SEPSIS

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UHCW

Case 1

A young woman arrives in the medical admissions unit with several days' history of diarrhoea.

She also has:

- a macular rash
- a temperature of 38.9 C
- systolic BP - 70 mmHg
- pulse 130 bpm.
- elevated urea and creatinine
- low platelets.

What is your immediate management?

Relative incidence of sepsis:

USA

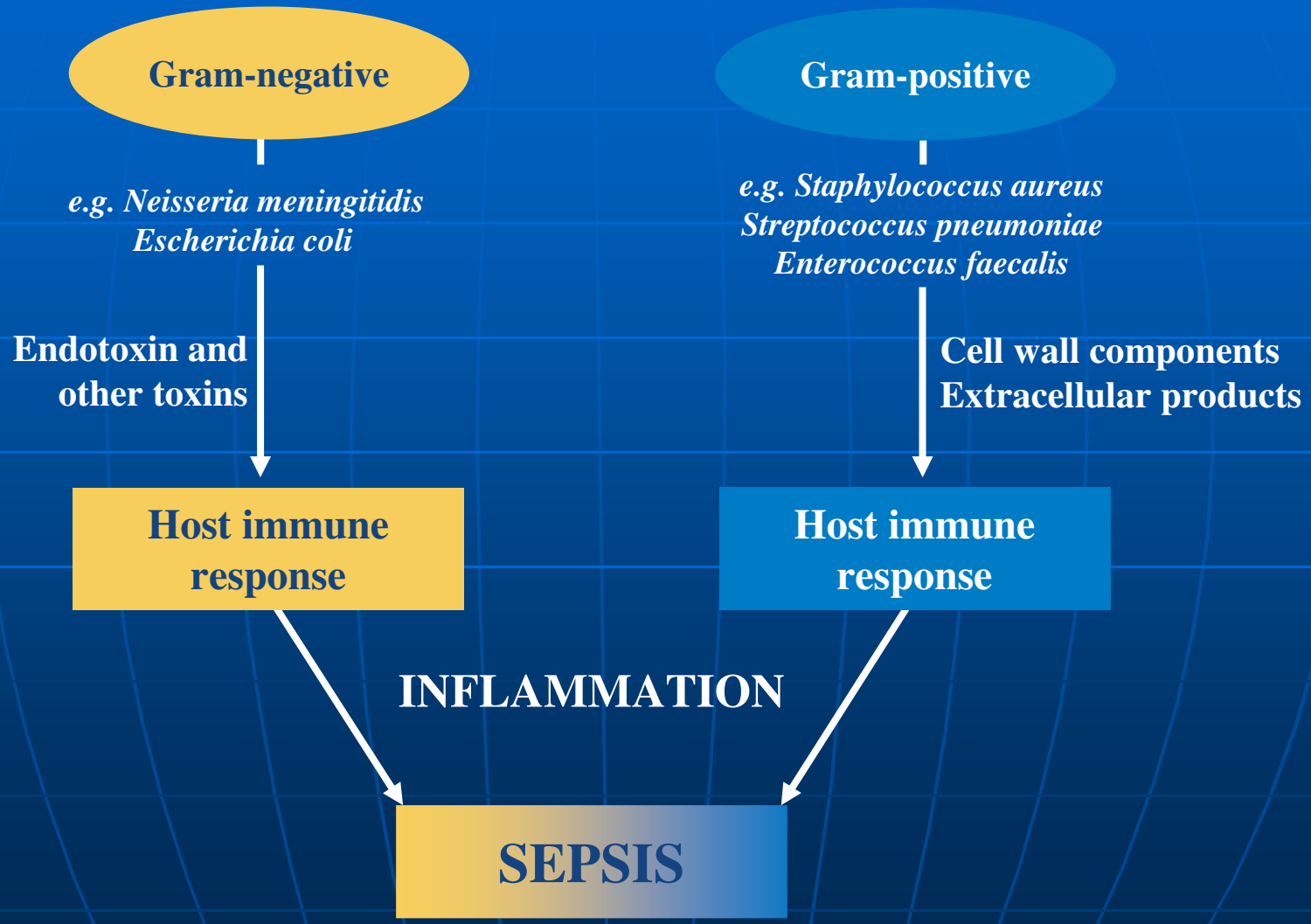
	Per 100,000 population
•AIDS	17
•Colon cancer	50
•Breast cancer	110
•Congestive heart failure	130
•Sepsis	300

UK

- 33% of all ICU admissions are due to severe sepsis.

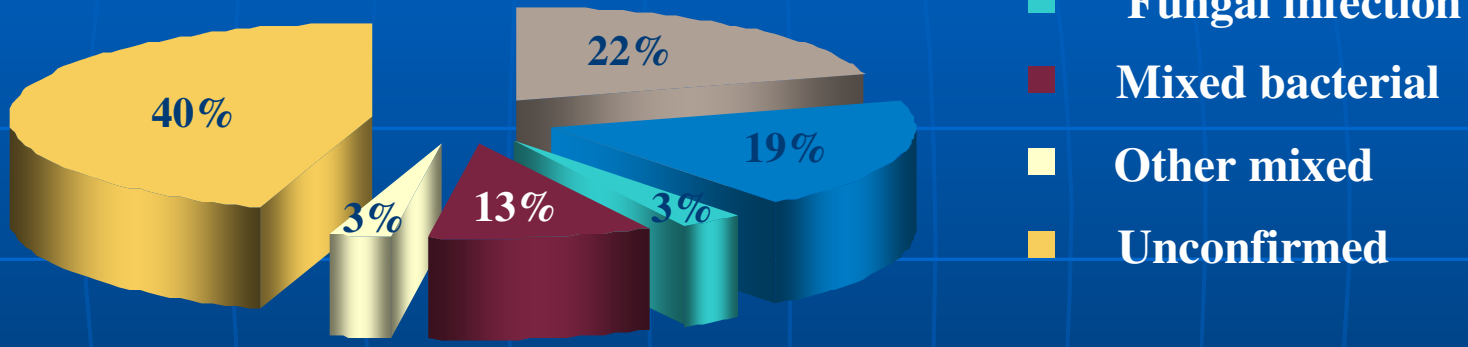
Bacterial pathogens in sepsis

A final common pathway?



