Sepsis

Amjad Bani Hani
Associate Prof. of Cardiac Surgery and Intensive Care
The University Of Jordan

Which patient has the highest risk of death?

A. 59yo male – large inferior STEMI

B. 27yo male – multi trauma (ISS >15)

C. 65yo female – bleeding gastric ulcer & BP 90/60

D. 74yo female – HR 96, BP 98/50, RR 28, T 35.6oC, mildly confused

E. 32yo female – DKA, pH 6.90, BSL 45, HCO3 9

Which patient has the highest risk of death?

A. 59yo male – large inferior STEMI
B. 27yo male – multi trauma (ISS >15)
C. 65yo female – bleeding gastric ulcer & BP 90/60
D. 74yo female – HR 96, BP 98/50, RR 28, T 35.6oC, mildly confused
E. 32yo female – DKA, pH 6.90, BSL 45, HCO3 9

Mortality

A. Inferior AMI < 10%

B. Trauma ISS16-24 7%

C. GI haemorrhage with low BP 11%

D. Septic shock 25%

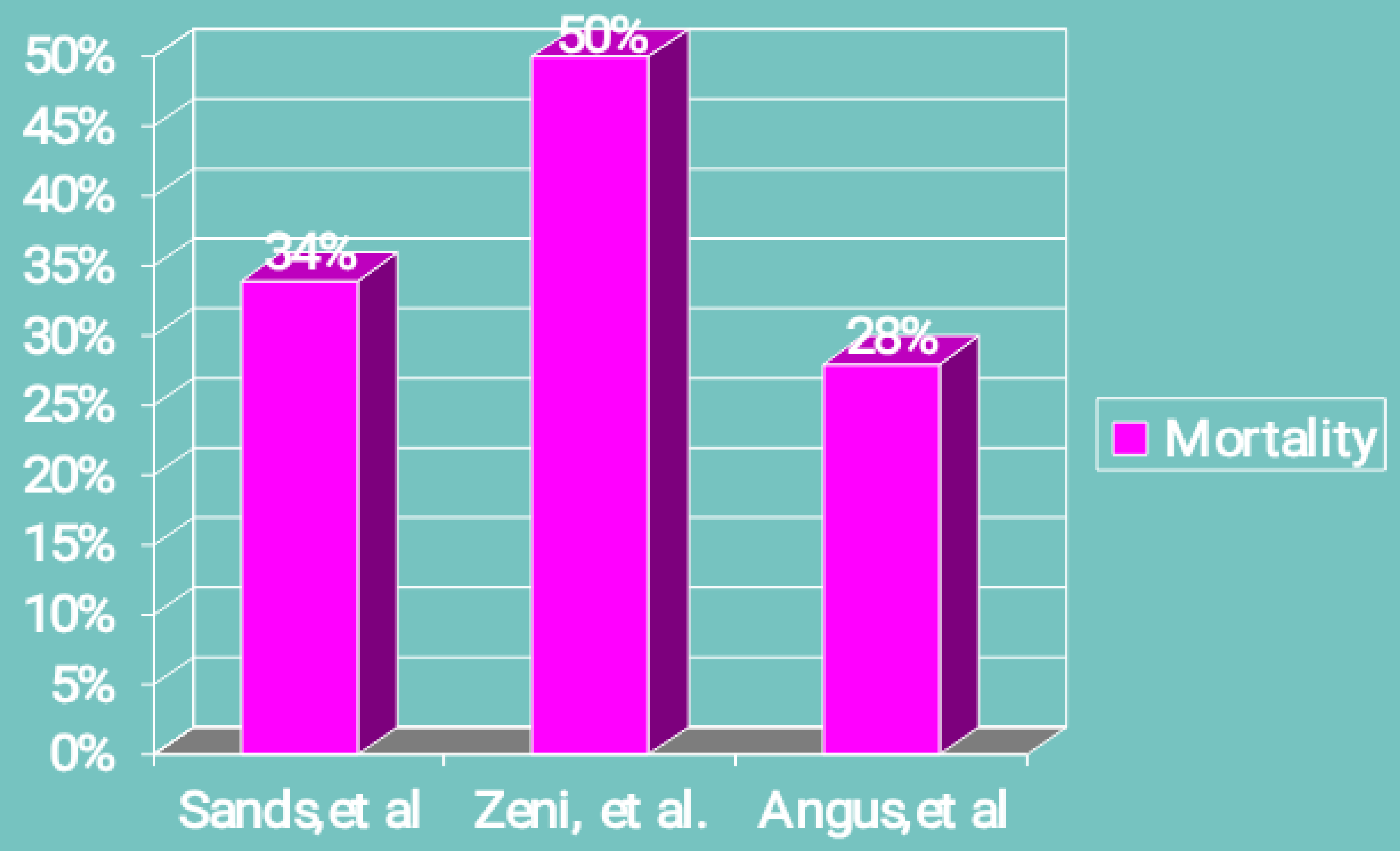
E. Severe DKA < 1%

1) Armstrong PW et al., JAMA, 2007;297:43–51. 2) Clemet N, SJTREM28:18 2010 3) Rockall TA BMJ. 311(6999):222-6, 1995 July 22 4) Mitchell M et al Crit Care Med2010 Vol. 38, No. 2 5) Hamdy O, Sep 2009

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

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

Sepsis is deadly



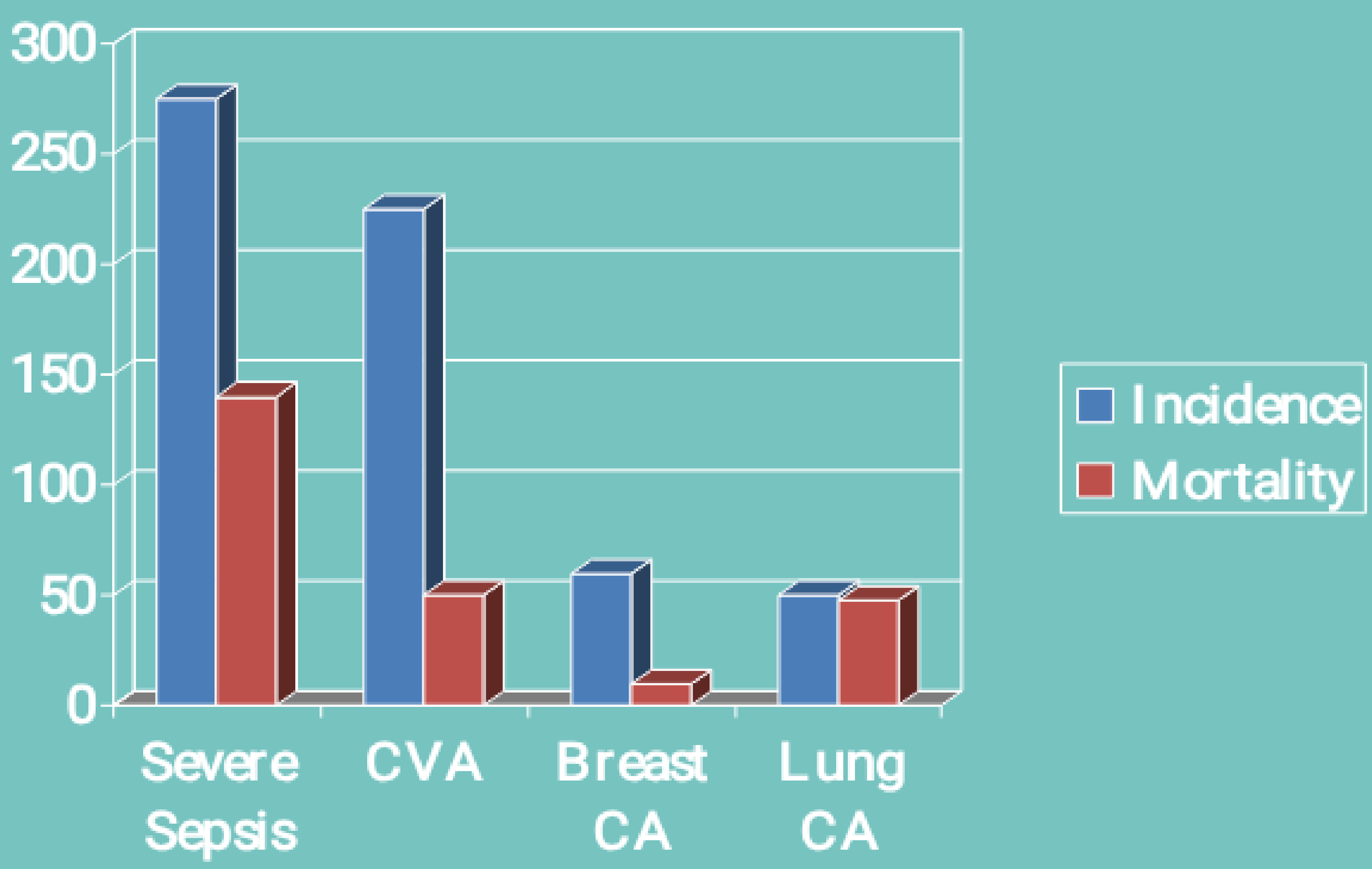
Mortality Rates

- Overall = 30% - 50%

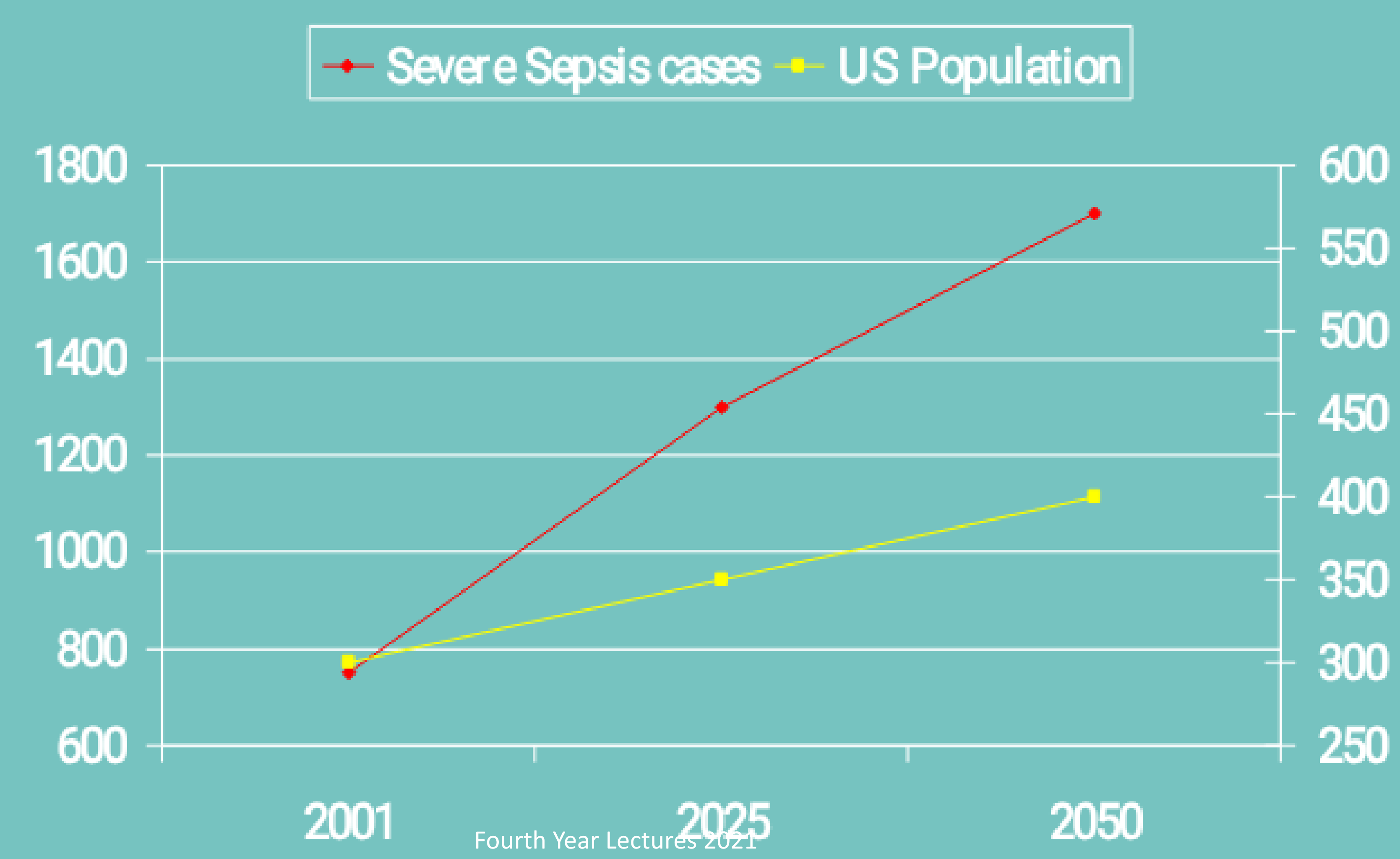
- By syndrome definition:
  - Sepsis = 16%
  - Septic shock = 46%

