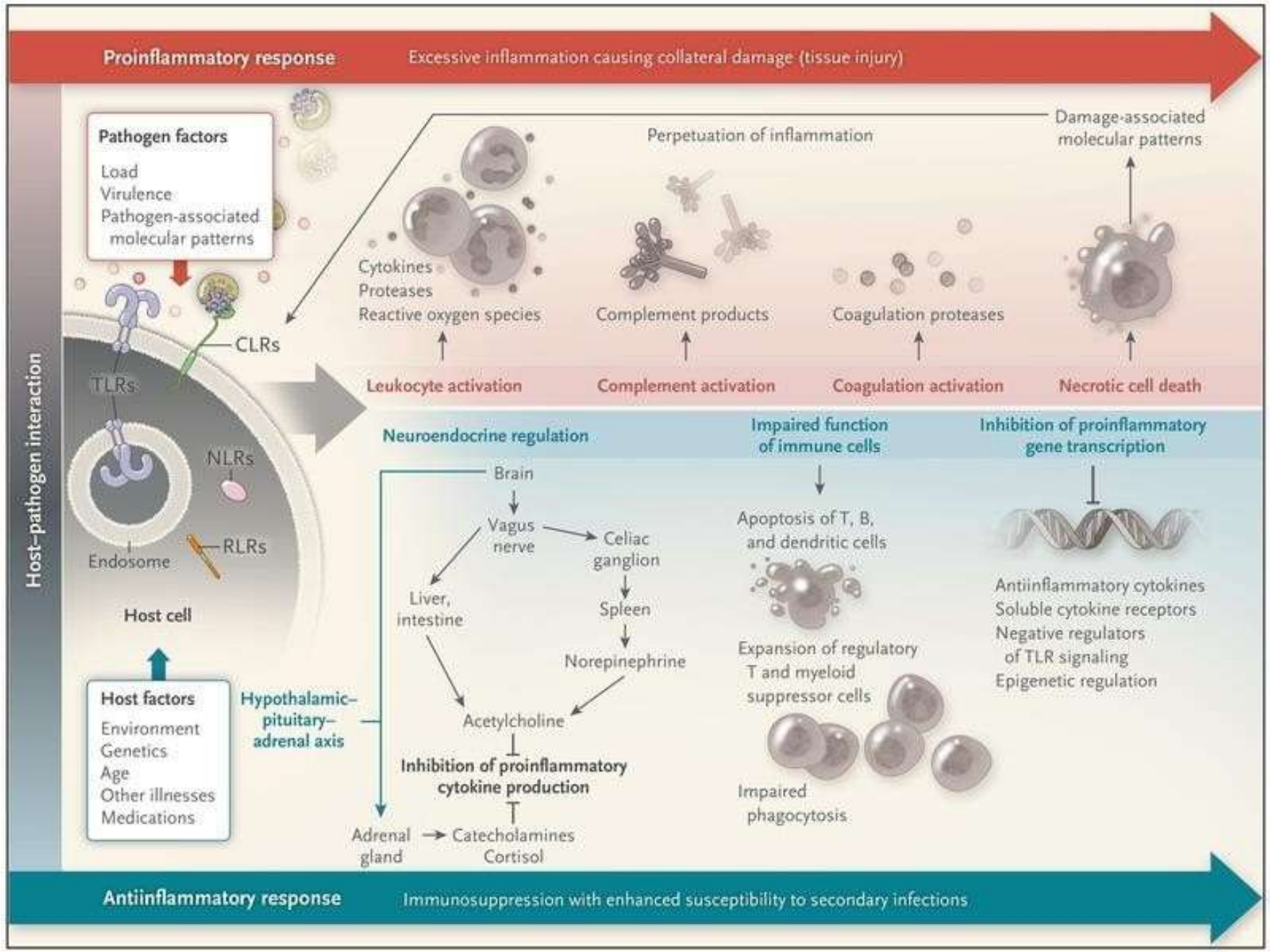


Figure Legend:

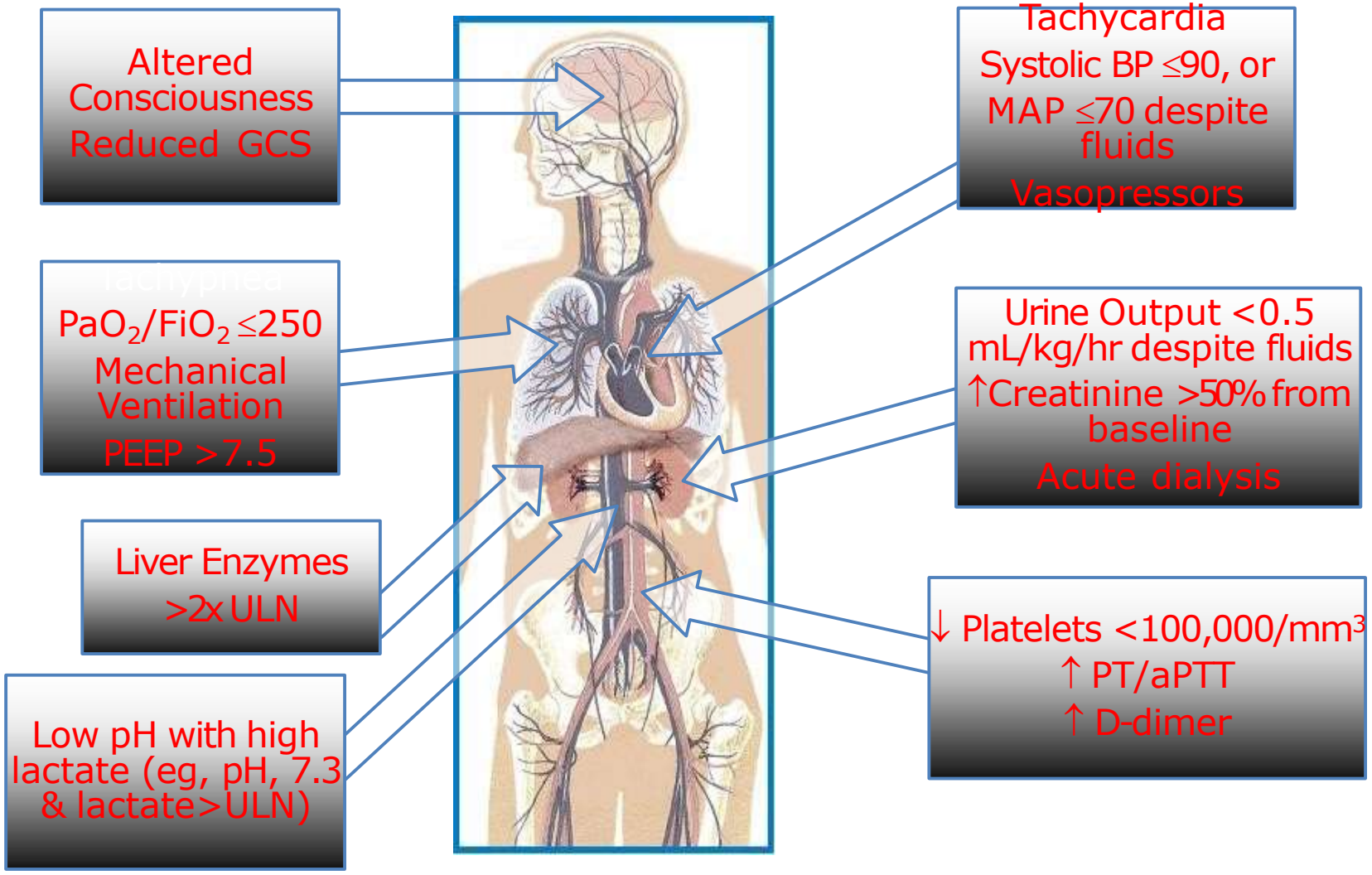
Fig. 2. Trauma-induced injury actives innate immune responses to produce pro- and antiinflammatory cytokines. Imbalance between the systemic inflammatory response syndrome and the compensatory antiinflammatory response (immunosupression) increases morbidity of trauma patients. In the first hours, the magnitude of the systemic inflammatory response syndrome is correlated with early multiple organ failure and infections. In the following days, immunosupression contributes to the increased incidence of nosocomial infections and late sepsis. CARS = compensatory anti-inflammatory response; MOF = multiple organ failure; SIRS = systemic inflammatory response syndrome.


