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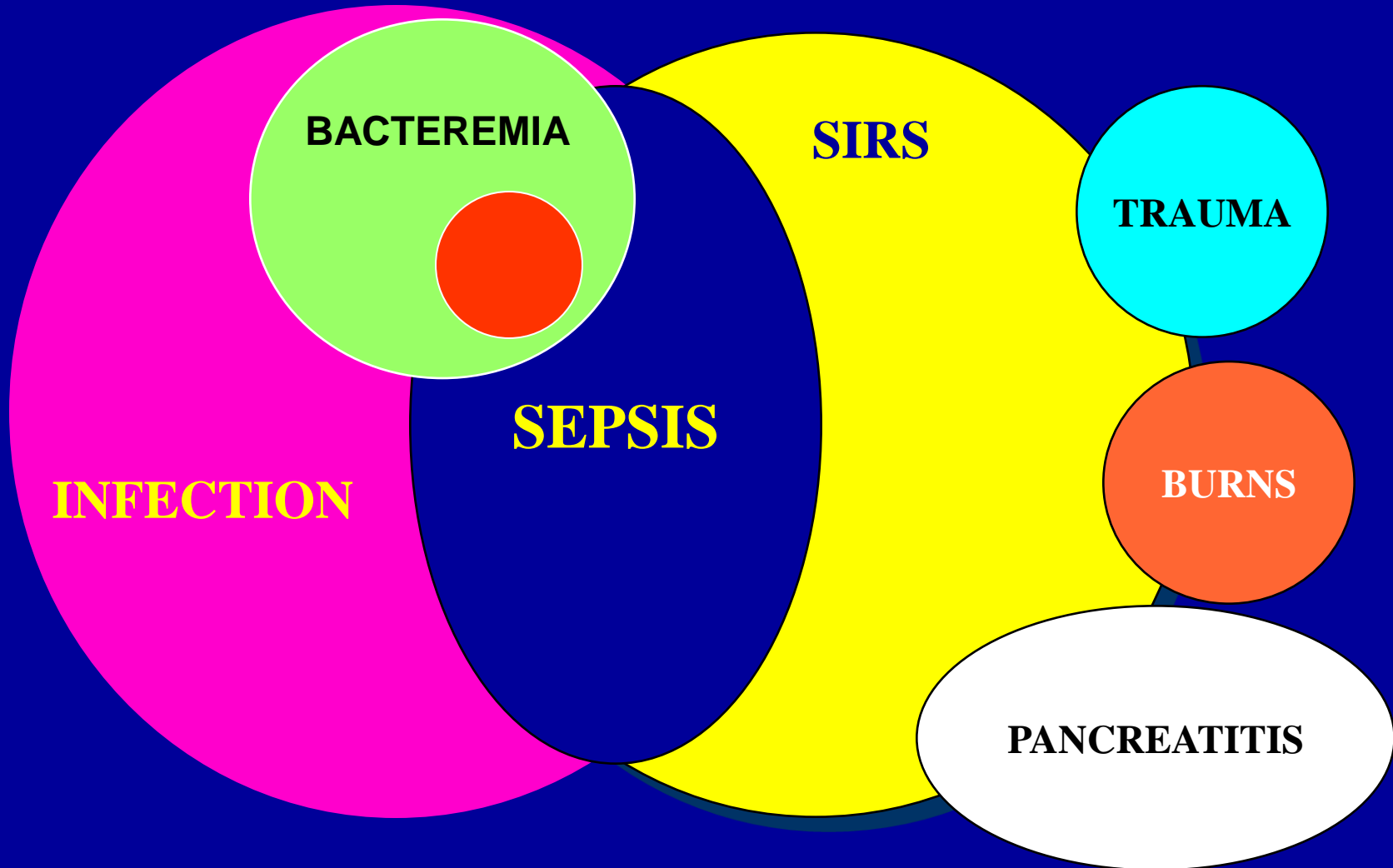
University Hospital Birmingham

Objectives

- **The definitions of Sepsis and the Sepsis Syndromes.**
- **The factors that precipitate and perpetuate the Sepsis Cascade.**
- **The Pathogenesis of Multiple Organ Dysfunction in Sepsis.**
- **Treatment options in Sepsis**

What is Sepsis?

Relationship Between Sepsis and SIRS



Definitions

- **Systemic Inflammatory Response Syndrome (SIRS):**
- The systemic inflammatory response to a variety of severe clinical insults

- **Sepsis:**
- The systemic inflammatory response to infection.

SIRS is manifested by two or more of the following conditions:

- **Temperature $>38^{\circ}\text{C}$ or $<36^{\circ}\text{C}$.**
- **Heart rate >90 beats per minute.**
- **Respiratory rate >20 breaths per minute or $\text{PaCO}_2 < 32\text{mmHg}$.**
- **White blood cell count $> 12,000/\text{cu mm}$, $<4,000/\text{cu mm}$, or $>10\%$ band forms.**

Definitions (ACCP/SCCM)

- **Sepsis:**
 - Known or suspected infection, plus
 - ≥ 2 SIRS Criteria.
- **Severe Sepsis:**
 - Sepsis plus >1 organ dysfunction.
 - MODS.
 - Septic Shock.

