MICROCIRCULATORY FAILURE

SHOCK, MODS, DIC

MAREK BRENISIN, MD., PHD.,

DEPARTMENT OF PATHOLOGICAL PHYSIOLOGY

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GENERAL CHARACTERISTICS OF SHOCK

- A pathological condition
- Discrepancies in oxygen supply and demand
  - Tissue hypoxia
- Leads to global hypoperfusion
  - Lactic acidosis development (MAC, HAGMA)
- Untreated leads to
  - Irreversible collapse of circulation
  - Organ systems dysfunction (multiple organ dysfunction syndrome, MODS)

PHASE/STAGES OF SHOCK

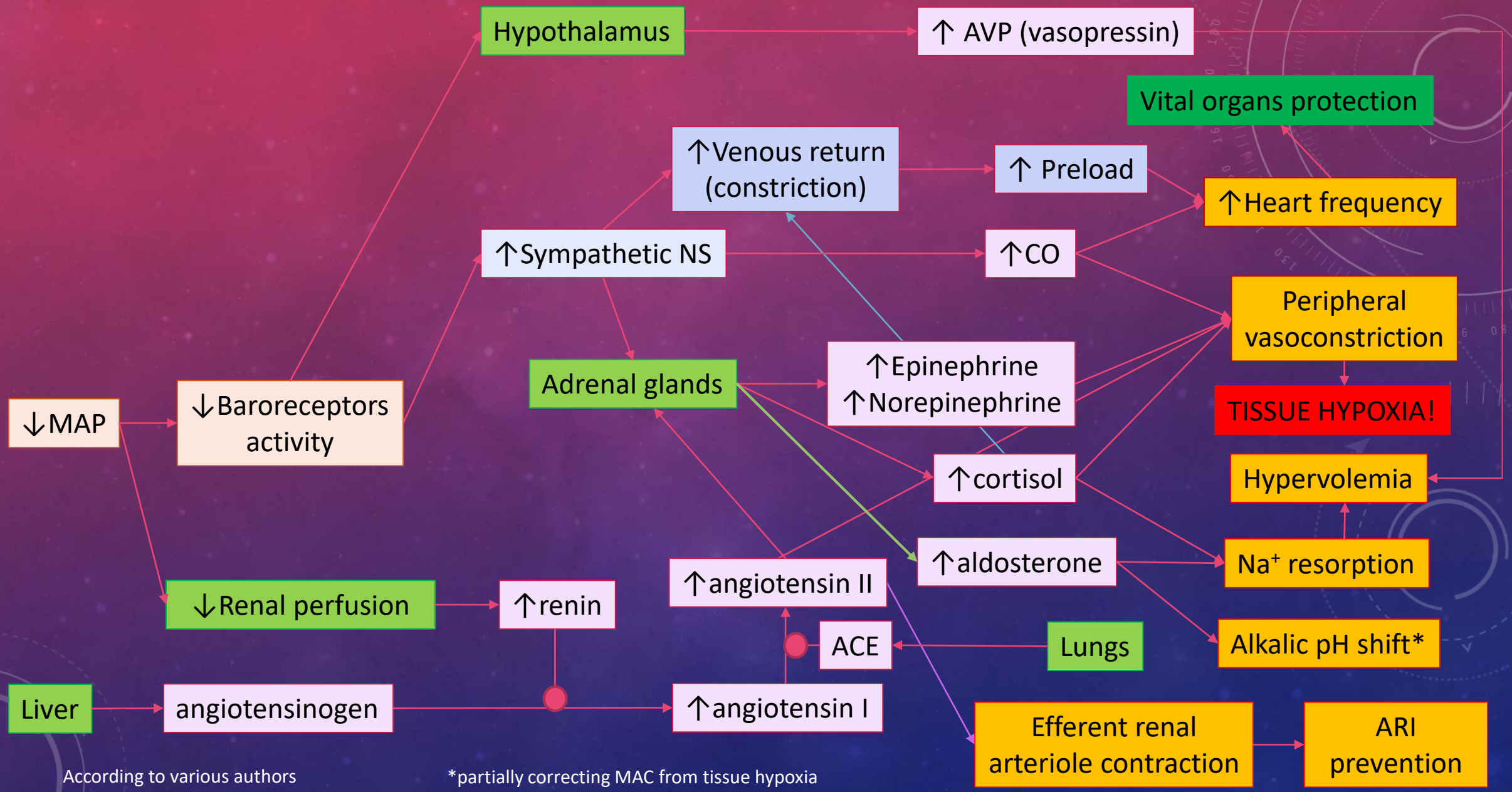
1. Initial
2. Compensatory (Compensated)
3. Progressive/Decompensed (Uncompensated)
4. Refractory (Irreversible)

INITIAL PHASE

- Drop in arterial pressure leads to failure of microcirculation support
- Transient tissue ischemia
  - Anaerobic glucose metabolism
  - Krebs cycle stopped -> pyruvate accumulation -> turning to lactic acid
- Cellular acidosis
  - Later lactate excreted to blood as well

COMPENSATORY PHASE (COMPENSATED SHOCK)

- Hypoperfusion triggers baroreceptors response (carotid sinus)
  - Increased sympathetic activity -> CO secretion -> vasoconstriction
  - Decreased parasympathetic activity
- Blood redistribution to heart and brain
  - Attempts to restore perfusion to kidney, lungs...
- Increased venous return
  - Increasing preload – mobilising reserves
- Adrenal secretion stimulation (by sympathetic NS)
  - norepinephrine and epinephrine
- Decreased renal perfusion -> renin secretion -> RAAS engaged



According to various authors

*partially correcting MAC from tissue hypoxia

SYSTEMIC HYPOTENSION COMPENSATORY MECHANISMS

Target action	Mechanism
Maintaining adequate circulating volume	*Vasoconstriction* via ↑ Sympathetic Tone, catecholamine release, angiotensin II release (RAAS) and vasopressin release
	Increased renal reabsorption via activation of RAAS and vasopressin release
Maximisation of cardiac output	*Increase in heart rate*
	Increase in contractility
	↑*Preload* ➔ ↑*CO* (Frank-Starling relationship)
Redirection of blood flow to vital organs	*Autoregulation* of blood flow to vital organs
Optimising oxygen unloaded settings	↑*RBC 2-3-DPG* concentration
	Bohr Effect (lactic acidosis)

https://www.intechopen.com/chapters/83503


Not to worry. We are still flying half a ship.

PROGRESSIVE/DECOMPENSATED (UNCOMPENSATED SHOCK)

- After prolonged hypoxia and anaerobic respiration
- Lactic acid accumulation
  - CVS – reduced cardiac contractility, ventricular arrhythmias
  - Hyperkalemia, hyponatremia
  - Prerenal azotemia
  - Lactic acidosis

PROGRESSIVE/DECOMPENSATED (UNCOMPENSATED SHOCK)

- ATP shortage
  - Intracellular acidosis interferes with pH dependent enzymes e.g. 6-P-fructokinase
  - ATP-ion pumps malfunction (Na^+/K^+-ATPase)
    - loss of membrane potential
    - cellular edema
  - Lysosomal ion channels malfunction -> lysosomal membrane broken
  - Toxic substances from dead cells into extracellular fluid

  } cell dysfunction and rupture

- Capillary endothelial damage and death

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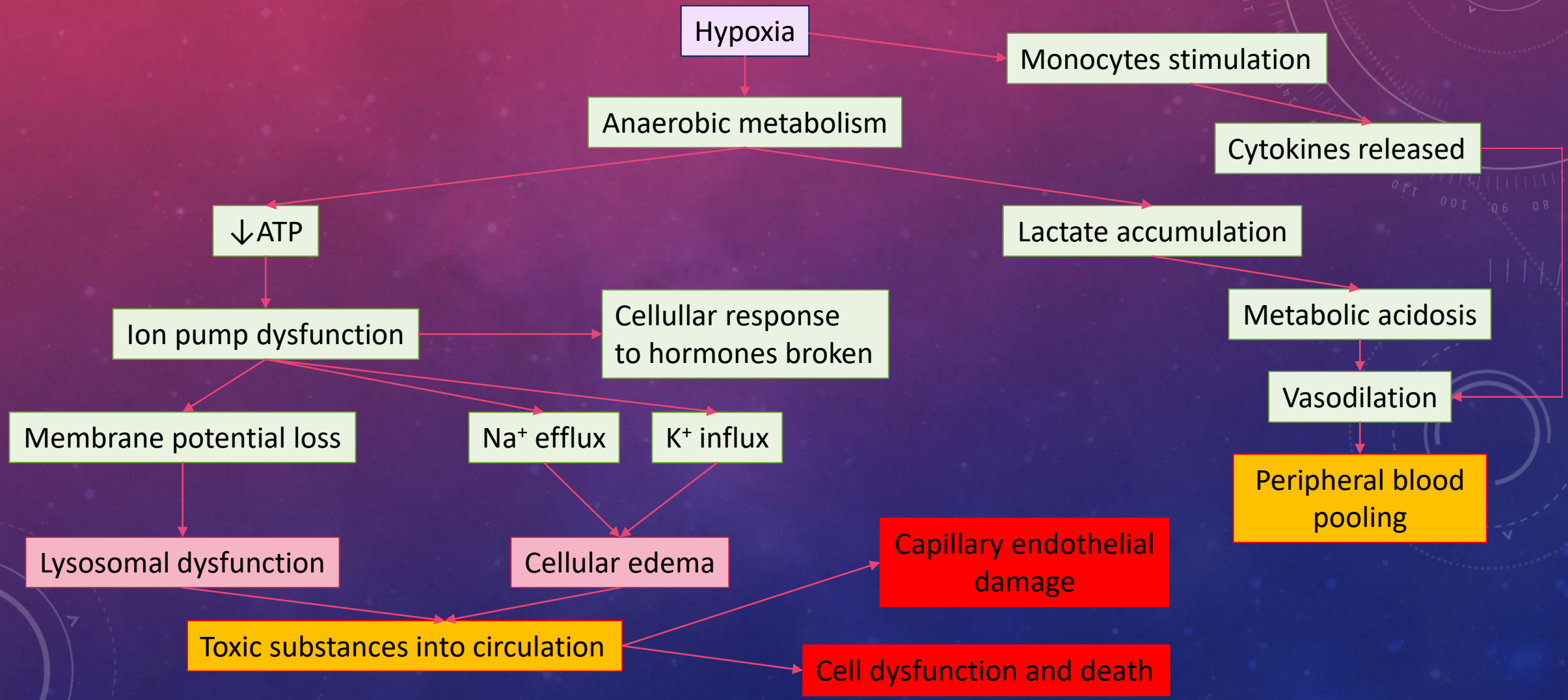
CELLULAR RESPONSE TO HYPOXIA



BODY FUNCTIONS DETERIORATING

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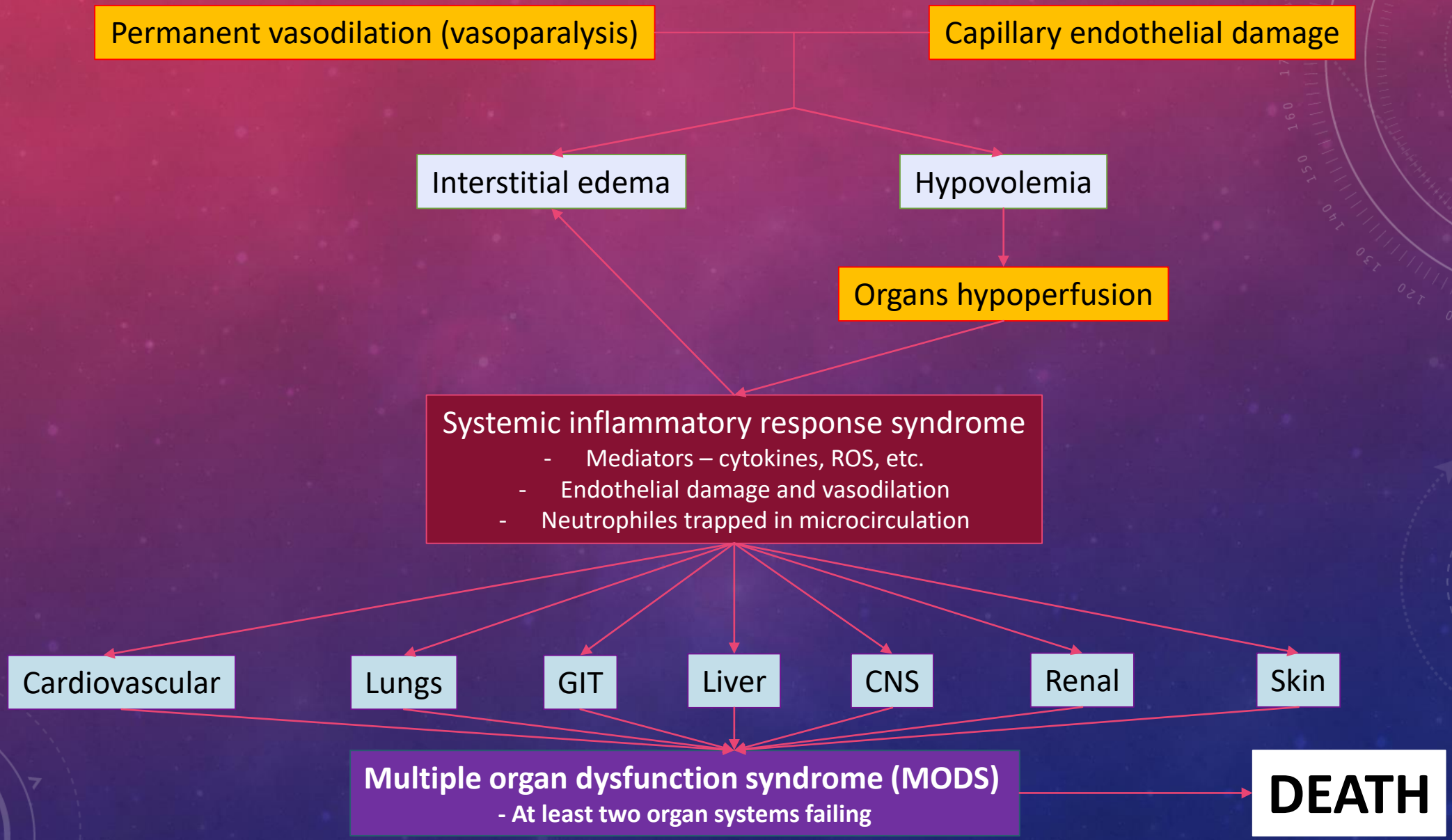
REFRACTORY (IRREVERSIBLE SHOCK)

- Cannot be reversed even via intense intervention
- Compensatory mechanisms lost
- Decreased organ perfusion
- Vasodilation + vascular permeability
  - Interstitial edema
  - Hypovolemia in circulation
- Refractory hypotension + organ ischemia
- Multiple organ dysfunction syndrome (MODS) developing


Permanent vasodilation (vasoparalysis)
Capillary endothelial damage
Interstitial edema
Hypovolemia
Organs hypoperfusion
Systemic inflammatory response syndrome
- Mediators – cytokines, ROS, etc.
- Endothelial damage and vasodilation
- Neutrophiles trapped in microcirculation
Cardiovascular
Lungs
GIT
Liver
CNS
Renal
Skin
Multiple organ dysfunction syndrome (MODS)
- At least two organ systems failing
DEATH