Proinflammatory response
Excessive inflammation causing collateral damage (tissue injury)
Host–pathogen interaction
Pathogen factors
Load
Virulence
Pathogen-associated molecular patterns
CLRs
TLRs
NLRs
RLRs
Endosome
Host cell
Host factors
Environment
Genetics
Age
Other illnesses
Medications
Hypothalamic–pituitary–adrenal axis
Perpetuation of inflammation
Damage-associated molecular patterns
Cytokines
Proteases
Reactive oxygen species
Complement products
Coagulation proteases
Leukocyte activation
Complement activation
Coagulation activation
Necrotic cell death
Neuroendocrine regulation
Brain
Vagus nerve
Celiac ganglion
Liver, intestine
Spleen
Norepinephrine
Acetylcholine
Inhibition of proinflammatory cytokine production
Adrenal gland
Catecholamines
Cortisol
Impaired function of immune cells
Apoptosis of T, B, and dendritic cells
Expansion of regulatory T and myeloid suppressor cells
Impaired phagocytosis
Inhibition of proinflammatory gene transcription
Antiinflammatory cytokines
Soluble cytokine receptors
Negative regulators of TLR signaling
Epigenetic regulation
Antiinflammatory response
Immunosuppression with enhanced susceptibility to secondary infections

Response

- Physiology
  - Heart rate
  - Respiration
  - Fever
  - Blood pressure
  - Cardiac output
  - WBC
  - Hyperglycemia
- Markers of Inflammation
  - TNF
  - IL-1
  - IL-6
  - Procalcitonin Biomarker of bacterial infection
  - PAF Platelet-Activating Factor

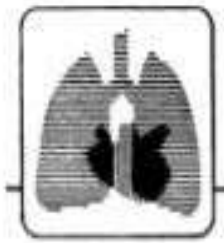
IDENTIFYING ACUTE ORGAN DYSFUNCTION AS A MARKER OF SEVERE SEPSIS



Organ Dysfunction

• Lungs	➢ Adult Respiratory Distress Syndrome
• Kidneys	➢ Acute Tubular Necrosis
• CVS	➢ Shock
• CNS	➢ Metabolic encephalopathy
• PNS	➢ Critical Illness Polyneuropathy
• Coagulation	➢ Disseminated Intravascular Coagulopathy
• GI	➢ Gastroparesis and ileus
• Liver	➢ Cholestasis
• Endocrine	➢ Adrenal insufficiency
• Skeletal Muscle	➢ Rhabdomyolysis

✓**Specific therapy exists**



accp/sccm consensus conference

Definitions for Sepsis and Organ Failure and Guidelines for the Use of Innovative Therapies in Sepsis

THE ACCP/SCCM CONSENSUS CONFERENCE COMMITTEE:

Roger C. Bone, M.D., F.C.C.P., Chairman
Robert A. Balk, M.D., F.C.C.P.
Frank B. Cerra, M.D.
R. Phillip Dellinger, M.D., F.C.C.P.
Alan M. Fein, M.D., F.C.C.P.
William A. Knaus, M.D.
Roland M. H. Schein, M.D.
William J. Sibbald, M.D., F.C.C.P.

2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference

Mitchell M. Levy, MD, FCCP; Mitchell P. Fink, MD, FCCP; John C. Marshall, MD; Edward Abraham, MD; Derek Angus, MD, MPH, FCCP; Deborah Cook, MD, FCCP; Jonathan Cohen, MD; Steven M. Opal, MD; Jean-Louis Vincent, MD, FCCP, PhD; Graham Ramsay, MD; For the International Sepsis Definitions Conference