Definitions (ACCP/SCCM):

- **Septic Shock:**
- **Sepsis with hypotension despite adequate resuscitation along with the presence of perfusion abnormalities which may include, but are not limited to lactic acidosis, oliguria, or an acute alteration in mental status.**

Definitions (ACCP/SCCM):

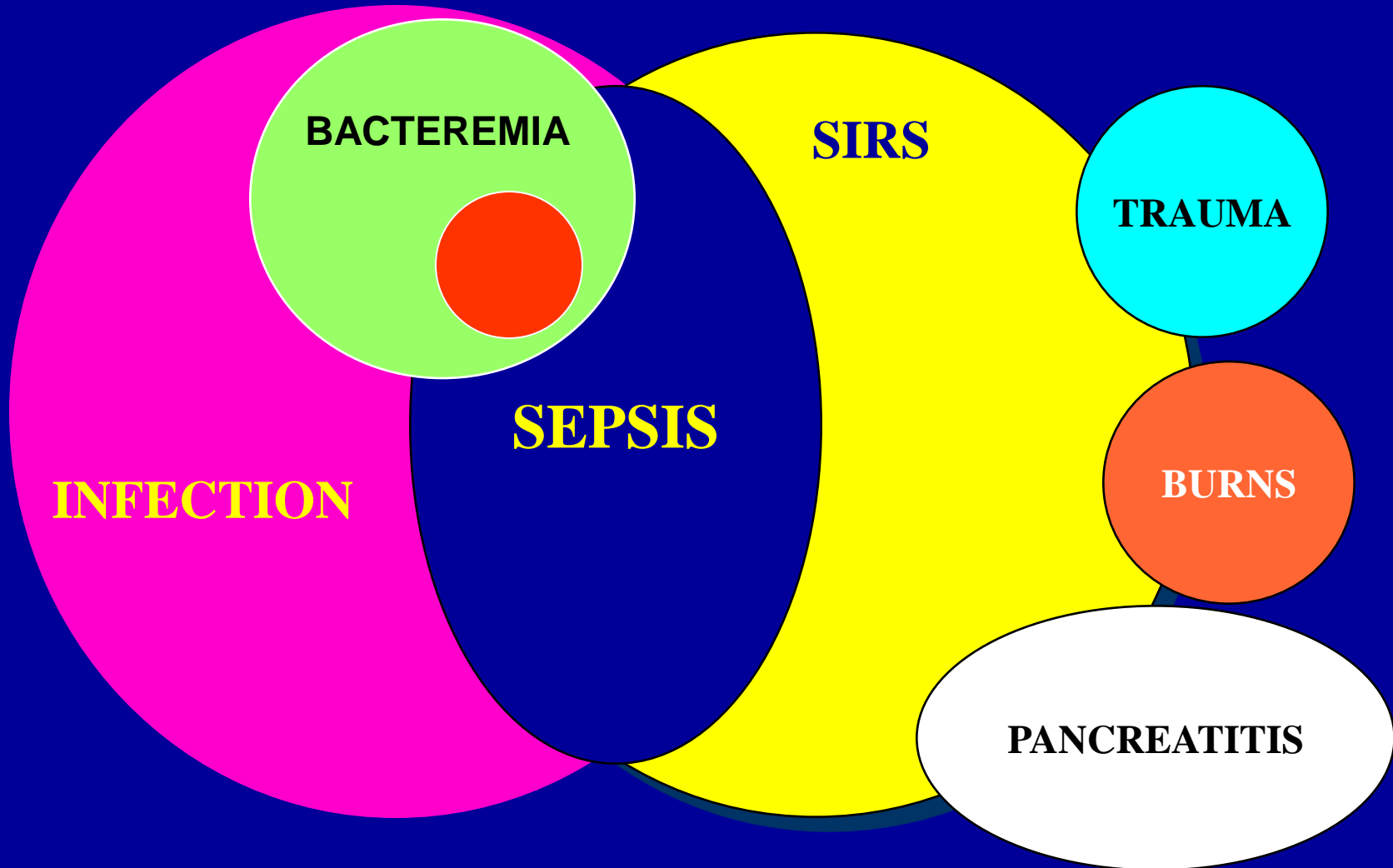
- **Septic Shock:**

Sepsis with **hypotension** despite adequate resuscitation along with the presence of **perfusion abnormalities** which may include, but are not limited to lactic acidosis, oliguria, or an acute alteration in mental status.

Definitions (ACCP/SCCM):

- **Multiple Organ Dysfunction Syndrome (MODS):**
- **The presence of altered organ function in an acutely ill patient such that homeostasis cannot be maintained without intervention.**

Relationship Between Sepsis and SIRS



Clinical Signs of Sepsis

- **Fever.**
- **Leukocytosis.**
- **Tachypnea.**
- **Tachycardia.**
- **Reduced Vascular Tone.**
- **Organ Dysfunction.**

Clinical Signs of Septic Shock

- **Hemodynamic Alterations**
 - **Hyperdynamic State (“Warm Shock”)**
 - Tachycardia.
 - Elevated or normal cardiac output.
 - Decreased systemic vascular resistance.
 - **Hypodynamic State (“Cold Shock”)**
 - Low cardiac output.