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CLASSIFICATION OF SHOCK

- Hypovolemic
- Cardiogenic
- Obstructive
- Distributive

HYPOVOLEMIC SHOCK

- Pathomechanism
  - Loss of blood volume due to bleeding, dehydration or leaking of fluids into extravascular space
- Causes
  - Absolute hypovolemia
    - Massive dehydration
    - Blood loss (hemorrhage)
    - Gastrointestinal – vomiting, diarrhea, stoma or fistula
    - Kidney – hyperglycemic states, diuretics treatment, salt-wasting nephropaties, diabetes insipidus
    - Skin – burns, skin lesions (ulcerations), perspiration (hot climate)
  - Relative hypovolemia (third spacing)
    - Intestinal obstruction, pancreatitis, major venous system obstruction, endothelial damage, massive or systemic inflammatory response

HYPOVOLEMIC SHOCK CLASSES

Class	Volume loss	Pulse	Blood pressure	Capillary refill	Respiratory rate	Urine output (mL/kg/h)
I	0 – 15 %	Normal	Normal	Normal	Normal	1 – 2
II	15 – 30 %	Mild tachycardia	Mildly Low	Mildly prolonged	Mild Tachypnea	0.5 – 1
III	30 – 40 %	Tachycardia	Low	Prolonged	Tachypnea	0.25 – 0.5
IV	>40 %	Tachycardia, Bradycardia or even absent	Very low	Greatly prolonged	Severe Tachypnea	<0.25 or non-existing

Shock Index (SI)	Group I No shock	Group II Mild Shock	Group III Moderate shock	Group IV Severe Shock
$SI = \frac{heart\ rate}{systolic\ blood\ pressure}$	<0.6	0.6 – 1.0	1.0 - 1.4	≥1.4

Hypovolemic Shock: *Pathogenesis, Complications, and Clinical Findings*

Authors:
Dean Percy
Miranda Schmidt
Reviewers:
Yan Yu
Tristan Jones
Frank Spence*
Ben Campbell
Ayaaz Sachedina*
** MD at time of publication*

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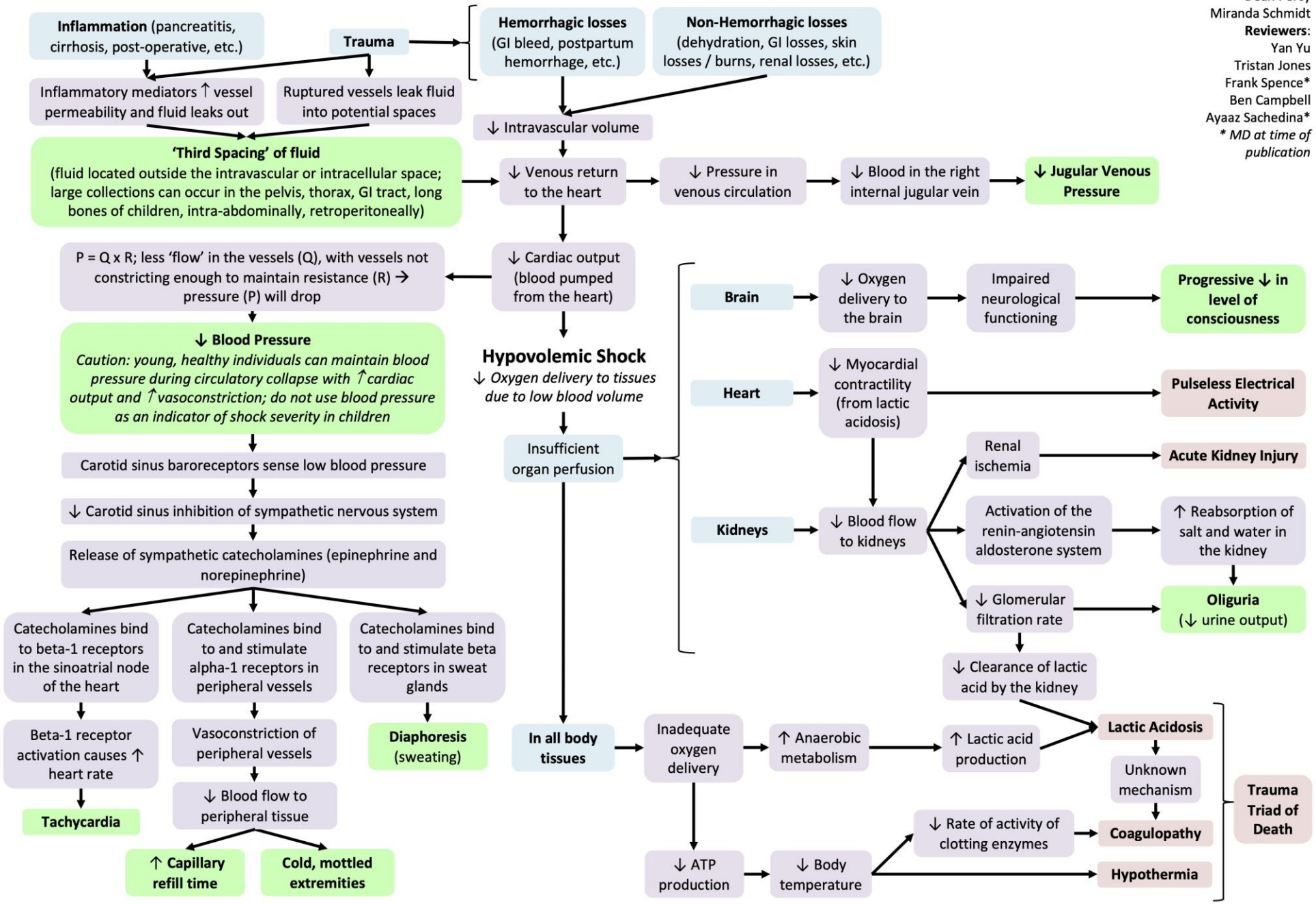

Legend: Pathophysiology | Mechanism | Sign/Symptom/Lab Finding | Complications

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CARDIOGENIC SHOCK

- Pathomechanism
  - Heart fails to pump enough blood to peripheries due to impaired myocardial contractility
- Causes
  - Myocardial infarction
  - Malignant arrhythmia
    - Myocardial ischemia, right arrhythmogenic ventricular dysplasia
  - Myocarditis (mostly Coxsackie B virus infection)
  - Dilated cardiomyopathy (systolic dysfunction)
  - Valvular dysfunction
    - Aortic valve stenosis, mitral valve stenosis
  - Tachy- and bradarrhythmias (>180–200 bpm or <20 respectively)

Cardiogenic Shock: *Pathogenesis, complications and clinical findings*

Author:
Dean Percy
Reviewers:
Yan Yu
Tristan Jones
Jason Waechter*
** MD at time of publication*

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Cardiac Arrhythmia*
- Severe bradycardia → ↓ Heart rate (HR)
- Severe tachycardia → ↓ diastolic time → ↓ time for L ventricle to fill

Cardiac Valve dysfunction*
- Valvular *regurgitation* → In systole, some blood goes backward
- Valvular *stenosis* → Forward flow of blood is obstructed

Cardiomyopathy*
- Hypertrophic cardiomyopathy → Forward flow of blood is obstructed
- Myocyte dysfunction or loss → ↓ Cardiac contractility (less blood is pushed forward when ventricles contract

Myocardial infarction*
→ Death of cardiac muscle → ↓ Cardiac contractility (less blood is pushed forward when ventricles contract

↓ Heart rate (HR) + ↓ time for L ventricle to fill + ↓ Cardiac contractility → **↓"Forward" Stroke Volume (SV)**

Low cardiac output → Cardiogenic shock!
(Think: CO = SV x HR)

- Build-up of blood (and thus pressure) in the venous system
  - Blood from right ventricle backs up into right atrium and SVC → **↑ JVP, Distended neck veins** → ↑ Hydrostatic pressure in peripheral veins → fluid pushed out of veins → **Peripheral edema**
  - Blood from left ventricle backs up into lungs → **↑ Pulmonary BP *(pulmonary capillary wedge pressure)*** → **Pulmonary Edema*** → **Dyspnea, Tachypnea**
- BP = CO x SVR; less 'flow' in vessels (CO) will lower BP → **↓ Blood Pressure**
- Heart tries to compensate by ↑ HR → **Tachycardia**
- Insufficient organ perfusion → **Skin**
  - Body preferentially vasoconstricts extremities, to preserve blood/warmth to key vital organs
  - ↓ Arterial blood (red) and ↑ venous blood (blue)

  → **Cold, pale, or mottled extremities**
- **Brain** → ↓ cerebral blood flow → cerebral hypoxia → **Progressive ↓ LOC**
- **Heart** → ↓ Coronary perfusion → **PEA if severe** / **Myocardial ischemia**
- **Kidneys** → ↓ Blood flow to kidneys
  - ↓ GFR → **1. Oliguria 2. ↑ Cr**
  - Renal ischemia → **ATN** → **1. Oliguria 2. ↑ Cr**

*See corresponding Calgary Guide slides for more details

Abbreviations:
ATN: acute tubular necrosis
JVP: Jugular venous pressure
LOC: level of consciousness
Cr: Creatinine
PEA: Pulseless Electrical Activity

Legend: Pathophysiology | Mechanism | Sign/Symptom/Lab Finding | Complications

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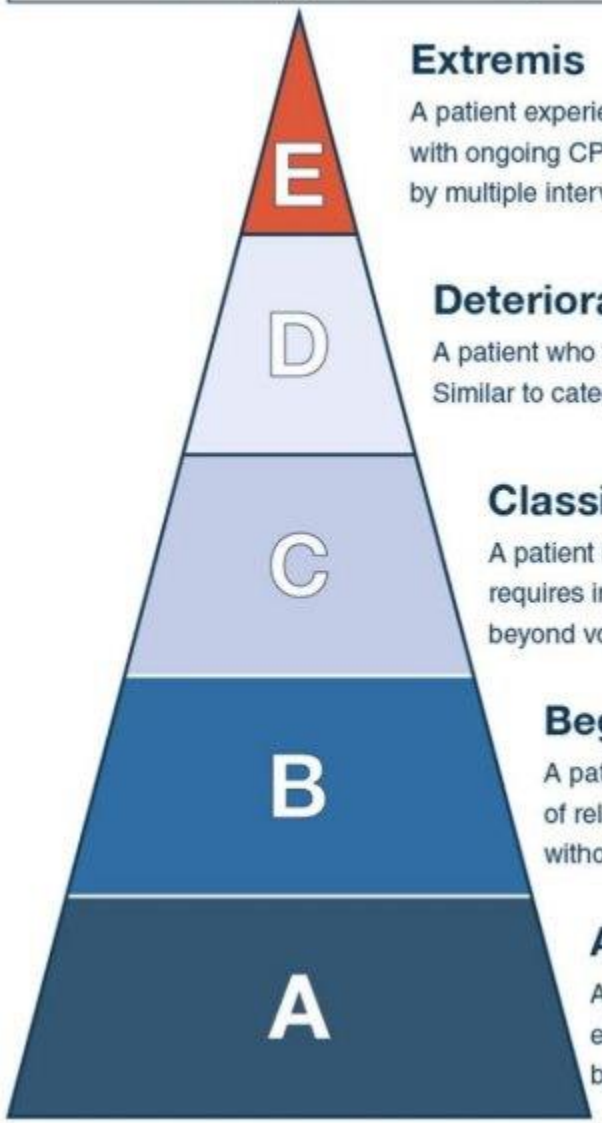

The SCAI pyramid of cariogenic shock classification[1]

Extremis

A patient experiencing cardiac arrest with ongoing CPR and/or ECMO, being supported by multiple interventions.

Deteriorating

A patient who fails to respond to initial interventions. Similar to category C but getting worse.

Classic

A patient manifests with hypoperfusion that requires intervention (inotrope, pressor or TCS) beyond volum resuscitation to restore perfusion.

Beginning

A patient who has clinical evidence of relative hypotension or tachycardia without hypoperfusion.

At risk

A patient who is not currently experiencing signs or symptoms of CS, but is at risk of developing CS.

Physical exam	Biochemical markers	Hemodynamics
Near pulselessness Cardiac collapse Mechanical ventilation Defibrillator used	CPR (A-modifier) pH ≤ 7.2 Lactate ≥ 5 mmol/L	No SBP without resuscitation PEA or refractory VT/VF Hypotension despite maximal support
<u>May include any of:</u> Look unwell, panicked ashen, mottled, dusky cold, clammy Volume overload Extensive rales Killip class 3 or 4 NIV or MV Altered mental status Urine output <30 mL/h	Stage C and deteriorating	Stage C and need for multiple pressors or TCS devices
	<u>May include any of:</u> Lactate ≥ 2 mmol/L Creatinine doubling > 50% drop in GFR Elevated LFTs Elevated BNP	SBP < 90 or MAP < 60 mmHg and need for drugs/device to maintain BP Cardiac index < 2.2 L/min/kg PCWP > 15 mmHg RAP/PCWP ≥ 0.8 mmHg PAPi < 1.85 Cardiac power output ≤ 0.6 W
Elevated JVP Rales in lung fields No sign of peripheral hypoperfusion	Normal lactic acid Minimal renal function impairment Elevated BNP	SBP < 90 or MAP < 60 mmHg Pulse > 100 bpm Cardiac index ≥ 2.2 L/min/kg PA sat ≥65%
Normal JVP Normal physical exam	Normal lactic acid Normal renal function	Normal BP Cardiac index ≥ 2.5 L/min/kg CVP < 10 mmHg PA sat ≥ 65%

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OBSTRUCTIVE SHOCK

- Pathomechanism
  - A barrier or an obstacle in circulation prevents proper heart filling
    - Decreased preload, high central venous pressure
- Causes
  - Cardiac tamponade
  - Tension pneumothorax
  - Pulmonary embolism
  - Abdominal compartment syndrome
    - Intraabdominal pressure >20 mmHg
    - Cause – sepsis, abdominal trauma
  - *Aortic stenosis**

*depending on the classification, but due to normal preload is mostly put into cardiogenic shock causes

Obstructive Shock: Pathogenesis, complications and clinical findings

Author:
Dean Percy
Reviewers:
Yan Yu
Tristan Jones
Jason Waechter*
* MD at time of publication

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Cardiac Tamponade
- Fluid in pericardium UNDER PRESSURE
- ↑ pericardial pressure compresses all chambers of the heart, eventually exceeds cardiac venous filling pressure
- ↓ venous return to heart

Pulmonary Embolism
- Obstruction of pulmonary blood flow
- ↑ R Ventricle afterload
- ↓ R Ventricle stroke volume

Tension Pneumothorax
- ↑ pressure in the pleural cavity
- Intrathoracic pressure > venous filling pressures
- ↓ venous return to heart

Underfilled L ventricle

Low stroke volume = ↓ cardiac output

BP = CO x SVR; less 'flow' in vessels (CO) will lower BP → **↓ Blood Pressure**

Obstructive Shock

↑ Venous pressure "backs up"
- ↑ Pressure distends veins (since veins have high compliance)
  - **↑↑ JVP**
  - Fluid under pressure extravasates out of veins and into tissue
    - **Peripheral edema**
    - Pulmonary edema
      - Poor gas exchange in lungs
        - **Dyspnea, Tachypnea**