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

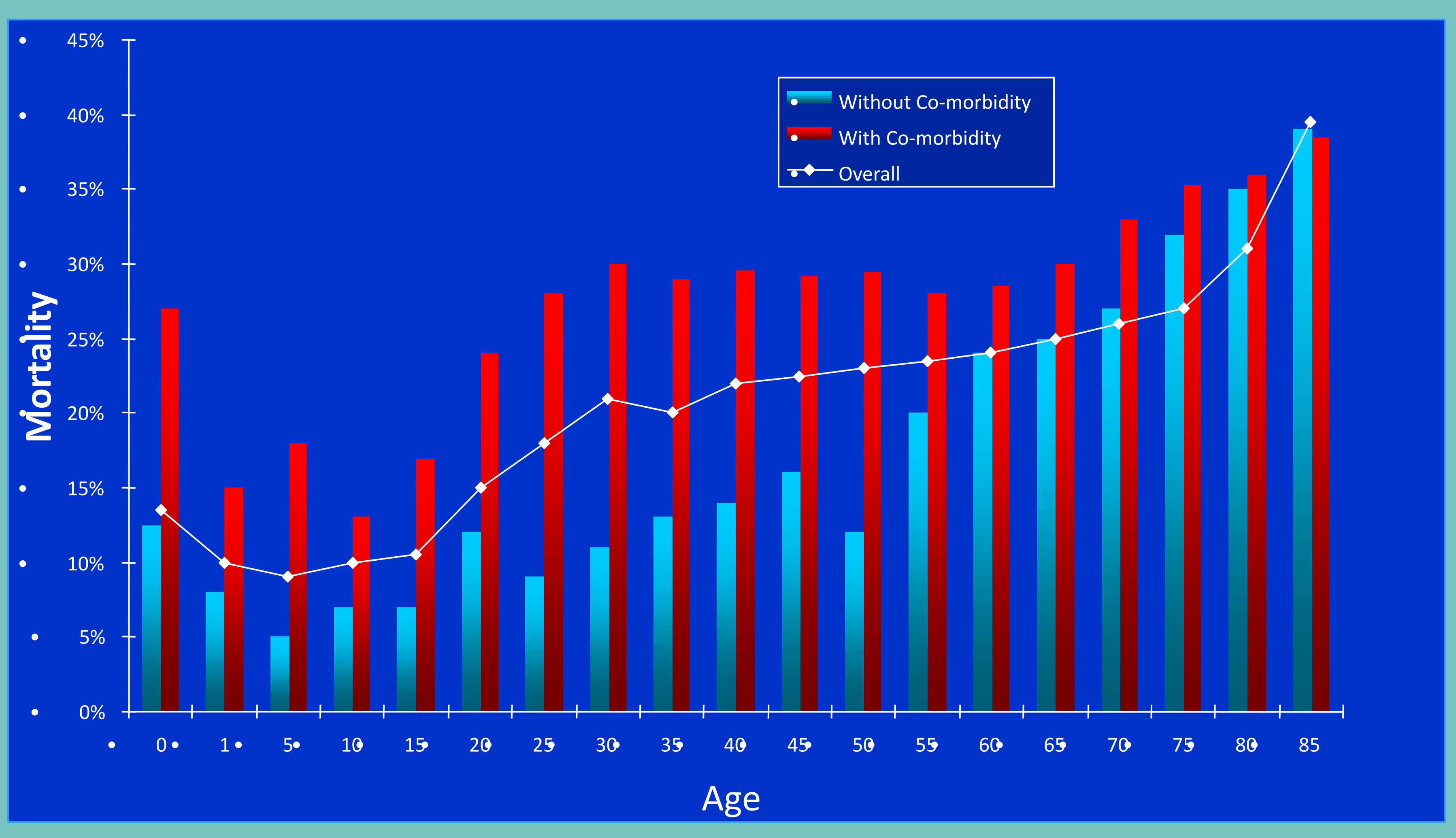
Sepsis is Common



Sepsis is increasing in incidence

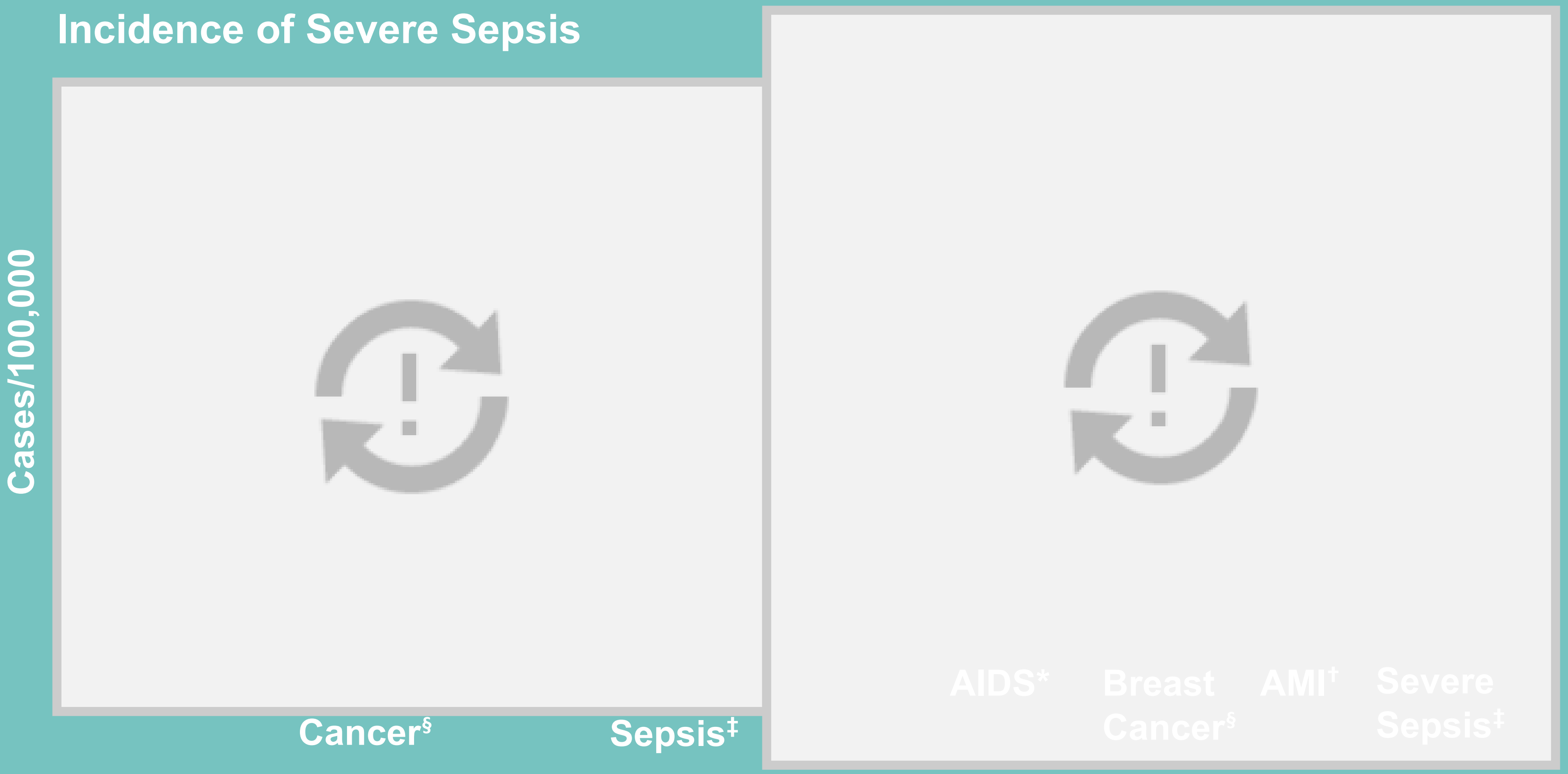


Mortality of Severe Sepsis by Age in the United States



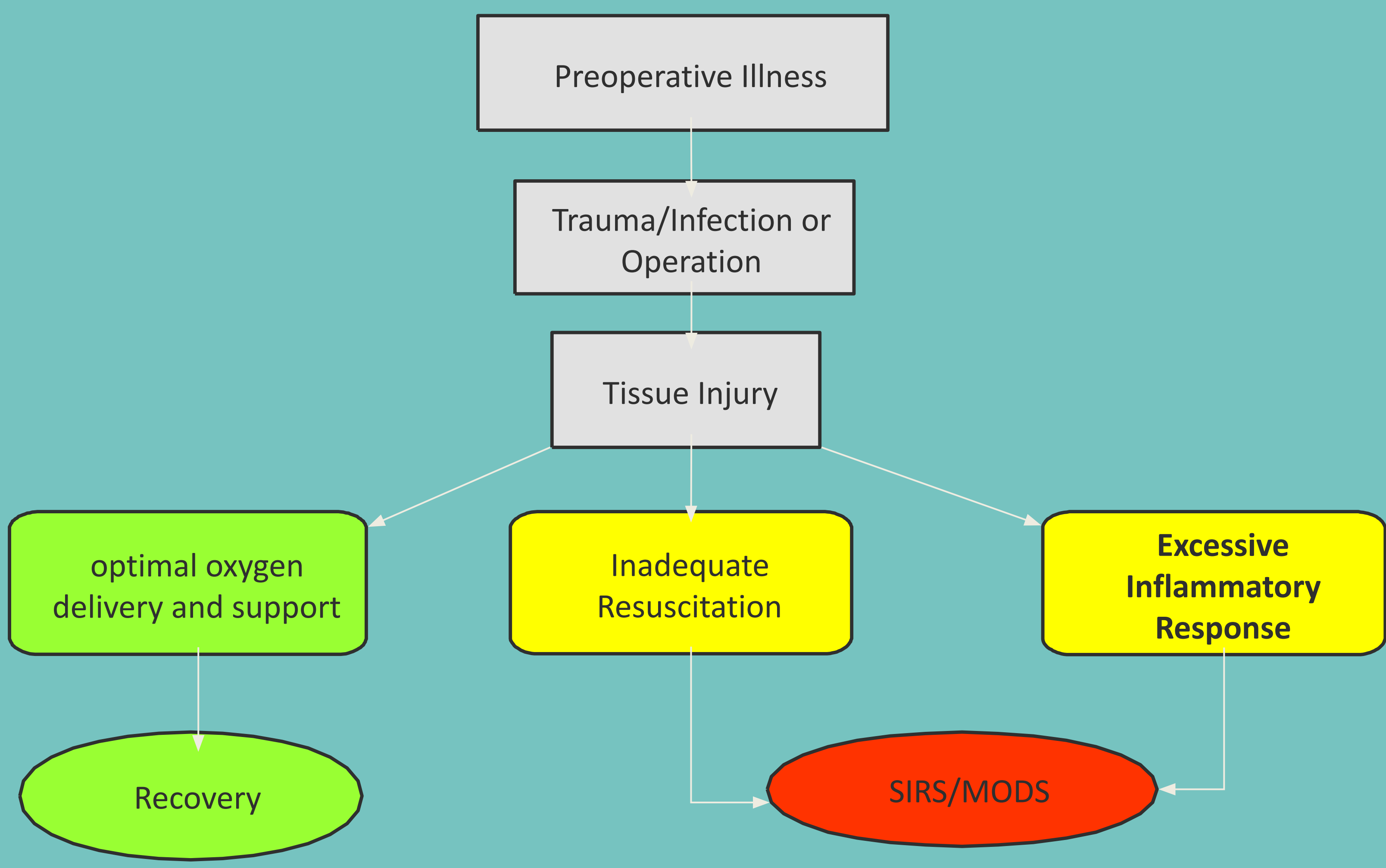
Angus DC, et al. Crit Care Med. 2001.

Comparison With Other Major Diseases

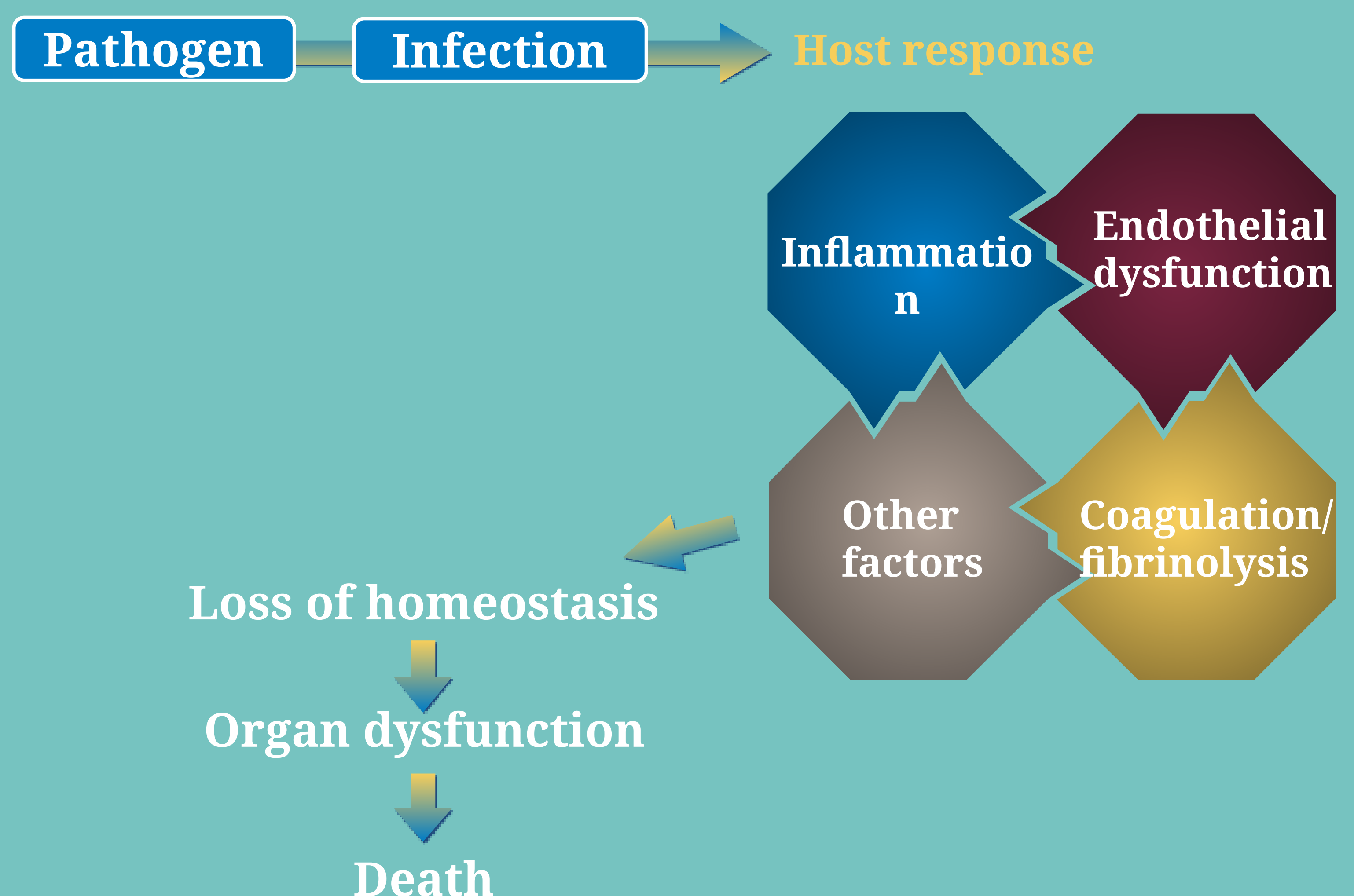


†National Center for Health Statistics, 2001. §American Cancer Society, 2001. *American Heart Association. 2000. ‡Angus DC et al. *Crit Care Med.* 2001;29(7):1303-1310.