Clinical Signs of Septic Shock

- Myocardial Depression.
- Altered Vasculature.
- Altered Organ Perfusion.
- Imbalance of O₂ delivery and Consumption.
- Metabolic (Lactic) Acidosis.

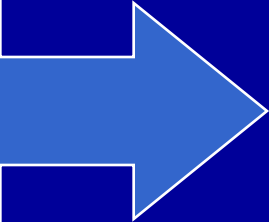
Locally Controlled



Leukocytosis



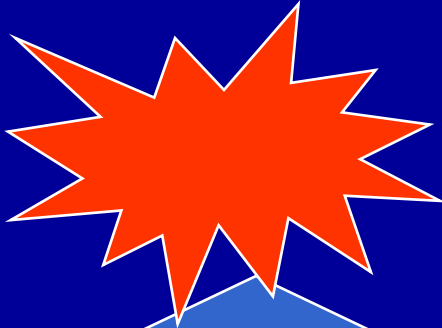
**Systemic
Hyperdynamic
Response**



**Oxygen metabolism
becomes uncoupled**



**Shock,
Organ Failure.**

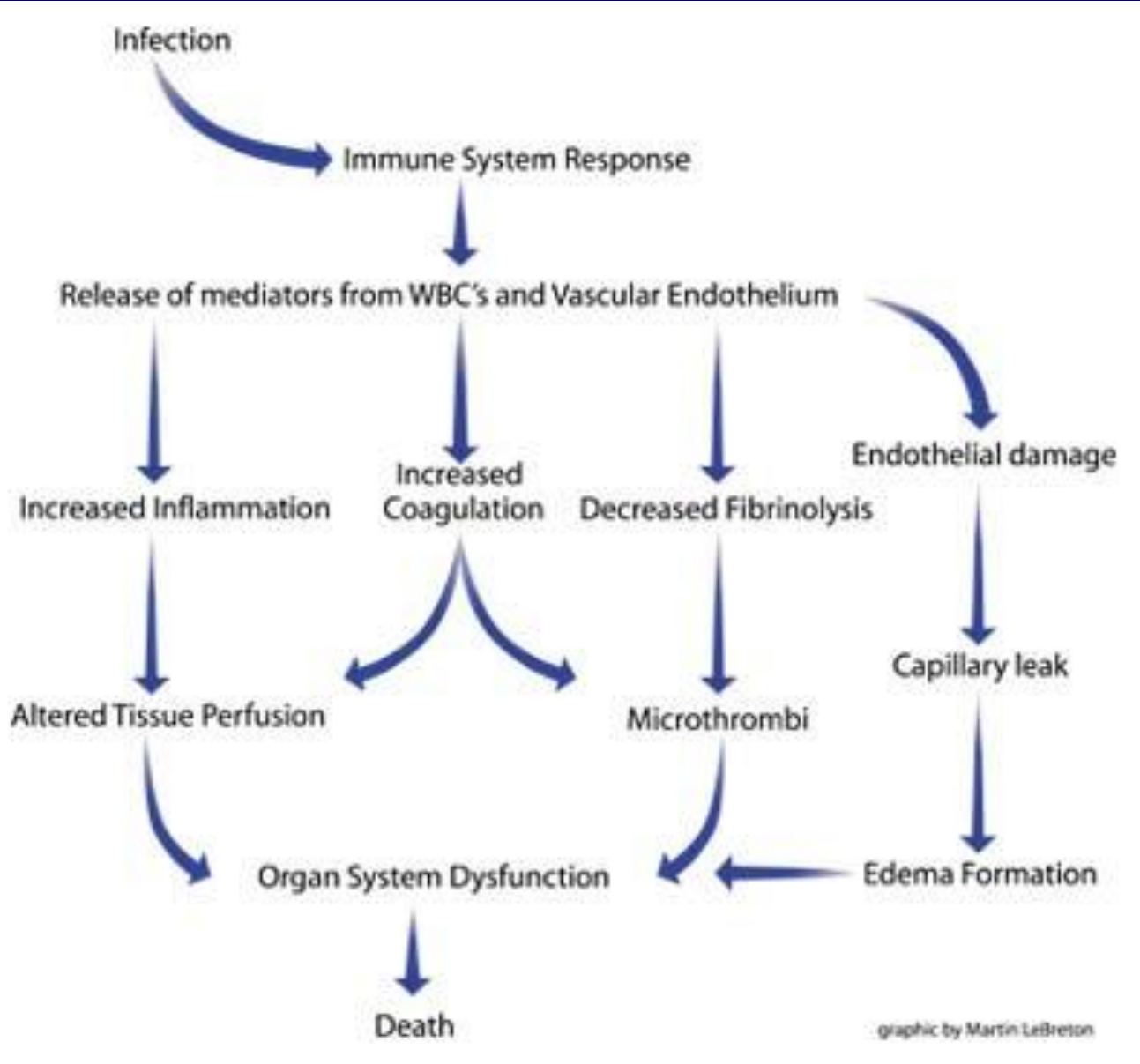


Stages In the Development of SIRS

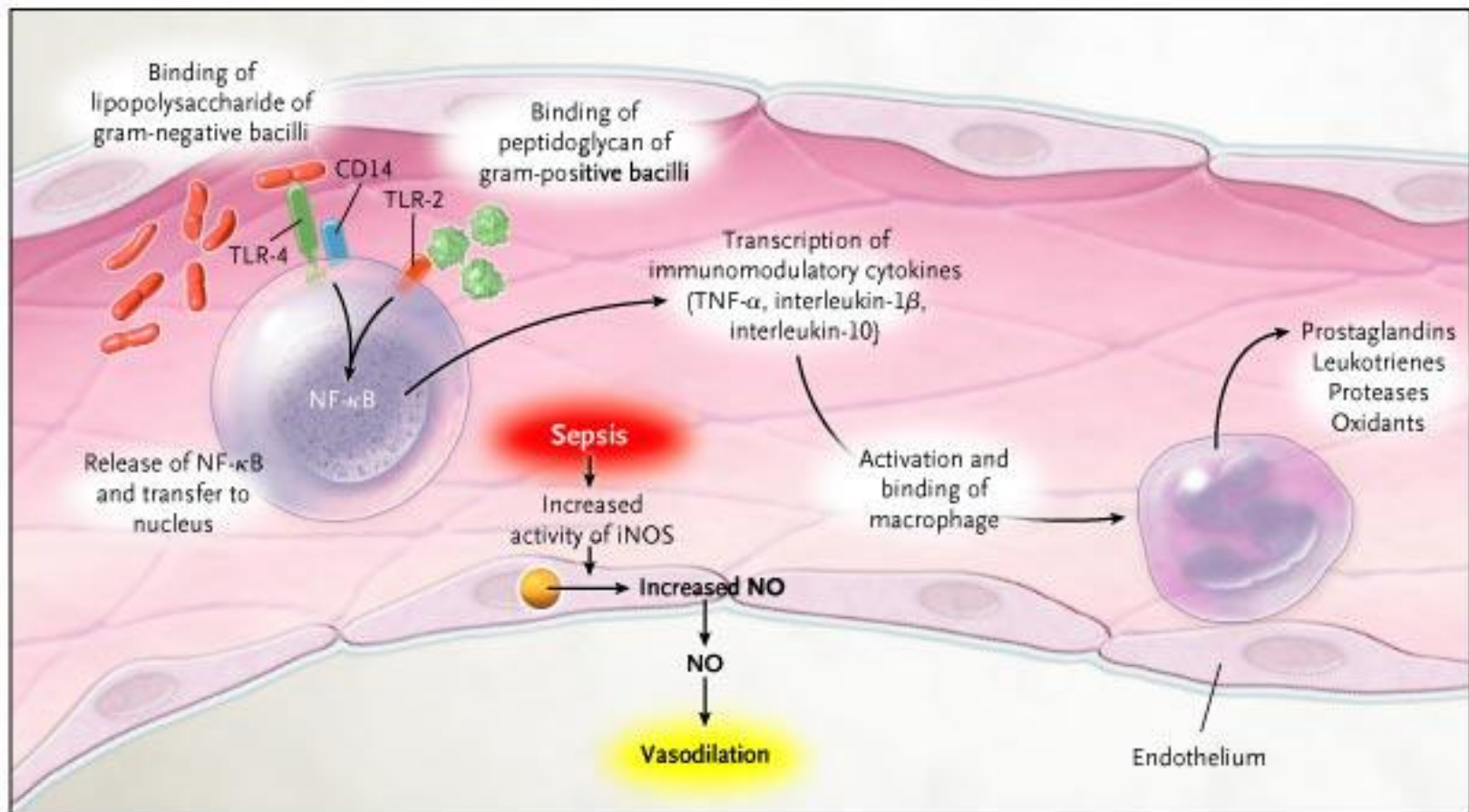
- **Stage 1.** In response to injury / infection, the local environment produces cytokines.
- **Stage 2.** Small amounts of cytokines are released into the circulation:
 - Recruitment of inflammatory cells.
 - Acute Phase Response.
 - Normally kept in check by endogenous anti-inflammatory mediators (IL-10, PGE2, Antibodies, Cytokine receptor antagonists).

Stages In the Development of SIRS

- **Stage 3.** Failure to control inflammatory cascade:
 - Loss of capillary integrity.
 - Stimulation of Nitric Oxide Production.
 - Maldistribution of microvascular blood flow.
 - Organ injury and dysfunction.