Insufficient organ perfusion
- Heart tries to compensate by ↑ HR
  - **Tachycardia**
- **Skin**
  - Body preferentially vasoconstricts extremities to preserve blood/warmth to key vital organs
  - ↓ Arterial blood (red) and ↑ venous blood (blue)
  - → **Cold, mottled extremities**
- **Brain**
  - ↓ cerebral blood flow → cerebral hypoxia
    - **Progressive ↓ LOC**
- **Heart**
  - ↓ Coronary perfusion
    - **PEA if severe**
    - **Myocardial ischemia**
- **Kidneys**
  - ↓ Blood flow to kidneys
    - ↓ GFR → **Oliguria ↑ Cr**
    - Renal ischemia → **ATN** → **Oliguria ↑ Cr**

Abbreviations:
ATN: acute tubular necrosis
JVP: Jugular venous pressure
LOC: level of consciousness
Cr: Creatinine
PEA: Pulseless Electrical Activity

Legend: Pathophysiology | Mechanism | Sign/Symptom/Lab Finding | Complications

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DISTRIBUTIVE SHOCK

- Pathomechanism
  - Inappropriate distribution of blood volume to capillaries
  - Sympathetic nervous system unable to maintain vascular tone
- Causes
  - Sepsis
  - Anaphylactic
  - Neurogenic

Distributive Shock: *Pathogenesis, complications and clinical findings*

Author:
Dean Percy
Reviewers:
Tristan Jones
Yan Yu
Jason Waechter*
** MD at time of publication*

https://calgaryguide.ucalgary.ca/wp-content/uploads/2015/05/Distributive-Shock.jpg

Pancreatitis
Anaphylaxis
Sepsis
Systemic inflammation
↑ vessel permeability
Fluid leaks out of intravascular space and pools in extremities
Warm extremities
↓ Intravascular volume → ↓ venous return → ↓ stroke volume → ↓ cardiac output (CO)

Vasodilatory Drugs
I.e. nitroglycerin, anesthetics, Ca^{2+}-channel blockers

Liver failure
↓ liver clearance of vasodilatory molecules

Adrenal insufficiency
↓ cortisol levels → ↓ ability to appropriately vasoconstrict vessels

"Neurogenic Shock": Injury to C- or upper T-spine
Sympathetic nerve connections below lesion are disrupted
↓ sympathetic constriction of smooth muscle around blood vessels
If injury is above T4, vagal inhibition of heart rate becomes unopposed!
Brady*cardia** ***(only in neurogenic shock)

Vasodilation (both arteriolar and venous)

Distributive shock ***Think: BP = CO x SVR***

Note: BP = CO x SVR is the cardio-vascular system's version of: Pressure (P) = Flow (Q) x Resistance (R)

SVR (systemic vascular resistance) is low → Vessel tone is what maintains blood pressure during diastole → BP ↓ during diastole → ↑ Difference between systolic and diastolic BP → **"Bounding Pulses" (↑ pulse pressure)**

Insufficient organ perfusion

↓ Blood Pressure → ↓ venous return to heart

↓ venous return to heart:
- Heart pumps faster to try to raise CO (CO = HR x SV), so as to maintain BP → ***Tachy*cardia**
- ↓ pressure in venous circulation → **↓ JVP**

Brain
↓ cerebral blood flow → cerebral hypoxia → **Progressive ↓ LOC**

Heart
↓ Coronary perfusion → **Myocardial ischemia**

Kidneys
↓ Blood flow to kidneys
- Renal ischemia → ATN → **Renal Failure**
- ↓ GFR → **Oliguria, ↑ Cr**

In all body tissues
↑ lactic acid production due to inadequate delivery of oxygen
↓ clearance of lactate by the liver, kidneys, and skeletal muscle → **Lactic Acidosis**

Abbreviations:
ATN: acute tubular necrosis
JVP: Jugular venous pressure
LOC: level of consciousness
Cr: Creatinine

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DISTRIBUTIVE SHOCK - SEPSIS

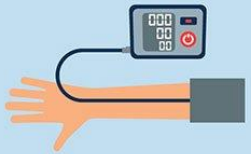
- Features
  - Septic-induced hypotension (SBP <90 mmHg or Δ40 mmHg from baseline), lactic acidosis, oliguria and/or alteration in mental status
  - Overproduction of inflammatory cytokines
  - Endotoxins from Gram- bacteria (K. pneumoniae, E. coli, Proteus spp.)
- SIRS present (definition criteria in the table below)

Finding	Value
Temperature	<36 °C (96.8 °F) or >38 °C (100.4 °F)
Heart rate	>90 bpm
Respiratory rate	>20/min or p_aCO_2 <4.3 kPa (32 mmHg)
WBC (Leukocytes)	<4000/mm^3 or >12000 mm^3 or ≥10 % bands

Sepsis

Symptoms of sepsis include:

Fast heart rate.



Low blood pressure.

Fever or hypothermia.

Shaking or chills.

Warm or clammy/ sweaty skin.

Confusion or disorientation.

Shortness of breath.

Sepsis rash.

Extreme pain or discomfort.

Cleveland Clinic

WHAT ARE THE SYMPTOMS?

SYMPTOMS IN CHILDREN

A child may have sepsis if he or she:

- Is breathing very fast
- Has a 'fit' or convulsion
- Looks mottled, bluish, or pale
- Has a rash that does not fade when you press it
- Is very lethargic or difficult to wake
- Feels abnormally cold to touch

SYMPTOMS IN ADULTS

An adult may have sepsis if they show any of these signs:

Slurred speech or confusion
Extreme shivering or muscle pain
Passing no urine (in a day)
Severe breathlessness
It feels like you're going to die
Skin mottled or discoloured

https://my.clevelandclinic.org/-/scassets/images/org/health/articles/12361-sepsis
https://sepsistrust.org/wp-content/uploads/2022/03/FM8EEKDWQAA4e4N.jpg

DISTRIBUTIVE SHOCK - ANAPHYLAXIS

- Features
  - Type I hypersensitivity reaction occurs
    - IgE mediated, evidences also for IgG (IgG1 and IgG3)
    - Pre-sensitised mast cells degranulation
      - Mainly histamine
    - Possible role of complement parts – C3a, C4a, C5a

DISTRIBUTIVE SHOCK – ANAPHYLAXIS PATHWAYS

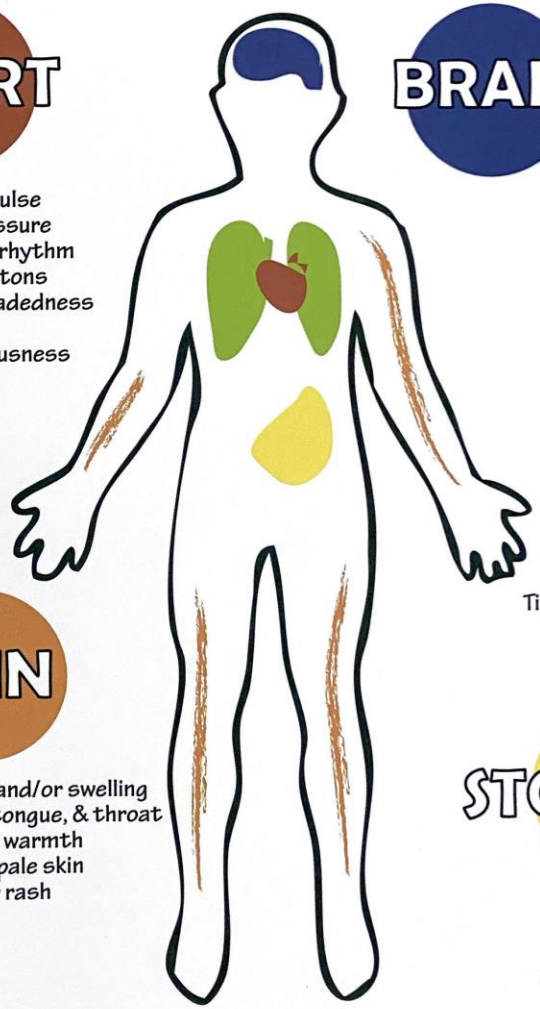
	IgE-dependent	IgG-dependent
Ig involved	IgE	IgGs (IgG1, IgG3)
Antigen concentration	Low	High
Fc receptor	FcεRI	FcγRI, FcγRIIA, FcγRIIB, FcγRIIC, FcγRIIIA, FcγRIIIB
Effector cells	Mast cells	**Macrophages**, monocytes, neutrophils
Mediators	Histamine (leukotrienes, prostaglandins, **serotonin**, etc.)	Platelet-activating factors (leukotrienes, prostaglandins, **serotonin**, etc.)
Triggering factors	Pollen particles, food, drugs (e.g. beta-lactam atb), insect sting and bites, exercise (food dependent)	Food, drugs (monoclonal antibodies – omalizumab or infliximab), dextrans, etc.

Serotonin and macrophages (bold) are hypothesised as novel players in anaphylaxis pathogenesis

https://www.frontiersin.org/files/Articles/262272/fimmu-08-00515-HTML/image_m/fimmu-08-00515-t001.jpg

SYMPTOMS OF ANAPHYLAXIS

SYMPTOMS CAN OCCUR WELL AFTER INITIAL EXPOSURE



HEART

Weak, rapid pulse
Low blood pressure
Abnormal heart rhythm
Heart palpitatons
Dizziness, lightheadedness
Shock
Loss of consciousness

BRAIN

Headache
Anxiety
Confusion
Weakness
Slurred speech
Feeling of impending doom

LUNGS

Wheezing
Chest pain
Difficulty breathing
Trouble swallowing
Fluid in the lungs
Tightness in chest and throat
Cough

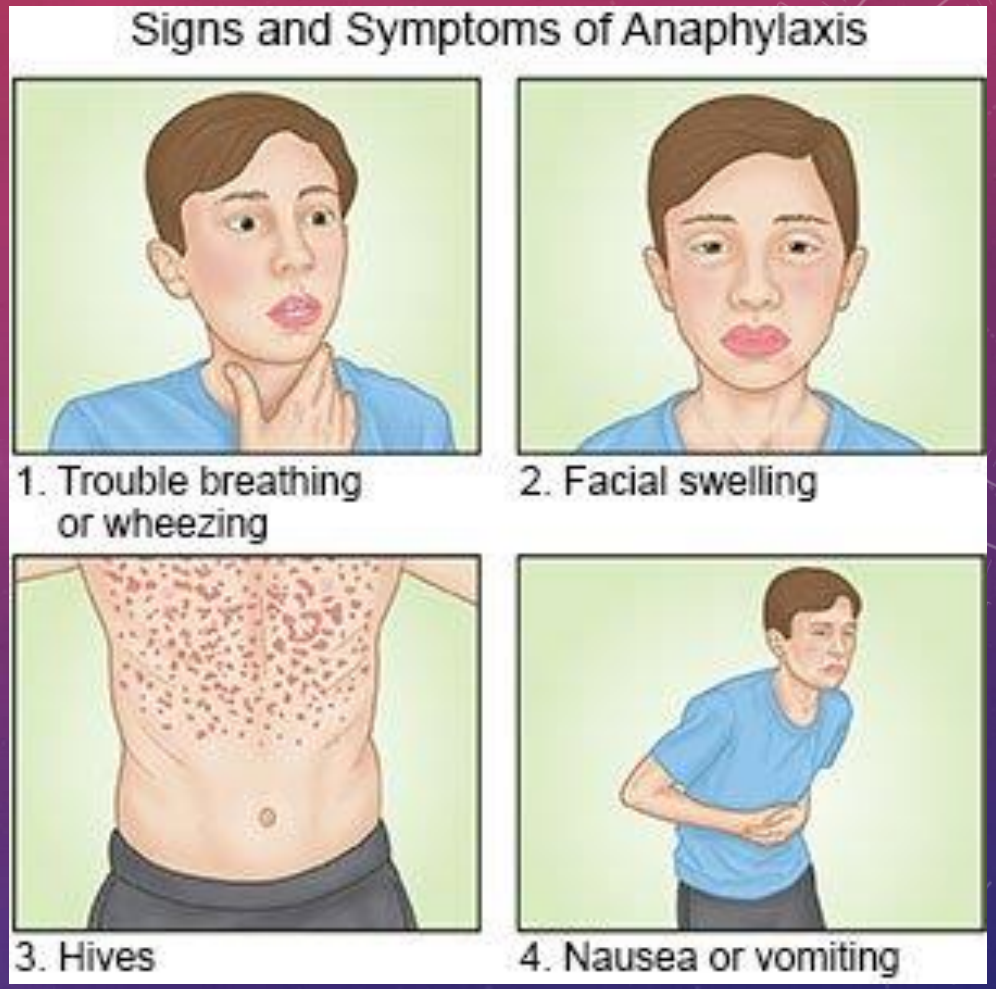
SKIN

Itching, redness, and/or swelling of face, eyes, lips, tongue, & throat
A feeling of warmth
Flushed or pale skin
Hives or rash

STOMACH

Nausea
Vomiting
Diarrhea
Abdominal pain

IF EXPERIENCING ANAPHYLAXIS CALL 911 & USE EPI-PEN



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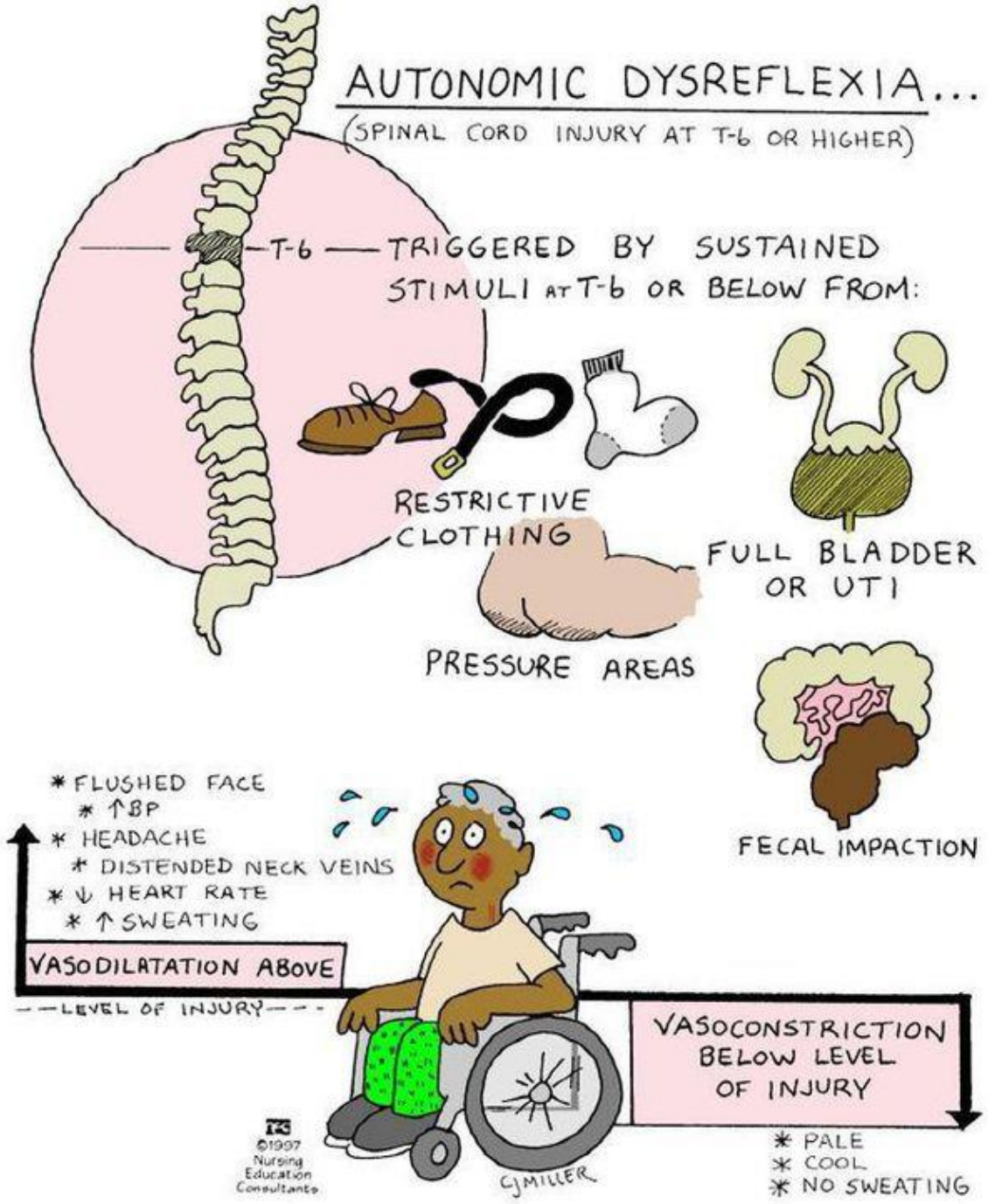
DISTRIBUTIVE SHOCK - NEUROGENIC

- Features
  - Brain or spinal cord trauma above T6 level
  - Sympathetic innervation disrupted
    - Drop in peripheral vascular resistence
    - Sudden blood pressure drop
- Different from spinal shock (see next slide!)