Pathogens involved in sepsis

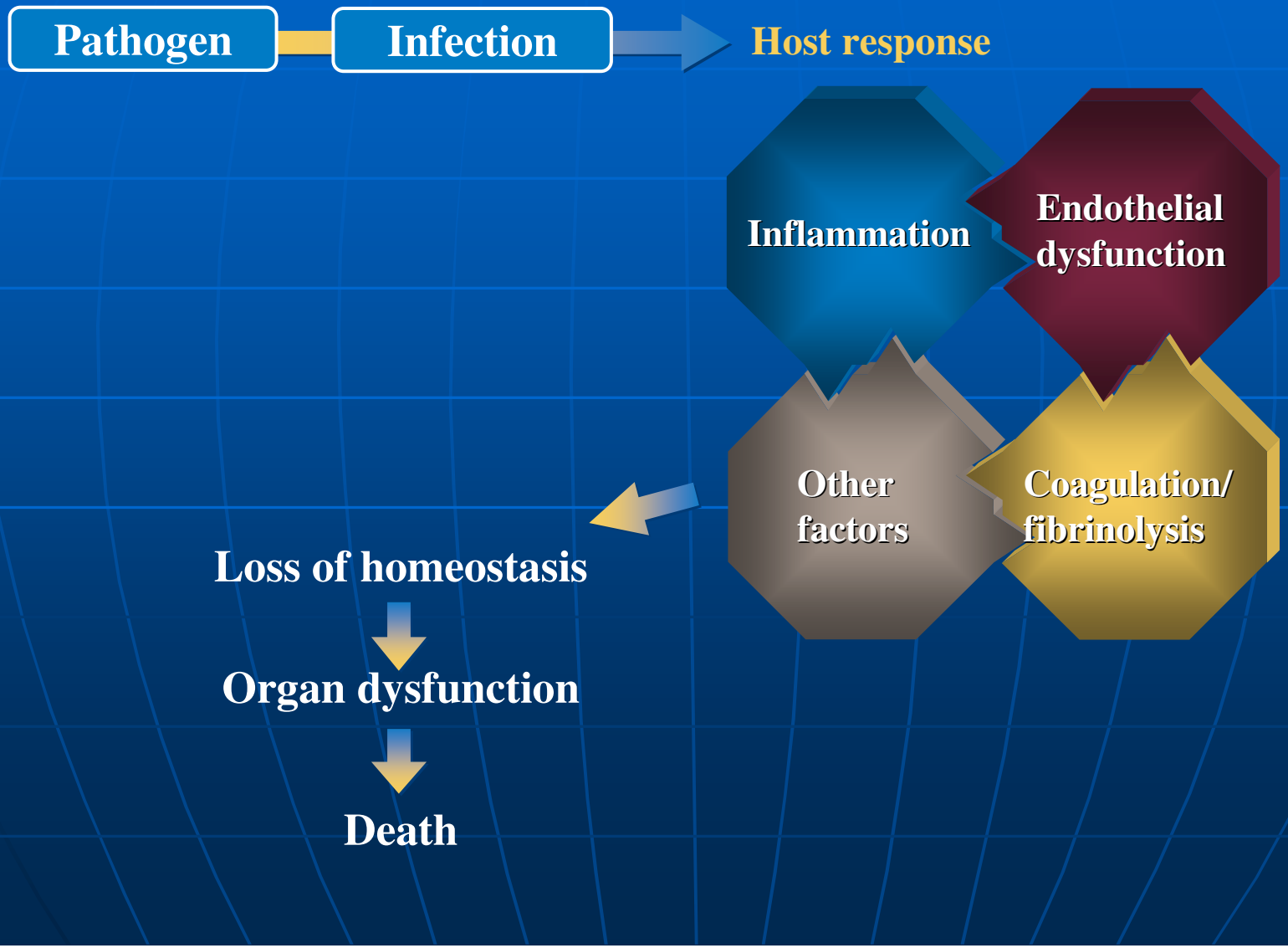
An overview



- Only 60% of severe sepsis/septic shock cases are associated with confirmed infection
- The most common infection sites are: the lung, abdomen or urinary tract.

