Sepsis – The Unseen Killer

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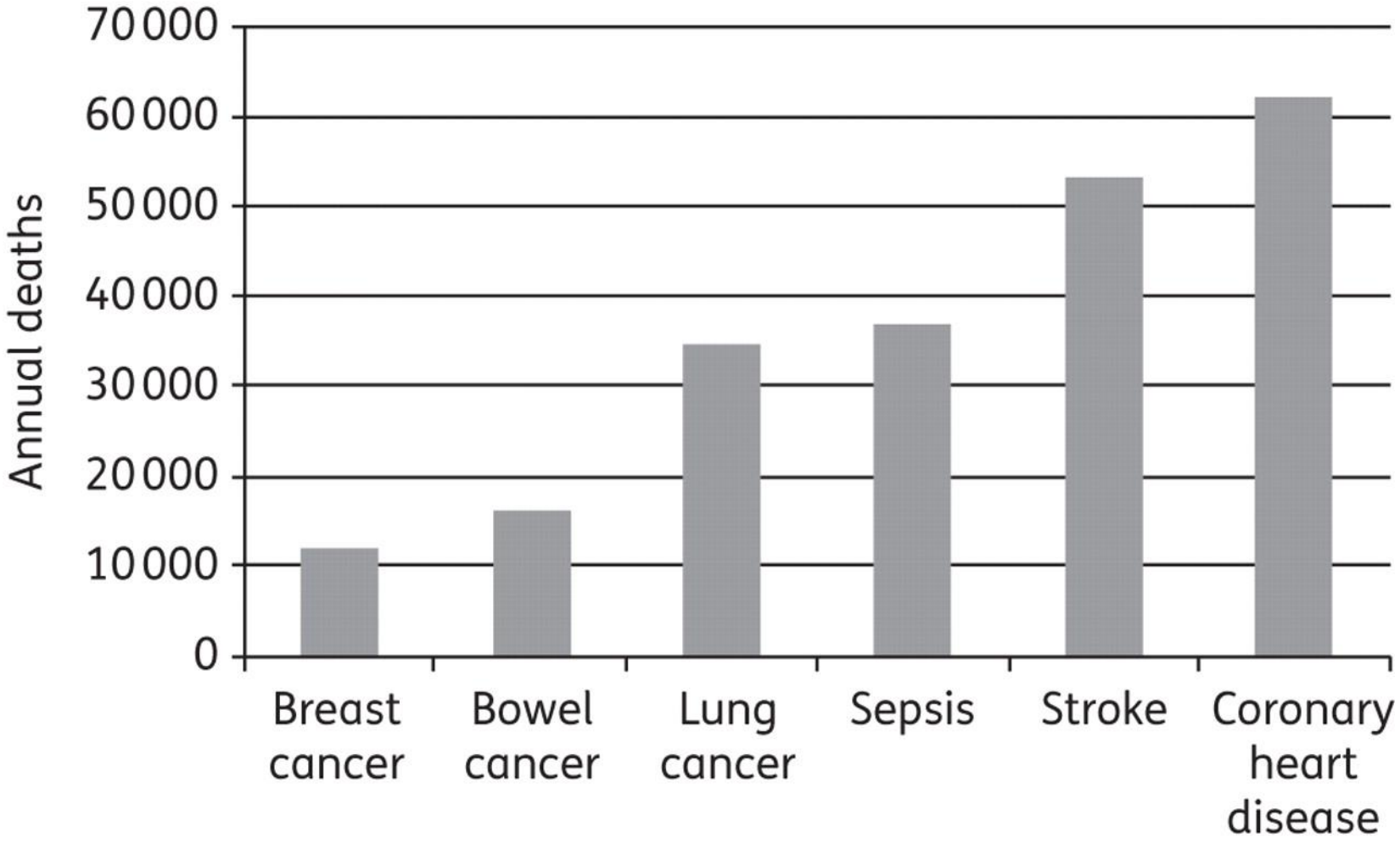
Lecture Content & Outcomes

- Identify the current incidence of sepsis globally in terms of occurrence and mortality figures
- Brief overview of the immune system
- Define what is sepsis, describe the physiology and pathophysiology surrounding sepsis, specifically the sepsis cascade
- Identify clinical signs of sepsis; how do we recognise it in our patients
- Identify and describe the latest treatment and management strategies surrounding sepsis

Epidemiology of Sepsis

- 18 - 20 million of cases of sepsis worldwide with an estimated 20,000 deaths a day globally. (Angus et al. 2001)
- In the developing world sepsis accounts for 60-80% of lost lives in childhood, killing more than 6 million neonates and children annually and is responsible for more than 100,000 cases of maternal sepsis (Angus 2010)
- Accounts for 37,000 deaths a year in the UK
- Sepsis is and remains a lingering public health disaster

Chart showing relative mortality figures in 1year for the UK for common conditions



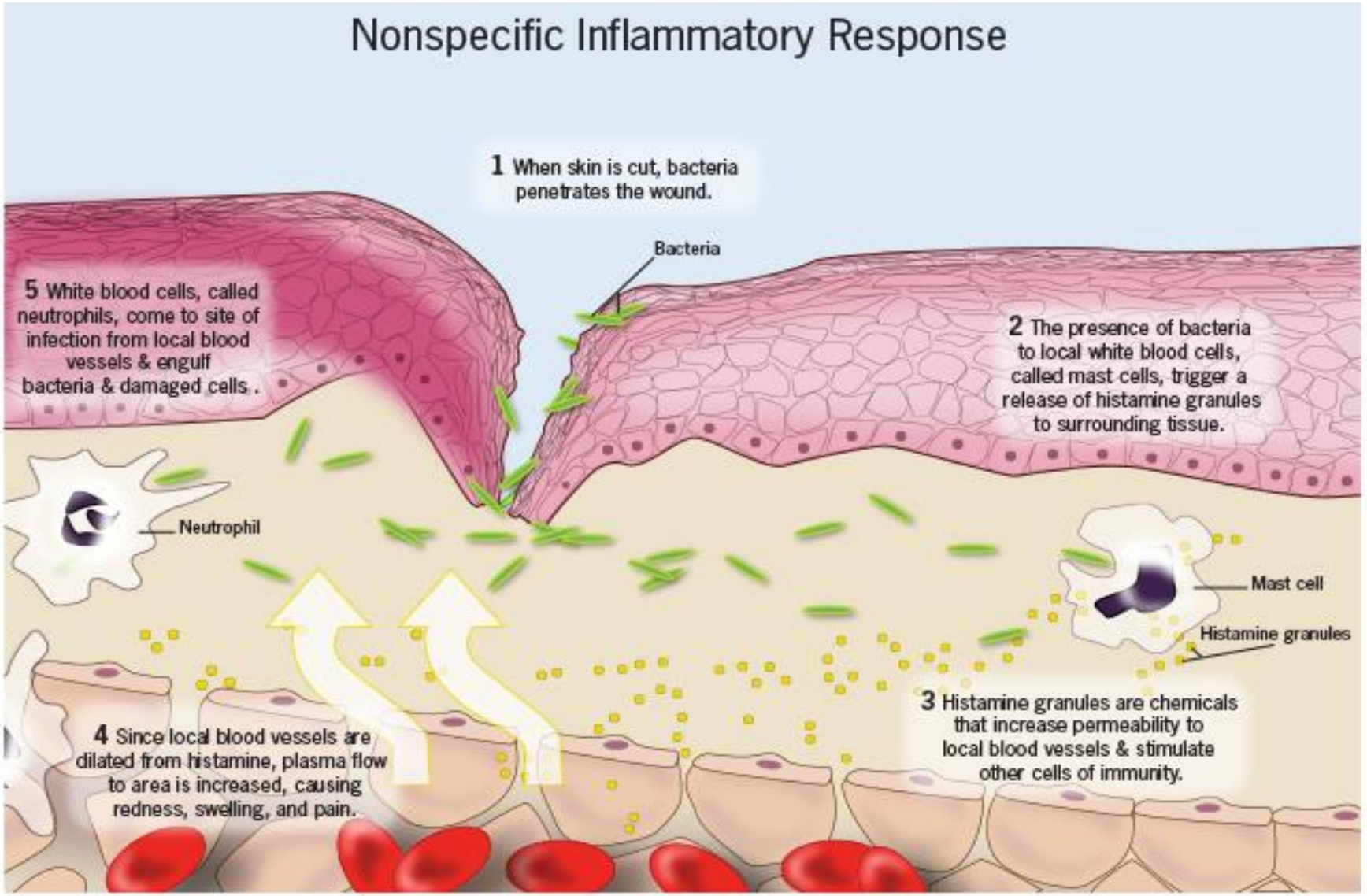
Daniels R J. Antimicrob. Chemother. 2011;66:ii11-ii23