graphic by Martin LeBreton

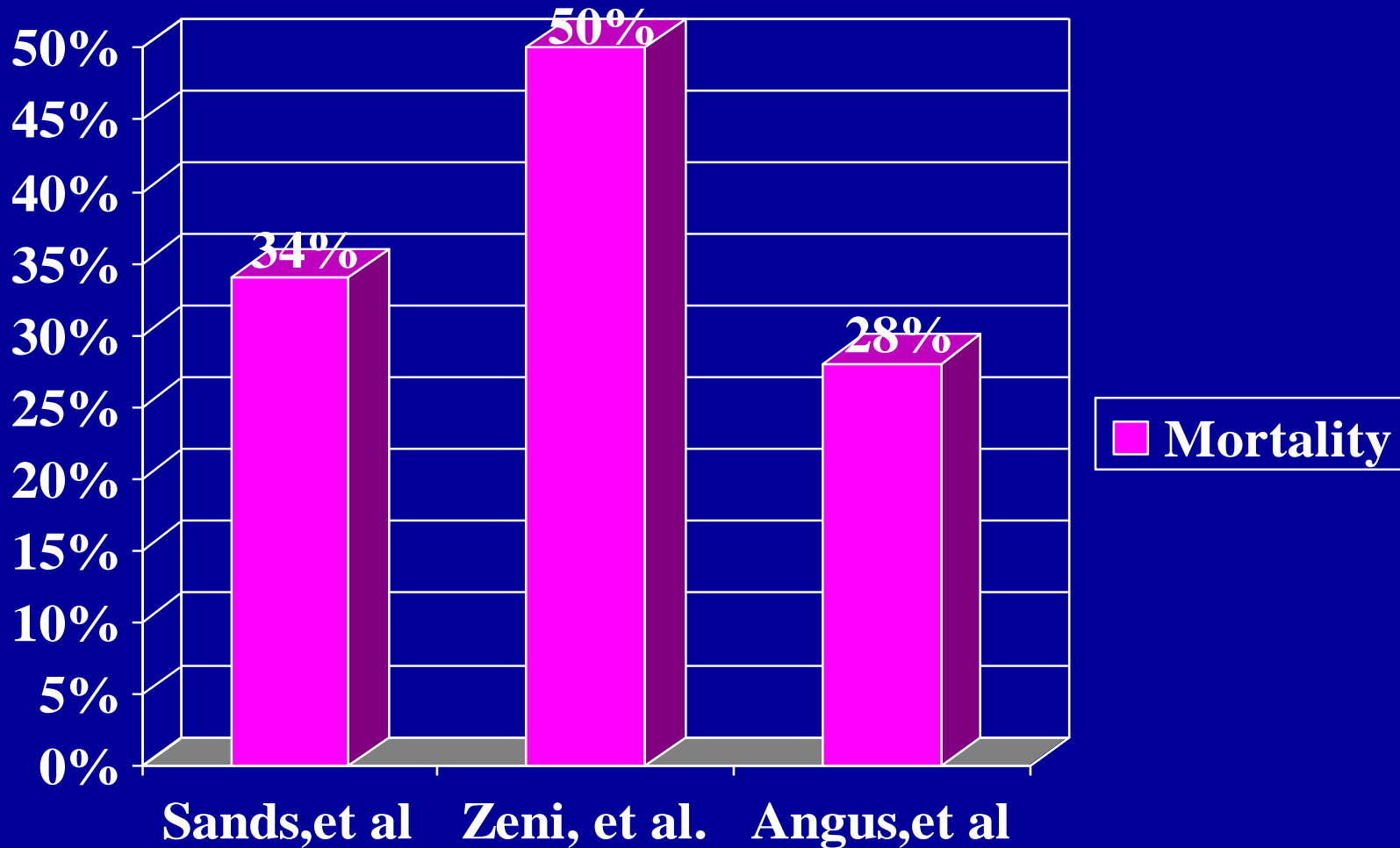


Why is Sepsis Important?