Pathogenesis of sepsis

An overview

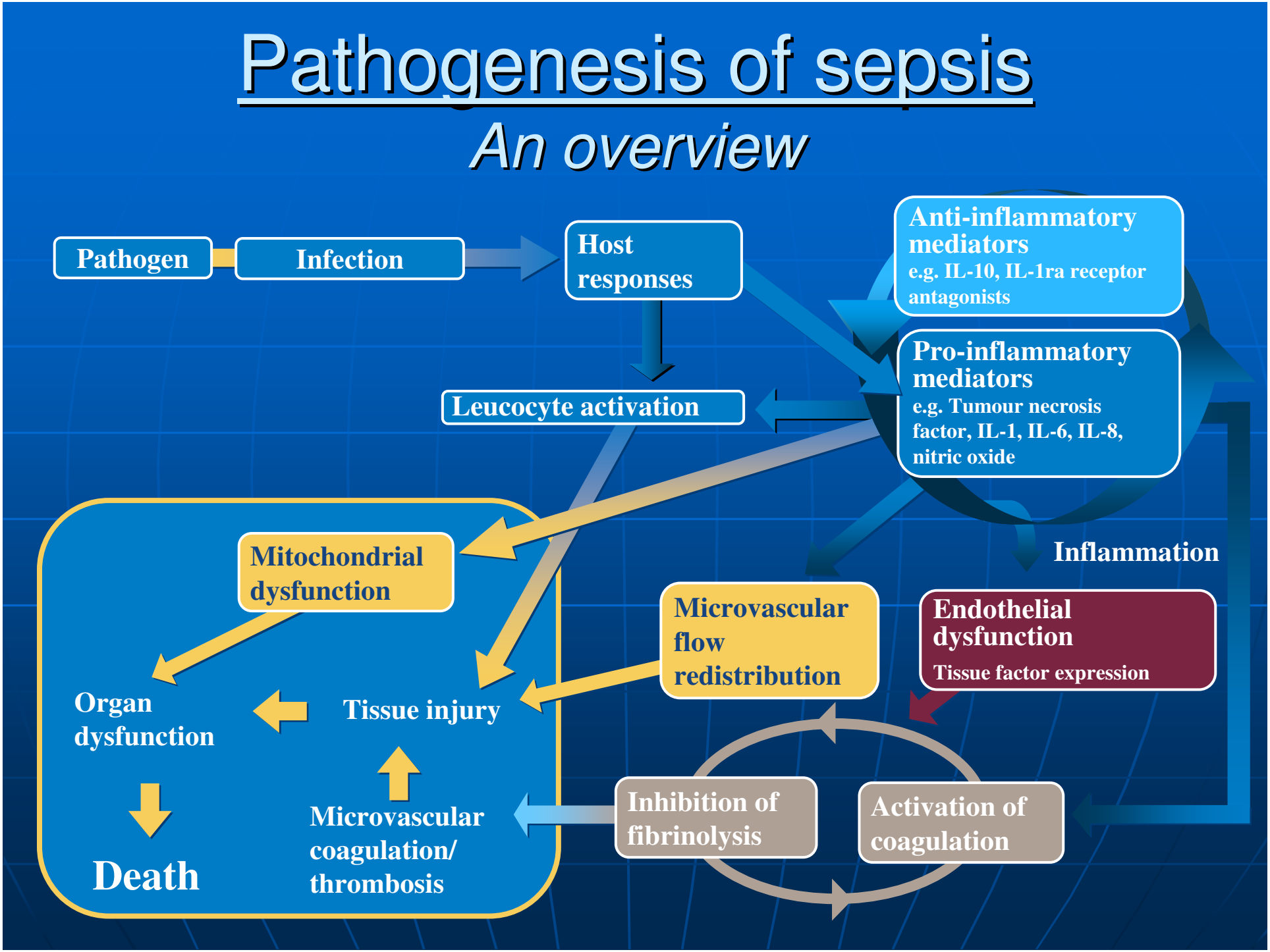


Pathogenesis of sepsis

- 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.

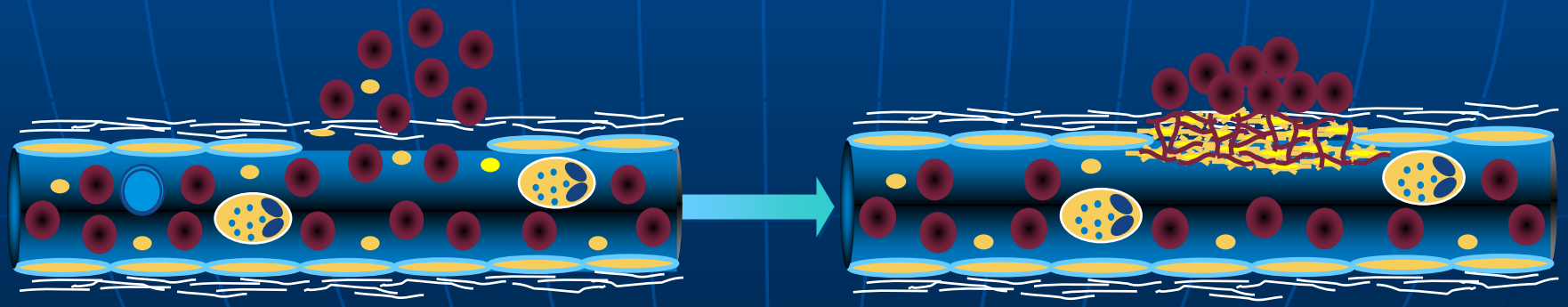
Pathogenesis of sepsis

An overview



The role of the endothelium

- Release of mediators of vasodilatation and/or vasoconstriction
- 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