Pathogenesis of SIRS/MODS

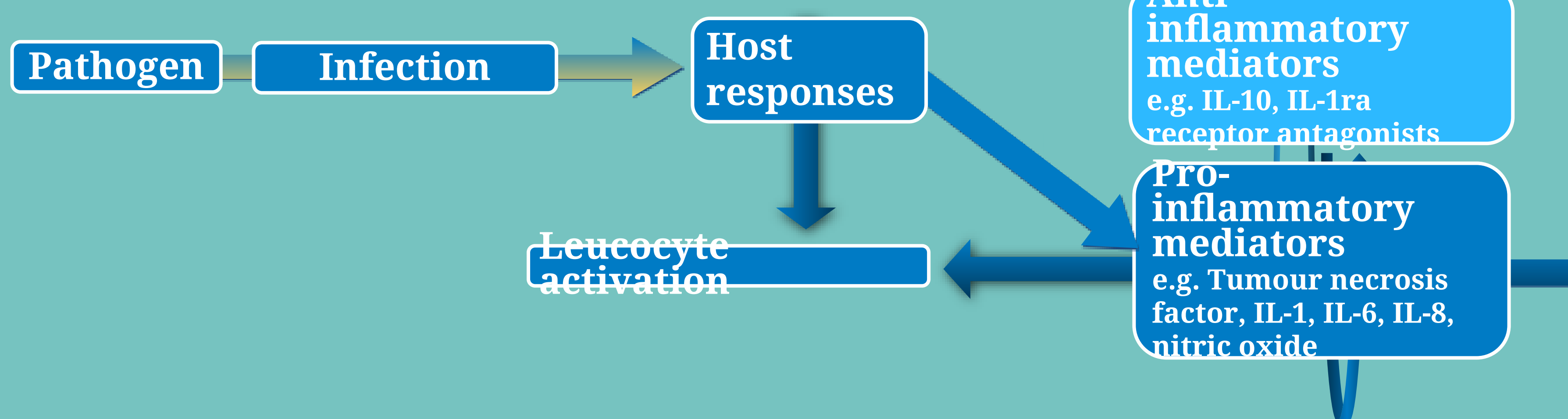


Pathogenesis of sepsis



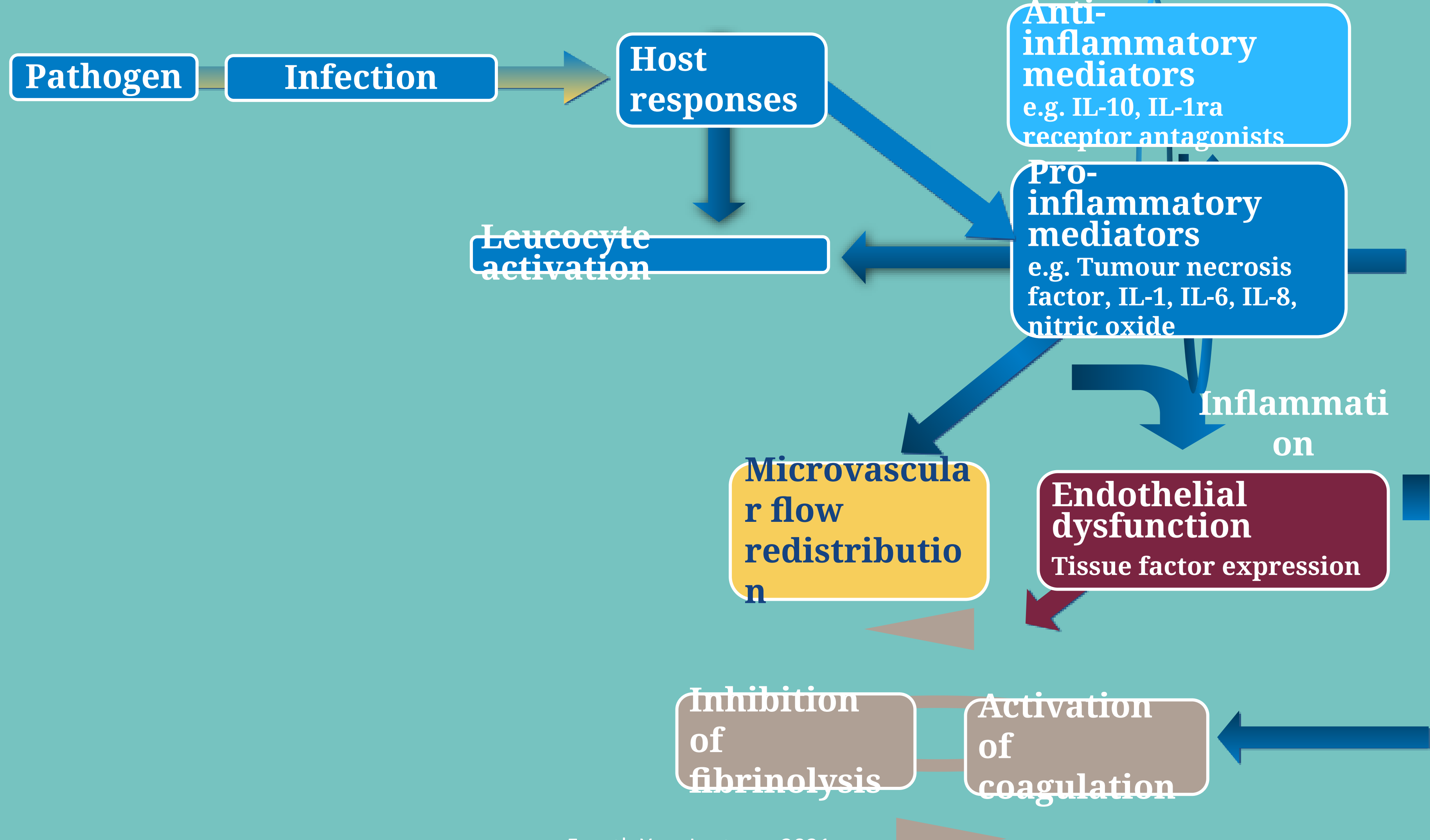
Pathogenesis of sepsis

An overview



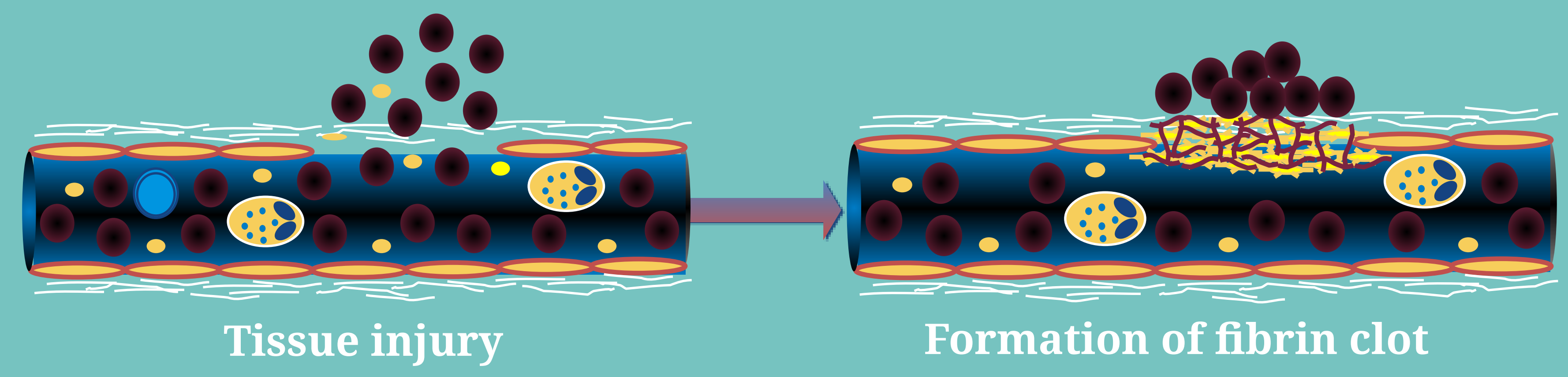
Pathogenesis of sepsis

An overview



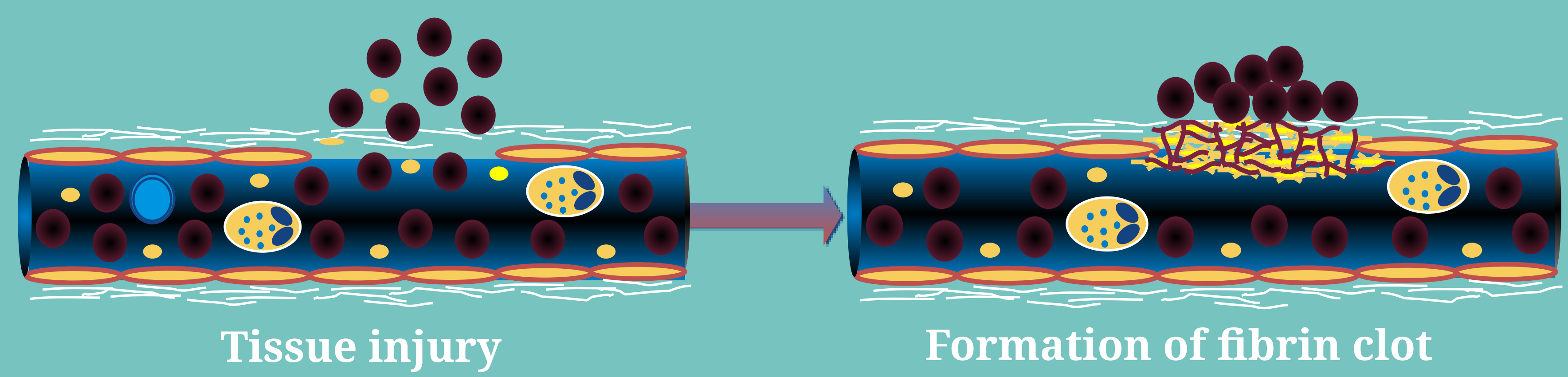
The role of the endothelium

- Release of mediators of vasodilatation and/or vasoconstriction
- 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

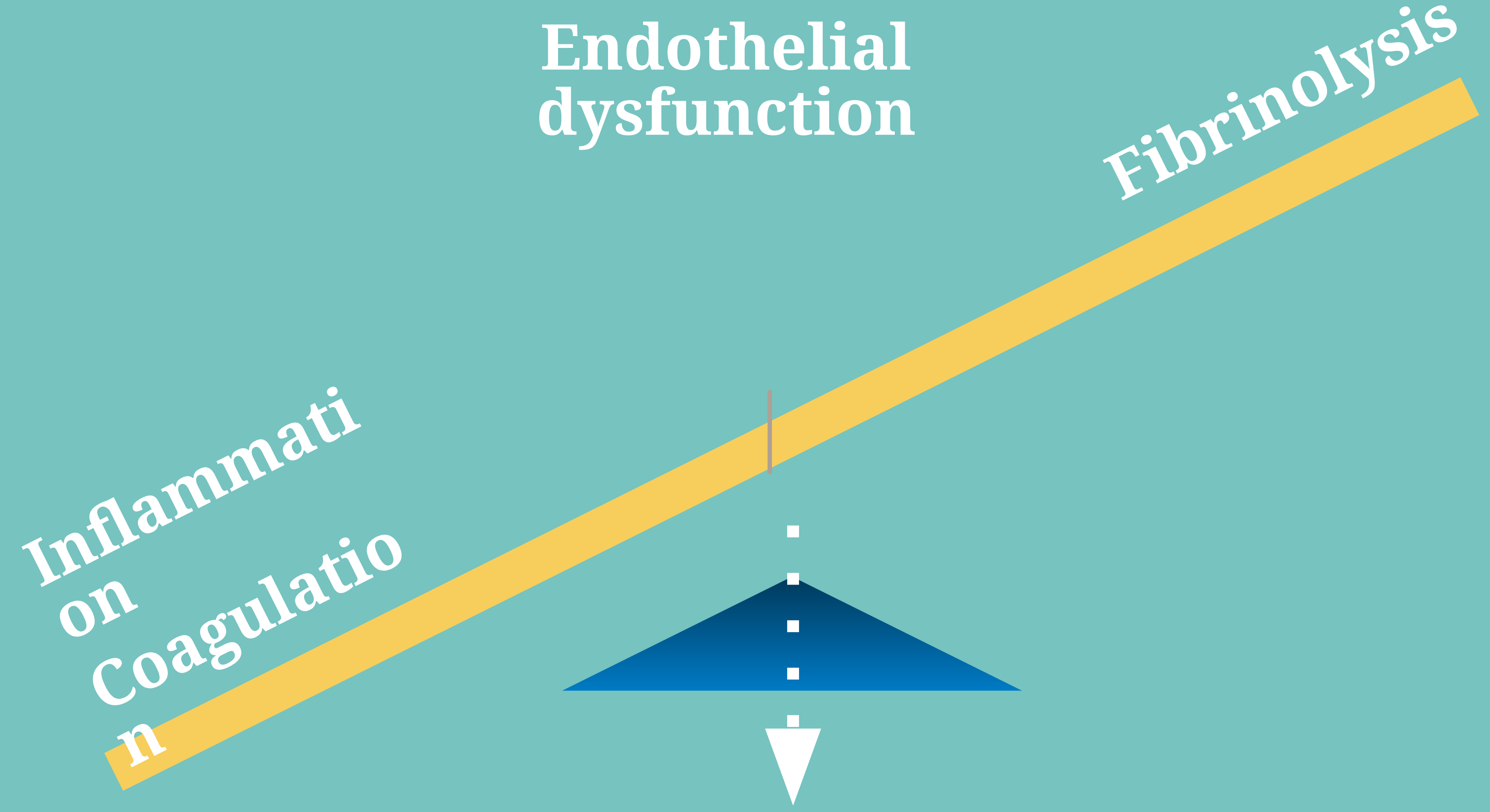


The role of the endothelium

- In sepsis, the regulatory function of the endothelium fails, leading to:
  - Excessive vasodilation and relative hypovolaemia
  - Leaking capillaries and generalised tissue damage
  - Tissue factor (TF) release initiates **procoagulant state**
  - Micro-thrombus formation compromising blood supply and leading to tissue necrosis
  - Inactivation of Protein C and suppression of fibrinolysis



Loss of homeostasis in sepsis



Pro-coagulant state

Disseminated Intravascular Coagulation (DIC)

DIC can cause:

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

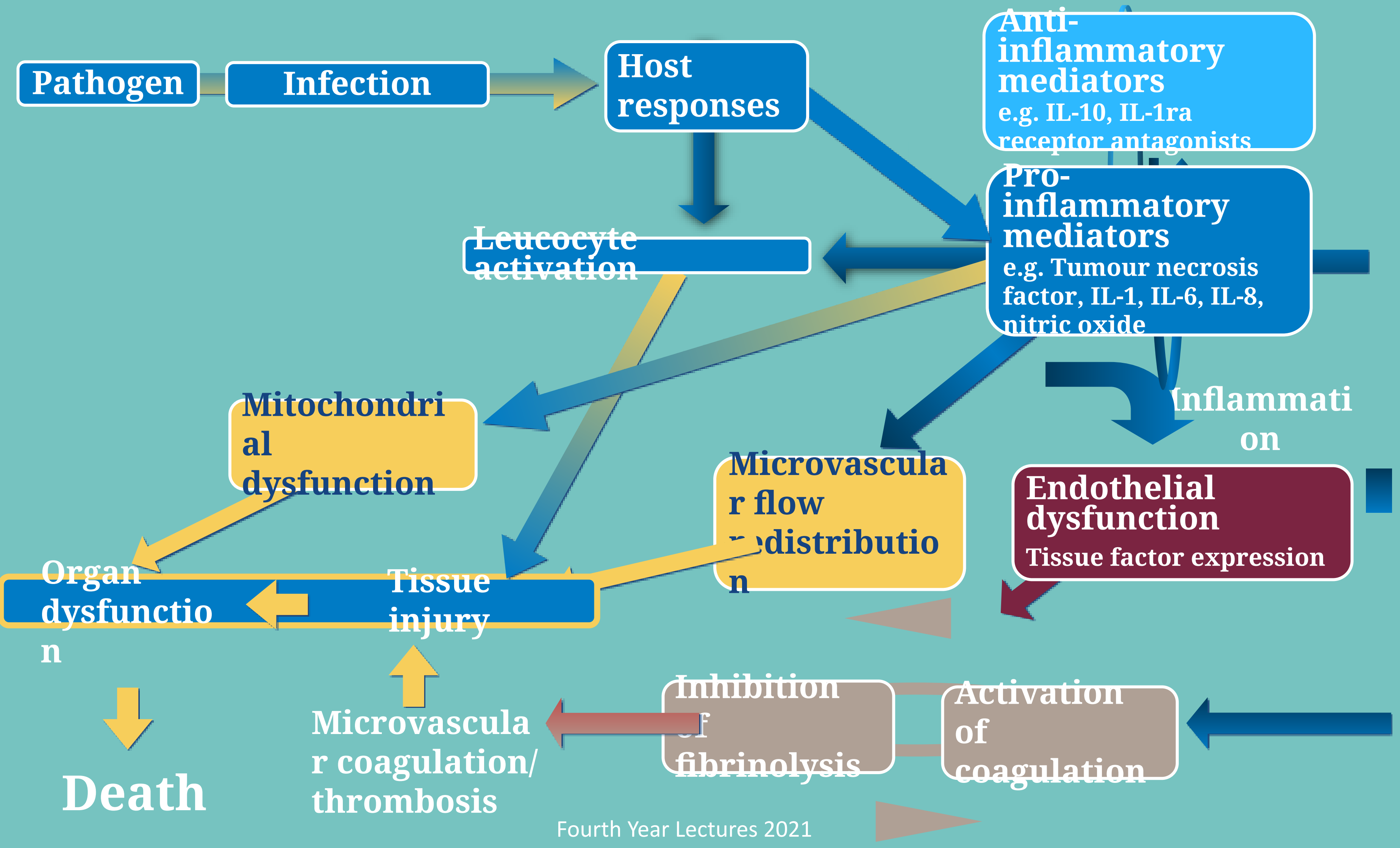
Widespread clotting causes consumption of:

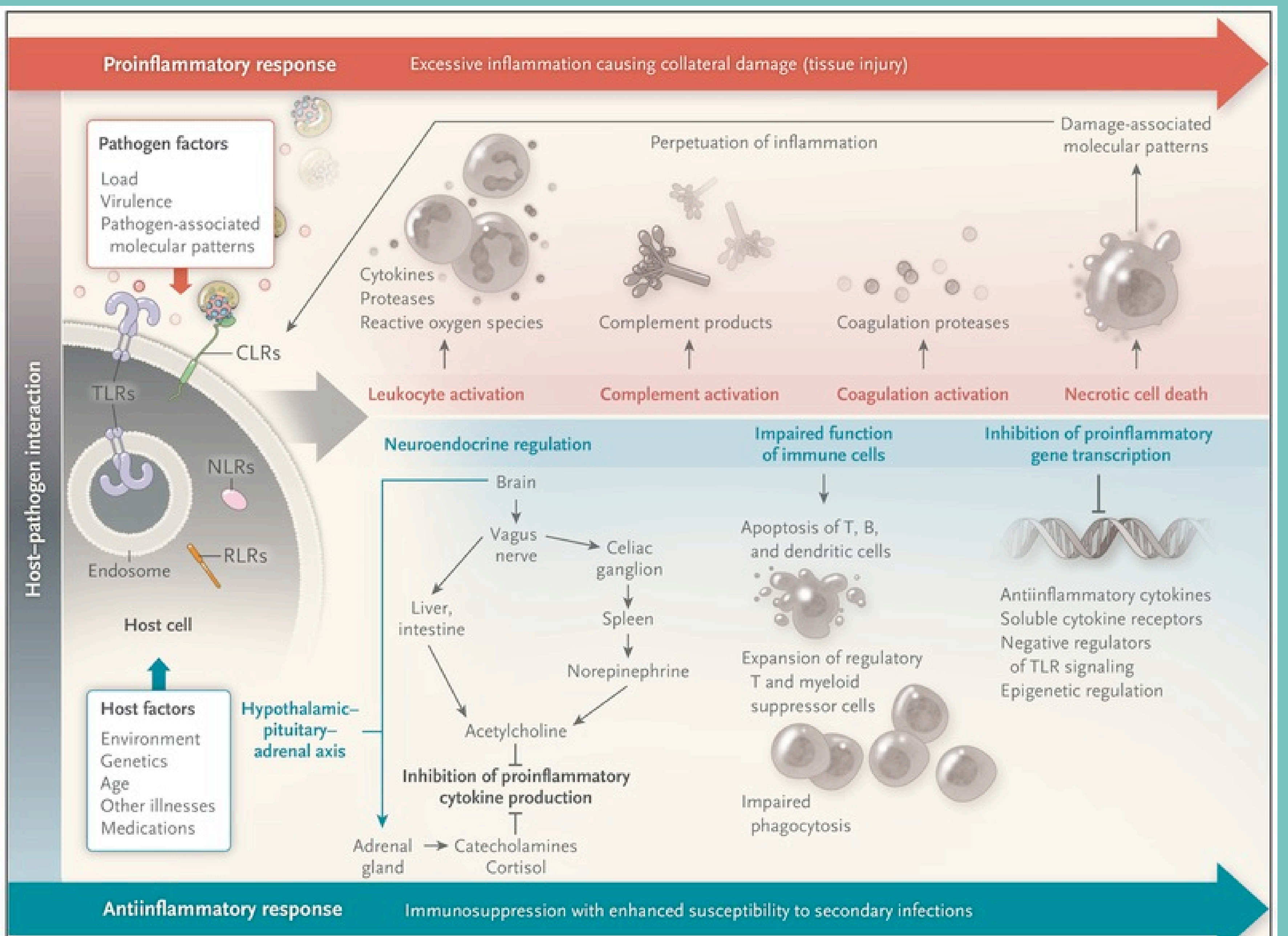
- Low platelets
- clotting factors long clotting time
- fibrinogen

As a result, bleeding risk increases

Pathogenesis of sepsis

An overview



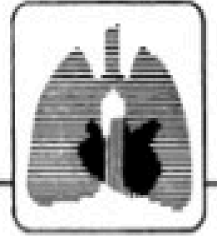


Compensatory Anti-inflammatory Response System Attempts to down regulate the SIRS response IL-4, IL-10, transforming growth factor beta, CSF, soluble receptors to TNF, antagonists to TNF-alpha and IL-1

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%

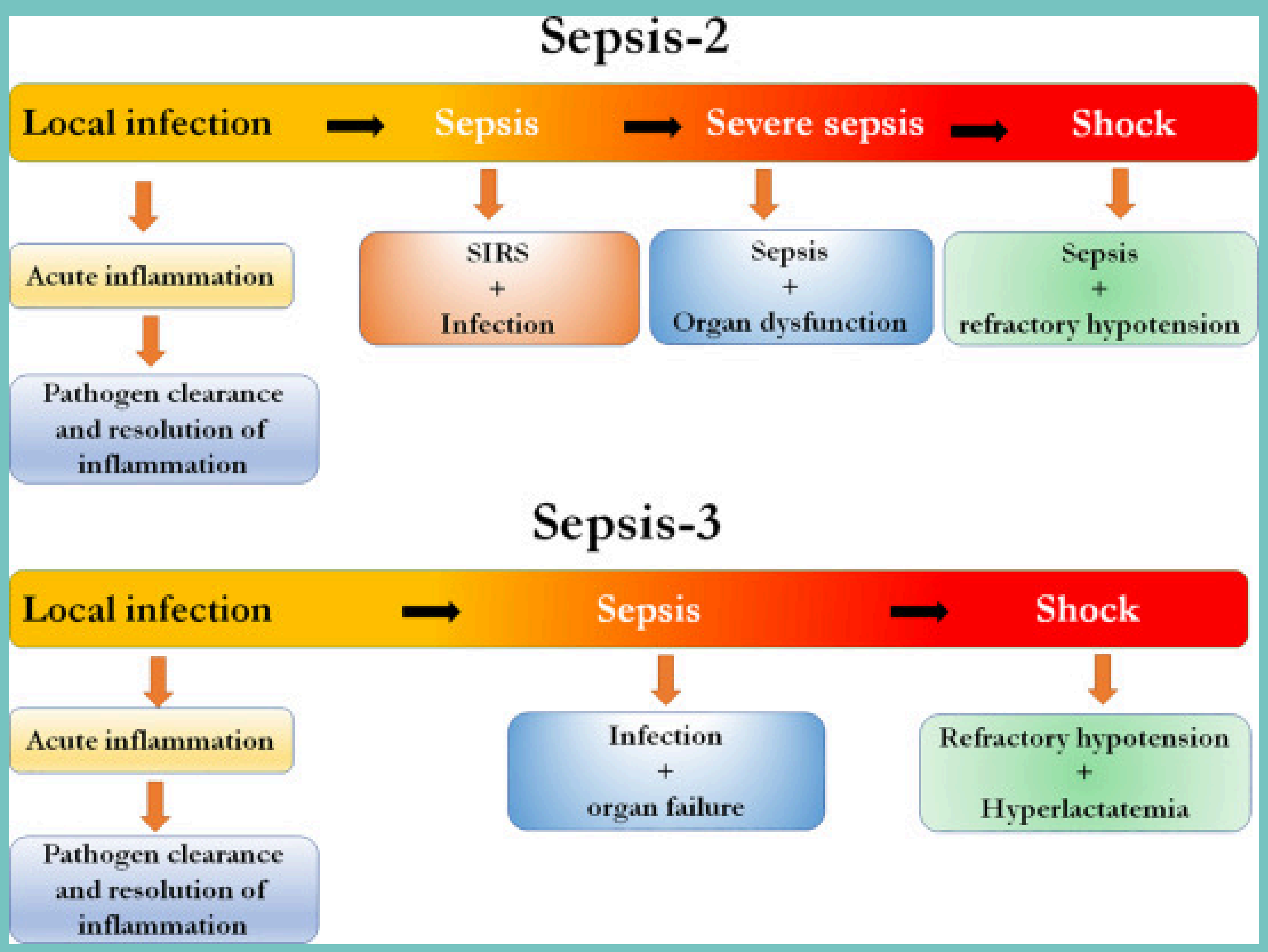
TWO out of four criteria
acute change from baseline

- 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

Sepsis Redefinition (Sepsis-3)
February 23, 2016

- Announced at the SCCM meeting in Orlando on February 22, 2016
- Published in JAMA on February 23, 2016

ESICM News

- The beginning of a new era for sepsis?

Sepsis-3: International Consensus Definitions for Sepsis and Septic Shock

Despite the wide implementation of life support measures in ICU, sepsis remains the leading cause of death from infection. This syndrome, especially in the absence of early recognition and prompt treatment, may evolve into septic shock, which is a more severe illness with a much higher mortality rate. The clinical picture of sepsis, as a syndrome, is shaped by an entire cohort of physiopathological and biochemical abnormalities that occur during the complex interaction between pathogen virulence and host immune-inflammatory response [1]. An up-to-date definition of sepsis, with precise clinical characterisation, is of paramount importance to aid physicians in daily clinical practice and investigators in designing trials for new therapeutic approaches or in reporting epidemiological surveys.

http://www.tinyurl.com/2016sepsis

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.

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

Editorial page 757

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

Related articles pages 762 and 775

CME Quiz at jamanetworkcme.com and CME Questions page 816

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.