	Neurogenic shock	Spinal shock
Definition	Sudden loss of sympathetic signals	Immediate temporary total loss of power, sensation and reflexes below the level of injury
Location of lesion	Above T6	Anywhere
Mechanism	Autonomic innervation disruption	Peripheral neurons temporarily unresponsive
Blood pressure	Hypotension	Normal or hypotension
Circulation collapse	Imminent	Possible
Pulse	Bradycardia	Bradycardia
Bulbocavernous reflexes	Variable	Absent
Motorics	Variable	Flaccid paralysis (later spastic)
Time after injury	48 – 72 hours	48 – 72 hours
Resolution	Short	Long
Temporary/Self-limiting	No	Yes



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An Approach to Shock

	Hypovolemic	Distributive	Cardiogenic	Obstructive
JVP	Low	Low	High	High
Temperature of extremities	Cold	Usually warm	Cold	Cold
Effect of passive leg raise on pulse pressure	Increased	Increased	No effect	No effect
IVC on ultrasound	Non-dilated Collapsing with respiration	Non-dilated Collapsing with respiration	Dilated Non-collapsing with respiration	Dilated Non-collapsing with respiration
LV function on ultrasound	Hyperdynamic	Usually hyperdynamic	Decreased	Usually normal
Other findings	History of bleeding or dehydration Low Hemoglobin → Hemorrhagic (can be misleadingly normal early) High hemoglobin → Non-hemorrhagic (hemoconcentration)	Infectious symptoms → Sepsis Fever, high or low WBC, new focal opacities on CXR → Sepsis New medication or food → Anaphylaxis	History of cardiac disease and/or CV risk factors S3 on exam Elevated BNP, troponin Signs of ischemia on ECG (Blood pressure is occasionally normal In cardiogenic shock)	History of malignancy or DVT risk factors DVT on exam → Massive PE Soft heart sounds, pulsus paradoxus, pericardial effusion on ultrasound or CXR → Tamponade Unilateral absence of breath sounds, pneumothorax on CXR → Tension pneumothorax
Next steps:	General mechanism usually obvious GI bleed → EGD and/or colonoscopy If hemorrhagic, but not GI/trauma → Consider CT abdomen	If septic shock suspected → Blood, urine, +/- sputum cultures Consider Abdominal CT	Formal echocardiogram Serial troponins and ECGs If acute MI likely → Cardiac cath	If PE suspected → CTA thorax If tamponade suspected → Echo

https://img.grepmed.com/uploads/6968/table-findings-shock-symptoms-differential-original.jpeg

MULTIPLE ORGAN DYSFUNCTION SYNDROME (MODS)

- Definition
  - When at least two organ systems are malfunctioning
  - CRITICAL CONDITION!
- Characteristics
  - Increases duration of hospitalisation and mortality
    - Average length of MODS patients hospitalisation was three times longer than without MODS
  - Incidence in critically ill trauma patients 22 – 88 %
  - One of factors leading to multiorgan failure (MOF)
  - Mechanism still unclear, hypotheses exist

MECHANISM OF MODS DEVELOPMENT

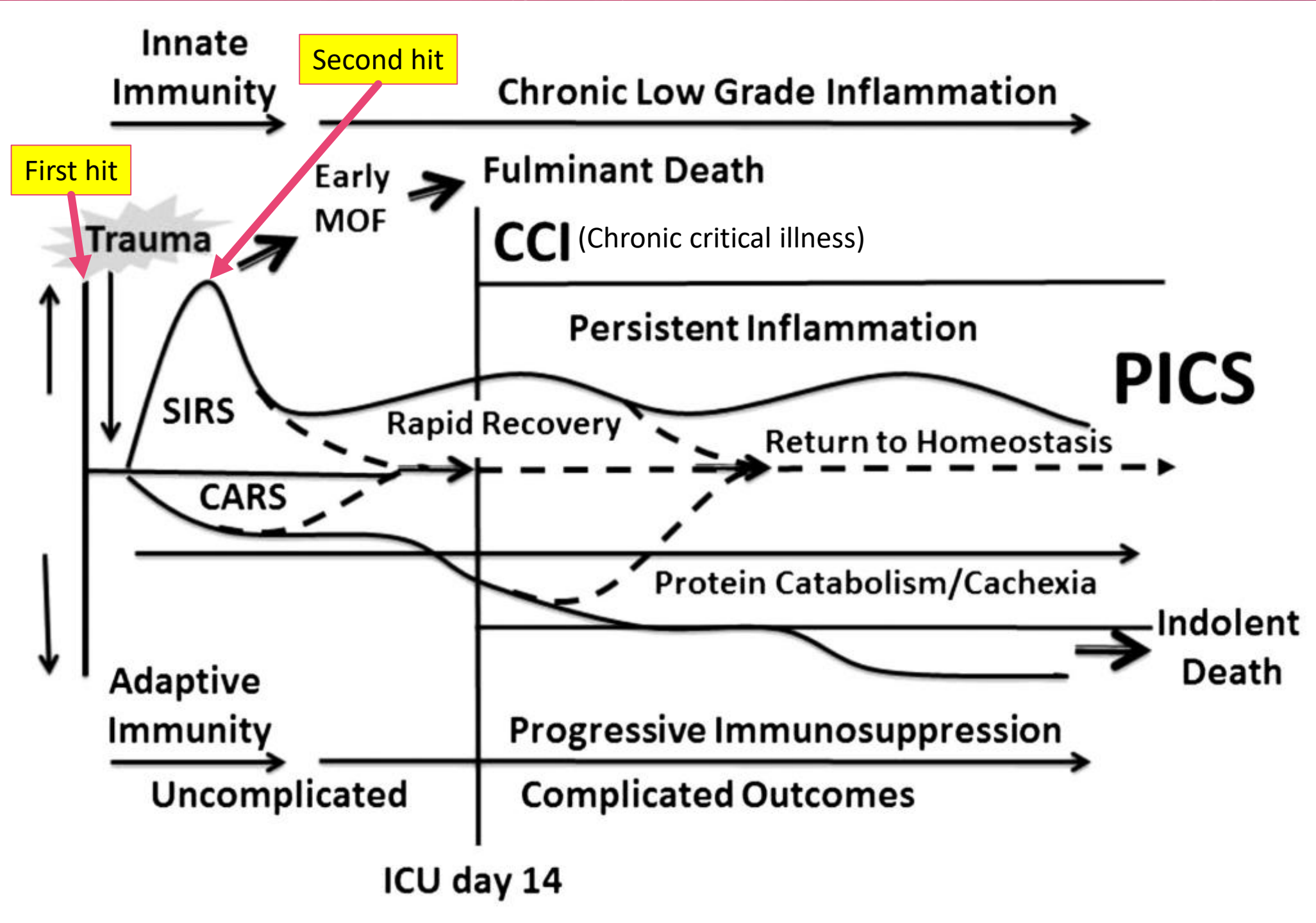
- „Two-hit“ theory process
  - First hit – excessive proinflammatory response (sepsis, injury, burns, hypoperfusion)
  - Second hit – bacterial infection/invasion, surgical intervention, etc.
- ↑immune response -> ↑free radicals -> vascular endothelial damage
- ↓perfusion -> ↑ROS, RNS -> oxidative stress -> mitochondrial damage
- Multifactorial process

- Deregulated immune response + mitochondrial damage -> background for MODS
  - Early phase -> ↑TNF-α, IL-1β, VCAM-1, endothelial leukocyte adhesion molecule-1
  - Late phase -> upregulation of immune response in affected organs
    - MAPK, Rho-activated kinase, TGF-β -> fibrosis -> cumulative damage

MECHANISM OF MODS DEVELOPMENT

- Balance between SIRS and CARS
  - SIRS – systemic inflammatory response syndrome
    - Proinflammatory cytokines, local inflammation to systemic
  - CARS – compensatory anti-inflammatory response syndrome
    - Anti-inflammatory cytokines and immunosuppresion
  - MARS – mixed antagonist response syndrome – (dys)balance of SIRS and CARS

- Pulmonary dysfunction -> cardiac, renal, hepatic dysfunction
- Sepsis may contribute, but SIRS is main factor for MODS development
  - Sepsis causes cca 66 % MODS cases



(Persistent inflammation, immunosuppresion and catabolism syndrome)

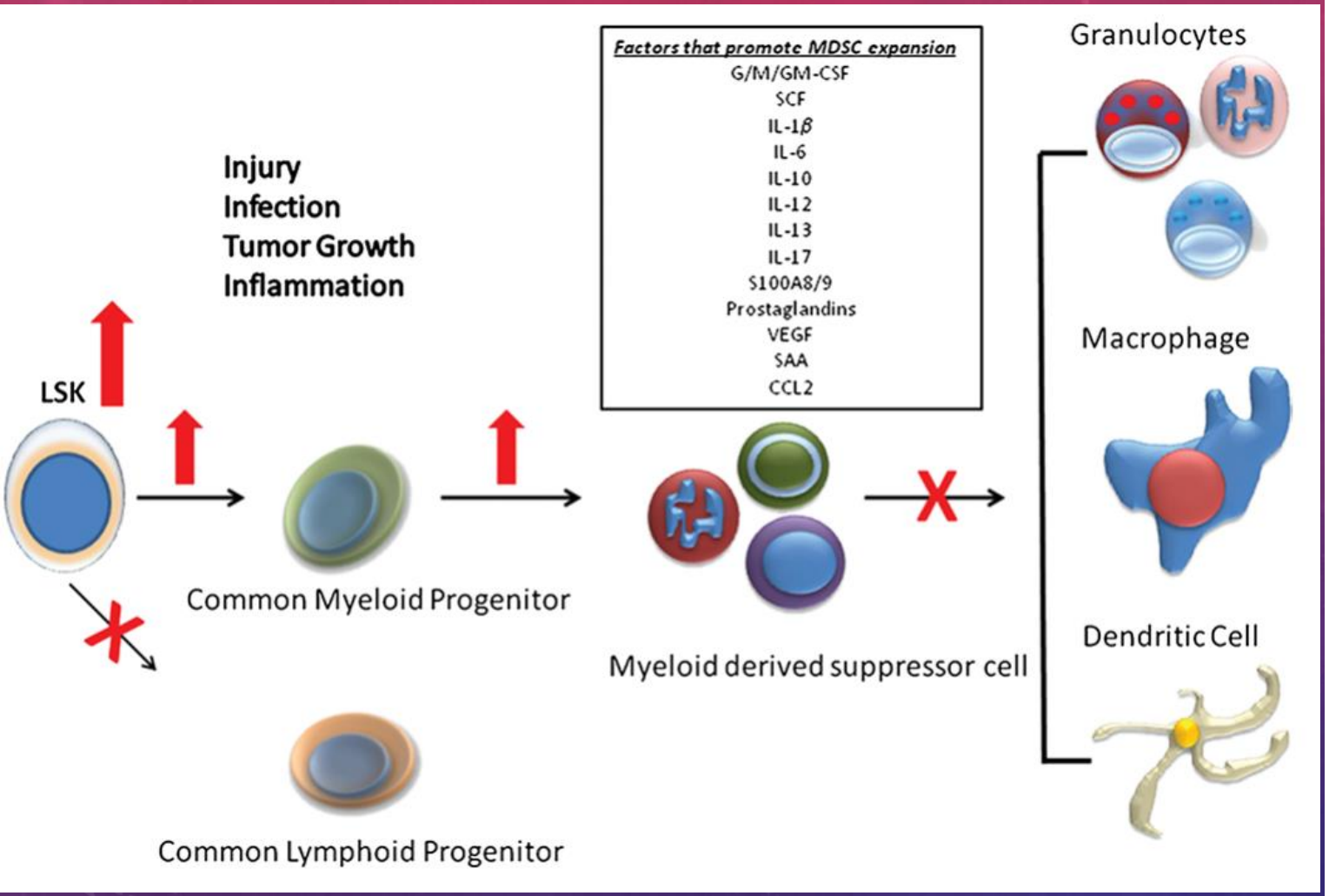
https://scirc.med.ufl.edu/files/2014/09/Vanzant-et-al-PICS-blunt-trauma-JTrACS-2014.pdf

CELLULAR ACTIVITY DURING MODS

- Early changes in 0 – 24 hours
  - Inflammatory stimuli
    - Neutrophils proliferation -> PMN (polymorphonuclears) priming
    - NK cell production
    - ↓γδ-T cells
    - ↑INF-γ
  - MODS and lymphopenia
    - Persistent lymphopenia increases mortality

CELLULAR ACTIVITY DURING MODS

- Emergency myelopoiesis
  - Under influence of G/GM-CSF, IL-6, IL-17, etc.
  - Emptying of bone marrow and lymphocytes apoptosis in secondary lymphoid organs
  - Myelopoietic precursors production favoured -> granulocytes, macrophages, dendritic cells
  - MDSC (myeloid-derived suppressor cells)
    - Role - T-cell suppresion
    - Mechanism – iNOS, arginase, ROS
  - Inflammatory response enhanced