Journal of Antimicrobial Chemotherapy

Contributing Factors to Increase

- Aging population
- Growing numbers of immunosuppressed patients
- Use of life-sustaining technology
- Resistance to antimicrobial agents

An infection



The immune system

Immune system

Inflammatory mediators

Inflammation

The Immune system

- Innate immunity (inbuilt)
- Complement system
- Phagocytes (neutrophils, monocytes, macrophages)
- B and T lymphocytes (cytotoxic helper T cell)

Innate immunity system

Non-specific inbuilt immune response

Toll-like receptors on immune cells recognise bacteria

Cytokine release

Neutrophil and macrophage activation

Complement system

- Usually inactive group of plasma proteins
- Activated directly or by antigen-antibody complexes
- Activate each other → cascade of reactions
- Leukocyte (white blood cell) activation
- Can insert “pores” that burst microbes
- Further cytokine release

Adaptive immunity

B lymphocytes

remember microbes and create antibodies

Helper T cells

Activate by macrophages

Secrete cytokines (chemical messengers)

↑production of B and cytotoxic T lymphocytes

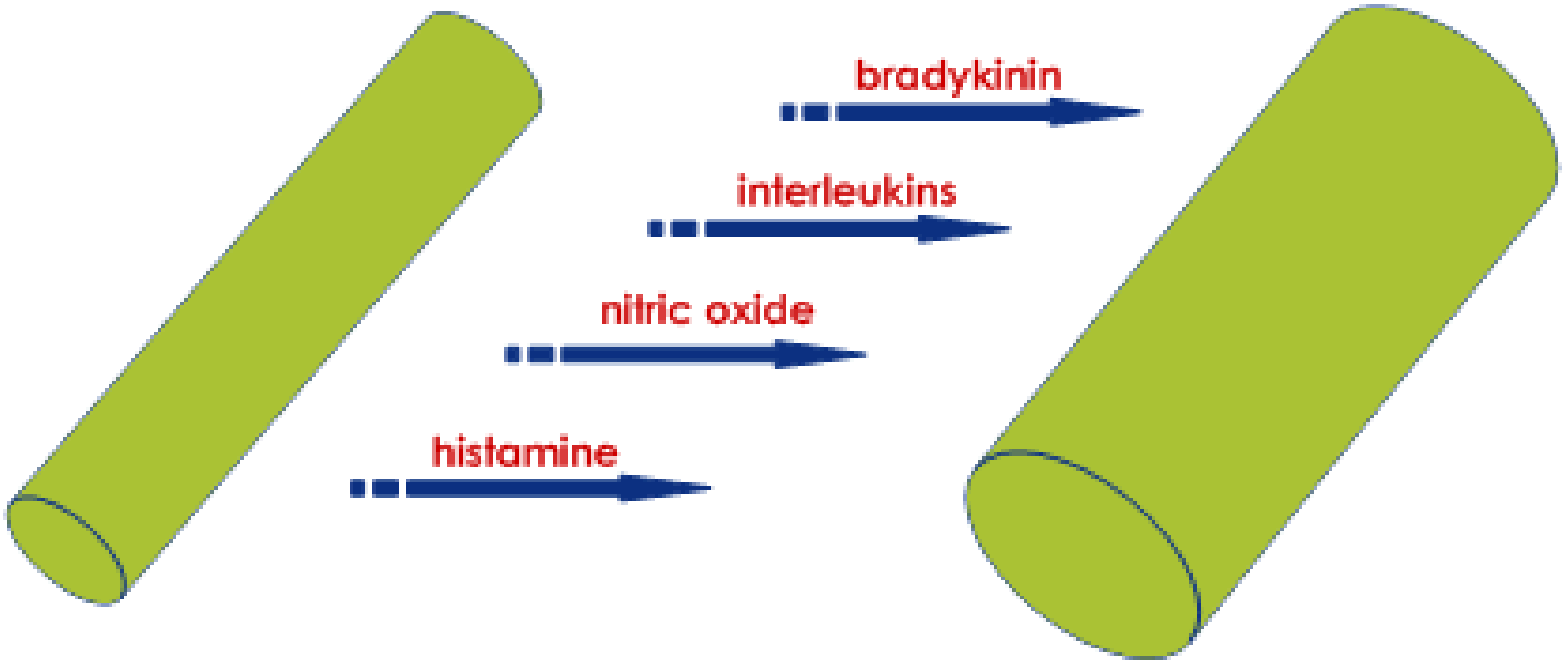
Cytotoxic T cells

Activated by antigens (protein on infected cell surface)

Secretes perforins to create pores and burst cell

Inflammatory mediators

Histamine
Cytokines (interleukin)
Complement system Kinin system (bradykinins)
Serotonin
Prostaglandins
Leukotrienes platelet Activating Factor
Nitric oxide
These cause ↑vascular permeability and vasodilation



Circulating mediators such as interleukins and nitric oxide cause vasodilatation, particularly in arterioles, and precapillary sphincter dysfunction. This leads to loss of systemic vascular resistance and contributes to hypotension. Additionally, regulation of blood flow to organs is impaired leading to hypoperfusion, shock and ultimately organ failure.

Stages of inflammation

- Vasodilatation
- ↑permeability of blood vessels
- Migration of leukocytes to site of injury