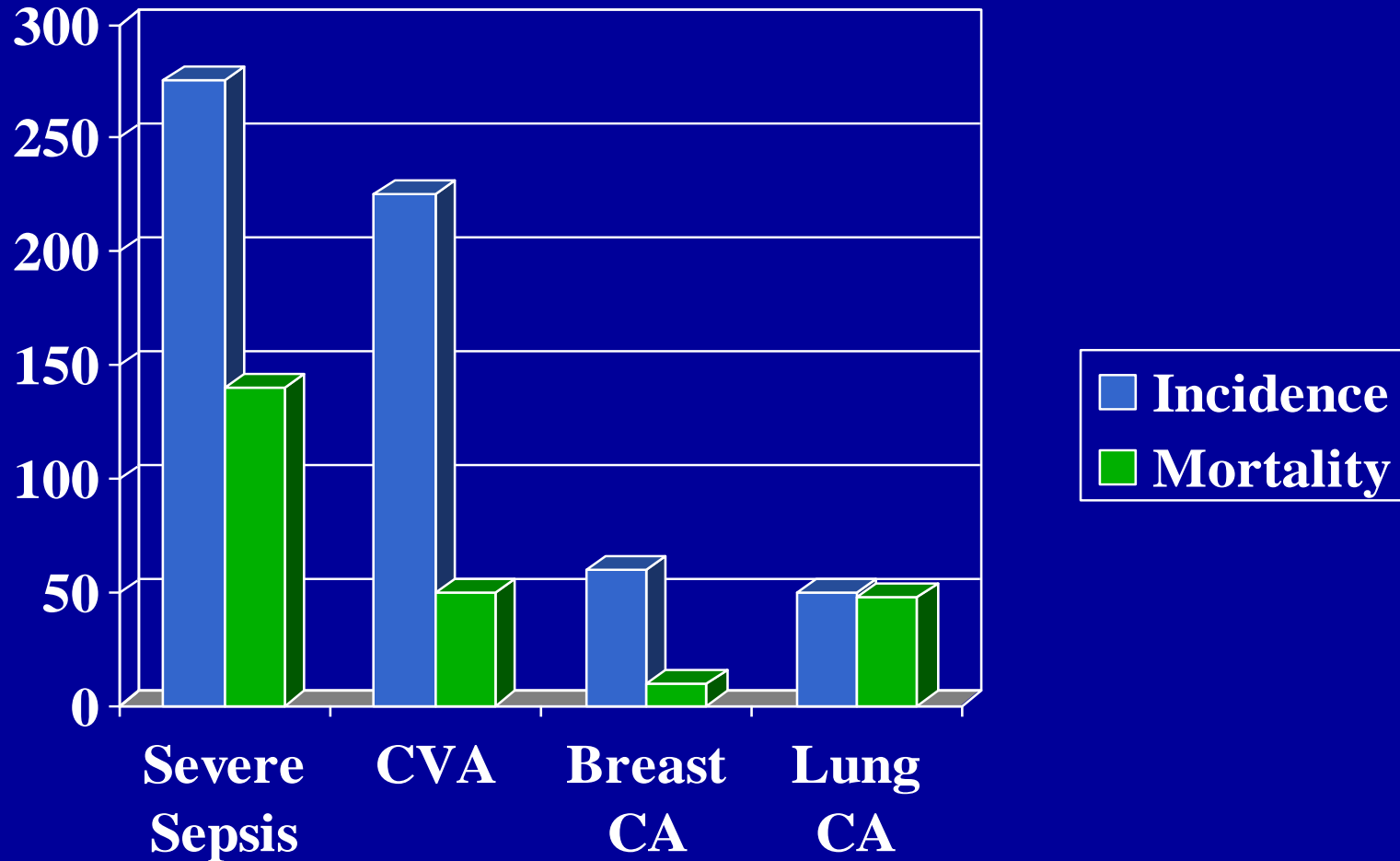
Severe Sepsis

- **Major cause of morbidity and mortality worldwide.**
 - **Leading cause of death in noncoronary ICU.**
 - **11th leading cause of death overall.**
- **More than 750,000 cases of severe sepsis in US annually.**
- **In the US, more than 500 patients die of severe sepsis daily.**