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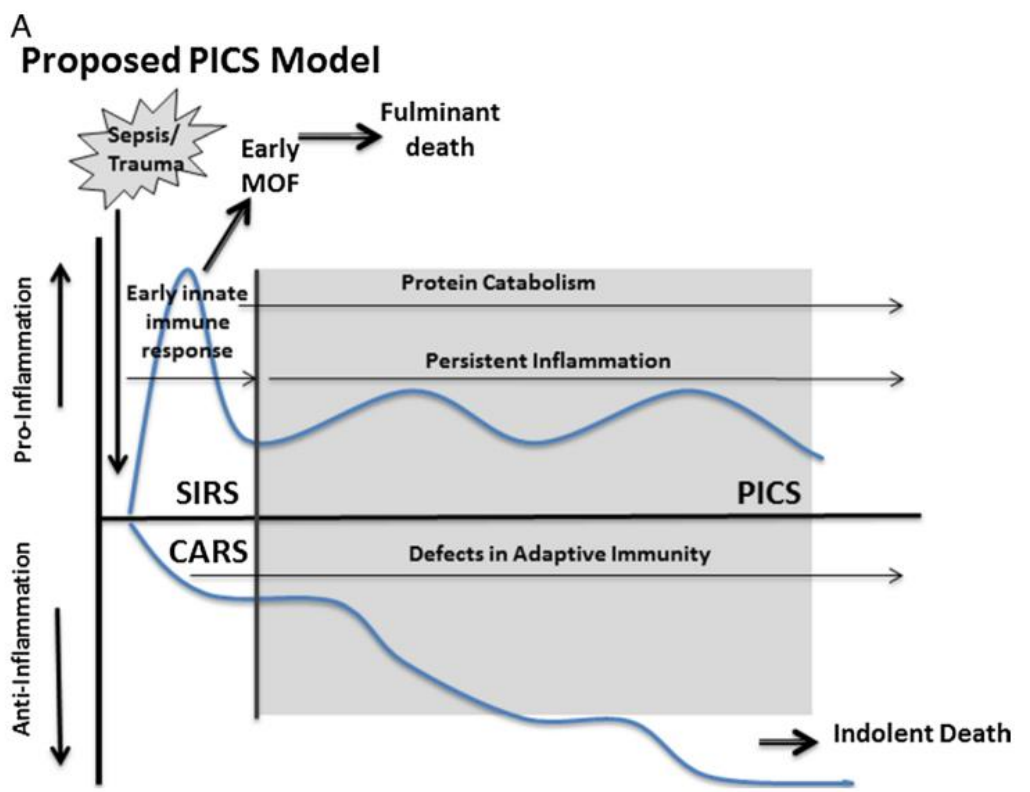
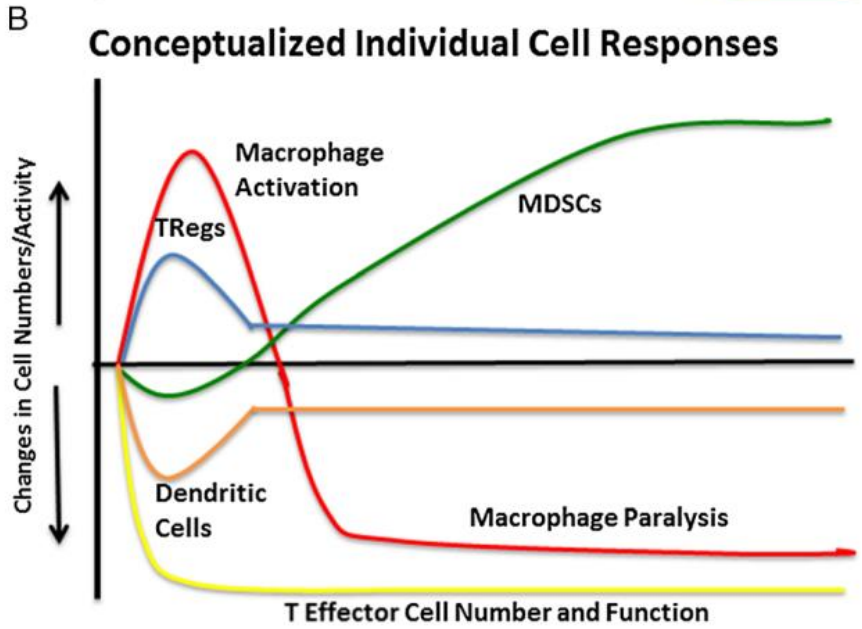




CARDIOVASCULAR SYSTEM IN MODS

- Frequent among critical patients
- Causes
  - Septic shock, sepsis, SIRS
- Pathomechanism (see next slide)
  - Primary ischemia-reperfusion injury
  - Inflammatory response
  - Adrenergic response
  - Treatment of CVS

Determinant	Description	Damage mechanism

Myocardial ischemia-reperfusion injury	O_2 not meeting demands of cardiac muscle
	• Myocardial infarction
	• Circulatory arrest
	• Hypovolemic shock
		• Ischemia
		  • ATP depletion
		  • Lactic acidosis
		  • Intracellular Ca^{2+} overload
		  • Apoptosis stimulation
		  • Impaired diastolic relaxation
		  • Prone to arrhythmias
		• Reperfusion
		  • ROS production
		  • Aggravation of cardiac injury

SIRS	Oxidative stress
	Deregulated immunity
		• TNF-α, IL-1β and IL-6
		  • Myocardial depression
		• NF-κB
		  • Inflammatory response upregulation in myocardium
		• ROS
		  • Mitochondrial damages and more ROS produced

Catecholamine induced cardiac dysfunction	↑plasma catecholamines Autonomic dysfunction Increased sympathetic activity	• Intracellular Ca^{2+} overload • ATP depletion • Mitochondrial damage • ROS produced
CVS treatment	Norepinephrine (vasopressor)	Cumulative damage with endogenous catecholaminergic reponse
	Propofol (and sedatives)	• Cardiac depression, vasodilation and hypotension • More vasopressors required to stabilise

	Mechanical ventilation	• Positive end exspiration pressure and positive pressure ventilation reduce venous return and cardiac output
		  • Paradoxal decline in CO_2 instead of induced O_2 increase
		  • Less oxygen delivery available

	Dobutamine	• ↑ cardiac output and contractility • May result into cardiac ischemia (increased O_2 demands)

CARDIOVASCULAR SYSTEM IN MODS

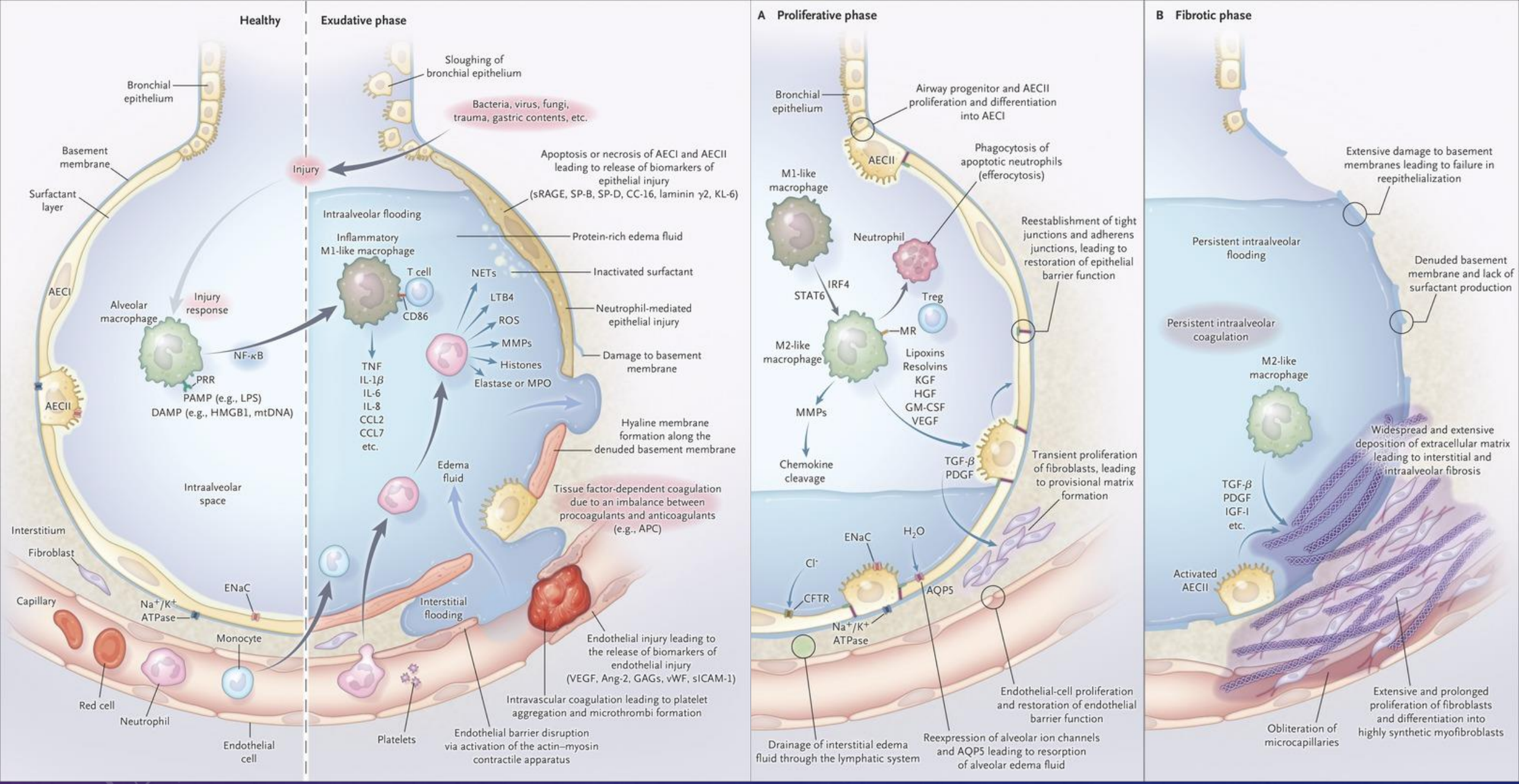
- Features
  1. Altered contractility
  2. Decreased ejection fraction
  3. Diastolic dysfunction
  4. Systolic dysfunction
  5. Ventricular dilation
     - Presence of both 4. and 5 is detected in 50 % septic shock patients and may increase mortality up to 70 %
     - Both 4. and 5. may occur even in normal or high cardiac output

LUNGS IN MODS

- Acute respiratory distress syndrome (ARDS) – The first malfunction in MODS usually
  - Acute inflammatory response with diffuse infiltrates
  - Characteristics
    - Lung edema
    - Poor oxygenation
    - Pulmonary hypertension and acute cor pulmonale (25 % patients)
  - Associated with apoptosis of cells in distant organs and their dysfunction
    - Kidney, colonic villi

LUNGS IN MODS

- „Two-hit“ theory
  - First hit – pneumonia, acid aspiration, contusion, etc.
  - Second hit – mechanical ventilation -> more intense inflammatory response
- Cca 10 % patients are dying from mechanical ventilation injury
  - SIRS usually starts with intubation even hours before ICU admission
  - Mechanical ventilation may solely deregulate immune response and start SIRS!
  - Proper ventilation regime needs to be set



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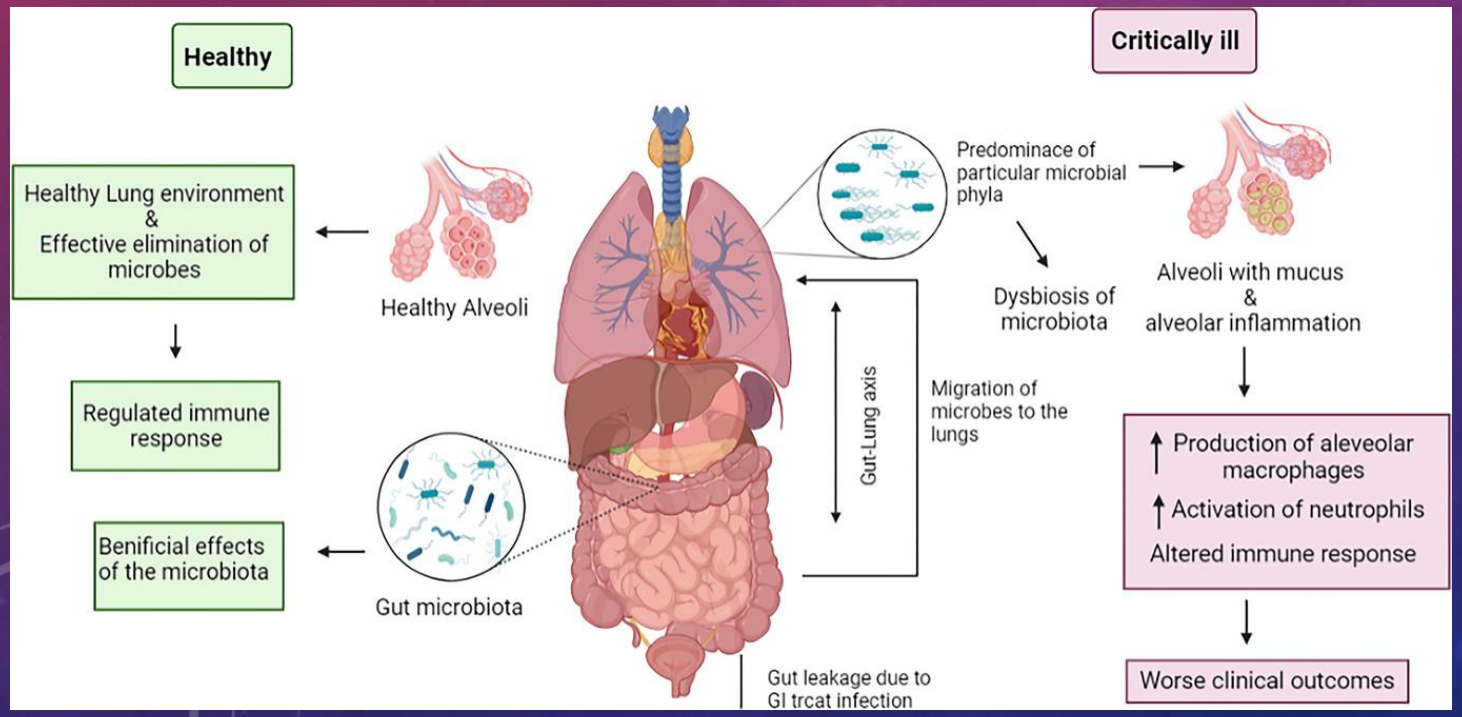
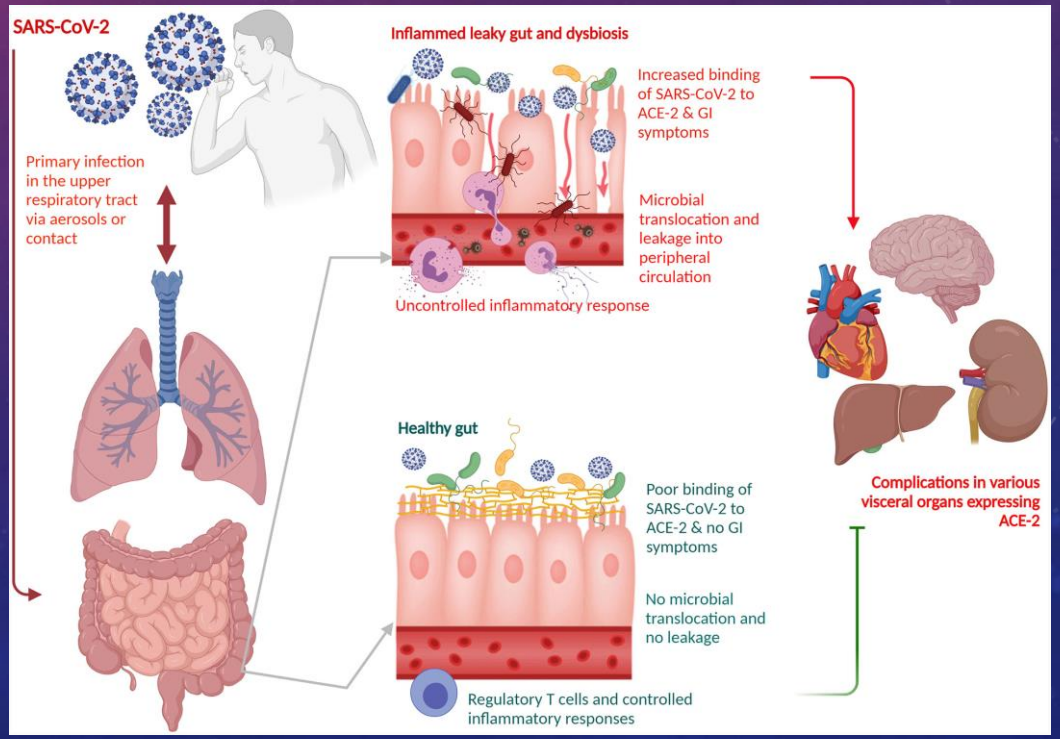
https://www.frontiersin.org/files/Articles/590874/fcimb-11-590874-HTML-r1/image_m/fcimb-11-590874-g001.jpg