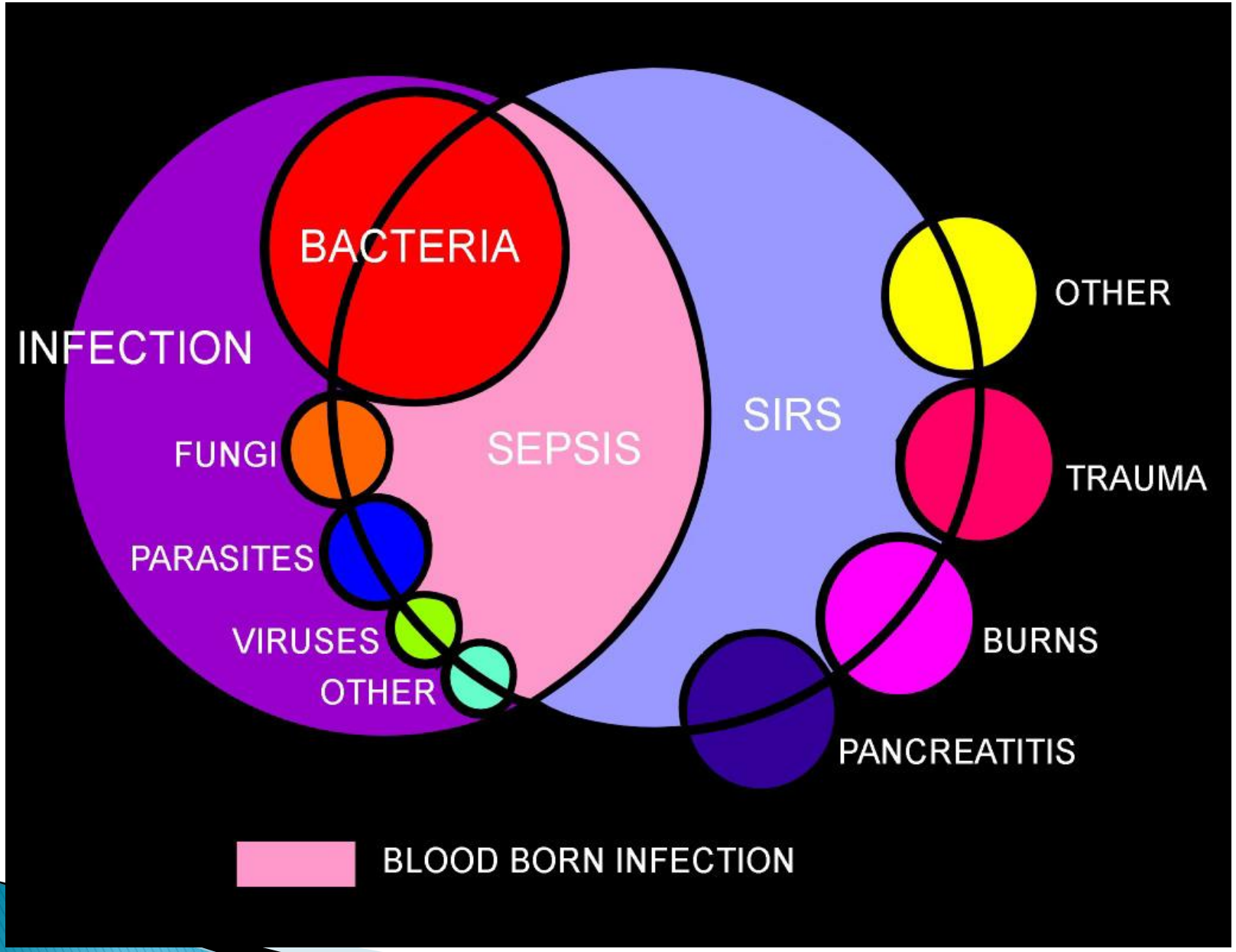
Infection/Sepsis

- An infection or tissue injury triggers a local immune response. This is a desired part of host defence and wound healing. In some patients, however, *a* systemic spillover of inflammatory mediators triggers a more generalized reaction.
- The manifestations of this can cause a systemic inflammatory response syndrome (SIRS).
- SIRS symptoms can include fever or hypothermia, leukocytosis or leukopenia, tachycardia, and tachypnea.
- The symptoms of SIRS may arise from infection, trauma, burns, pancreatitis, and other inflammatory conditions.
- Patients with SIRS and a presumed or known infection are considered to have sepsis.

Systemic Inflammatory Response Syndrome

This syndrome is clinically recognized by the presence of TWO or more of the following:

- Temperature >380C or < 360C
- Heart rate > 90 beats/min
- Respiratory rate > 20 breaths/min or PaC02 > 32mmHg
- WBC > 12,000 cells/mm3, <4000 cells/mm3, or >10% immature forms
- Hyperglycaemia in the absence of Diabetes Mellitus


BACTERIA
INFECTION
FUNGI
SEPSIS
SIRS
OTHER
TRAUMA
PARASITES
VIRUSES
OTHER
BURNS
PANCREATITIS
BLOOD BORN INFECTION

Key Pathophysiology of the Sepsis Syndrome

- The sepsis syndrome is a complex systemic inflammatory condition associated with infection
- It is not the infective pathogen that directly causes the sepsis syndrome, but the host response to that pathogen
- The pathophysiology surrounding sepsis can be divided into 4 main areas:
  - The individual host response
  - The role of the endothelium
  - The imbalance of the pro-inflammatory and anti-inflammatory mechanisms
  - Activation of the coagulation pathways

Pathophysiology of Sepsis

Bacteria enters

↓

Colonisation

↓

Triggers a nonspecific response
Via the Tollgate Receptors (TLR)

↓

Chemical signals trigger cytokine release

↓

Neutrophil activation

↓

Activated neutrophils adhere to each other and to the endothelium, resulting in tissue injury

B and T cell response and release of cytokines, including tumour necrosis factor (TNF) x, interleukins and prostaglandins

↓

Activation of cell mediators causes vascular permeability and vasodilation

↓

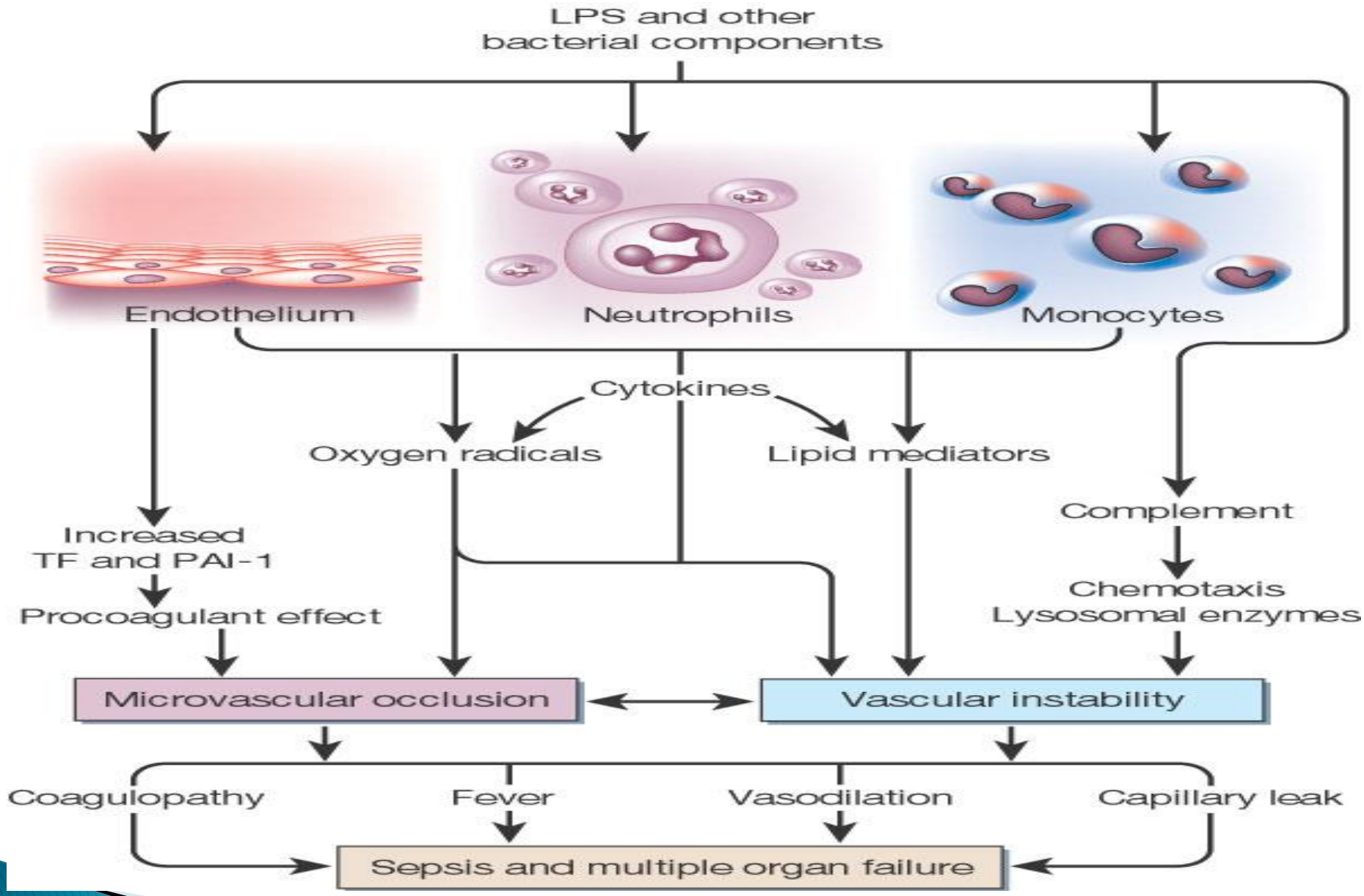
The cytokines also activate the extrinsic coagulation cascade and inhibit fibrinolysis.