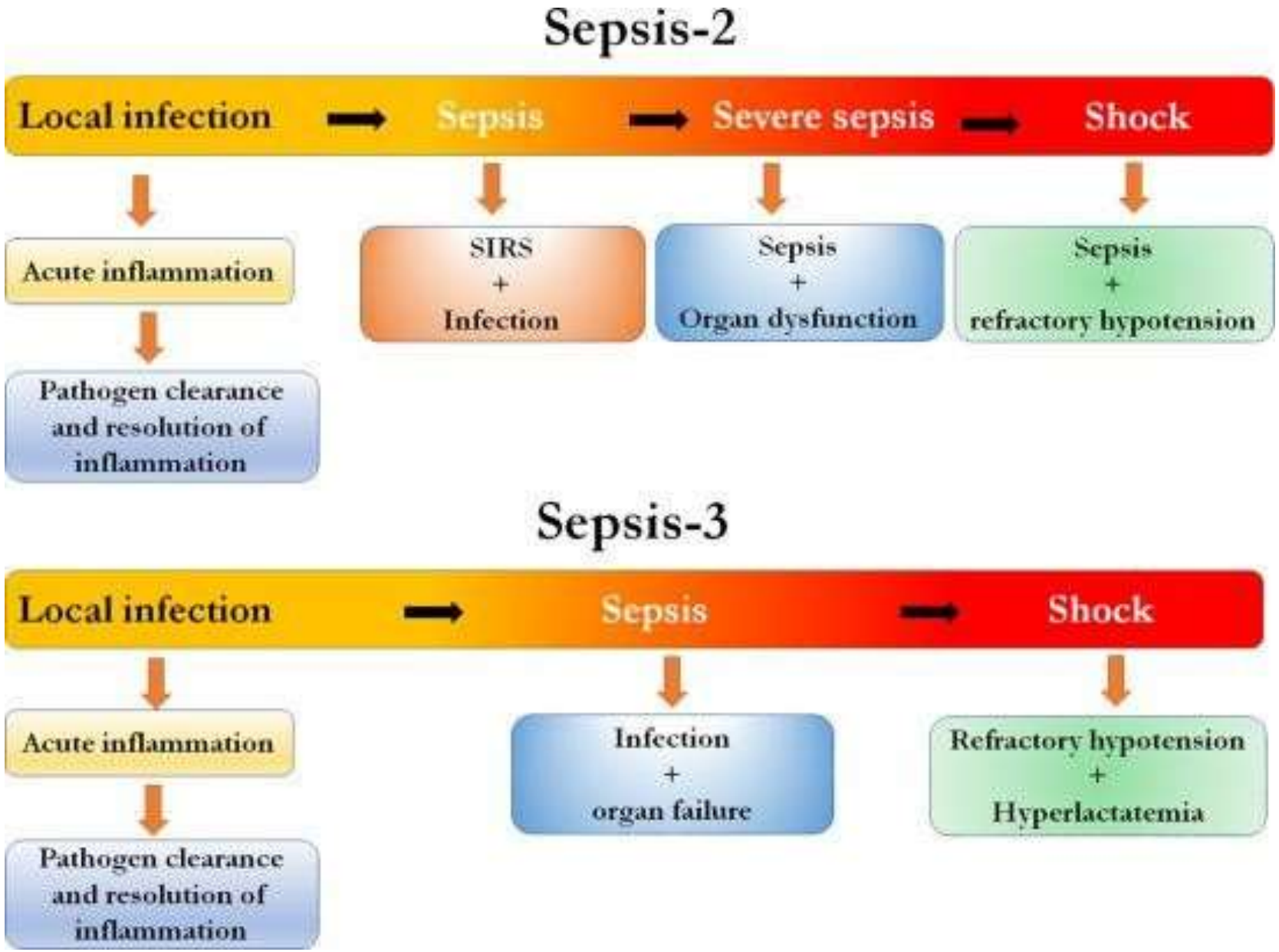
Terminology

- Systemic Inflammatory Response Syndrome (SIRS)
  - Temp > 38 or < 36
  - HR > 90
  - RR > 20 or PaCO2 < 32
  - WBC > 12 or < 4 or Bands > 10%

TWO out of four criteria
acute change from baseline

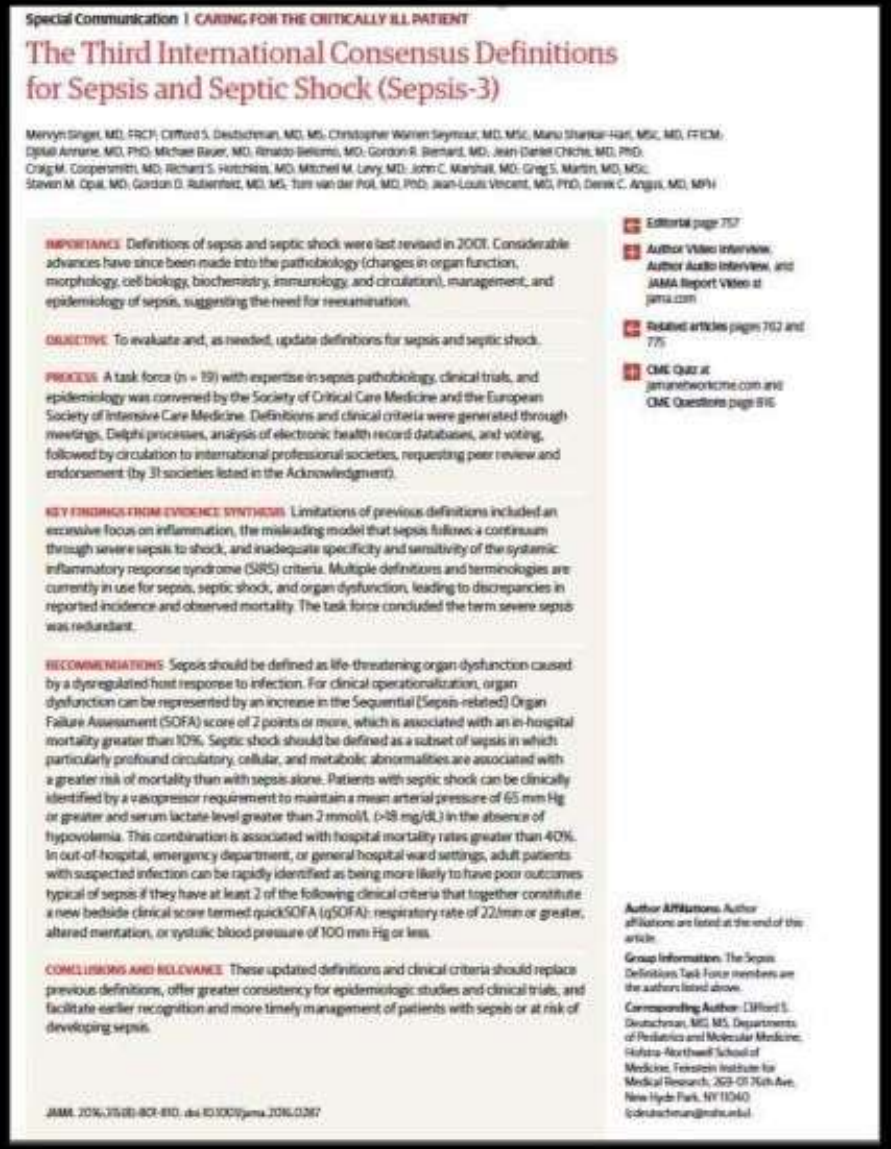
- Sepsis
  - The systemic inflammatory response to infection.
- Severe Sepsis
  - Organ dysfunction secondary to Sepsis.
  - e.g. hypoperfusion, hypotension, acute lung injury, encephalopathy, acute kidney injury, coagulopathy.
- Septic Shock
  - Hypotension secondary to Sepsis that is resistant to adequate fluid administration and associated with hypoperfusion.

Bone, R., Balk, R., Cerra, F., Dellinger, R., Fein, A., Knaus, W., Schein, R., et al. (1992). 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*, *101*(6), 1644–1655.


Sepsis-2
Local infection
Sepsis
Severe sepsis
Shock
Acute inflammation
Pathogen clearance and resolution of inflammation
SIRS + Infection
Sepsis + Organ dysfunction
Sepsis + refractory hypotension
Sepsis-3
Local infection
Sepsis
Shock
Acute inflammation
Pathogen clearance and resolution of inflammation
Infection + organ failure
Refractory hypotension + Hyperlactatemia

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

The Sepsis Definitions Task Force



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.

PROCESS A task force (n = 19) with expertise in sepsis pathobiology, clinical trials, and epidemiology was convened by the Society of Critical Care Medicine and the European Society of Intensive Care Medicine. Definitions and clinical criteria were generated through meetings, Delphi processes, analysis of electronic health record databases, and voting, followed by circulation to international professional societies, requesting peer review and endorsement (by 31 societies listed in the Acknowledgment).

KEY FINDINGS FROM EVIDENCE SYNTHESIS Limitations of previous definitions included an excessive focus on inflammation, the misleading model that sepsis follows a continuum through severe sepsis to shock, and inadequate specificity and sensitivity of the systemic inflammatory response syndrome (SIRS) criteria. Multiple definitions and terminologies are currently in use for sepsis, septic shock, and organ dysfunction, leading to discrepancies in reported incidence and observed mortality. The task force concluded the term severe sepsis was redundant.

RECOMMENDATIONS Sepsis should be defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. For clinical operationalization, organ dysfunction can be represented by an increase in the Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score of 2 points or more, which is associated with an in-hospital mortality greater than 10%. Septic shock should be defined as a subset of sepsis in which particularly profound circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone. Patients with septic shock can be clinically identified by a vasopressor requirement to maintain a mean arterial pressure of 65 mm Hg or greater and serum lactate level greater than 2 mmol/L (>18 mg/dL) in the absence of hypovolemia. This combination is associated with hospital mortality rates greater than 40%. In out-of-hospital, emergency department, or general hospital ward settings, adult patients with suspected infection can be rapidly identified as being more likely to have poor outcomes typical of sepsis if they have at least 2 of the following clinical criteria that together constitute a new bedside clinical score termed quickSOFA (qSOFA): respiratory rate of 22/min or greater, altered mentation, or systolic blood pressure of 100 mm Hg or less.