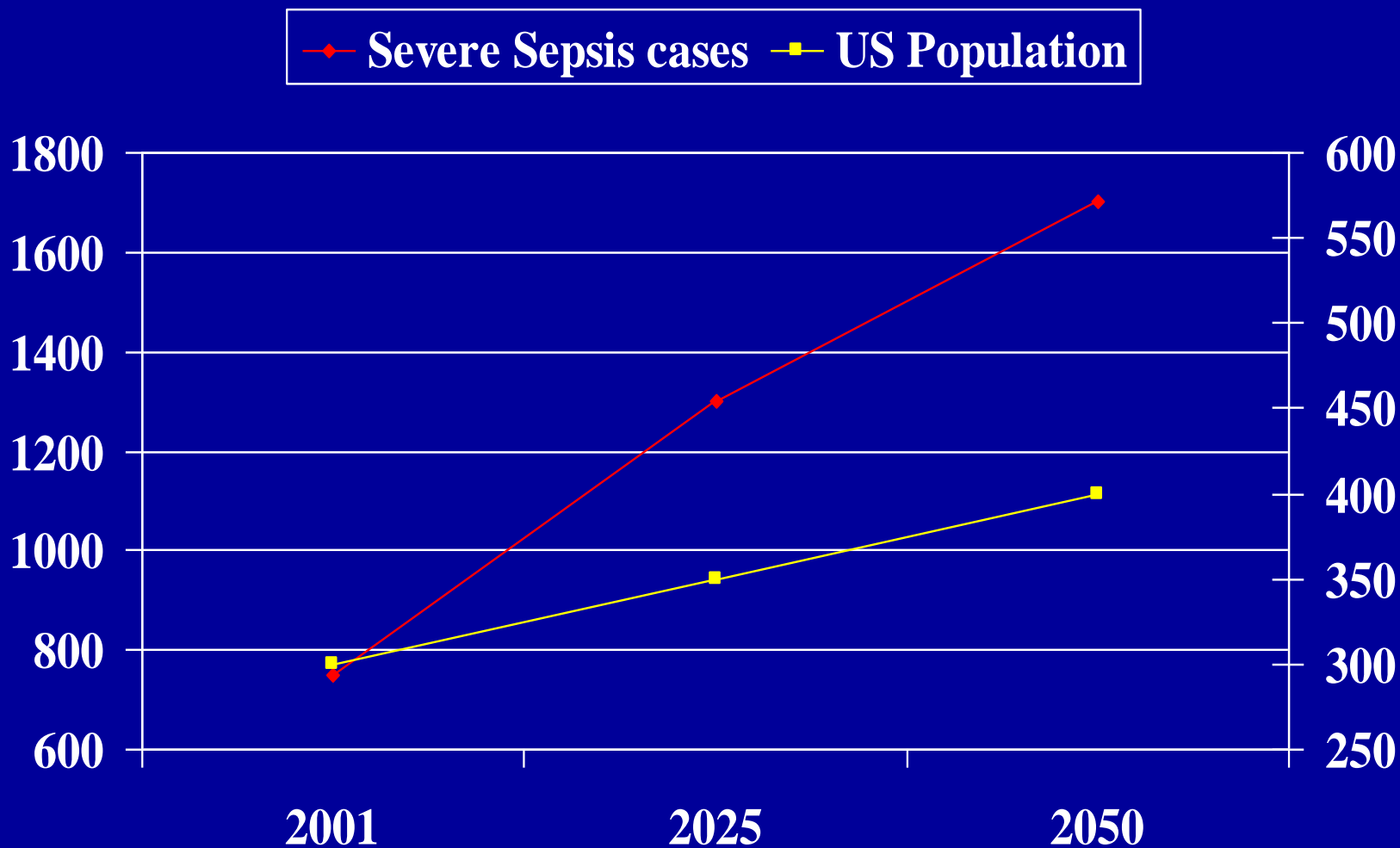
Severe Sepsis is deadly



Severe Sepsis is Common



Severe Sepsis is increasing in incidence



Severe Sepsis is Significant Healthcare Burden

- **Sepsis consumes significant healthcare resources.**
- **In a study of Patients who contract nosocomial infections, develop sepsis and survive:**
 - **ICU stay prolonged an additional 8 days.**
 - **Additional costs incurred were \$40,890/patient.**
- **Estimated annual healthcare costs due to severe sepsis in U.S. exceed \$16 billion.**

Mediators of Septic Response

Pro-inflammatory Mediators

- **Bacterial Endotoxin**
- **TNF- α**
- **Interleukin-1**
- **Interleukin-6**
- **Interleukin-8**
- **Platelet Activating Factor (PAF)**
- **Interferon-Gamma**
- **Prostaglandins**
- **Leukotrienes**
- **Nitric Oxide**

Anti-inflammatory Mediators

- Interleukin-10
- PGE2
- Protein C
- Interleukin-6
- Interleukin-4
- Interleukin-12
- Lipoxins
- GM-CSF
- TGF
- IL-1RA

Why do Septic Patients Die?

Organ Failure and Mortality

•Knaus, et al. (1986):

•Direct correlation between number of organ systems failed and mortality.

•Mortality Data:

	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%

Pathophysiology of Sepsis-Induced Organ Injury

- **Multiple Organ Failure (MOF) results from diffuse cell injury / death resulting in compromised organ function.**
- **Mechanisms of cell injury / death:**
 - **Cellular Necrosis (ischemic injury).**
 - **Apoptosis.**
 - **Leukocyte-mediated tissue injury.**
 - **Cytopathic Hypoxia**

Pathogenesis of Vasodilation in Sepsis

- **Loss of Sympathetic Responsiveness:**
 - Down-regulation of adrenergic receptor number and sensitivity, possible altered signal transduction.
- **Vasodilatory Inflammatory Mediators.**
- **Endotoxin** has direct vasodilatory effects.
- **Increased Nitric Oxide Production.**

Vasodilatory Inflammatory Mediators

- **Vasoactive Intestinal Peptide**
- **Bradykinin**
- **Platelet Activating Factor**
- **Prostanoids**
- **Cytokines**
- **Leukotrienes**
- **Histamine**
- **NO**

Microvascular Plugging in Sepsis

- Decreased red cell deformability in inflammatory states.
- Microvascular sequestration of activated leukocytes and platelets.
- Sepsis is a Procoagulant State.
 - The extrinsic pathway may be activated in sepsis by upregulation of **Tissue Factor** on monocytes or endothelial cells.
 - Fibrinolysis appears to be inhibited in sepsis by upregulation of **Plasminogen Activator Inhibitor**.
 - A variety of pathways result in reduced **Protein C** activity in sepsis.

In septic shock,
we are designed to die

The herd must survive

Surviving Sepsis



Surviving Sepsis

A global program to:

Reduce mortality rates in severe sepsis

**Surviving Sepsis Campaign (SSC)
Guidelines for Management of Severe
Sepsis and Septic Shock**

25 % reduction in sepsis mortality by 2009



Dellinger RP, Carlet JM, Masur H, et al.

Surviving Sepsis Campaign Guidelines for management of severe sepsis and septic shock.

Critical Care Medicine. 2004;32:858-873.

Sponsoring Organizations

- **American Association of Critical Care Nurses**
- **American College of Chest Physicians**
- **American College of Emergency Physicians**
- **American Thoracic Society**
- **Australian and New Zealand Intensive Care Society**
- **European Society of Clinical Microbiology and Infectious Diseases**
- **European Society of Intensive Care Medicine**
- **European Respiratory Society**
- **International Sepsis Forum**
- **Society of Critical Care Medicine**
- **Surgical Infection Society**

Care Bundles

A "bundle" is a group of interventions related to a disease process that, when executed together, result in better outcomes than when implemented individually.

Care Bundles

The individual bundle elements are built on upon evidence-based practices.

The science behind the elements of a bundle is so well-established that their implementation should be considered a generally accepted practice.

How to treat?