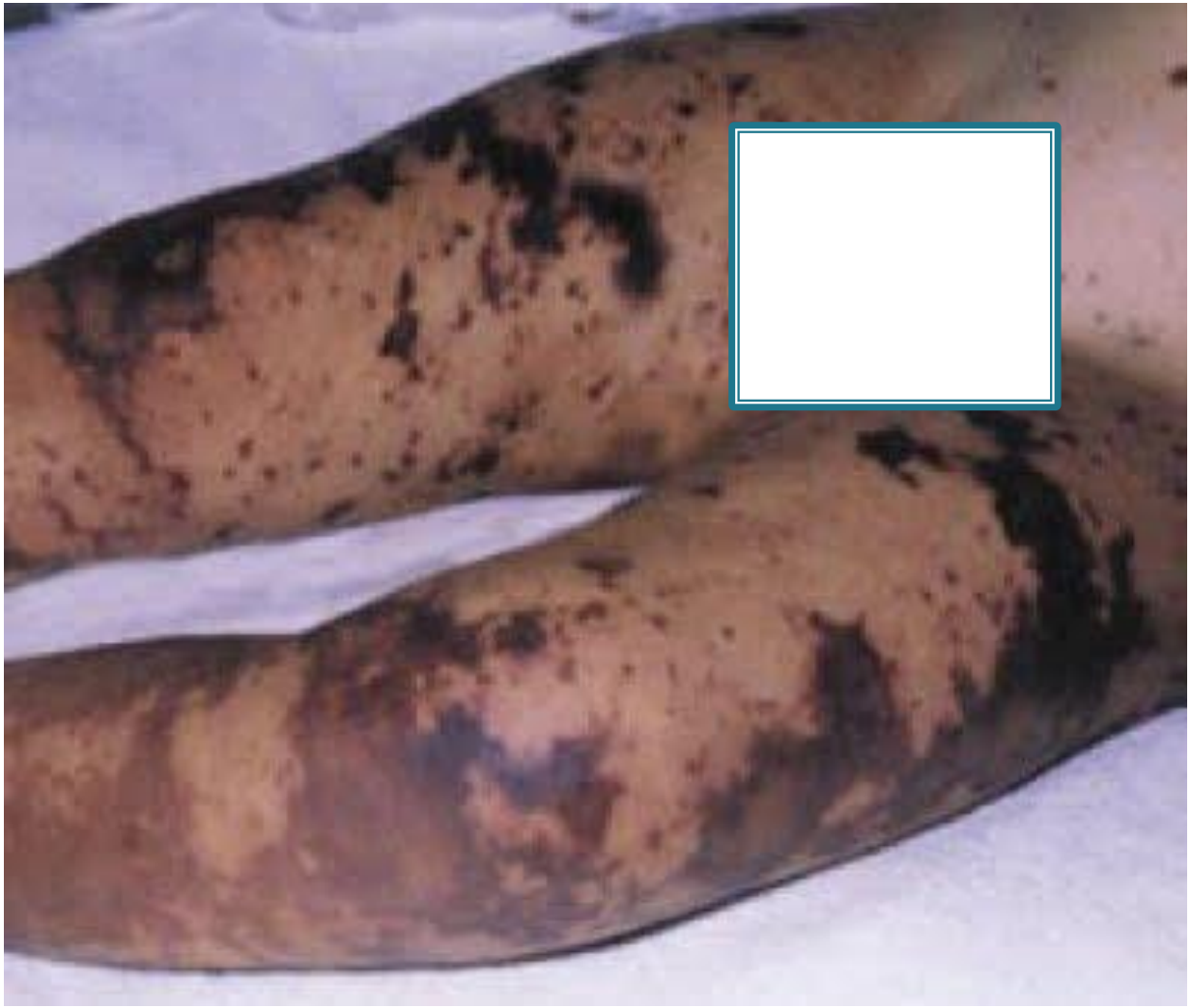
↓

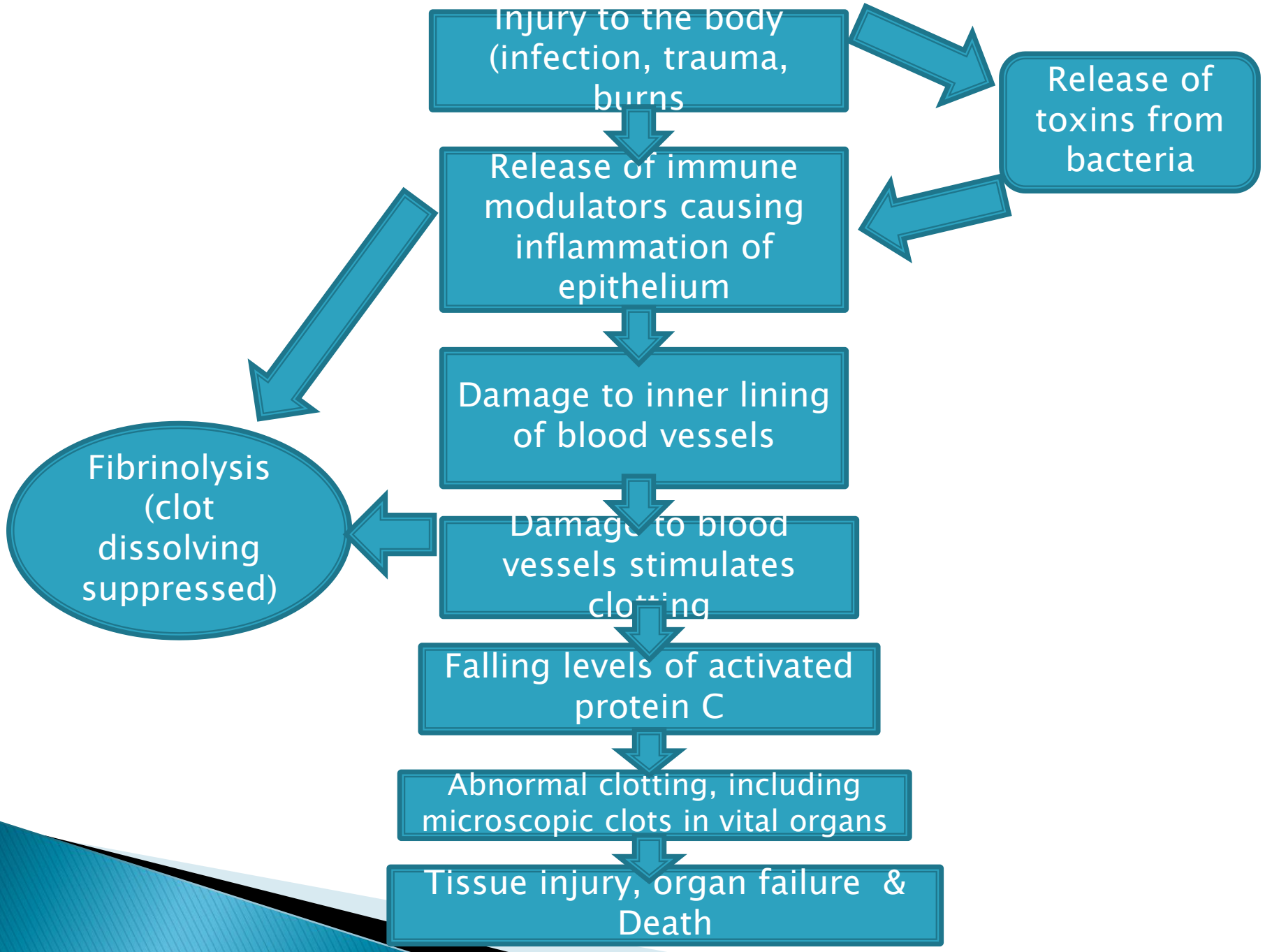
Activation of the coagulation system leads to consumption of endogenous anticoagulants (protein C and antithrombin)