CONCLUSIONS AND RELEVANCE These updated definitions and clinical criteria should replace previous definitions, offer greater consistency for epidemiologic studies and clinical trials, and facilitate earlier recognition and more timely management of patients with sepsis or at risk of developing sepsis.

Editorial page 757

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

Related articles pages 762 and 775

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Author Affiliations. Author affiliations are listed at the end of this article.

Group Information. The Sepsis Definitions Task Force members are the authors listed above.

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

The Document

Singer M, Deutschman CS, Seymour CW, Shankar-Hari M et al.

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

JAMA 2016; 315: 801-10

The Definition of Sepsis

Sepsis is life-threatening organ dysfunction caused by a dysregulated host response to infection

The Definition of Septic Shock

- What tangibly differentiates septic shock from sepsis ?

- MORTALITY

  Septic shock is “really bad” sepsis

Septic shock is a subset of sepsis in which profound circulatory, cellular and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone

Clinical criteria for sepsis

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

System	0	1	2	3	4
Respiration PaO2/FiO2, mmHg (kPa)	≥400 (53.3)	<400 (53.3)	<300 (40)	<200 (26.7) with respiratory support	<100 (13.3) with respiratory support
Coagulation Platelets, x10³/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) <500	>5.0 (440) <200
*Catecholamine Doses = ug/kg/min for at least 1hr					

SOFA Score

The European Society of Intensive Care Medicine

Mortality	SOFA score
<10%	0-6
15-20%	7-9
40-50%	10-12
50-60%	13-14
>80%	15
>90%	15-24

Mortality	Score trend (First 48 hrs)
>50%	Increasing
27-35%	Unchanged
<27%	Decreasing

Clinical criteria for sepsis

- Infection plus 2 or more SOFA points (above baseline)

Please visit www.qsofa.org

Clinical criteria for sepsis

- Infection plus 2 or more SOFA points (above baseline)

Prompt outside the ICU to consider sepsis

Please visit www.qsofa.org

qSOFA


Hypotension
Systolic BP
<100 mmHg
Altered
Mental
Status
Tachypnea
RR >22/Min
Score of ≥2 Criteria Suggests a Greater Risk of a Poor Outcome

Clinical criteria for sepsis

- Infection plus 2 or more SOFA points (above baseline)

Prompt outside the ICU to consider sepsis

- Infection plus 2 or more qSOFA points

Please visit www.qsofa.org

Outside the ICU, patients with suspected or presumed infection who are highly likely to have poor outcomes can be clinically identified using qSOFA

- SBP < 100mm Hg
- RR > 22 breath/min
- Altered mental status

❖ In the ICU, patients with suspected or presumed infection who are highly likely to have poor outcomes can be clinically identified by the presence of 2 or more SOFA points

Patients with a SOFA score of 2 or more had an overall mortality risk of approximately 10% in a general hospital population with presumed infection.