Corresponding Author: Clifford S. Deutschman, MD, MS, Departments of Pediatrics and Molecular Medicine, Hofstra-Northwell School of Medicine, Feinstein Institute for Medical Research, 269-01 76th Ave, New Hyde Park, NY 11040 (cdeutschman@nshs.edu).

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

Definition of Sepsis

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

- What tangibly differentiates septic shock from sepsis ?

- MORTALITY

  Septic shock is “really bad” sepsis

The Definition of Septic Shock

A subset of sepsis where circulatory, cellular, and metabolic abnormalities are profound enough to significantly increase mortality.

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, $x10^3$/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

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

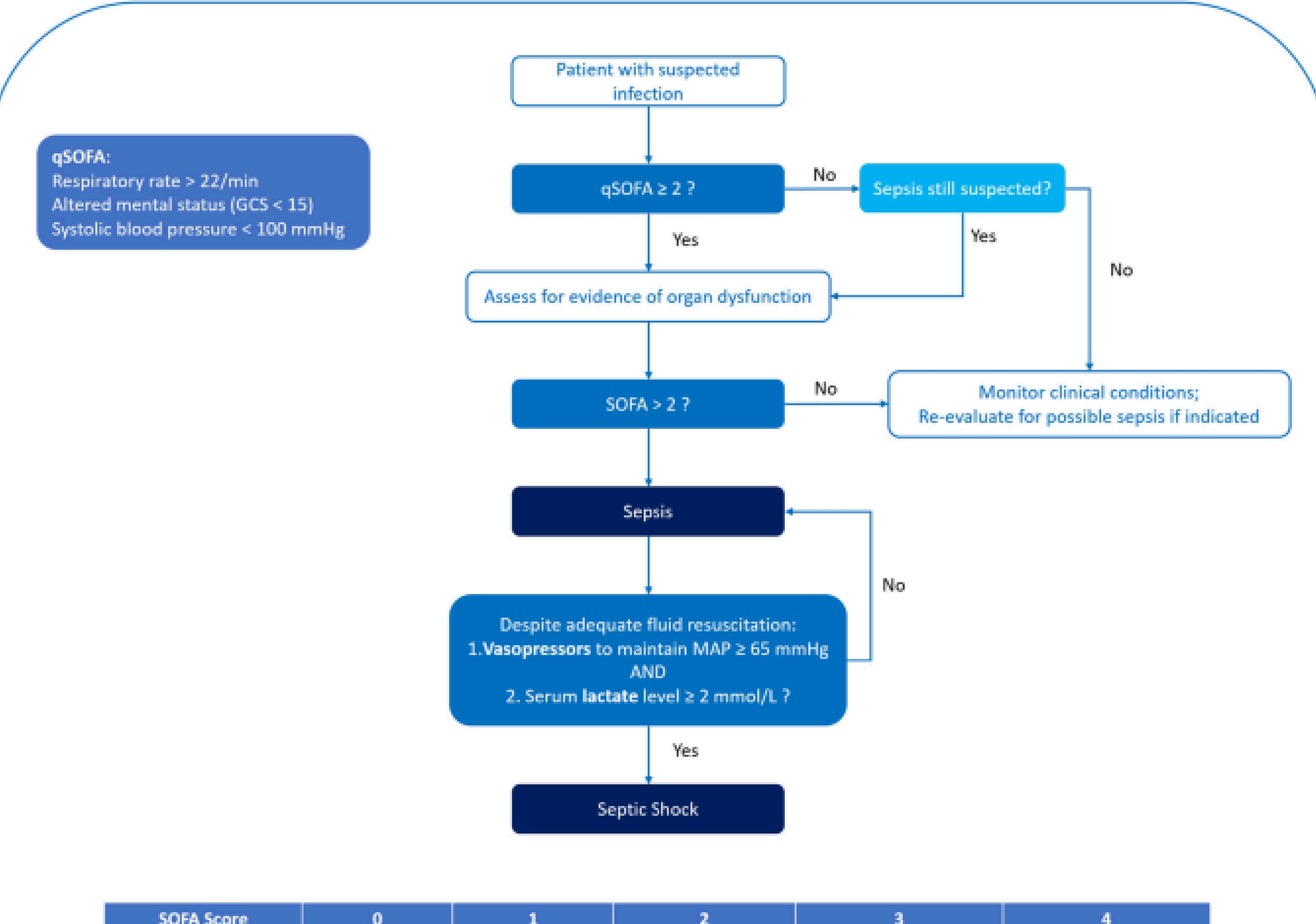
Please visit www.qsofa.org

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.

Septic Shock Criteria

- The need for vasopressors to maintain a mean arterial pressure (MAP) above 65 mm Hg
- Serum lactate level greater than (2) mmol/L (>18) mg/dL)
- Despite adequate fluid resuscitation.

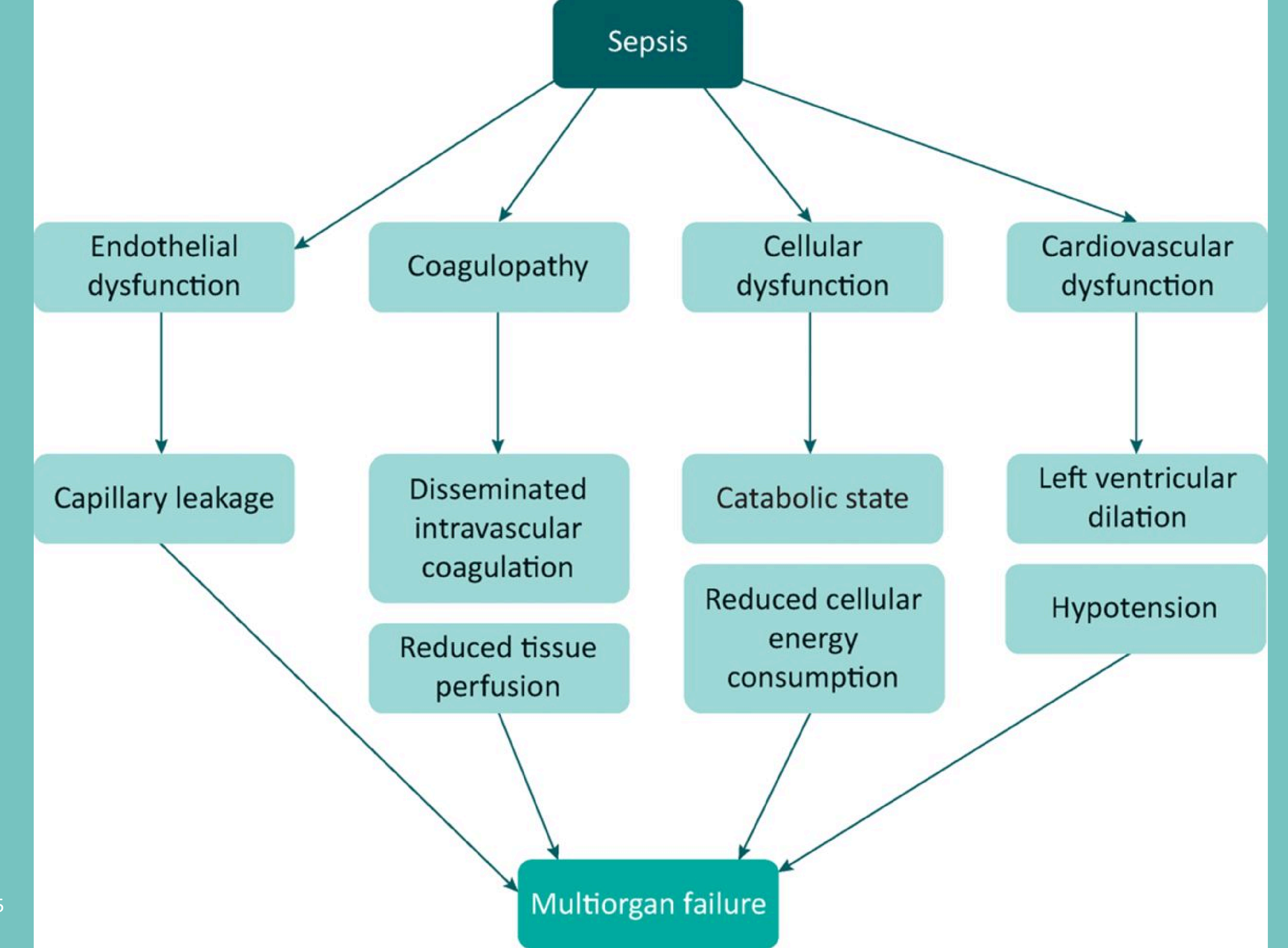
Mortality of Septic shock exceeds 40 %



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

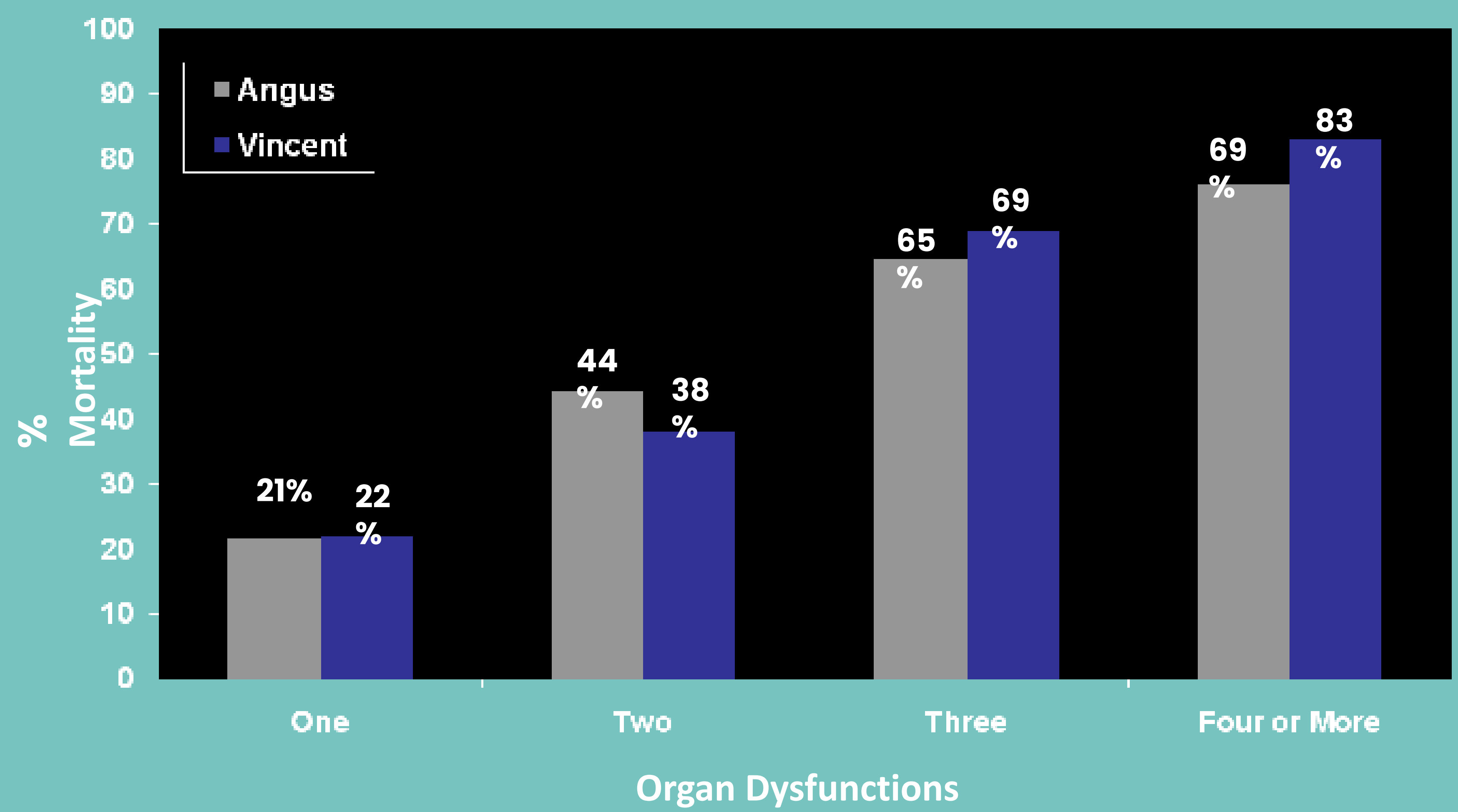

Sepsis
Endothelial dysfunction
Coagulopathy
Cellular dysfunction
Cardiovascular dysfunction
Capillary leakage
Disseminated intravascular coagulation
Reduced tissue perfusion
Catabolic state
Reduced cellular energy consumption
Left ventricular dilation
Hypotension
Multiorgan failure