↓

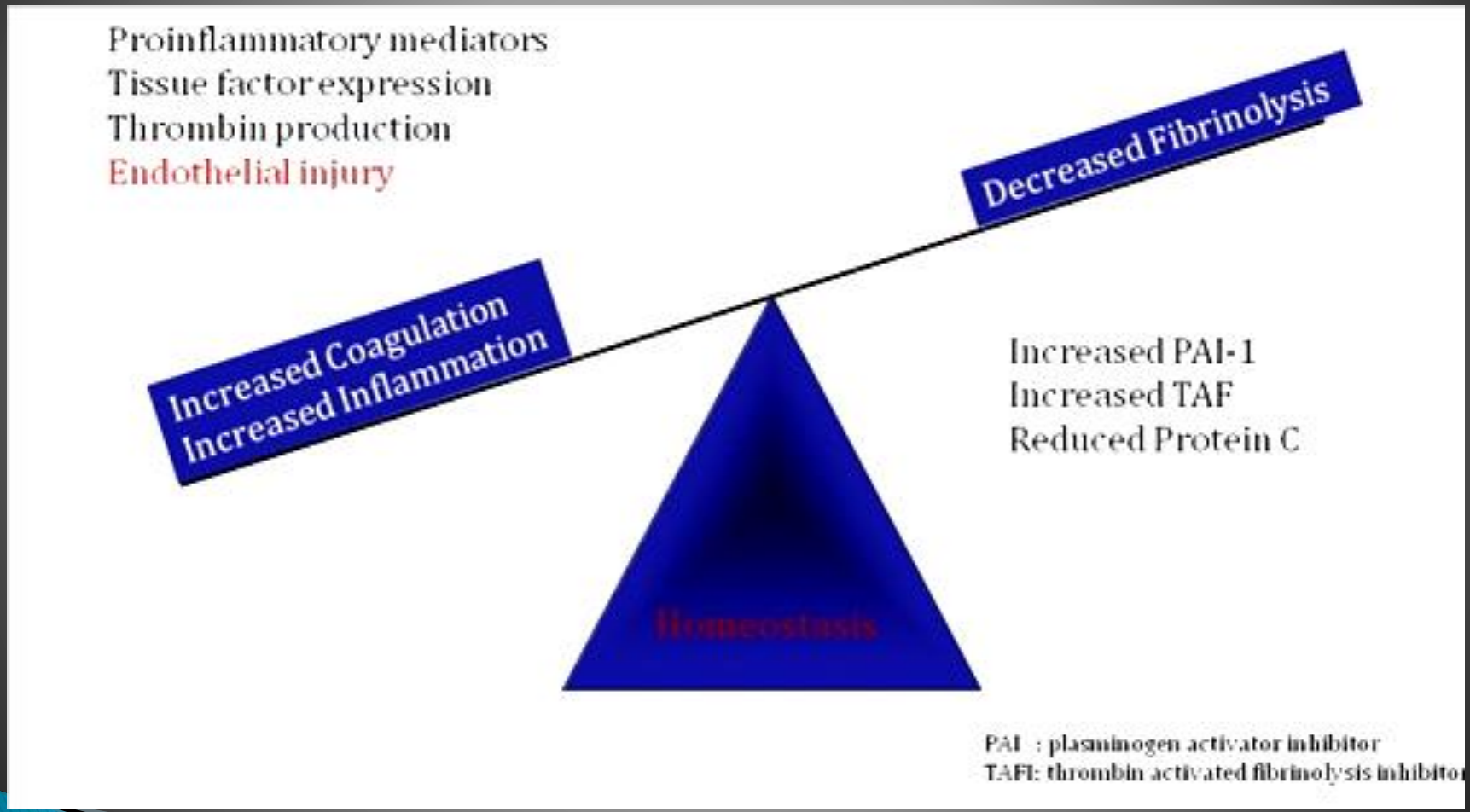
Anti-inflammatory mediators as well as inflammatory mediators have a role to play in sepsis


LPS and other
bacterial components
Endothelium
Neutrophils
Monocytes
Cytokines
Oxygen radicals
Lipid mediators
Increased
TF and PAI-1
Procoagulant effect
Complement
Chemotaxis
Lysosomal enzymes
Microvascular occlusion
Vascular instability
Coagulopathy
Fever
Vasodilation
Capillary leak
Sepsis and multiple organ failure




Injury to the body (infection, trauma, burns
Release of toxins from bacteria
Release of immune modulators causing inflammation of epithelium
Damage to inner lining of blood vessels
Fibrinolysis (clot dissolving suppressed)
Damage to blood vessels stimulates clotting
Falling levels of activated protein C
Abnormal clotting, including microscopic clots in vital organs
Tissue injury, organ failure & Death

The Loss of Homeostasis in Sepsis



The Disease Continuum

Infection ➡ SIRS ➡ Sepsis ➡ Severe Sepsis ➡ MOF ➡ Death

- In **1991** The American College of Chest Physicians and the Society of Critical Care Medicine (ACCP/SCCM) at a Consensus Conference developed clear clinical definitions for the **disease continuum**.
- These groups developed four terms for the progression of clinical symptoms: SIRS, ***sepsis, severe sepsis and septic shock.***
- It is important to realise that these stages do not necessarily imply an increasing **severity** of infection, but rather an increasingly **severe systemic response** to infection.

Stages of Sepsis

Systemic Inflammatory Response Syndrome (SIRS)

- Two or more of the following
- Temperature >380C or < 360C
- Heart rate > 90 beats/min
- Respiratory rate > 20 breaths/min or PaC02 > 32mmHg
- WBC > 12,000 cells/mm3, <4000 cells/mm3, or >10% immature forms
- Hyperglycaemia in the absence of Diabetes Mellitus

Sepsis

- SIRS plus a confirmed infection

Severe Sepsis

- Sepsis plus organ dysfunction, hypotension or hypoperfusion (included but not limited to lactic acidosis. Oliguria or acute mental status changes)

Septic Shock

- Hypotension (despite fluid resuscitation) plus hypoperfusion

Clinical Progression

Infection → SIRS → Sepsis → Severe Sepsis → MOF → Death

Severe sepsis: sepsis + one organ dysfunction

- Circulatory failure
- Respiratory failure
- Renal failure
- Haematological failure
- Hepatic failure
- "Brain failure"

Severe sepsis – organ failures

Circulatory *or*	Systolic BP <90mmHg *or* MAP <65mmHg reduction in SBP 40 mmHg from baseline
Respiratory	O_2 saturation <90% on air *or* oxygen *or* $P_aO_2:F_iO_2$ <40 kPa
Renal *or*	Urine output <0.5 ml/kg/hr for >2 hrs Creatinine >176 µmol/l acutely
Hepatic	Plasma lactate >4 mmol/l *or* Bilirubin >34 µmol/l
Haematological APTT>60s	Platelets <100x10^9 or INR >1.5 or
Mental	Acute alteration in mental status

Septic Shock

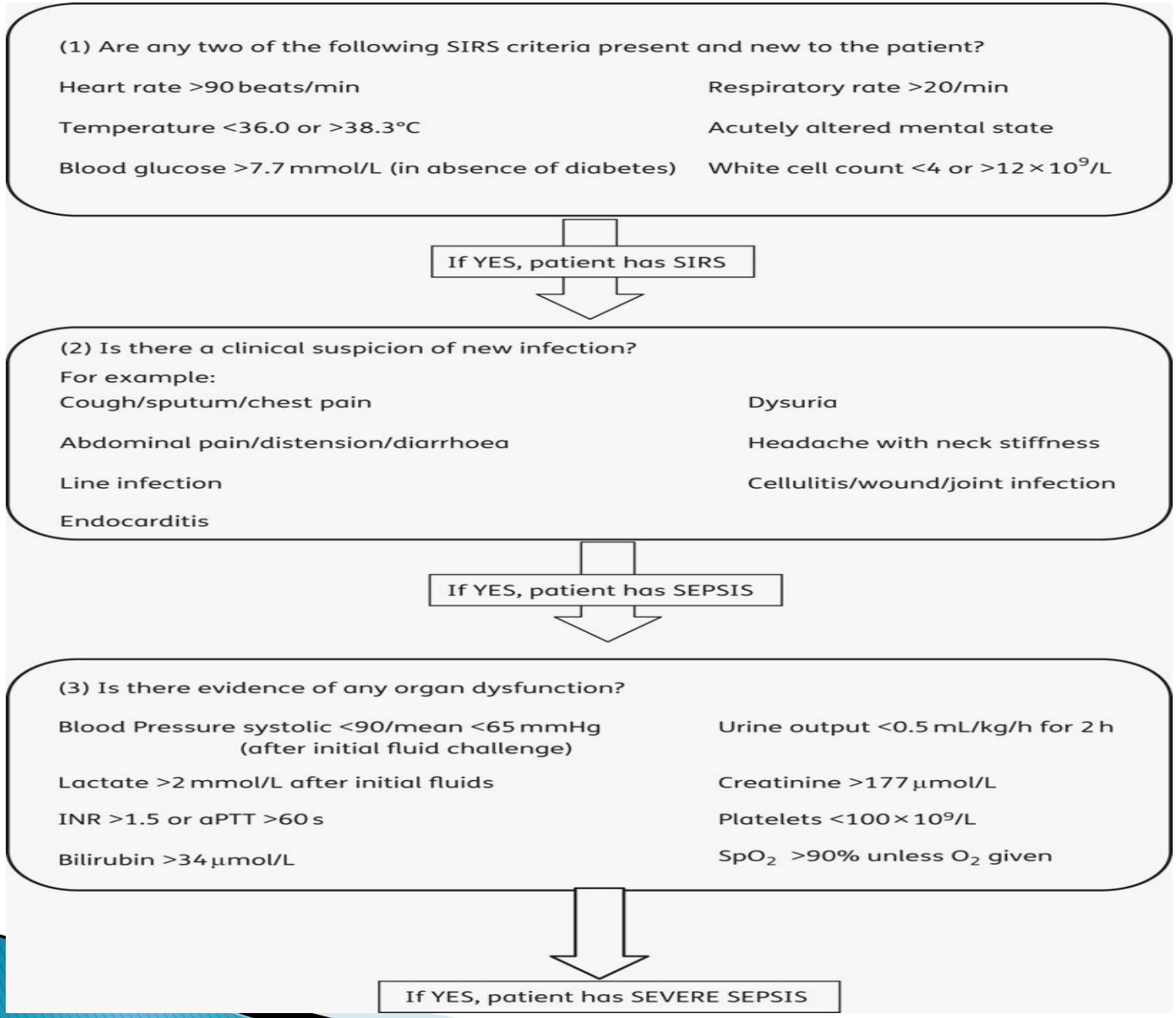
Initially is suggested by evidence of organ hypoperfusion:

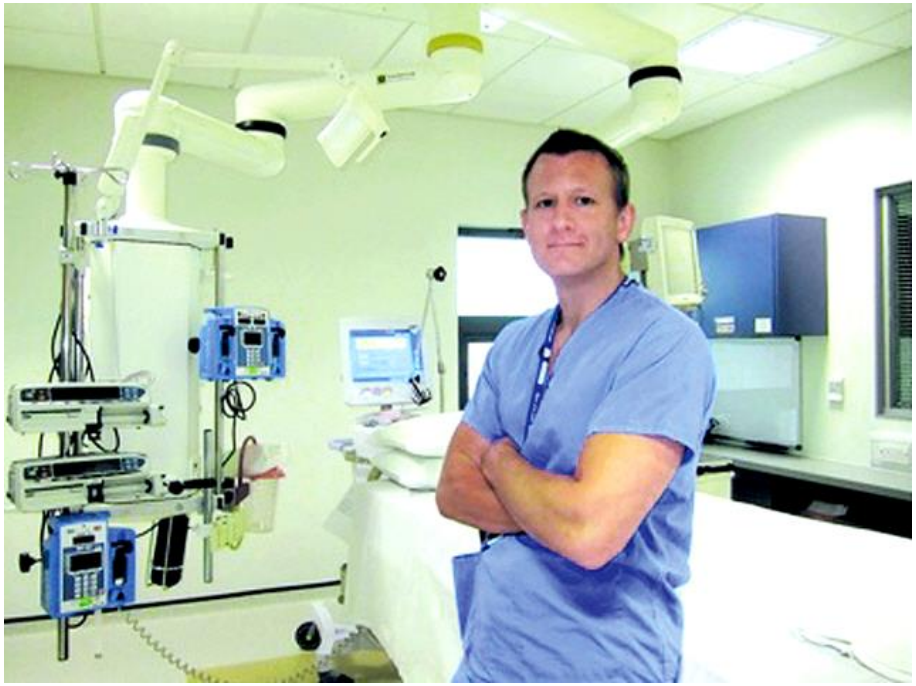
haemodynamic instability
mottled skin
decreased urine output
altered level of consciousness
lactic and metabolic acidosis

Later - circulatory failure leading to multi-organ failure:

reduced SVR, leaking capillaries
slightly increased and than decreased cardiac output
Deranged clotting with low platelet count.
ARF, liver failure, hypoglycaemia

Diagnostic criteria for sepsis, SIRS





‘Awareness is the number one cure for sepsis. Raising recognition of the disease and increasing the number of patients treated in the “Golden Hour” is the single biggest attempt we can make to save lives.’

Dr. Ron Daniels, CEO of the Global Sepsis Alliance

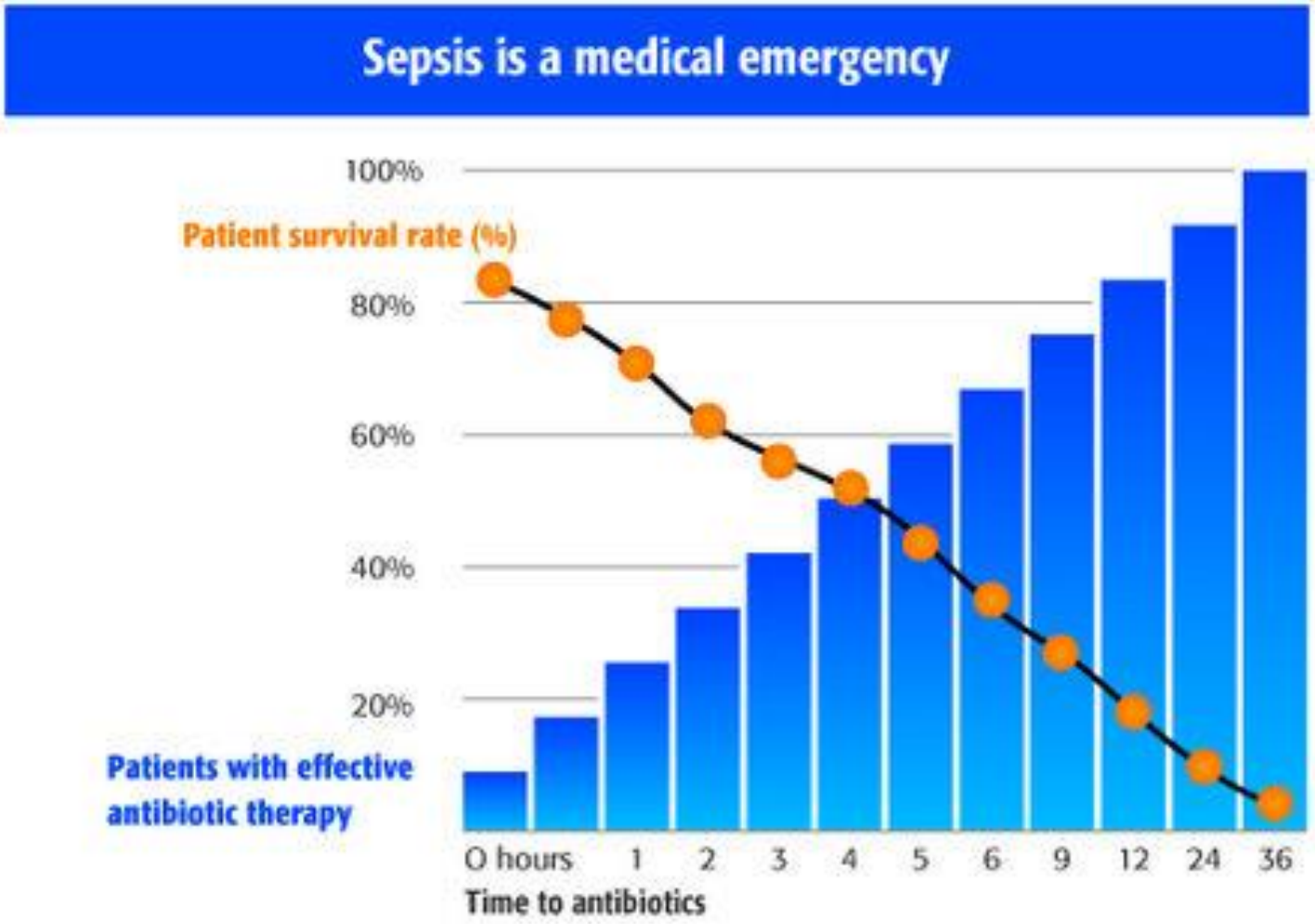
Early Goal Directed Therapy in Sepsis

- Early goal directed therapy (EGDT) is a clinical strategy which results in a more successful resuscitation, restoration of perfusion, and less tissue hypoxia.