2016 Septic Shock Criteria

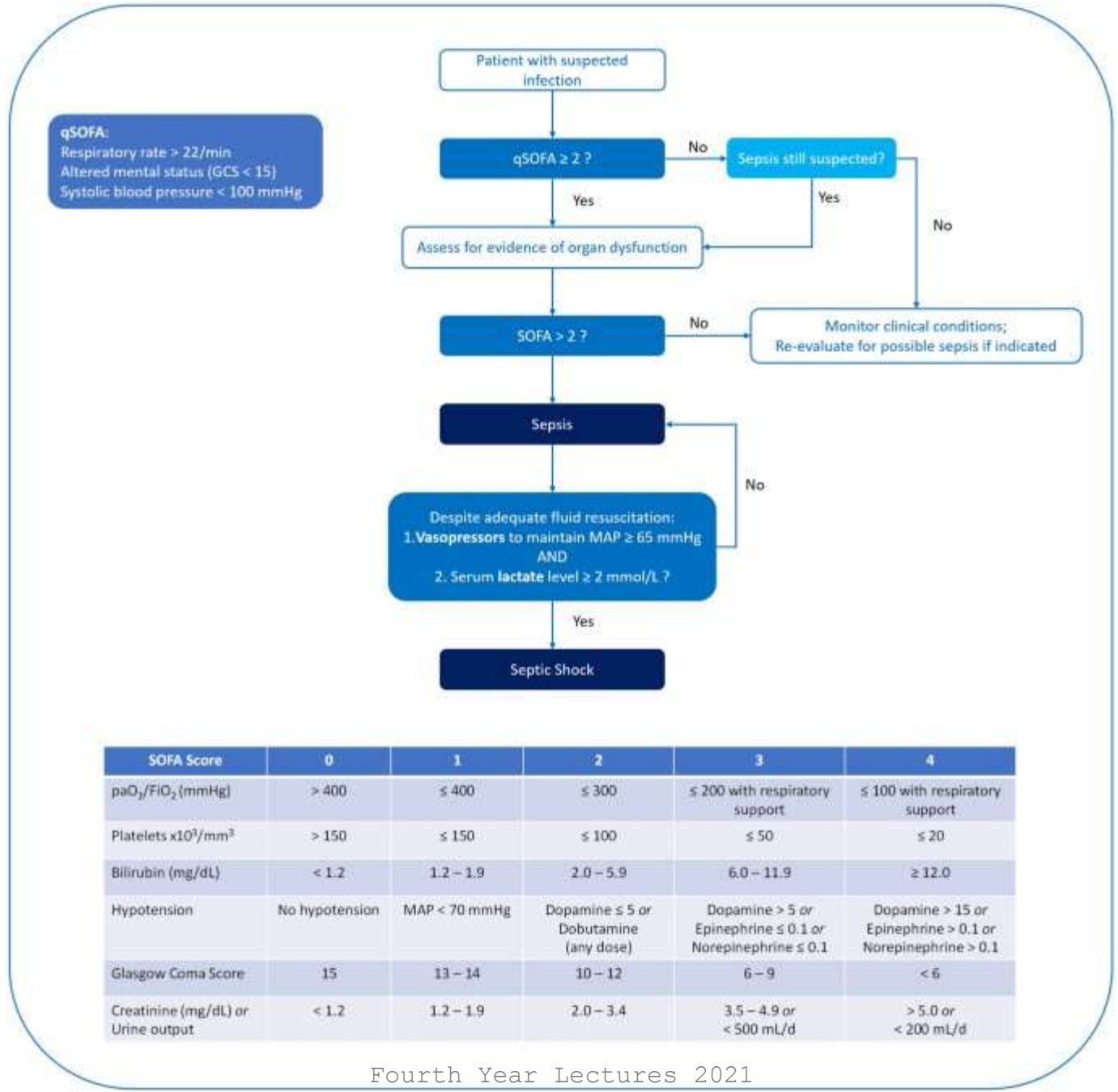
Despite adequate fluid resuscitation

- vasopressors needed to maintain MAP ≥65 mmHg

  AND

- lactate >2 mmol/l

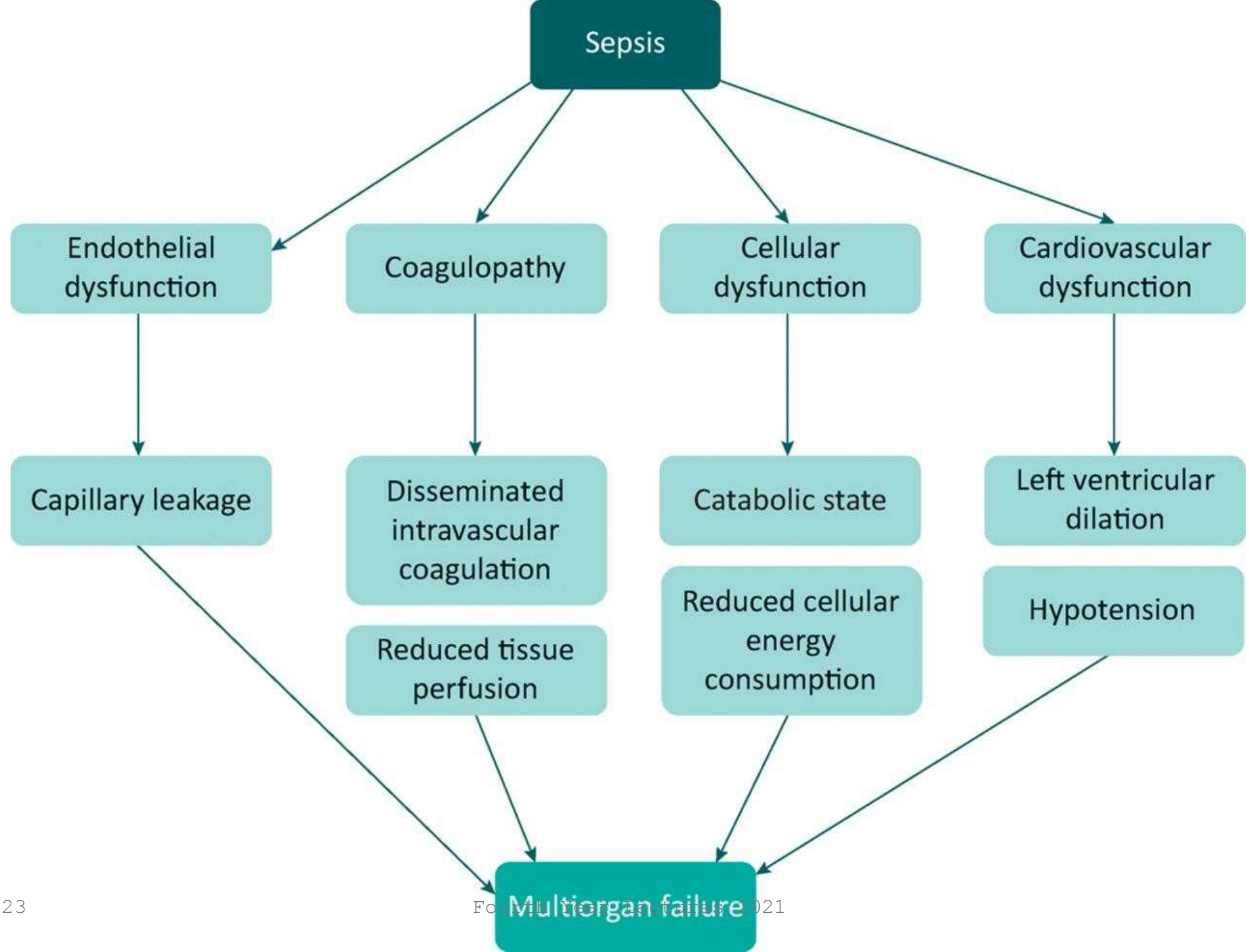
Mortality of Septic shock exceeds 40 %



SOFA Score	0	1	2	3	4
paO_2/FiO_2 (mmHg)	> 400	≤ 400	≤ 300	≤ 200 with respiratory support	≤ 100 with respiratory support
Platelets $x10^3/mm^3$	> 150	≤ 150	≤ 100	≤ 50	≤ 20
Bilirubin (mg/dL)	< 1.2	1.2 – 1.9	2.0 – 5.9	6.0 – 11.9	≥ 12.0
Hypotension	No hypotension	MAP < 70 mmHg	Dopamine ≤ 5 *or* Dobutamine (any dose)	Dopamine > 5 *or* Epinephrine ≤ 0.1 *or* Norepinephrine ≤ 0.1	Dopamine > 15 *or* Epinephrine > 0.1 *or* Norepinephrine > 0.1
Glasgow Coma Score	15	13 – 14	10 – 12	6 – 9	< 6
Creatinine (mg/dL) *or* Urine output	< 1.2	1.2 – 1.9	2.0 – 3.4	3.5 – 4.9 *or* < 500 mL/d	> 5.0 *or* < 200 mL/d

Why do Septic Patients Die?