ARDS AND DISTANT ORGANS DAMAGE

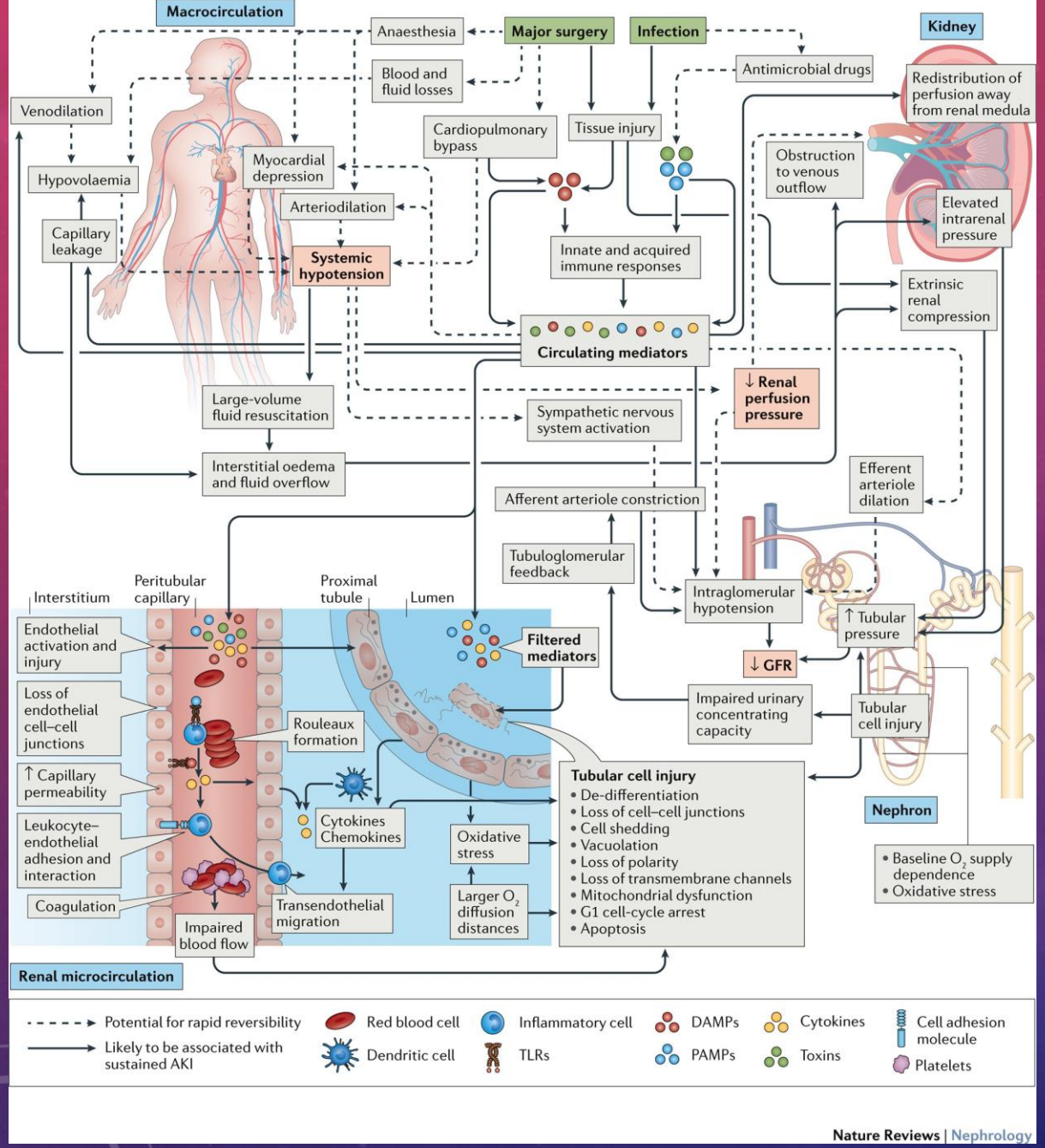
- Deregulated inflammation in ARDS -> cytokines into circulation -> bacteria and toxins from GIT to circulation -> worsening of outcome and distant organs damage
- *Note - Lung-gut axis can work in both ways, but ARDS is usually the primary change in MODS*

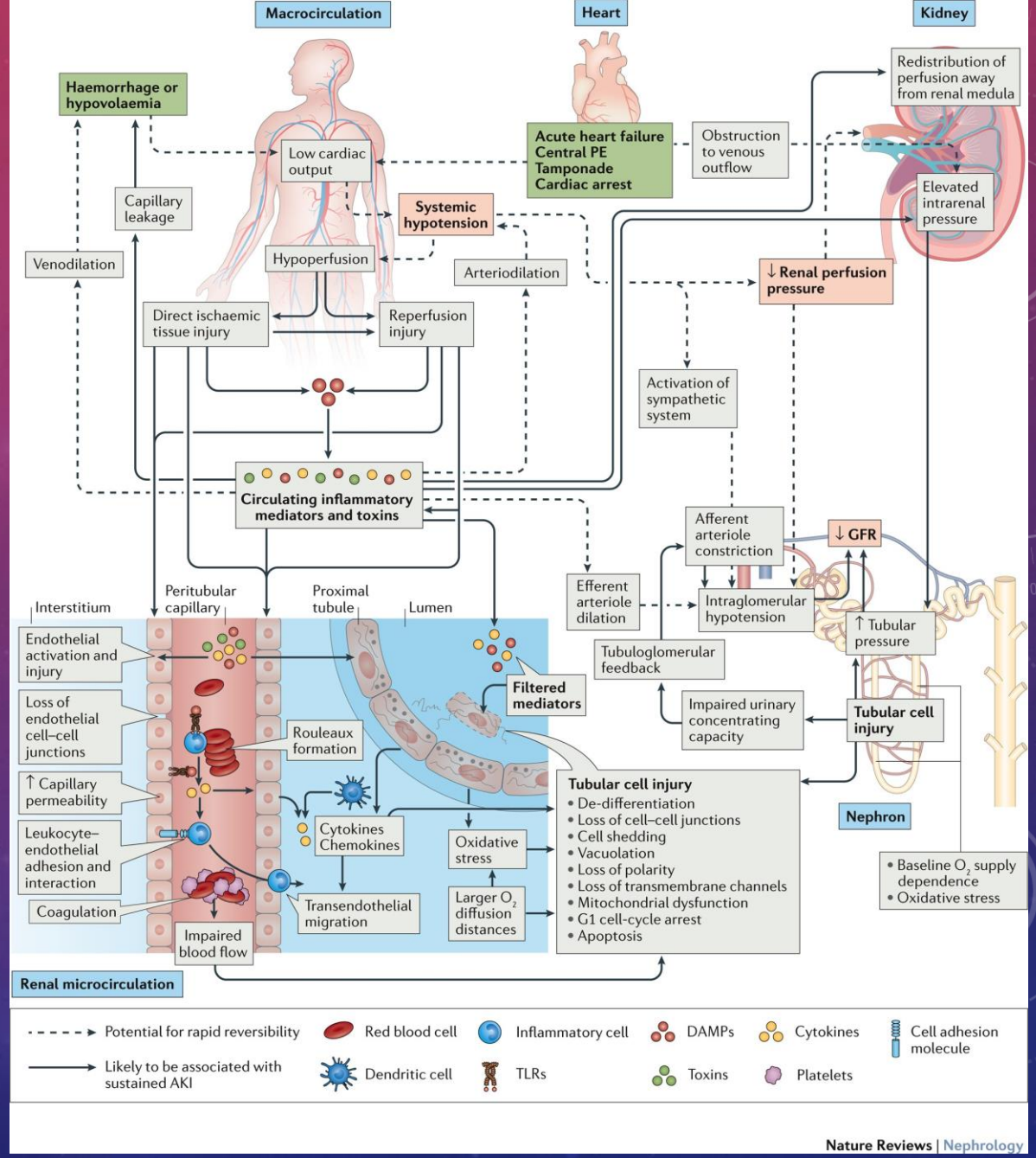




RENAL DYSFUNCTION IN MODS

- Occurs in 30 – 40 % critically ill patients (up to 60 % with mechanical ventilation)
- Acute kidney injury in MODS (see next slide)
  - Decreased filtration -> fluid dysbalance
  - Metabolic acidosis -> pulmonary vasoconstriction, systemic vasodilation
  - Increase of erythropoietin in 48 hrs, then drop
  - Immune response deregulation
    - Decreased cleavage of cytokines
    - Tissue injury lead to production of DAMPs (damage-associated molecular patterns) -> TLRs engaged -> pro-inflammatory cytokines secreted -> IL-2, -6, -8, -12, -18, INF-γ, TNF, CCL2 (monocytes) and CCL5 (monocytes, T-cells)
    - Deregulation of neutrophils, monocytes, T-cells
  - Perivascular infiltrate and microthrombi formation -> may spread to systemic circulation





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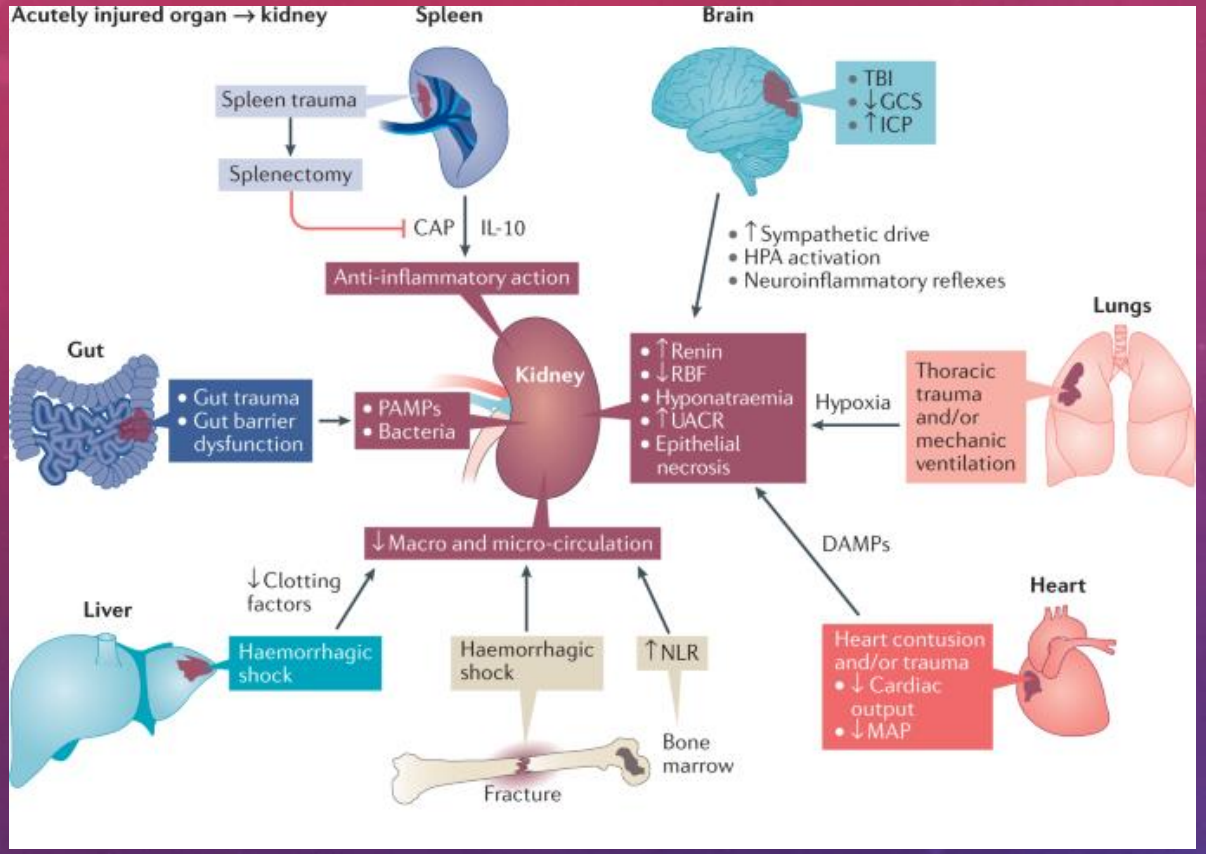

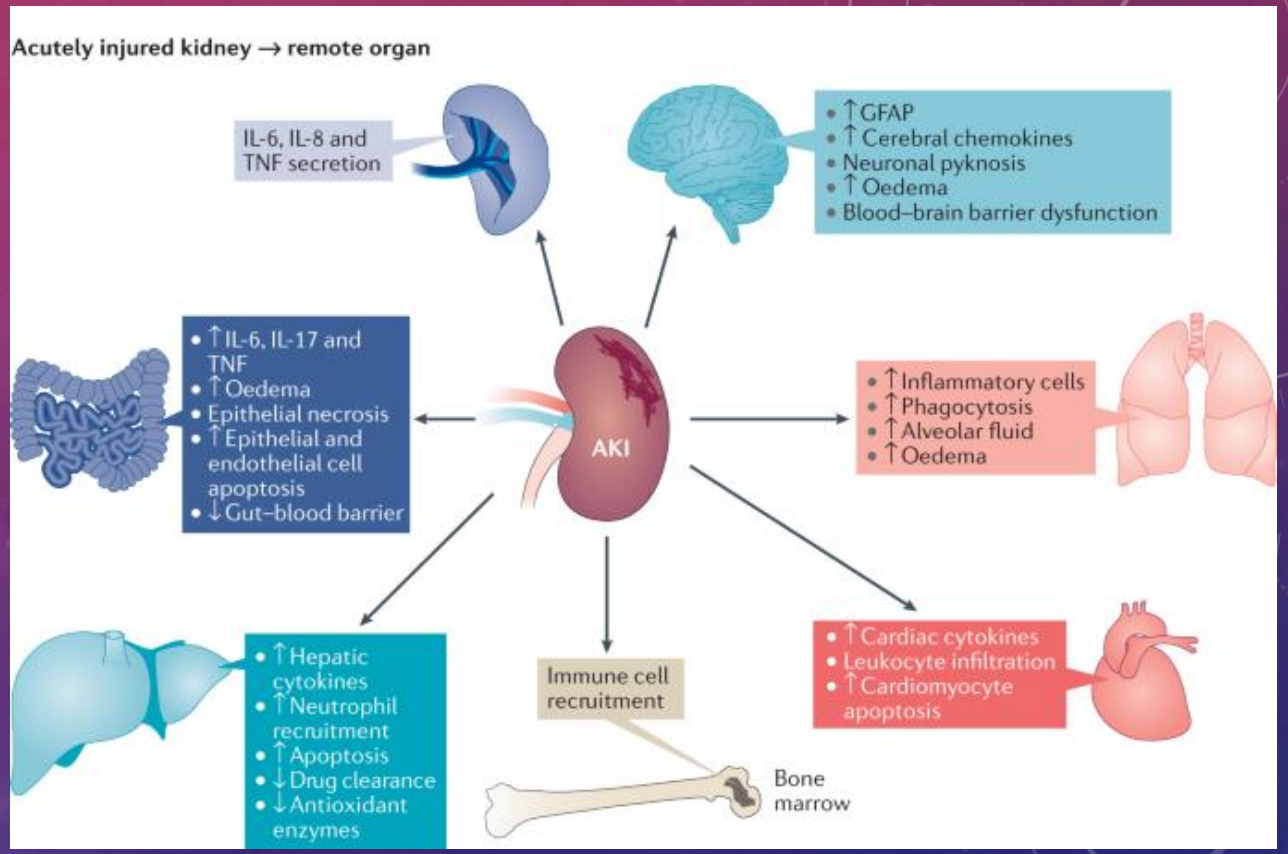

AKI and MODS

SIRS promotes renal damage ↔ AKI affects distant organs dysfunction

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GASTROINTESTINAL SYSTEM IN MODS