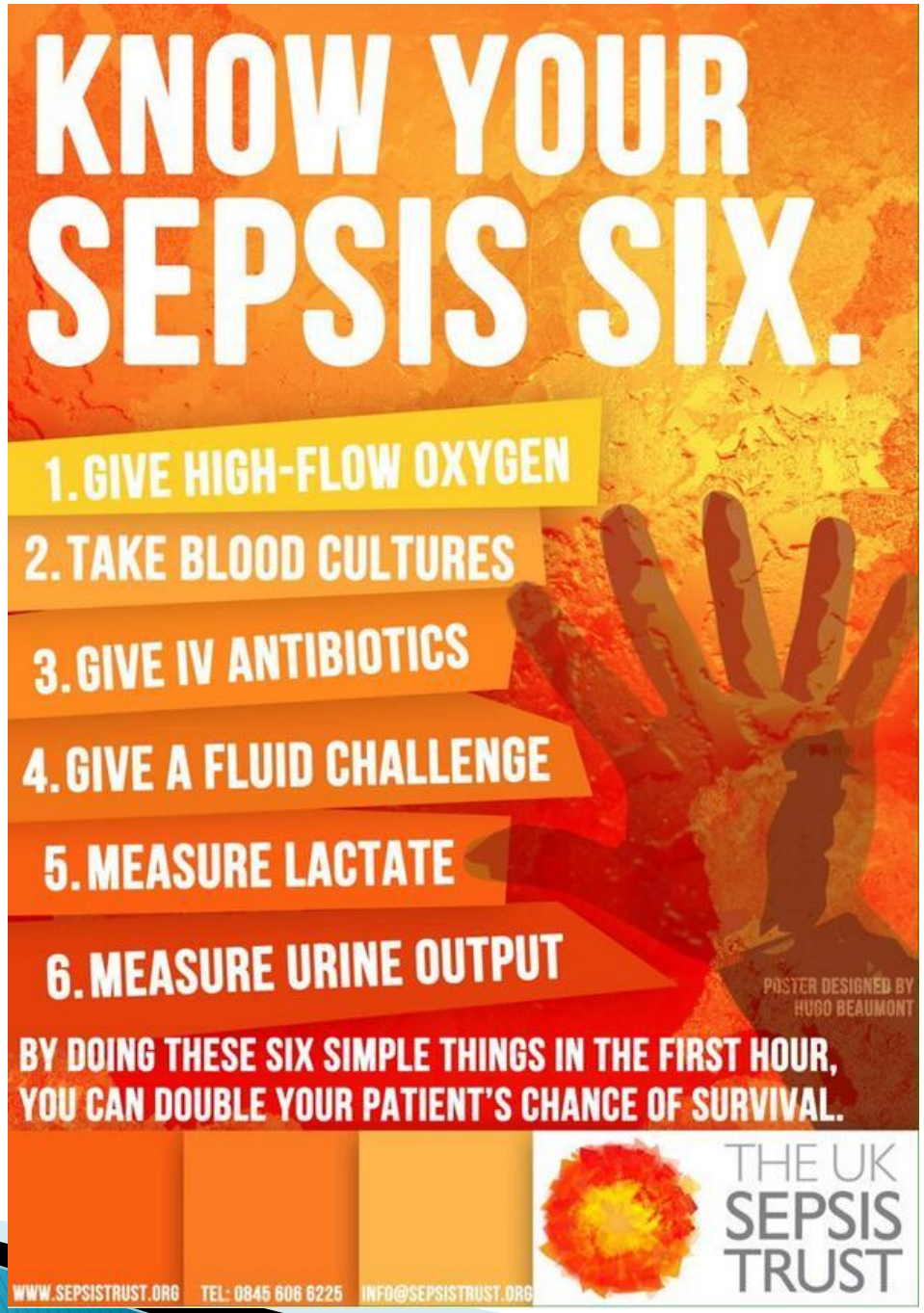
- It is a step by step process of giving oxygen, fluids, vasoactive agents, inotropic agents and blood products according to clinical signs, measurements and observations

EGDT - What are the goals?

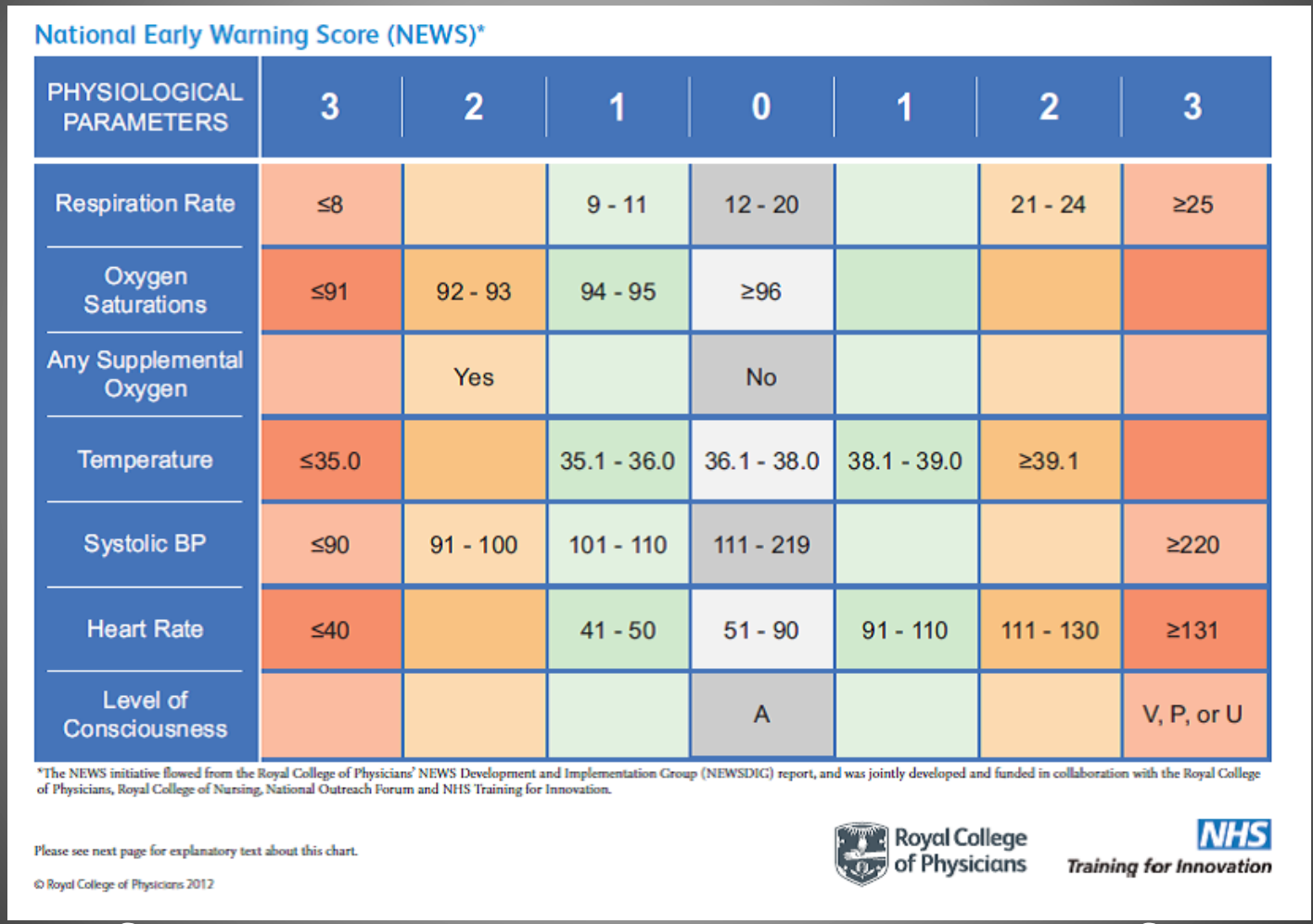
- To ensure the presumptive diagnosis is made within 2 hours of admission
- Fluid resuscitation 20 mls/kg within the recommended target of 6 hours from presentation
- Early CVP monitoring and central venous oxygen saturation measurement ($S_{cv}O_2$)
- Vasopressors given earlier after initial fluid resuscitation
- Cultures drawn before antibiotics administered
- Antibiotics within 3 hours of a presumptive diagnosis of a severe sepsis in ED, or 1 hour if patient already in hospital