Organ Failure and Mortality

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



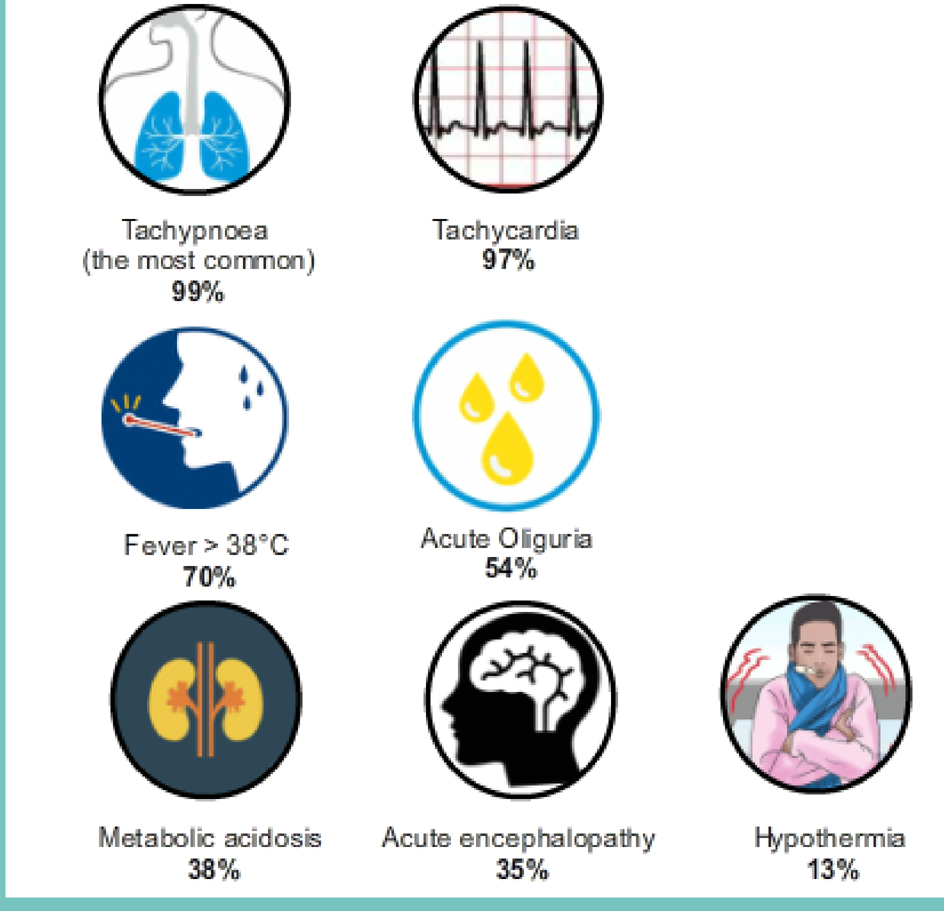
Angus DC, et al. *Crit Care Med.* 2001;29:1303-1310.
Vincent JL, et al. *Crit Care Med.* 1998;21:1793-1800.

Think sepsis!

- Sepsis is an **emergency**
- **You** can make a difference
- Time is **life**

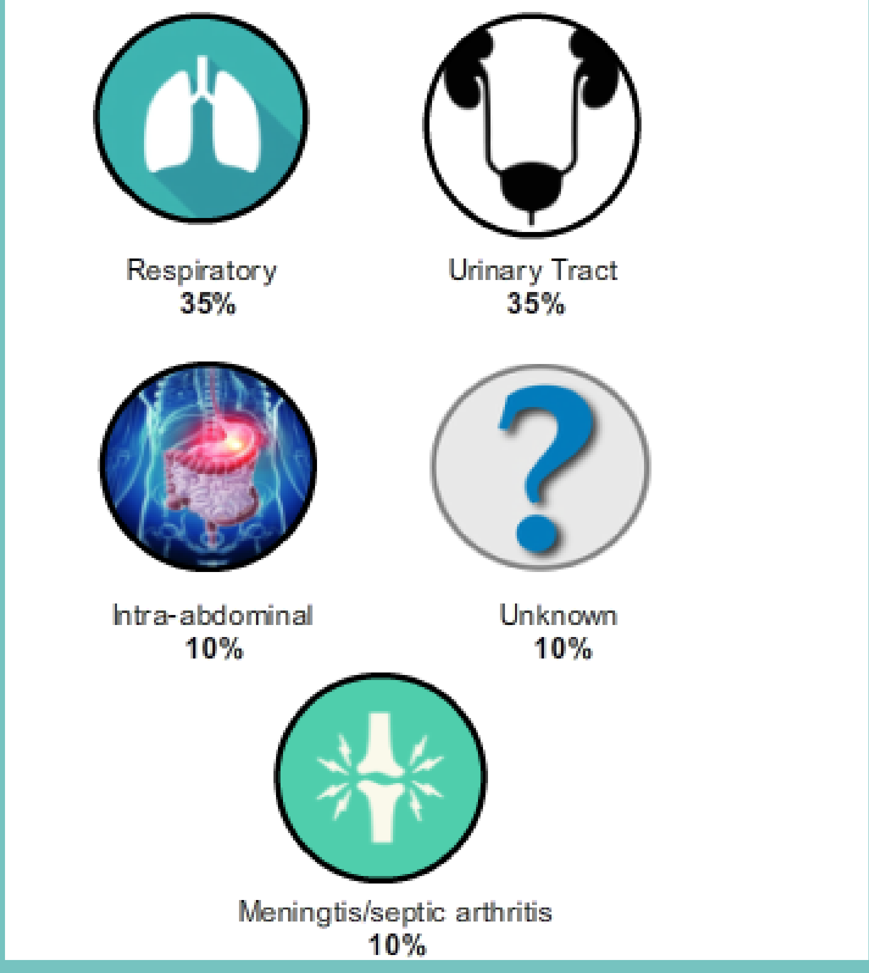
Common signs and symptoms

- Tachypnoea is most common
- Do not just look for a fever



Common sites of infection

- Can be community or hospital acquired
- The sepsis pathway contains antimicrobial recommendations for site of infection
-
- (Guthrie-Chu, 2009; Hartnett, 1989; Myers; 2007; Shelton, 1999)



Body Response to Shock

1. Sympathetic Nervous System (SNS) Activation
2. Activation of Renin-Angiotensin-Aldosterone System (RAAS)
3. Antidiuretic Hormone (ADH) Release
4. Redistribution of Blood Flow
5. Cellular Metabolism Changes
6. Inflammatory Response
7. Coagulation Activation (DIC risk)

1. 🔁 Sympathetic Nervous System (SNS) Activation

Triggered by baroreceptors detecting low BP

Releases catecholamines: **epinephrine** and **norepinephrine**

Effects:

- ↑ Heart rate (**tachycardia**)
- ↑ Cardiac output
- Vasoconstriction → ↑ systemic vascular resistance (SVR)
- Sweating (diaphoresis)
- Pupillary dilation

2. 💦 Activation of Renin-Angiotensin-Aldosterone System (RAAS)

Low blood flow to kidneys → renin release → angiotensin II → vasoconstriction

Aldosterone promotes:

- Sodium and water reabsorption → ↑ blood volume
- Potassium excretion

3.Antidiuretic Hormone (ADH) Release

Released from posterior pituitary

Promotes **water reabsorption** in kidneys

Helps maintain circulating volume

4. ❤️ Redistribution of Blood Flow

Body **prioritizes perfusion to vital organs**:

- **Brain**
- **Heart**
- **Lungs**

Blood flow is **reduced to skin, GI tract, kidneys, limbs**

→ **Pale, cold skin**
→ **Oliguria** (low urine output)
→ **Delayed capillary refill**

-

5. 🔬 Cellular Metabolism Changes

↓ Oxygen → switch from aerobic to **anaerobic metabolism**

Leads to:

- **Lactic acid buildup**
- **Metabolic acidosis**
- Impaired ATP production → **cell death**

•

6. Inflammatory Response

Particularly prominent in **septic shock**

Cytokine storm → vasodilation, capillary leak, coagulation changes

7.Coagulation Activation (DIC risk)

Shock can trigger **coagulation cascade**

Especially in sepsis → **disseminated intravascular coagulation (DIC)**

- Microthrombi formation
- Bleeding risk due to consumption of clotting factors

Why Are Surgical Patients at Risk?

- Invasive procedures and tissue injury
- Breach of physical barriers
- Use of catheters, drains, implants
- Immune suppression (e.g., diabetes, steroids)
- Hospital-acquired infections

Surgical Site Infections	Wound infections, dehiscence
Intra-abdominal Infections	Abscesses, peritonitis, leaks
Catheter-Related Infections	Central line, urinary catheter
Ventilator-Associated Pneumonia	Intubated post-op ICU patients
Necrotizing Soft Tissue Infection	Fasciitis, gas gangrene
Post-op Pneumonia	Especially after abdominal surgery
Gut Flora Translocation	Bowel ischemia, obstruction
Foreign Body Infections	Mesh, grafts, prosthetic joints

Risk Factors for Sepsis in Surgical Patients

1. Patient-Related Risk Factors

- **Advanced age**
- **Immunosuppression**
  - Steroids
  - Chemotherapy
  - HIV/AIDS
  - Post-transplant status
- **Chronic illnesses**
  - Diabetes mellitus
  - Chronic kidney disease
  - Liver cirrhosis
  - Malnutrition
- **Obesity**
- **Smoking or alcohol abuse**
- **History of previous infections or colonization (e.g., MRSA)**

2. Surgery-Related Risk Factors

- **Emergency surgery** (vs. elective)
- **Long duration of surgery**
- **High blood loss during surgery**
- **Contaminated or dirty surgical field**
  - Trauma, bowel perforation, abscess
- **Improper sterile technique**
- **Multiple surgeries/reoperations**

3. Postoperative Risk Factors

- Complications and care-related issues after surgery:
- **Surgical site infections (SSIs)**
- **Anastomotic leaks**
- **Prolonged hospital stay or ICU stay**
- **Poor wound healing**
- **Ventilator support** → pneumonia
- **Presence of foreign materials** (e.g., mesh, prosthesis)
- **Immobility/bedrest** → risk of pneumonia, UTI

4. Device-Related Risk Factors

- **Central venous catheters**
- **Urinary catheters**
- **Drains**
- **Endotracheal tubes (mechanical ventilation)**
- **Feeding tube**

5. Treatment-Related Risk Factors

- **Inadequate or delayed antibiotic prophylaxis**
- **Inappropriate empiric antibiotics**
- **Delayed source control**
- **Overuse of broad-spectrum antibiotics** → resistance
- **Immunosuppressive therapy** (corticosteroids, cytotoxics)

Evolution of Sepsis care

Established Core Rx:
Source Control
Antibiotics
Resuscitation
Supportive Care

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

Mortalit
y

In general the process of care has improved

Steroids

No Steroids
- Endotoxin Antagonists
- LPS/LPS receptor an[illegible]
- anti-TNF
- NSAIDs
- Nitric Oxide Synthase Inhibitors
- Tissue Factor Pathway Inhibitors
- anti-TLR4

Xigri

Tight Glycemic Control [illegible]

Loose Glycemic Control [illegible]

Why a clinical pathway?