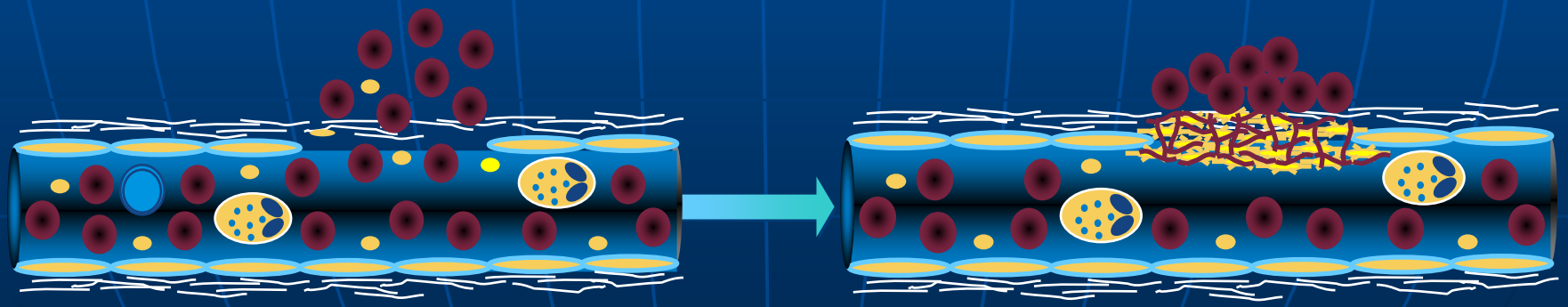


Tissue injury

Formation of fibrin clot

The role of the endothelium

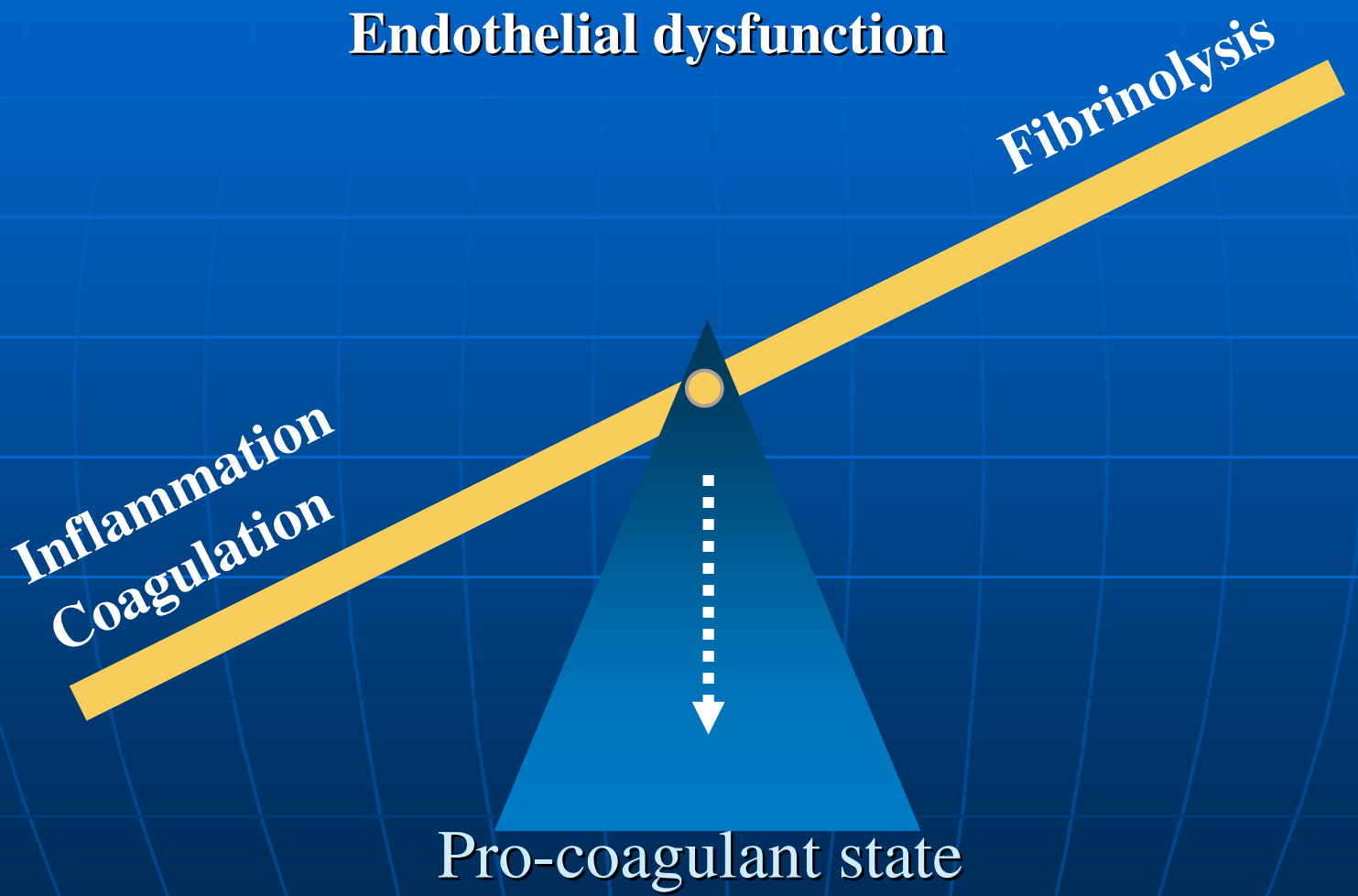
- In sepsis, the regulatory function of the endothelium fails, leading to:
  - Excessive vasodilation and releative hypovolaemia
  - Leaking capillaries and generalised tissue damage
  - Tissue factor (TF) release initiates **procoagulant state**
  - Micro-thrombus formation compromising blood supply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



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:

- platelets,
- clotting factors
- fibrinogen

As a result, bleeding risk increases

Disseminated Intravascular Coagulation (DIC)

Testing for DIC:

- APTT and INR are raised.
- platelets count low.
- fibrinogen level low.

After the increased coagulation and fibrin formation, *fibrinolysis* results in:

- raised FDP (fibrin degradation products)
- raised D-Dimer

Action of Activated Protein C

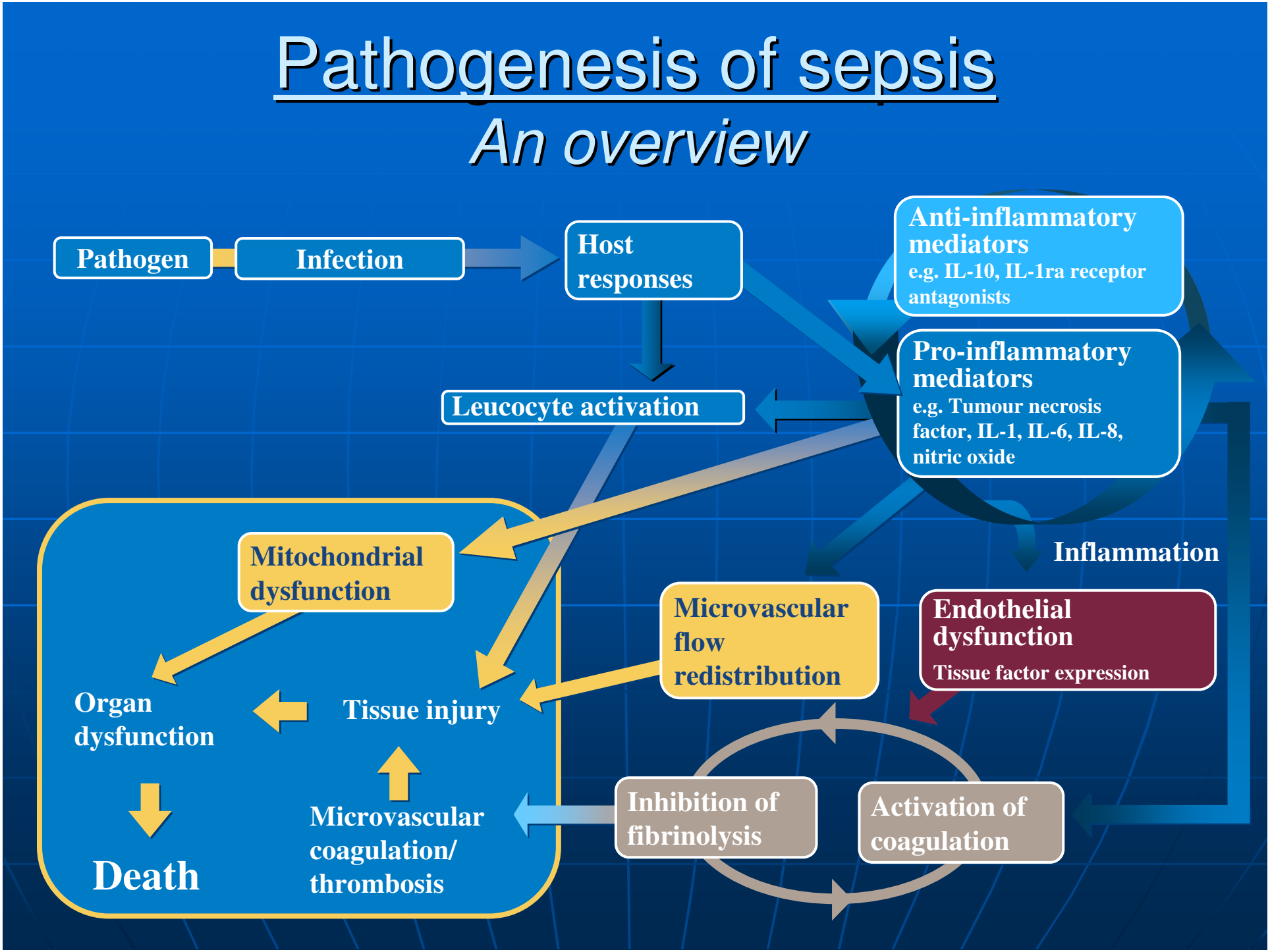
Activated protein C:

- Inactivates cofactors Va and VIIIa impeding the clotting process
- Enhancing fibrinolysis by neutralising PAI-1* and accelerating clot breakdown
- Direct anti-inflammatory effect, decreasing cytokine production
- Inhibiting leukocyte attachment to endothelium

*__P__lasminogen __A__ctivator __I__nhibitor-1

Pathogenesis of sepsis

An overview



Mitochondrial dysfunction in sepsis

- Mitochondrial inhibition is likely to have a role in organ dysfunction
- Organs may sometimes fail despite adequate perfusion with oxygenated blood
- Oxygen utilization at a cellular level may be impaired in sepsis – 'dysoxia'
- Mitochondrial function impaired by:
  - cytokines
  - nitric oxide
  - other reactive species

SSC -The disease continuum

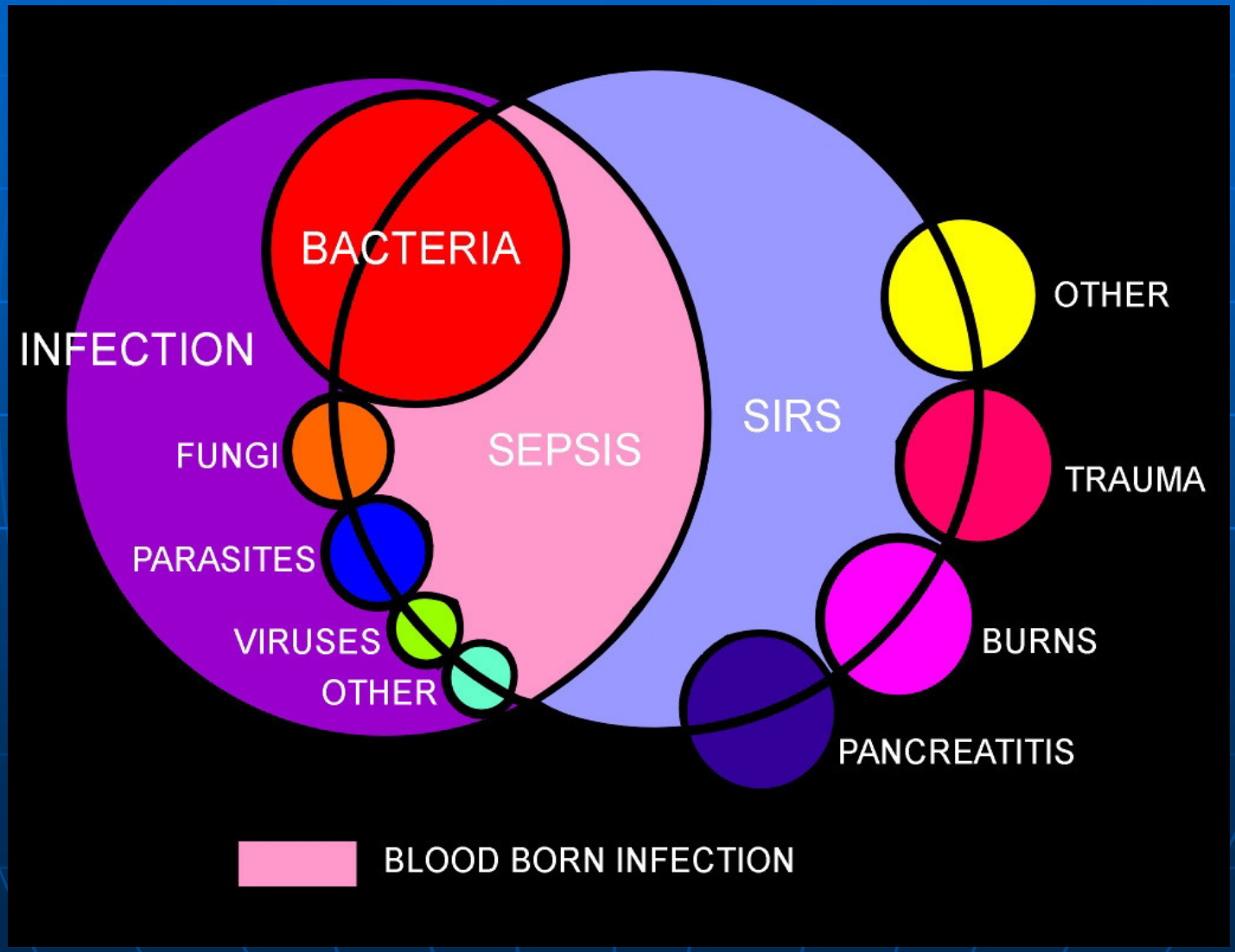
- In **1991** The American College of Chest Physicians and the Society of Critical Care Medicine (ACCP/SCCM) at a Consensus Conference developed clear clinical definitions for the **disease continuum**.
- These groups developed three terms for the progression of clinical symptoms: SIRS, ***sepsis, severe 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.

Systemic inflammatory response syndrome (SIRS)

Infection → **SIRS** → **Sepsis** → **Severe sepsis** → **Death**

- SIRS (systemic inflammatory response syndrome) represents the clinical presentation of the widespread inflammation that results from a variety of insults and can also be caused by **trauma, burns, pancreatitis and other insults…**
- The conference defined an initial **SIRS,** that requires evaluation of:
  - temperature,
  - heart rate,
  - respiratory rate and
  - white blood cell count.