Sepsis is a medical emergency
100%
Patient survival rate (%)
80%
60%
40%
20%
Patients with effective antibiotic therapy
O hours
1
2
3
4
5
6
9
12
24
36
Time to antibiotics
Made for World Sepsis Day by lingruen-gmbh.com


SEPSIS IS A RARE BUT SERIOUS CONDITION THAT CAN LOOK JUST LIKE FLU, GASTROENTERITIS OR A CHEST INFECTION.
SEEK MEDICAL HELP URGENTLY IF YOU DEVELOP ANY ONE OF THE FOLLOWING:
SLURRED SPEECH
EXTREME SHIVERING OR MUSCLE PAIN
PASSING NO URINE (IN A DAY)
SEVERE BREATHLESSNESS
"I FEEL LIKE I MIGHT DIE"
SKIN MOTTLED OR DISCOLOURED
THE UK SEPSIS TRUST
EMAIL: INFO@SEPSISTRUST.ORG FOR MORE INFORMATION


KNOW YOUR
SEPSIS SIX.
1. GIVE HIGH-FLOW OXYGEN
2. TAKE BLOOD CULTURES
3. GIVE IV ANTIBIOTICS
4. GIVE A FLUID CHALLENGE
5. MEASURE LACTATE
6. MEASURE URINE OUTPUT
POSTER DESIGNED BY
HUGO BEAUMONT
BY DOING THESE SIX SIMPLE THINGS IN THE FIRST HOUR,
YOU CAN DOUBLE YOUR PATIENT'S CHANCE OF SURVIVAL.
WWW.SEPSISTRUST.ORG
TEL: 0845 606 6225
INFO@SEPSISTRUST.ORG
THE UK
SEPSIS
TRUST

National Early Warning Score (NEWS)



National Early Warning Score (NEWS)*

PHYSIOLOGICAL PARAMETERS	3	2	1	0	1	2	3
Respiration Rate	≤8		9 - 11	12 - 20		21 - 24	≥25
Oxygen Saturations	≤91	92 - 93	94 - 95	≥96			
Any Supplemental Oxygen		Yes		No			
Temperature	≤35.0		35.1 - 36.0	36.1 - 38.0	38.1 - 39.0	≥39.1	
Systolic BP	≤90	91 - 100	101 - 110	111 - 219			≥220
Heart Rate	≤40		41 - 50	51 - 90	91 - 110	111 - 130	≥131
Level of Consciousness				A			V, P, or U

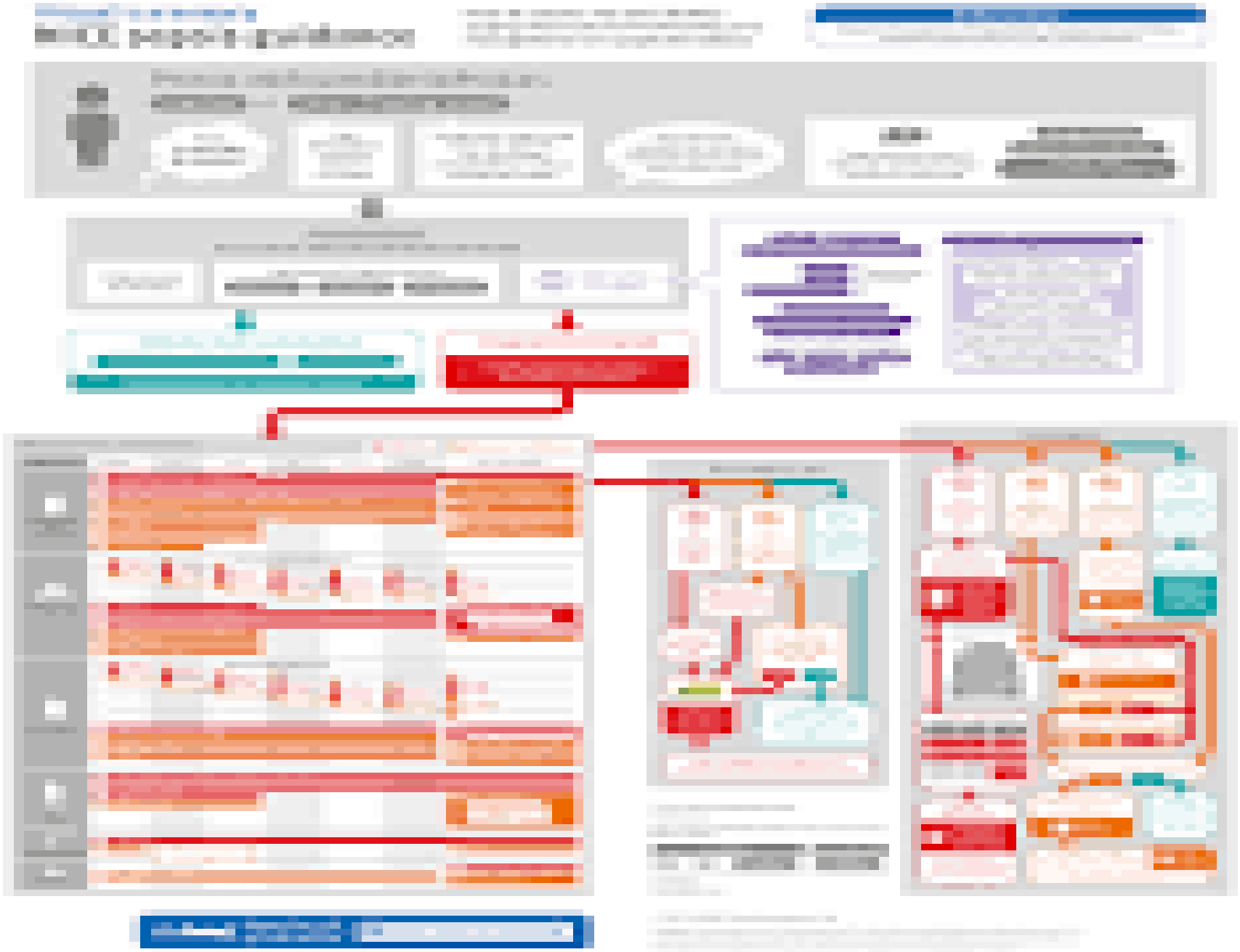
*The NEWS initiative flowed from the Royal College of Physicians' NEWS Development and Implementation Group (NEWSDIG) report, and was jointly developed and funded in collaboration with the Royal College of Physicians, Royal College of Nursing, National Outreach Forum and NHS Training for Innovation.

Please see next page for explanatory text about this chart.

Royal College of Physicians

NHS Training for Innovation

A score of *3 in any* ***one*** *category* or a score of *4 overall* should prompt a search for infection



The Health Professionals role

- Increasing awareness amongst patients and the public
- Recognising sepsis in it's early stages through noting abnormalities in clinical observations is vital
- Act fast – oxygen, blood cultures, antibiotics, fluid & fluid balance.

The Impact of Sepsis!

http://www.bbc.co.uk/news/health-35407340

Conclusion

- Sepsis is a systemic disease, probably triggered by over activation of the immune system
- Multiple pathways combine synergistically to produce the clinical picture
- Organ dysfunction secondary to systemic inflammation characterises sepsis

Sepsis – Tipping the balance!

Thank your for listening any questions

Useful Sepsis websites

- http://survivesepsis.org/what-is-sepsis/
- http://globalsepsisalliance.com/
- http://www.survivingsepsis.org/Pages/default.aspx

- Kleinpell, R., Aitken, L., Schorr, C. (2013) Implications of the New International Sepsis Guidelines for Nursing Care. American Journal of Critical Care, 22 (3) 212-222

http://wfccn.org/wp-content/uploads/Klienpell5_13pgs_212_222.pdf