- Sepsis is important
  - One of the world's leading causes of death in hospitalised patients
  - 25% mortality associated with septic shock
- Intervention saves lives
  - Delayed recognition and treatment increases mortality
- Reduced variation in practice
  - Standardised care and enhance communication
  - Empowerment of all team members to activate
  - All of the team 'on the same page'

Guidelines for sepsis

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

R. Phillip Dellinger, MD[1]; Mitchell M. Levy, MD[2]; Andrew Rhodes, MB BS[3]; Djillali Annane, MD[4]; Herwig Gerlach, MD, PhD[5]; Steven M. Opal, MD[6]; Jonathan E. Sevransky, MD[7]; Charles L. Sprung, MD[8]; Ivor S. Douglas, MD[9]; Roman Jaeschke, MD[10]; Tiffany M. Osborn, MD, MPH[11]; Mark E. Nunnally, MD[12]; Sean R. Townsend, MD[13]; Konrad Reinhart, MD[14]; Ruth M. Kleinpell, PhD, RN-CS[15]; Derek C. Angus, MD, MPH[16]; Clifford S. Deutschman, MD, MS[17]; Flavia R. Machado, MD, PhD[18]; Gordon D. Rubenfeld, MD[19]; Steven A. Webb, MB BS, PhD[20]; Richard J. Beale, MB BS[21]; Jean-Louis Vincent, MD, PhD[22]; Rui Moreno, MD, PhD[23]; and the Surviving Sepsis Campaign Guidelines Committee including the Pediatric Subgroup*

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?

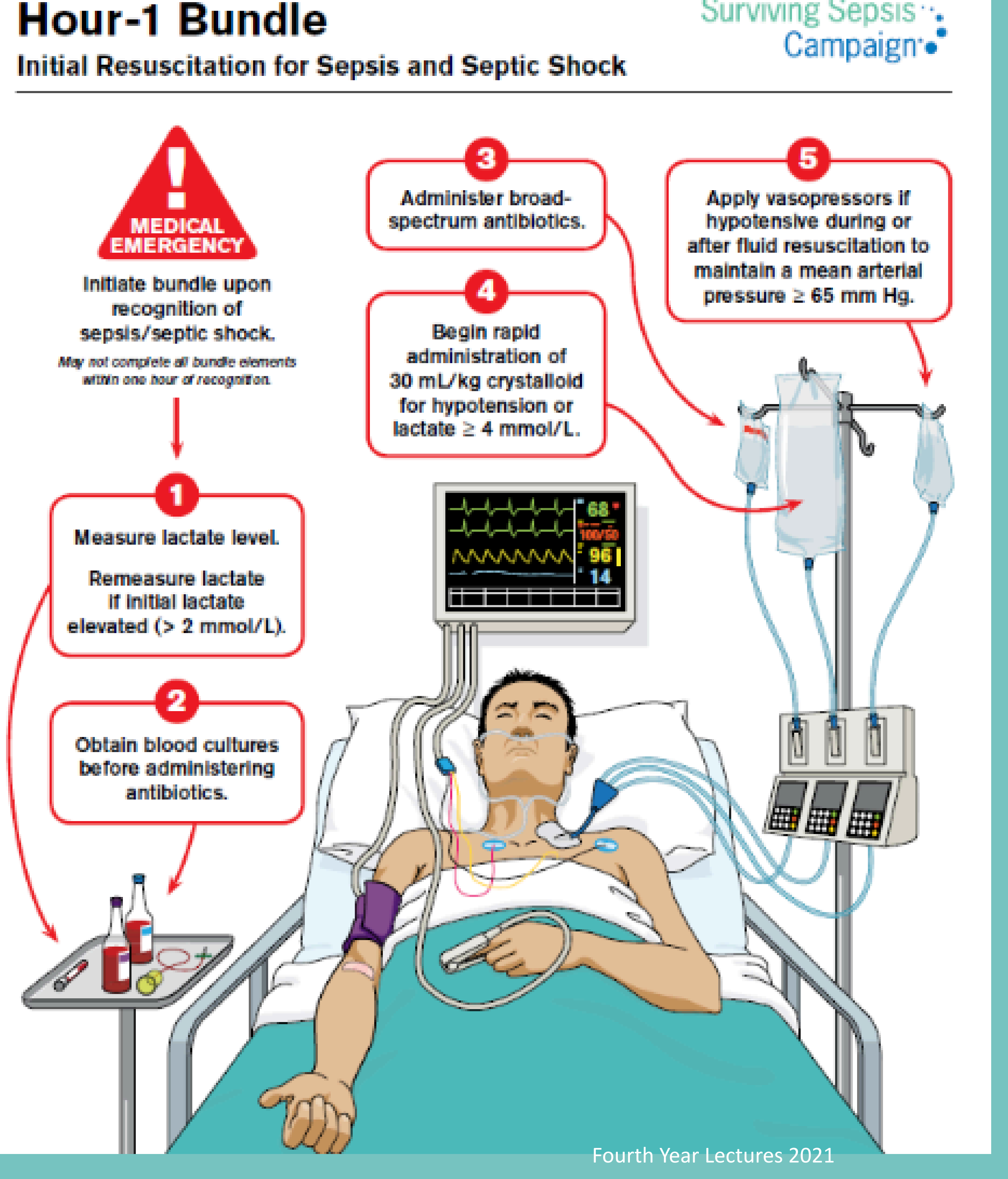
1) Investigate and treat sepsis
    - Try and find and treat source
    - Early blood cultures
    - Start antibiotics asap ideally within 1 hour and after cultures taken
2) Assess extent of end organ hypoperfusion and improve oxygen delivery

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:
    o Crystalloid 20ml/Kg
    o 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:
	    o 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

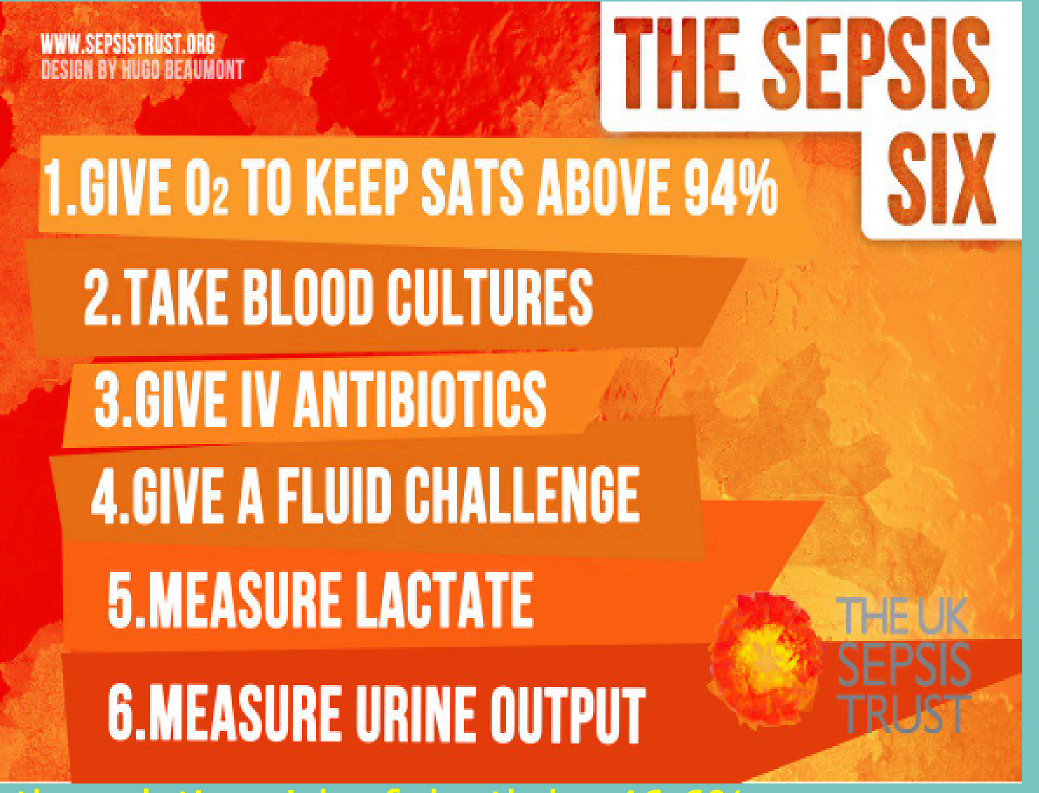
24-hour Management Bundle • Low dose steroids • Human activated protein C (rhAPC) • Maintain glucose 70 -150 mg/dL • Maintain median inspiratory plateau pressure < 30 cm H2O in mechanical ventilation	***24-hour Bundle no longer recommended***	

1 Hour Bundle



A bundle of medical interventions designed to reduce the mortality of septic patients

1. **Titrate oxygen to a saturation target of 94%**
2. **Take blood cultures**
3. **Administer empiric intravenous antibiotics**
4. **Measure serum lactate and send full blood count**
5. **Start intravenous fluid resuscitation**
6. **Commence accurate urine output measurement**



Compliance with the Sepsis 6 has been shown to reduce the relative risk of death by 46.6%

Achieving 80 percent compliance, therefore, would be expected to save an estimated 11,000 - 15,000 lives per year across the NHS

Surviving Sepsis targets of fluid resuscitation

What are they?

- SBP
- MAP
- CVP
- U/o
- Lactate
- $ScvO_2$
- 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
- $ScvO_2$ >70
- 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)

Resuscitation

- 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
  - $ScvO_2$

CVP

What does it mean?

CVP

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

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%

$ScvO_2$

What can I do if it's low?

$ScvO_2$

What can I do if it's low?

Delivery = [Hb] x SpO_2 x 1.34 x HR x SV

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%

Inotropes

“Time Zero”

- Time Zero = time of presentation
  - ED, Medical Floors, ICU
- 1 Hour Bundle

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

1.00
.80
.40
.20
0.0

14 ICUs; n = 2,731

% Survival

% Total receiving antibiotics

Only 50% of patients in Septic Shock

received antibiotics w/in 6 hrs.

0 - .5
.5 – 1.0
1 - 2
2 - 3
3-4
4 - 5
5 - 6
6 - 9
9 - 12
12 - 24
24 - 36
> 36

Time, hrs

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**

CORTICOSTEROIDS

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

Thank You