Organ Failure

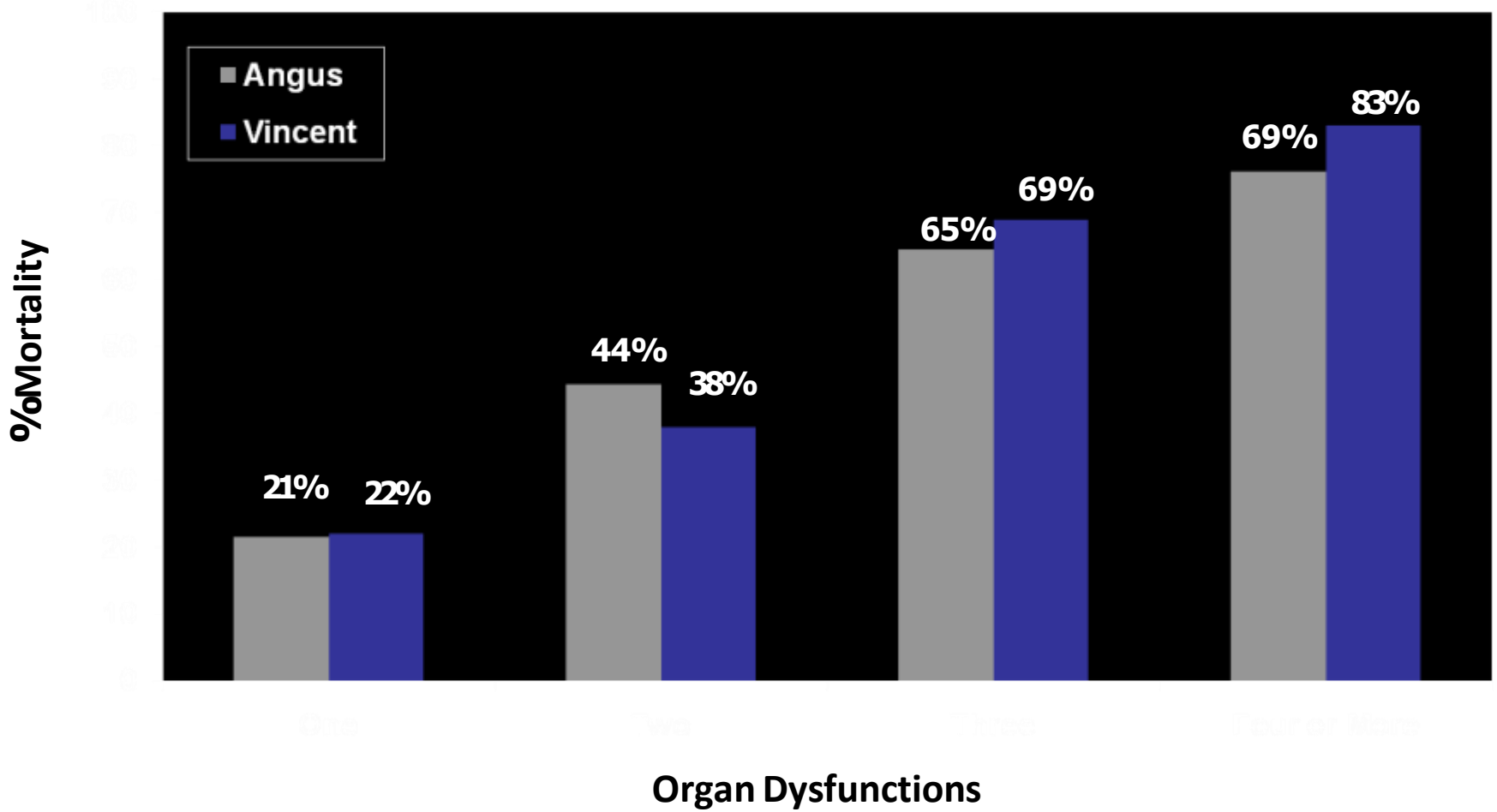

Sepsis
Endothelial dysfunction
Coagulopathy
Cellular dysfunction
Cardiovascular dysfunction
Capillary leakage
Disseminated intravascular coagulation
Catabolic state
Left ventricular dilation
Reduced tissue perfusion
Reduced cellular energy consumption
Hypotension
Multiorgan failure

Organ Failure and Mortality

- **Knaus, et al. (1986):**
  - **Direct correlation between number of organ systems failed and mortality.** +number of days
  - **Mortality Data:**

#OSF	D1	D2	D3	D4	D5	D6	D7
1	22%	31%	34%	35%	40%	42%	41%
2	52%	67%	66%	62%	56%	64%	68%
3	80%	95%	93%	96%	100 %	100%	100%

SEVERE SEPSIS-ASSOCIATED MORTALITY INCREASES WITH THE NUMBER OF ORGAN DYSFUNCTIONS



Evolution of Sepsis care

Established Core Rx:
Source Control
Antibiotics
Resuscitation
Supportive Care

Steroids

No Steroids
Endotoxin Antagonists
LPS/LPS receptor antagonists
anti-TNF
NSAIDs
Nitric Oxide Synthase Inhibitors
Tissue Factor Pathway Inhibitors
anti-TLR4

Established Core Rx:
Source Control
More Antibiotics
Faster Resuscitation
Better Supportive Care

In general the process of care has improved

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

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Dellinger RP, Levy MM, Rhodes A, et al. Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: 2012. Critical Care Medicine 2013;41(2):580–637.

How do we manage sepsis and septic shock?

1) Investigate and treat sepsis

- Try and find and treat source
  - Early blood cultures
  - Start antibiotics asap ideally within 1 hour and after cultures taken

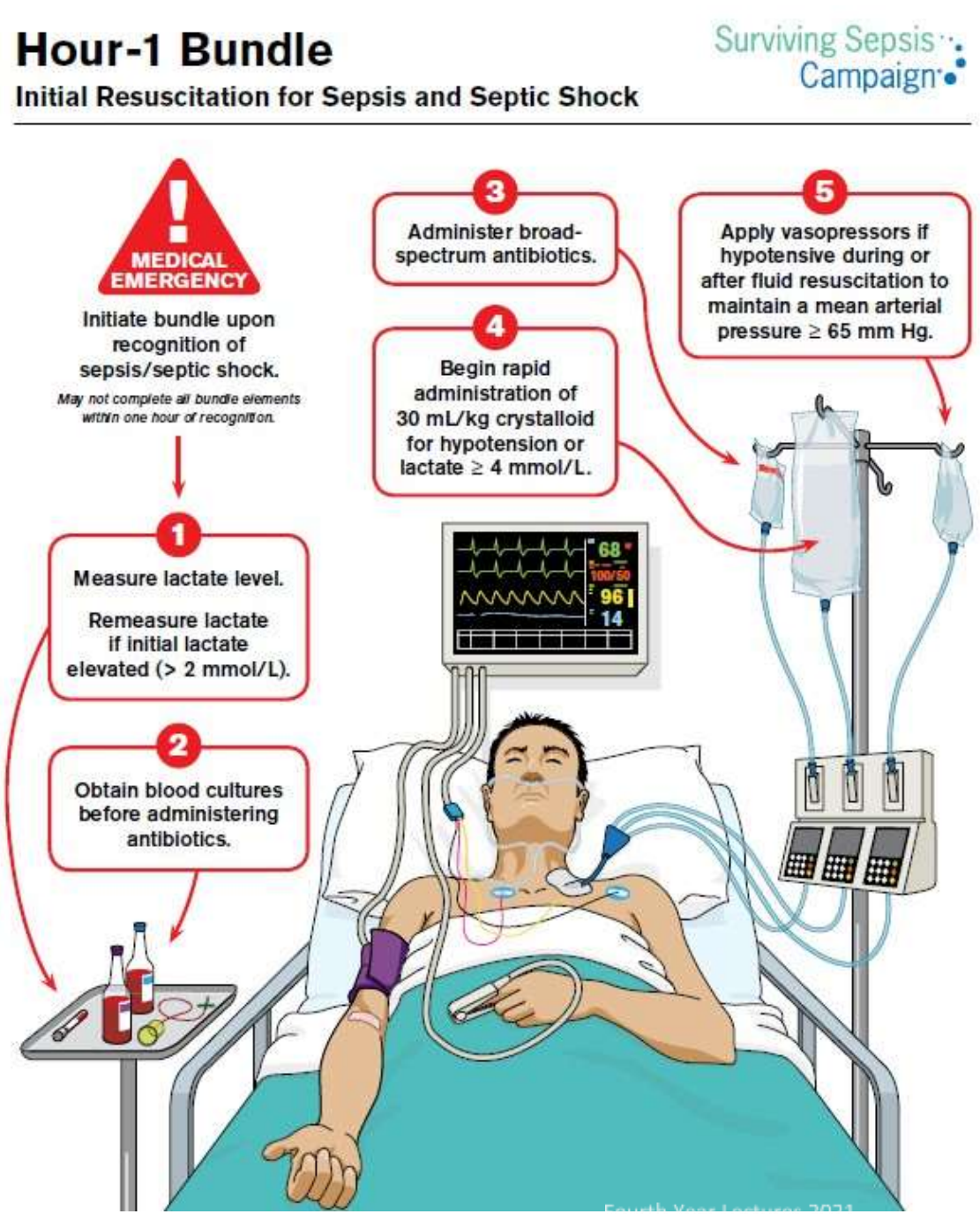
2) Assess extent of end organ hypoperfusion and improve oxygen delivery