- Changes in GIT function may be a motor of changes during MODS
  - Decreased absorption of nutrients
  - Increased gut permeability for bacteria and toxins
  - Alteration of a gut microbiome
- „Gut-lymph“ hypothesis to play the main role
  - Bacterial translocation may lead to deregulation of inflammatory response
  - Emergence of multiple-drug resistance bacteria in critically-ill patients
  - Result of both antibiotics and common treatment and/or surgery
  - Normalisation of gut microbiome decreased risk of MODS

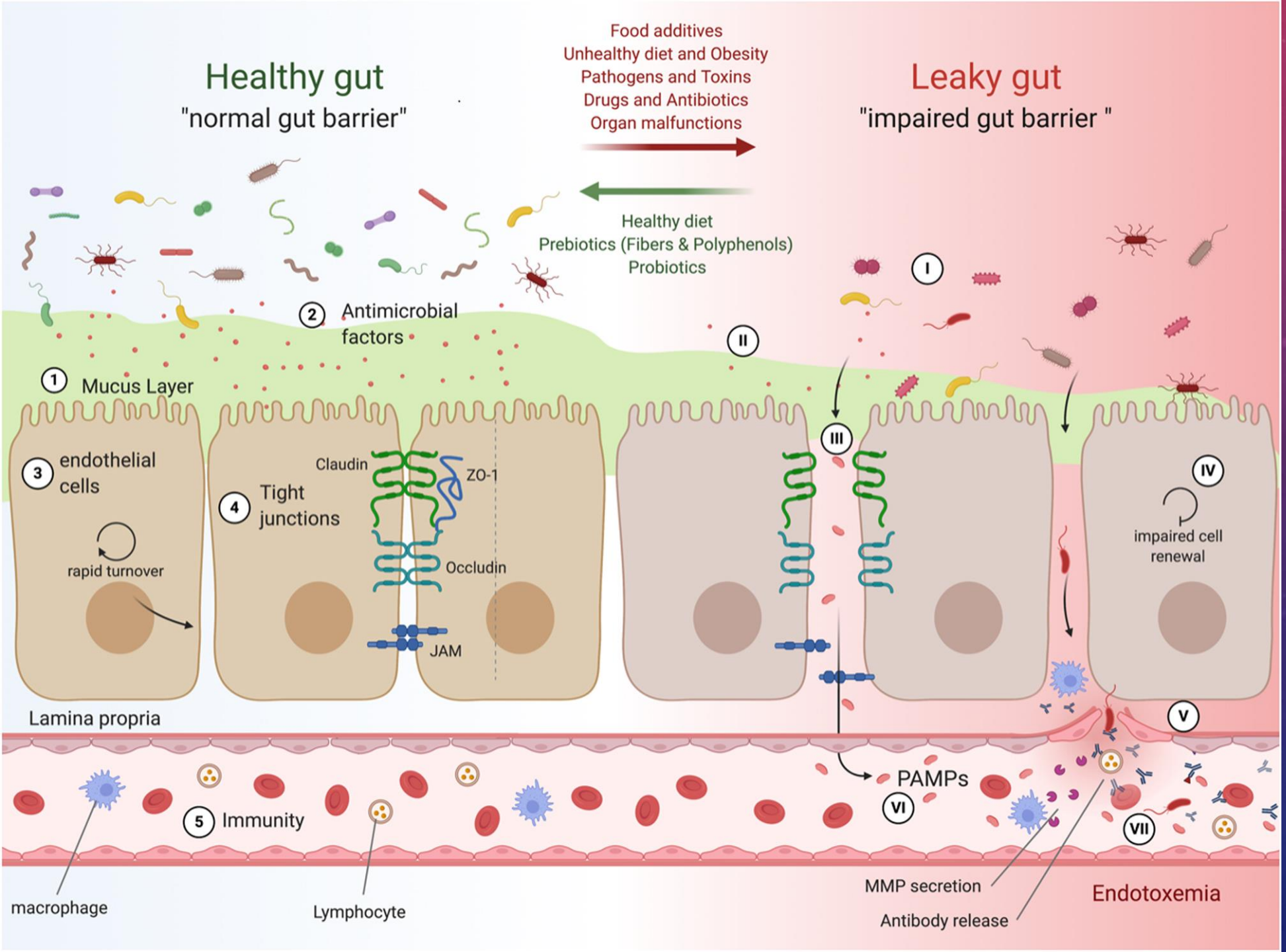
GASTROINTESTINAL BARRIER FUNCTIONS (PHYSIOLOGY)

1. Biological – bacteria provide
   - Metabolic
     - digestion assistance – indigestible oligosaccharides cleaved
     - synthesis of short-chain fatty acids (acetate, propionate, butyrate) for intestinal epithelium energy supply
     - vitamin Bs and K synthesis
     - regulation of entero-hepatic bile acids cycle
   - Immunologic
     - PAMPs production and interaction with innate and adaptive immunity
   - Gut-protective functions
     - countering pathological bacteria (nutrients consumption and prevention of colonisation)

GASTROINTESTINAL BARRIER FUNCTIONS (PHYSIOLOGY)

2. Immune – GALT (gut-associated lymphatic tissue)
   - T-cells
     - T_{regs} induced
     - Th to Th_{17} differentiation
   - B-cells
     - IgA production in response to microbiome
   - Group 3 innate lymphoid cells
   - Dendritic cells and macrophages

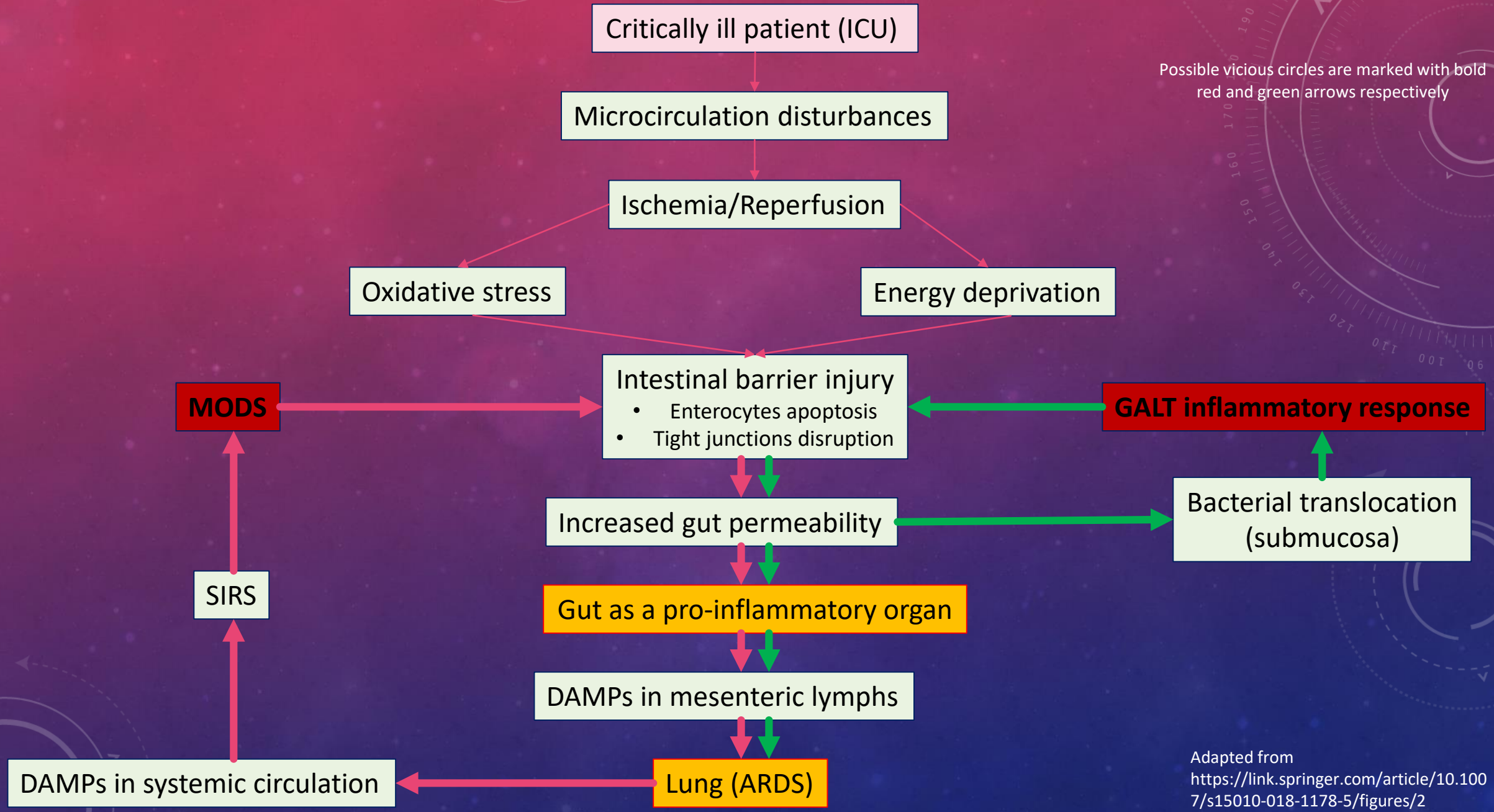
3. Mechanical
   - Closed-lining intestinal epithelium
     - „kissing-points“ – tight junction to prevent ions, molecules and cells unregulated transport (near apical part of cells)
   - Subendothelial cells
   - Vascular endothelium



https://joe.bioscientifica.com/view/journals/joe/248/2/images/JOE-20-0473fig1.jpeg

GUT-LYMPH HYPOTHESIS IN MODS

- „Three-hit (gut) theory“ – breakdown of GIT barrier
  1. Splanchnic hypoperfusion/ischemia
  2. Reperfusion injury
  3. Loss of gut function (leaky guts) -> luminal bacterial/endotoxin translocation
- Mesenteric lymph nodes as a crucial factors
  - Loss of maintenance of commensal bacteria -> pathological species prevail
  - PAMPs overload
  - DAMPs production (danger-associateed molecular patterns)
    - TLR4 and PRR (pattern-recognition receptors) stimulated -> deregulated immune response
  - Drained by cisterna chyli –> left subclavian vein –> lung circulation exposed as first -> possible acceleration of ARDS
  - Ligation of major mesenteric lymphatic duct in animal models improved survival



Possible vicious circles are marked with bold red and green arrows respectively

Adapted from https://link.springer.com/article/10.1007/s15010-018-1178-5/figures/2

LOW CITRULLINE AS A MARKER OF INTESTINAL INSUFFICIENCY?

- Intestinal cells produce citrulline (concentration dependent on mass of cells
  - Intestinal transplantation succes possible predictor
    - Increase after surgery indicates better prognosis
- Citrulline levels correlate
  - Severity of disease – negative and strong
  - Absorption – positive and weak

- Decreased citrulline <20 mmol/L -> intestinal dysfunction
  - Short-bowel syndrome
    - Parenteral nutrition lead to more intense citrulline drop
    - Teduglutide (GLP-2 analogue, growth factor) lead to increase of citrulline
  - Possible negative marker of inflammation
    - Necrotising enterocollitis
    - Coeliac disease (intestinall vill atrophy)
    - Critical illness and sepsis
      - Also possible due to inflammatory reaction affection (possible synergy)

LIVER DYSFUNCTION IN MODS

- Three main pathomechanisms
  1. Hypoxic liver injury
  2. Cholestatic dysfunction
  3. Sclerosing cholangitis in critically ill
- Protective liver mechanisms
  - Hepatic arterial buffer response
    - Blood supply of liver – Portal vein (75 – 80 %) vs. hepatic artery (20 – 25 %)
    - ↓portal vein blood flow
      - hepatic artery dilation (and vice versa)
      - Increased oxygen extraction (up to 90 %)
    - Able to compensate 25 – 60 % of portal vein blood flow loss

HYPOXIA LIVER INJURY (HLI)

Ischemia
- Malperfusion, shock

Impaired oxygen extraction
- Sepsis, shock

Passive venous congestion
- Cardiac insufficiency, heart failure

Systemic hypoxia
- COPD, pneumonia, respiratory failure, ARDS

Inflammatory signals (e.g. endotoxin)

↓iNOS function

↓eNOS phosphorylation

↓hepatic vasodilation

Drug-induced liver injury (e.g. acetaminophen)

Hepatic damage/ Centrilobular necrosis

↑AST, ALT > 20x ULN*

Acute Conditions complicating HLI
- Acute heart failure/cardiogenic shock (50 – 70 %)
- Sepsis (13 – 32 %)

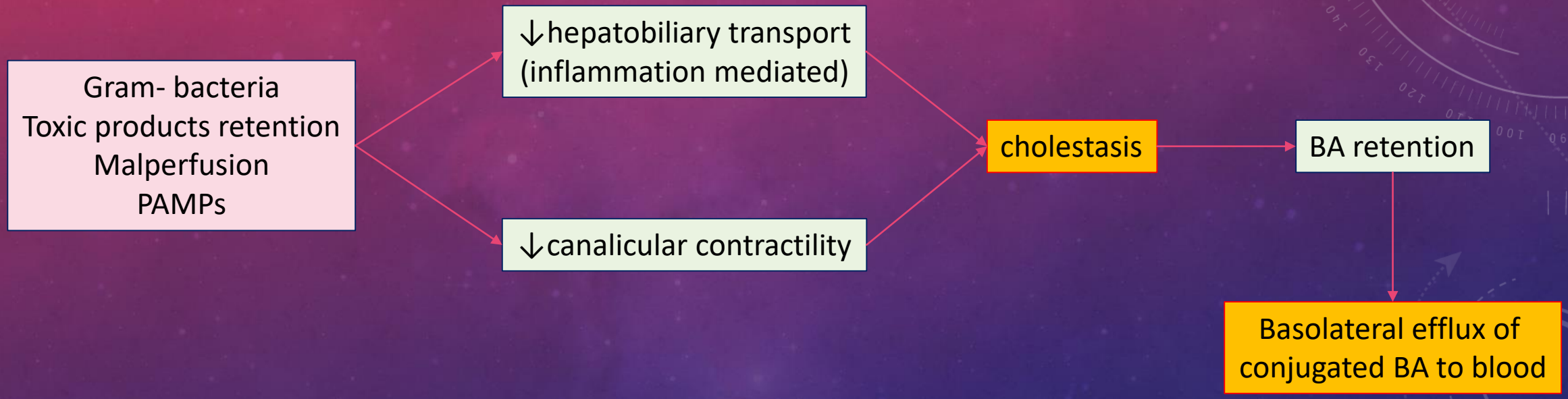
Chronic conditions in HLI process
- Cardiomyopathy (<40 %)
- COPD (20 %)
- Cirrhosis (15 %)