Systemic inflammatory response syndrome



Systemic Inflammatory Response Syndrome

Diagnosis comprises ***2 or more*** of the following:

- Tachycardia — >90 bpm
- Core temperature — <36°C *or* >38°C
- Tachypnoea — >20 bpm *or* P_aCO_2 <4.2 kPa
- WCC — >12,000 *or* <4,000 *or* >10% immature neutrophils
- Hyperglycaemia — in the absence of Diabetes Mellitus

- NB: The term *'Signs and Symptoms of Infection' (SSI)* is appearing in the context of sepsis, but means essentially the same thing

Clinical Progression

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

Sepsis :

1) - two or more of SIRS, plus

2) - documented or suspected infection

(presence of commonly recognised signs of infection without an identifiable pathogen being isolated)

Possible sites of a new infection

- Pneumonia or empyema
- Urinary tract infection
- Acute abdominal infection
- Meningitis
- Skin/soft tissue inflammation
- Born/joint infection
- Catheter or device infection
- Endocarditis
- Wound infection*

*May also be known as *Surgical Site Infection (SSI)* – confusingly!

Modified Early Warning Score (MEWS)

Score	3	2	1	0	1	2	3
Central nervous system		Confused or agitated		**A**lert	Respond to **V**oice	Respond to **P**ain	**U**: No response
Respiratory rate (breaths/min)	‹8			8-20	21-30		›30
Heart rate (beats/min)	‹40		40-50	51-100	101-110	111-130	›130
Systolic blood pressure (mm Hg)	‹70	71-80	81-100	101-180	181-200	201-220	›220
Temperature (°C)	‹34	34.0-35.0		35.1-37.5	37.6-38.5	38.6-40.0	›40

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

What is VitalPAC?

VitalPAC® CLINICAL

- Patients
- Clinical trends
  - Summary
  - TPR chart
  - EWS chart
  - Specialty chart
  - Custom chart
- Pathology
- Radiology
- Past admissions
- Listening service
- Patient details
- PatientFlow

BLOOD PRESSURE =

TEMP = ●

PULSE = X
(i = irregular)

PULSE APEX = +

TIME	44 01	47 06	01 10	43 13	11 14	15 18	16 19	43 20	27 01	07 03	51 03	59 04	07 06	00 10	35 10	49 11	45 12	43 13	42 14
Respiratory Rate	16	17	18	18	16	17	18	20	20	24	22	17	20	30	36	30	25	32	32
AVPU	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A
SaO2 (Oxygen Saturation)	95	94	94	96	97	95	95	96	96	93	93	93	97	90	98	98	94	96	97
FiO2 (Ltrs/Min or %)	Air	2L	Air	2L	2L	2L	2L	2L	2L	2L	2L	2L	2L	2L	15L	15L	60%	40%	60%
Pain Score (0=no pain-3=severe)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Nausea / Vomiting	N N	N N	N N	N N	N N	Y N	Y N	N N	N Y	N Y	N Y	N N	N N	N N	N N	N N	Y N	Y Y	N N
Bowels opened																			
Weight (kg)			66.9																
EARLY WARNING SCORE (EWS) AVPU	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
EARLY WARNING SCORE (EWS) RESPS	0	0	0	0	0	0	0	0	0	1	1	0	0	2	3	2	1	3	3
EARLY WARNING SCORE (EWS) Pulse	0	0	0	2	1	2	2	1	2	2	2	2	2	3	2	2	3	2	2
EARLY WARNING SCORE (EWS) BP Systolic	1	1	1	1	1	1	1	0	0	1	1	1	0	1	0	1	1	1	1
EARLY WARNING SCORE (EWS) Temperature	0	0	0	0	0	1	1	0	2	2	2	0	0	2	2	2	2	0	0
EARLY WARNING SCORE (EWS) TOTAL EWS	1	1	1	3	2	4	4	1	4	6	6	3	2	8	7	7	7	6	6
LOW SCORE (GCS) Best Eye Open																			
LOW SCORE (GCS) Best Verbal Response																			

Target weight: not set

Height: 1.78m.
(14/06/2009 10:01)
Weight: 66.9kg.
(14/06/2009 10:01)
BMI: 21.1.

Key

OW = Off ward
Uc = Unmeas. condition
Ue = Unmeas. equipment
U = Other unmeasurable
R = Refused