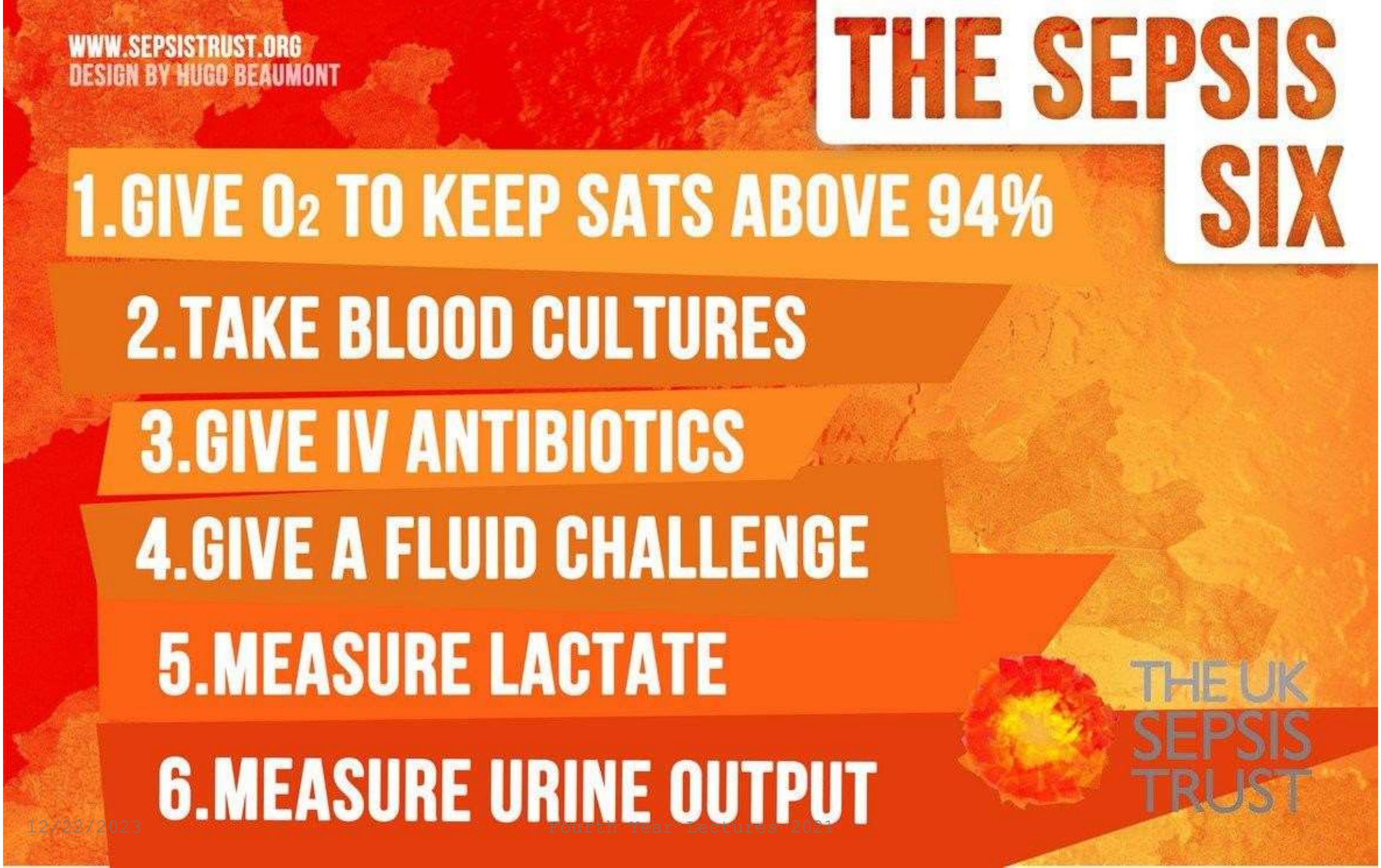
2005	2013	2018

6-hour Resuscitation Bundle
• Measure serum lactate
• Obtain blood cultures prior to antibiotics
• Administer broad spectrum antibiotics within 3 hours of ED or 1 hour non-ED admission
• With hypotension &/or serum lactate > 4 mmol/L:
  ○ Crystalloid 20ml/Kg
  ○ Vasopressors if unresponsive
• Persistent hypotension &/or lactate > 4 mmol/L achieve:
  • CVP ≥ 8 mm Hg
  • ScvO2 ≥ 70 % or SvO2 ≥ 65%
	3-hour Bundle
	• Measure serum lactate
	• Obtain blood cultures prior to antibiotics
	• Administer broad spectrum antibiotics
	• With hypotension &/or serum lactate > 4 mmol/L:
	  ○ Crystalloid 30ml/Kg
	6-hour Bundle
	• Vasopressors for hypotension after fluid
	• For persistent arterial hypotension after fluid or with lactate > 4 mmol/L;
	  • Measure CVP
	  • Measure ScvO2
		1-hour Bundle
		• Measure serum lactate. Re-measure if initial > 2 mmol/L
		• Obtain blood cultures prior to antibiotics
		• Administer broad spectrum antibiotics
		• Begin rapid crystalloid 30 ml/kg
		• Apply vasopressors if hypotension remains after fluid resuscitation to MAP ≥ 65 mm Hg

24-hour Management Bundle • Low dose steroids • Human activated protein C (rhAPC) • Maintain glucose 70 -150 mg/dL • Maintain median inspiratory plateau pressure < 30 cm H2O in mechanical ventilation	***24-hour Bundle no longer recommended***	

1 Hour Bundle




WWW.SEPSISTRUST.ORG
DESIGN BY HUGO BEAUMONT
THE SEPSIS SIX
1.GIVE O_2 TO KEEP SATS ABOVE 94%
2.TAKE BLOOD CULTURES
3.GIVE IV ANTIBIOTICS
4.GIVE A FLUID CHALLENGE
5.MEASURE LACTATE
6.MEASURE URINE OUTPUT
THE UK SEPSIS TRUST

Surviving Sepsis targets of fluid resuscitation

What are they?

- SBP
- MAP
- CVP
- U/o
- Lactate
- ScvO2
- HCt

Surviving Sepsis targets of fluid resuscitation

What are they?

- SBP > 90
- MAP > 65
- CVP 8 - 12
- U/o > 0.5 ml/kg/hr
- Lactate < 1
- ScvO2 >70 (Central Venous Oxygen Saturation)
- HCt > 30

30 mL/kg of IV crystalloid fluid be given within the first 3 h

- additional fluids be guided by frequent reassessment of hemodynamic status (BPS)

Crystalloids are favored as the initial fluid

- Hydroxyethyl starches are likely harmful
- Albumin may have a role, particularly if alot of fluid is given

Markers of perfusion

What are they?

- Clinical signs
  - Warm skin, conscious level, u/o
- Haemodynamic variables
  - CVP
- Bloods
  - Serum Lactate
  - ScvO2

CVP

What does it mean? pressure in the right atrium

CVP

pressure in the right atrium (preload)
-low CVP --> patient need fluid

- What does it mean?
- Starling's Law
- Estimate of LVEDV (i.e. preload)
- Not always a good correlation with volume-responsiveness However if low strongly suggestive of hypovolaemia

Lactate

What does it mean?

Lactate

sign of switch from aerobic to anerobic (no oxygen enough)

What does it mean?

- Increased production (anaerobic glycolysis)
  - Tissue hypoperfusion
  - Tissue dysoxia
- Reduced metabolism
  - Hepatic
  - Renal
- <1 is normal, 1-2 is a concern, >2 is bad,
  >4 is very bad

ScvO2

What does it mean?