- Pathogen
- Fluid shift
- Impaired vasoconstriction
- Rampant inflammation
- Oxygen consumption
- Abnormal coagulation
- Break down of homeostasis
- Antibiotics
- Fluids
- Steroids / pressors
- Statins/ steroids
- Oxygen/ hb
- Clotting products
- Take control

Sepsis *Resuscitation* Bundle:

Evidence-based goals that must be completed within **6 hours** for patients with severe sepsis, septic shock and/or lactate > 4 mmol/L

Sepsis *Management* Bundle:

Evidence-based goals that must be completed within **24 hours** for patients with severe sepsis, septic shock and/or lactate > 4 mmol/L

Sepsis Resuscitation Bundle:

- Serum lactate measured
- Blood cultures obtained prior to antibiotic administration
- From the time of presentation, broad-spectrum antibiotics administered within 3 hours for ED admissions and 1 hour for non-ED ICU admissions

- In the event of hypotension and/or lactate > 4 mmol/L
 - Deliver an initial minimum of 20 ml/kg of crystalloid (or colloid equivalent)
 - Apply vasopressors for hypotension not responding to initial fluid resuscitation to maintain mean arterial pressure (MAP) > 65 mm Hg

- In the event of persistent hypotension despite fluid resuscitation (septic shock) and/or lactate > 4 mmol/L
 - Achieve central venous pressure (CVP) of > 8 mm Hg
 - Achieve central venous oxygen saturation (ScvO₂) of $> 70\%$

Initial Resuscitation

Goals during first 6 hours:

- Central venous pressure: 8–12 mm Hg
- Mean arterial pressure ≥ 65 mm Hg
- Urine output ≥ 0.5 mL kg⁻¹/hr⁻¹
- Central venous (superior vena cava) or mixed venous oxygen [SvO₂] saturation $\geq 70\%$

Grade B

Initial Resuscitation

Goals during first 6 hours:

- Central venous or mixed venous O₂ sat < 70% after CVP of 8–12 mm Hg
 - Packed RBCs to Hct 30%
 - Dobutamine to max 20 µg/kg/min

Grade B

Sepsis Management Bundle:

- Low-dose steroids administered for septic shock in accordance with a standardized ICU policy
- Drotrecogin alfa (activated) administered in accordance with a standardized ICU policy
- Glucose control maintained $>$ lower limit of normal, <8.3 mmol/L
- Inspiratory plateau pressures maintained < 30 cm H₂O for mechanically ventilated patients

Diagnosis

- **Appropriate cultures**
- **Minimum 2 blood cultures**
 - **1 percutaneous**
 - **1 from each vascular access ≥ 48 hrs**

Grade D

Antibiotic Therapy

- **Begin intravenous antibiotics within first hour of recognition of severe sepsis.**

Grade E

Antibiotic Therapy

- **One or more drugs active against likely bacterial or fungal pathogens.**
- **Consider microorganism susceptibility patterns in the community and hospital.**

Grade D

Antibiotic Therapy

Reassess antimicrobial regimen at 48-72 hrs

- **Microbiologic and clinical data**
- **Narrow-spectrum antibiotics**
- **Non-infectious cause identified**
- **Prevent resistance, reduce toxicity, reduce costs**

Grade E

Source Control

- **Evaluate patient for a focused infection amendable to source control measures including abscess drainage or tissue debridement.**
 - **Move rapidly**
 - **Consider physiologic upset of measure**
 - **Intravascular access devices**

Grade E

Statins

- Statins in the intensive care unit.
Curr Opin Crit Care. 2006 Aug;12(4):309-14
- Association of statin therapy and increased survival in patients with multiple organ dysfunction syndrome.
Intensive Care Med. 2006 Aug;32(8):1248-51.
- Statins and sepsis.
Lancet. 2006 May 20;367(9523):1651
- Review
- Brit J Anaes 2007;98(2):163

Do it fast

- Recognise
- Access
- Antibiotics
- Oxygen
- (Hb)
- Fluid
- vasopressors

Other bundles

- Ventilator bundles
- Nutrition
- Central line care

Rivers E, Nguyen B, Havstad S, et al.

Early goal-directed therapy in the treatment of severe sepsis and septic shock.

New England Journal of Medicine.
2001;345:1368–1377.

Vincent JL, Gerlach H.

Fluid resuscitation in severe sepsis and septic shock: An evidence-based review.

Critical Care Medicine.
2004;32(11):(Suppl.)S451-S454.

Bernard GR, Vincent JL, Laterre PF, et al.

Efficacy and safety of recombinant human activated protein C for severe sepsis.

New England Journal of Medicine.
2001;344:699–709.

Van den Berghe G, Wouters P, Weekers F, et al.

Intensive insulin therapy in the critically ill patients.

New England Journal of Medicine.
2001;345:1359–1367.

Sepsis

*It is neither necessary nor
desirable to be too clever*

Infection/
Trauma

SIRS

Sepsis

Severe Sepsis



Systemic Inflammatory Response Syndrome

A clinical response arising from a nonspecific insult, including ≥ 2 of the following:

- Temperature $\geq 38^{\circ}\text{C}$ or $\leq 36^{\circ}\text{C}$
- Heart rate ≥ 90 beats/min
- Respirations ≥ 20 /min
- WBC count $\geq 12,000/\text{mm}^3$ or $\leq 4,000/\text{mm}^3$ or $>10\%$ immature neutrophils

SIRS with a presumed or confirmed **infection**

Sepsis with ≥ 1 sign of **organ failure**

- Cardiovascular (refractory hypotension)
- Renal
- Respiratory
- Hepatic
- Hematologic
- CNS
- Unexplained metabolic acidosis



Septic Shock