AVPU Key

A = Alert
V = Voice
P = Pain
U = Unresponsive

Clinical Progression

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

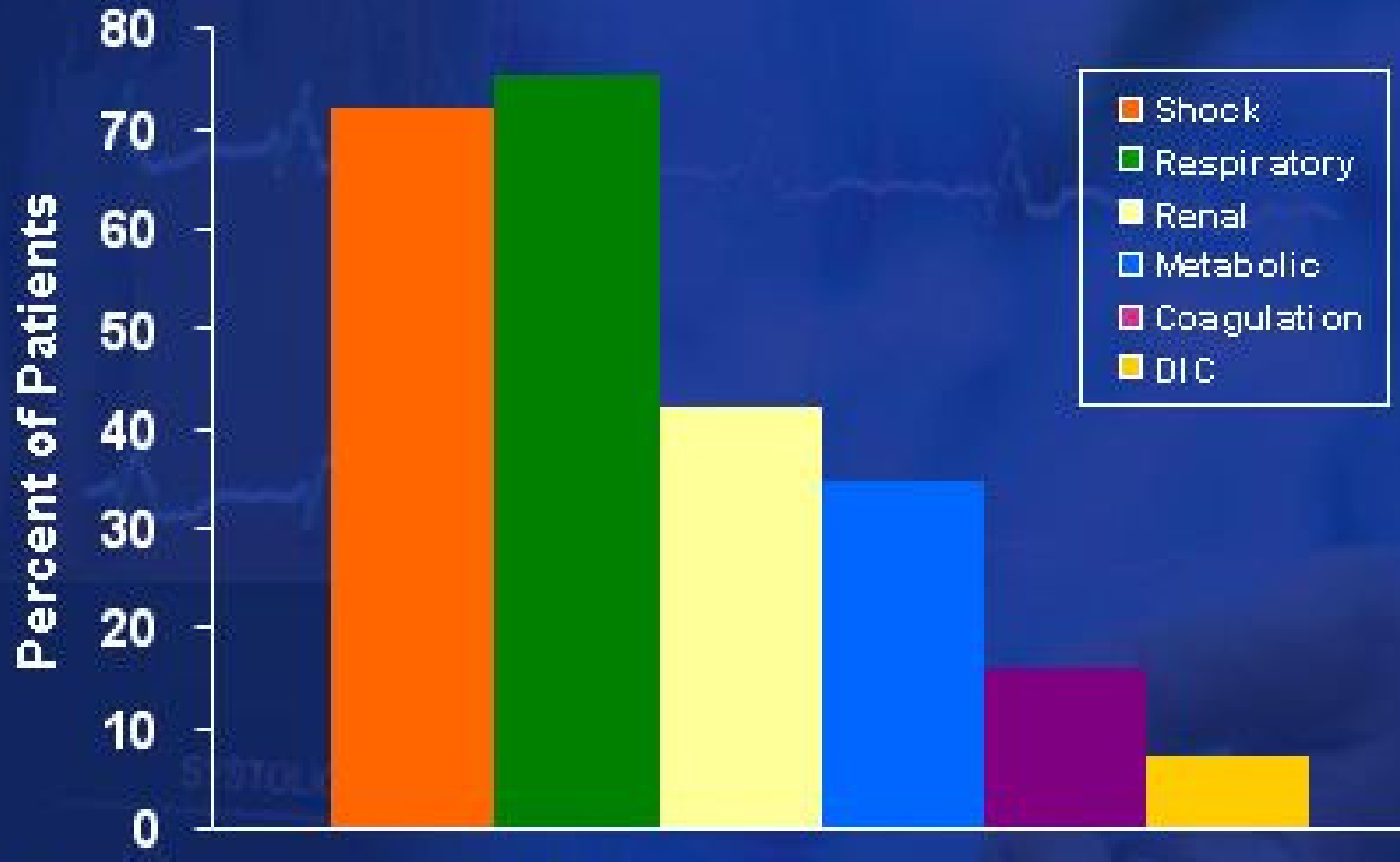
Severe sepsis: sepsis + one organ dysfunction

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

Severe sepsis – organ failures

- Circulatory — Systolic BP <90mmHg *or* MAP <65mmHg *or* 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 — Urine output <0.5 ml/kg/hr for >2 hrs *or* Creatinine >176 µmol/l acutely
- Haematological — Platelets <$100x10^9$ or INR >1.5 or APTT >60s
- Hepatic — Plasma lactate >4 mmol/l *or* Bilirubin >34 µmol/l
- Mental — Acute alteration in mental status

Organ Dysfunctions at Time of Severe Sepsis Recognition



Bernard G et al. *N Engl J Med.* 2001;344:699-709.

Clinical Progression

Infection ➡ SIRS ➡ Sepsis ➡ Severe Sepsis ➡ MOF ➡ Death
Septic Shock

Septic shock: Acute circulatory failure unexplained by other causes.

Circulatory failure is defined as:

persistent arterial hypotension (SBP < 90 mmHg, MAP< 65, or a reduction in SBP 40 mmHg from baseline) *despite adequate volume resuscitation*.

Septic Shock

Initially is suggested by evidence of end 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
- coagulopathy with thrombocytopenia.
- ARDS, ARF, liver failure, hypoglycaemia,

Although most patients in shock will be hypotensive, some patients will have preserved systolic pressure early in shock as a result of excessive catecholamine release.

Case 2

- A 50-year-old lady was seen in ED and treated for urinary tract infection on the basis of symptoms and a positive urine dipstick. She was discharged home the same day.
- The next day she returned having collapsed. On arrival her observations were as follows:
  - alert
  - pulse 150bpm
  - temperature 38°C
  - BP 80/50 mmHg,
  - RR 20 per minute
  - S_a0_2 94% on air,
  - urine output normal.

What is your diagnosis, management and what other immediate tests do you perform?

Goal directed therapy in Sepsis

Surviving Sepsis Campaign Guidelines
2004 – 2007

Guidelines on Intravenous Fluid Therapy for Adult Surgical Patients
GIFTASUP 2008

Trial of Early Goal-Directed Therapy

- *263 pts* presented to ED with sepsis
- Randomized into two groups:

  I - Early Goal Directed Therapy Group (EGDT)
  II - Control Group (similar, excluding $S_{cv}O_2$ data)

- Initial resuscitation was performed in ED over the first 6 hour period then transferred to in-patient bed or ICU
- Evaluated for a further 72 hours

Rivers et al., New Eng J Med 2001, 345

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

EGTD: What are the end points?

- Aims to avoid or reverse impaired perfusion and oxygen delivery (DO_2) and prevent vital organ failure:
  - Indicators of adequate perfusion:
    - CVP 8-12 mmHg
    - MAP >65 mmHg
    - UO >0.5 ml/kg/hr
  - Indicators of DO_2 insufficiency:
    - $S_{cv}O_2$ <70 %
    - Lactate >4.0 mmol/L

Trial results

- The EGDT group received significantly more iv fluids (4.5l vs 3.0l), blood products and inotropic support at the end of the 6 hour period
- After 6 hrs, the EGDT group had:
  - higher blood pressure
  - higher $S_{cv}O_2$
  - lower Base Deficit (BE)
- By the end of 72 hrs both group had received the same volume of fluid and amount of inotropic support

In-hospital mortality 30% *vs* 46%
60 day mortality 50% *vs* 70%

Surviving Sepsis Campaign

Phase 1 Barcelona declaration 2002

Collaboration between US and European Critical Care Societies
(Definitions, Studies and Trials)

Phase 2 Evidence based guidelines 2004-07

- Resuscitation bundles – for the first 6 hours
- Management bundles – for the first 24 hours

Phase 3 Implementation and education

Surviving Sepsis Campaign

Goals of the SSC:

- Build awareness of sepsis
- Improve diagnosis
- Increase the use of appropriate treatment
- Educate healthcare professionals
- Improve post-ICU care
- Develop guidelines of care
- Facilitate data collection for the purposes of audit and feedback

Surviving Sepsis Campaign

6 hour bundle
(Resuscitation bundle)

24 hour bundle
(Management bundle)