ScvO2

What does it mean?

- Balance between oxygen delivery and consumption (VO2)
- ScvO2 = SaO2 - $\frac{VO2}{CO}$
- Target > 70% if it is low the patient need resuscitation

ScvO2

What can I do if it’s low?

ScvO2

What can I do if it’s low?

Delivery = [Hb] x SpO2 x 1.34 x HR x SV

if it is low
hemogplbin / oxygen content / cardiac pump / preload and afterload are optimized for this

ScvO2

What can I do if it's low?

Delivery = [Hb] x SpO2 x 1.34 x HR x SV

Fluid optimise

Transfuse packet cells

HCt > 30% not needed anymore

Inotropes

“Time Zero”

- Time Zero = time of presentation
  - ED, Medical Floors, ICU
- 1 Hour Bundle within one hour from time zero we have to achieve all things

microbiologic cultures (including blood) be obtained before starting antimicrobial therapy in patients with suspected sepsis or septic shock if doing so results in no substantial delay in the start of antimicrobials.

Antibiotic therapy

- intravenous antimicrobial therapy as early as possible and within the first hour of recognition
- empiric broad-spectrum therapy with one or more antimicrobials to cover all likely pathogens (including bacterial and potentially fungal or viral coverage)
- antimicrobial therapy to be narrowed once pathogen identification and sensitivities are established and/or adequate clinical improvement is noted .

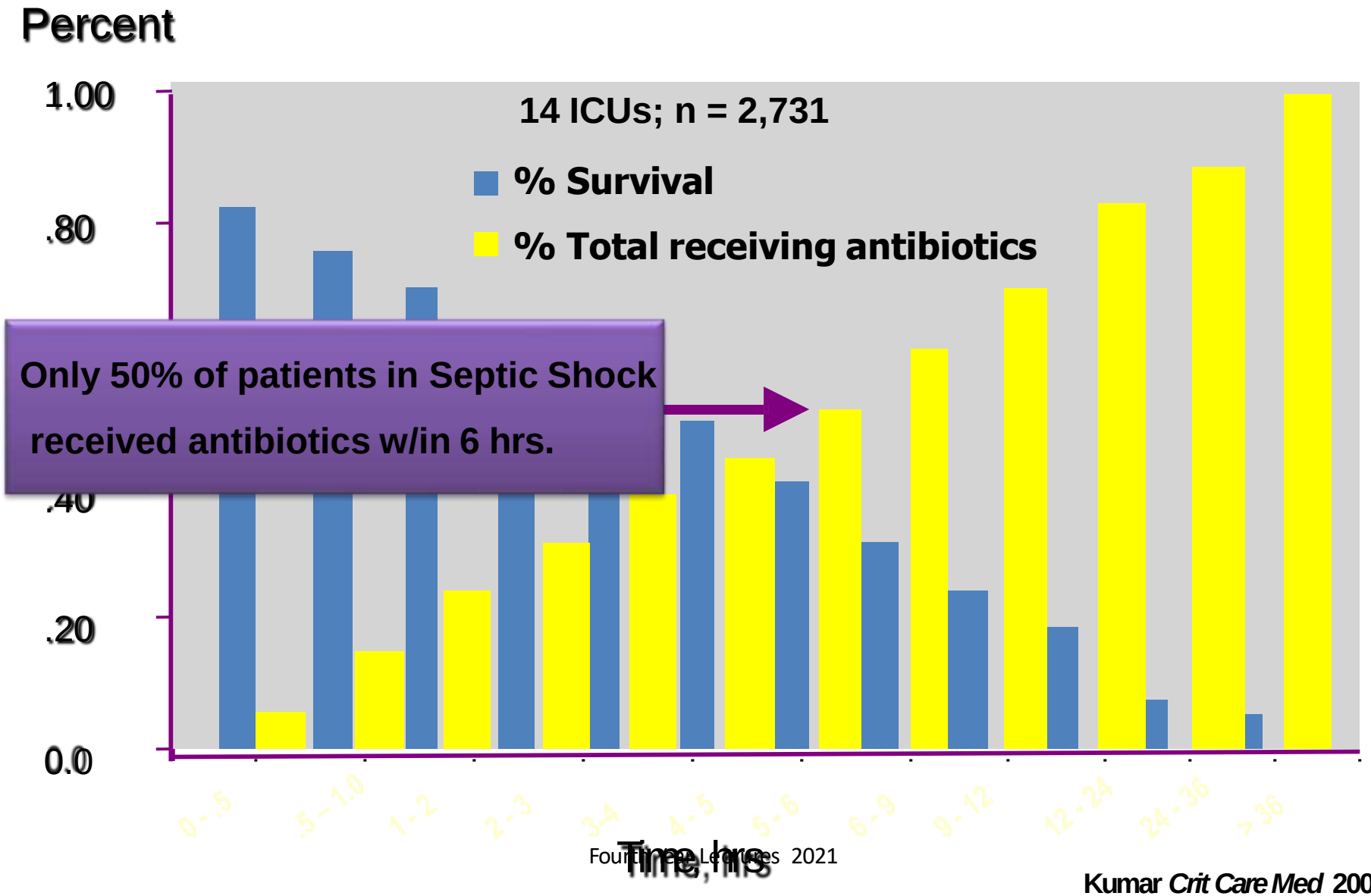
Hospital Mortality by Time to Antibiotics

Time to ABX[1], hrs	OR[2]	95% CI		*p*-value	Probability of mortality[3]	95% CI	
0 (ref)	1.00	---	---	---	18.7	17.5	19.9
1	1.05	1.02	1.07	< 0.001	19.3	18.3	20.4
2	1.09	1.04	1.15	< 0.001	20.0	19.1	21.0
3	1.14	1.06	1.23	< 0.001	20.8	19.7	21.8
4	1.19	1.08	1.32	< 0.001	21.5	20.3	22.8
5	1.25	1.11	1.41	< 0.001	22.3	20.7	23.9
6	1.31	1.13	1.51	< 0.001	23.1	21.2	25.1

[1]Time to ABX is based on 15,948 observations that are greater than or equal to zero

[2]Hospital mortality odds ratio referent group is 0 hours for the time to ABX and is adjusted by the number of baseline organ failures, infection type (community vs. nosocomial), and geographic region (Europe, North America, and South America)

Septic Shock: Timing of Antibiotics



Kumar *Crit Care Med* 2006

Source Control

a specific anatomic diagnosis of infection requiring emergent source control to be identified or excluded as rapidly as possible and that any required source control intervention be implemented as soon as medically and logistically practical after the diagnosis is made.

Vasoactive agents

- **Norepinephrine is the first choice vasopressor**

second choice --> adrenaline if he doesn't have cardiac problem
dobutamine if he has cardiac problems
or we can use vasoprosile ?

CORTICOSTEROIDS

in patient who need vasopressor
-we give steroids we think due to shock the patient suffer from adrenal gland insufficiency and don't secrete cortisol

intravenous hydrocortisone to treat septic shock patients if adequate fluid resuscitation and vasopressor therapy are UNABLE to restore hemodynamic stability.

GLUCOSE CONTROL

We recommend a protocolized approach to blood glucose management in ICU patients This approach should target an upper blood glucose level ≤180 mg/dL

Hit fast and hit Hard

- IV fluids
- Antibiotics
- Source control

give them very early and very hardly and as soon as possible

Thank You