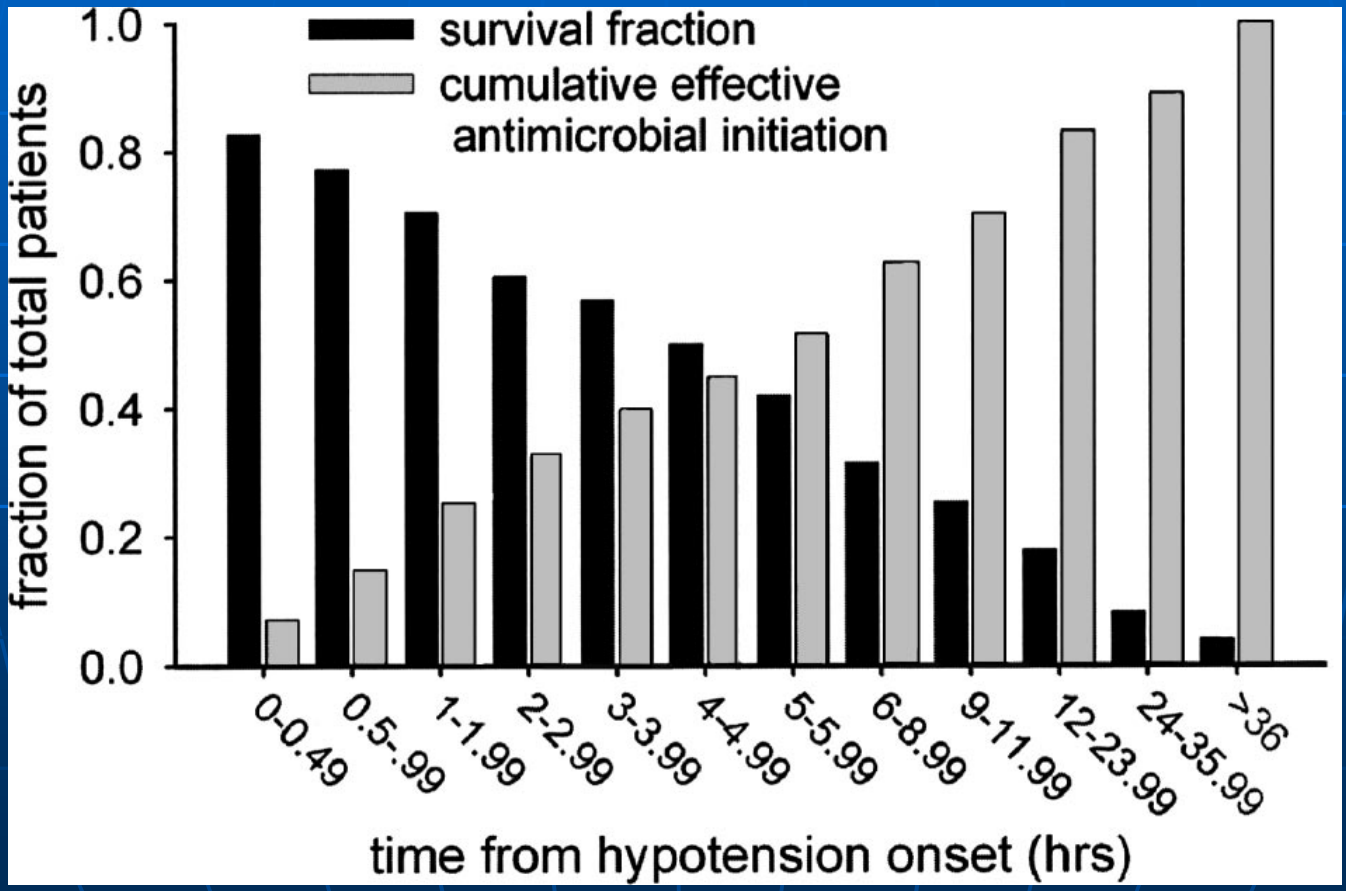
Bundles

- *Definition:*
  - A "bundle" is a group of therapies for a given disease that, when implemented together, may result in better outcomes than if implemented individually
- Individual elements are evidence-based
- All elements must be completed to be 'compliant' with the bundle for measurement purposes by organizations (eg DoH, SSC, etc)
- They are NOT a substitute for physician decision-making

6 Hour Sepsis Bundle

- Immediate **fluid resuscitation** using crystalloids or colloids
- Obtain **blood cultures and lactate** ASAP after diagnosis of sepsis
- **Antibiotics** administered within **3 hours (1 hour** if inpatient) of presumptive diagnosis
- Obtain **CVP** if bp is not responsive to fluids or if serum lactate is elevated
- Repeated boluses of crystalloid/colloid (250-500 ml) every 30 min until CVP >8mmHg (>12 mmHg if ventilated)
- **Vasopressors** via central line if MAP < 65 mm Hg during and after adequate fluid resuscitation - eg Noradrenaline or Dopamine
- If $S_{cv}O_2$ <70 % after fluid replacement and Noradrenaline - start **inotropes** (Dobutamine or Adrenaline infusion via central line) and/or give **RBC's** (to keep Hb above 10g/dl)

Initiation of Antibiotic Therapy in Severe Sepsis



Kumar A, Roberts D, Wood KE, *et al.*: *Crit Care Med*. 2006 , **34:**1589-1596

24 Hour Sepsis Bundle (Management Bundle)

- Applies to patients in Critical Care
- Consider use of Recombinant human Activated Protein C using local guidelines
- Low dose steroids (Hydrocortisone 200-300mg/day i.v.) for adult septic shock patients requiring continued use of vasopressors
- Glucose control (<10 mmol/l)
- For ventilated patients – inspiratory peak airway pressure <30 cmH2O

Case 3

- A 29 year old lady arrives in the Resuscitation room. She is drowsy, with the following vital signs:
  - bp: 80/50 mmHg
  - pulse 130 bpm
  - RR 28 per minute
  - Temp. 38.5°C
  - Sa02 95% on 10 l/min O_2 via a reservoir bag mask
  -

ABG:	
pH	7.31
$Pa0_2$	35.5 kPa
$PaC0_2$	3.5 kPa
Bicarb	12.7mmol/l
BE	-10.0mmol/l

- She has a petechial rash on her trunk.
- She responds to voice and there is no neck stiffness.
- Her bedside glucose measurement is 6.2 mmol/L

What is your management?

Questions