*often in setting of cardiac, circulatory or respiratory failure

CHOLESTATIC DYSFUNCTION

- Occuring in early hours in critically ill patients
- No clear definition
- Up to 20 % ICU patients
  - Mainly in septic shock, cardiogenic shock, less cases after surgery
- Cause or symptom?
  - Bile acids inhibit hepatic iNOS
- Bile acids have pro- and anti-inflammatory effects
  - Neonatal hyperbilirubinemia as a protective factor against S. agalactiae sepsis

CHOLESTATIC DYSFUNCTION SCHEME

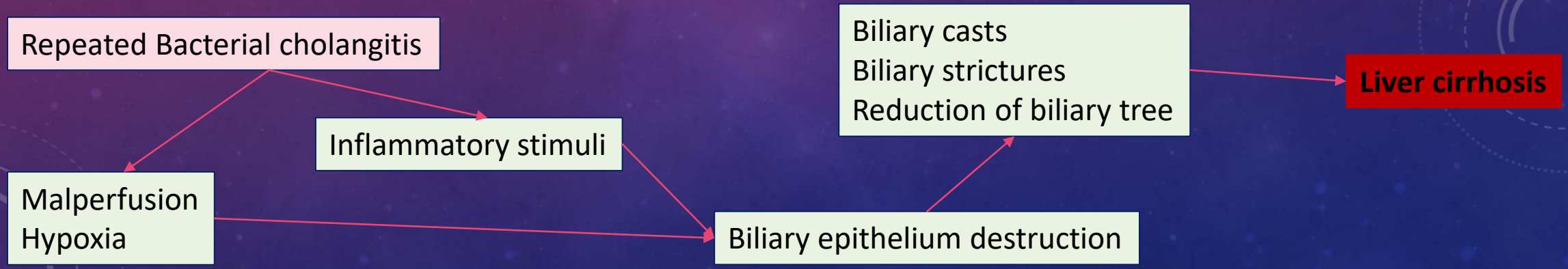


To be considered when

- ALP >6.8 µkat/l (>400 IU/L)
- GGT >1.3 µkat/l (>80 IU/L)
- T-bilirubin >265 µmol/l (or >3 mg/dl)

SCLEROTISING CHOLANGITIS OF CRITICALLY ILL PATIENTS

- Only 0.6 % of critically ill patients
- Progressive condition
- ATB treatment may reduce or prevent progression
- When liver cirhhosis develop only minority eligible for transplantation
  - Median of survival without transplantation is cca 13 months

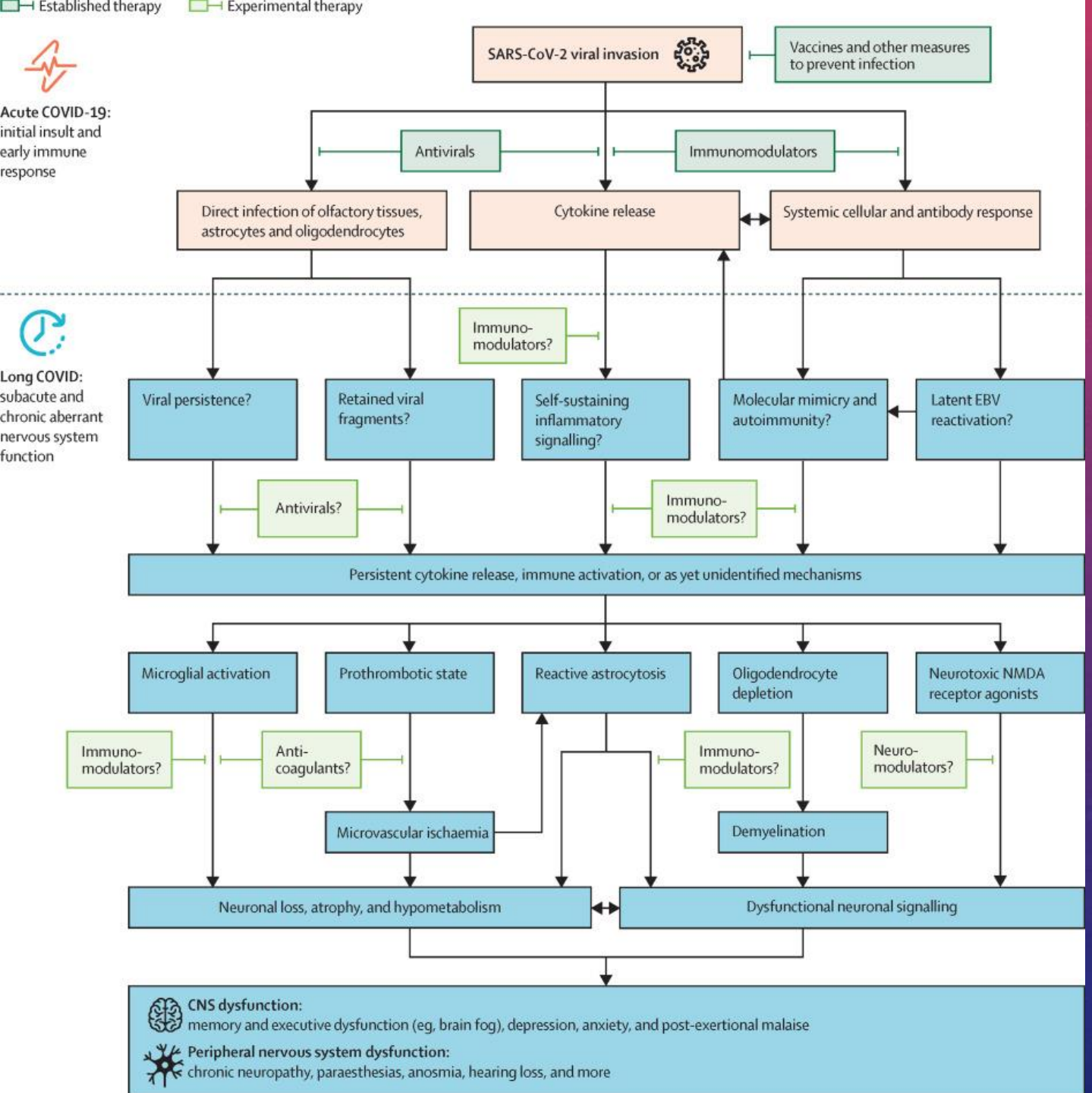


NEURAL SYSTEM IN MODS

- Affected in 70 % of critically ill patients
- Pathomechanism
  - Local inflammatory activation (IL-1, -2, -6, TNF-α) -> systemic
  - Rolling neutrophils, activation of coagulation, microthrombi creation
  - Vasoparalysis -> capillary dilation reduces cerebral blood flow
    - Mitochondrial production halted -> ATP depletion
  - Microglia and astrocytes activated
  - Blood-brain barrier may become leaky – cytokines and immune cells into cerebrospinal liquor
  - Loss of oligodendrocytes – demyelination
  - Neurotransmitter dysbalance

NEURAL SYSTEM IN MODS

- Both central and peripheral may be affected
- Acute disorders are mostly reversible when sepsis or SIRS is resolved
- Central
  - Behavioural changes
    - Depression, psychosis
  - Consciousness alterations
    - Pre-coma, coma; delirium
  - Sepsis-induced encephalopathy
  - Long-term cognitive dysfunction may occur
- Peripheral
  - Critical illness myopathy
  - Critical illness polyneuropathy



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SKIN CHANGES IN MODS

- Acute skin failure
  - Life threatening condition
  - Affect skin and adjacent tissues
    - Cells cannot survive in zones of hypoxia, mechanical stress, lack of nutrients and toxic products and metabolites accumulation
  - Skin cannot regulate
    - Body core temperature
    - Percutaneous loss of fluid, electrolytes and protein (fluid and ion dysbalance)
    - Penetration of foreign bodies and pathogens (mechanical and immune barrier compromised)
- Pathomechanism
  - Combination of hypoxia, hypoperfusion, inflammatory response, ↑vascular permeability -> cellular acidosis, hypermetabolic state -> loss of cellular functions

SCORING SYSTEMS IN MODS

- SOFA (Sequential Organ Failure Assessment)
  - Best mortality predictor in initial 48 hours

Score	CNS (GCS)	CVS (MAP or vasopressors)	Respiratory PaO2/FiO2 (mmHg/kPa)	Coagulation Platelets (x103/µl)	Liver Bilirubin (mg/dl / µmol/l)	Renal Creatinine (mg/dl / µmol/l) or urine output
+0	15	MAP ≥70 mmHg	≥400/53.3	≥150	<1.2/20	<1.2/110
+1	13 – 14	MAP <70 mmHg	<400/53.3	<150	1.2 – 1.9/20 – 32	1.2 – 1.9/ 110 - 170
+2	10 – 12	dopamine ≤ 5 µg/kg/min or dobutamine (any dose)	<300/40	<100	2.0 – 5.9/33 - 101	2.0 – 3.4/ 171 - 299
+3	6 – 9	dopamine > 5 µg/kg/min OR epinephrine ≤ 0.1 µg/kg/min OR norepinephrine ≤ 0.1 µg/kg/min	<200/(26.7 and mechanically ventilated including CPAP	<50	6.0 – 11.9/102 - 204	3.5 – 4.9/ 300 – 440 Or <500 ml/day
+4	3 - 5	dopamine > 15 µg/kg/min OR epinephrine > 0.1 µg/kg/min OR norepinephrine > 0.1 µg/kg/min	<100/(13.3 and mecha nically ventilated including CPAP	<20	>12.0/204	>5.0/440 Or <100 ml/day

Initial score	Average mortality
11 or less, then drop	<6 %
Constant	
2 - 7	37 %
8 – 11	60 %
11 - 24	91 – 95 %

SCORING SYSTEM IN MODS

- Quick SOFA (qSOFA)
  - When laboratory data not available/unable to be assessed
  - Orientational parameter
  - Prognosis
    - Initial score of 2 – 3 -> increased mortality or prolonged ICU stay

Parameter	0	1
Systolic BP (mmHg)	>100	≤100
Respiration (breaths/min)	<22	≥22
GCS	15	14 - 3

QUICK SOFA MNEMONICS – USE „HAT“

- **H**ypotension (systolic BP <100 mmHg)
- **A**ltered consciousness (GCS <15)
- **T**achypnea >22/min

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SCORING SYSTEMS IN MODS

- APACHE IV (Acute Physiology and Chronic Health Evaluation)
  - First APACHE model introduced in 1981
  - APACHE II
    - Acute physiology score + age points + chronic health points
  - APACHE III (1991)
    - 17 variables
  - APACHE IV released in 2006
    - Complex system – 142 variables
    - Web calculations can be done
    - Developed and validated in ICUs of USA only

ICU Calculators - RNSH

APACHE IV Score

https://intensivecarenetwork.com/Calculators/Files/Apache4.html

Age (ans)	
Temperature (°C)	37
MAP (mmHg)	70
HR (/min)	80
RR (/min)	15
Mecanical Ventilation	○ No ○ Yes
FiO2 (%)	
pO2 (mmHg)	90
pCO2 (mmHg)	40
Arterial pH	7.4
Na+ (mEq/L)	140
Urine Output (mL/24h)	
Creatinine (mg/dL)	1
Urea (mEq/L)	4
BSL (mg/dL)	100
Albumin (g/L)	40
Bilirubin (mg/dL)	1
Ht (%)	40
WBC (x1000/mm3)	10
GCS :	☐ Not available
- Eyes	4. Spontaneous
- Verbal	5. Oriented
- Motor	6. On Command

Change values used for AaDO2 calculation

Chronic Health Condition :

- ☐ CRF / HD
- ☐ Cirrhosis
- ☐ Hepatic Failure
- ☐ Metastatic Carcinoma
- ☐ Lymphoma
- ☐ Leukemia / Myeloma
- ☐ Immunosuppression
- ☐ AIDS

Admission Information :

Pre-ICU LOS (days)	
Origin	Other
Readmission	◉ No ○ Yes
Emergency Surgery	◉ No ○ Yes

Admission Diagnosis :

○ Non operative ○ Postoperative

System

Diagnosis

Thrombolysis : ◉ No ○ Yes

Calculate

APACHE IV Score		/286
APS Score		/239
Estimated Mortality Rate		%
Estimated Length of Stay		days

SCORING SYSTEMS IN MODS

- Marshall‘s MOD Score
  - Simple evaluation of organs dysfunction
  - More than 2 pts in each parameter -> organ failure
  - When staying at ICU - prognosis
    - 9 – 12 –> 25 % mortality
    - 13 – 16 –> 50 % mortality
    - 17 – 20 –> 75 % mortality
    - 21 – 24 –> 100 % mortality

Organ System	0	1	2	3	4
Respiratory PO_2/FiO_2 (mmHg)	>300	226–300	151–225	76–150	≤ 75
Renal serum creatinine (µmol/liter)	≤ 100	101-200	201–350	351–500	>500
Hepatic serum bilirubin (µmol/l)	≤ 20	21–60	61–120	121–240	>240
Cardiovascular PAR[1)]	≤ 10,0	10,1–15,0	15,1–20,0	20,1–30,0	>30,0
Hematologic platelets/nl	>120	81–120	51–80	21-50	≤ 20
Neurologic Glasgow Coma Score	15	13–14	10–12	7–9	≤ 6

https://epomedicine.com/wp-content/uploads/2015/10/Modified-marshall-score.jpg

SCORING SYSTEMS IN MODS

- Modified Marshall Scoring System for Organ Dysfunction

Table 7.4-1. Modified Marshall scoring system

Organ system	Score				
	0	**1**	**2**	**3**	**4**
Respiratory (PaO_2/FiO_2)	>400	301-400	201-300	101-200	≤101
Renal (serum creatinine, micromol/L)[a]	≤134	134-169	170-310	311-439	>439
Cardiovascular (systolic blood pressure, mm Hg)[b]	>90	<90 Fluid responsive	<90 Not fluid responsive	<90, pH <7.3	<90, pH <7.2

A score of ≥2 in any system defines the presence of organ failure.

[a] The score for patients with preexisting chronic renal failure depends on the extent of further deterioration of baseline renal function. No formal correction exists for a baseline serum creatinine ≥134 micromol/L or ≥1.4 mg/dL.

[b] Off inotropic support.

Source: Gut. 2013;62(1):102-11.

https://empendium.com/mcmtextbook/table/B31.5.1-2.

SCORING SYSTEMS IN MODS

- Denver MOF Score
  - In trauma patients with intensity severity score >15 and surviving 48 hours
  - Any parameter >3 indicates worse outcome

Dysfunction	Grade 0	Grade 1	Grade 2	Grade 3
Pulmonary PaO2/FiO2 ratio	> 208	208 - 165	165 - 83	< 83
Renal Creatinine (umol/L)	<159	160 - 210	211 - 420	> 420
Hepatic Total Bilirubin (umol/L)	< 34	34 – 68	69 - 137	> 137
Cardiac Inotropes	No inotropes	Only one inotrope at a small dose *	Any inotrope at moderate dose or >1 agent, all at small doses *	Any inotrope at large dose or > 2 agents at moderate doses *

*

* Inotrope doses (in ug/ Kg / min):

	Small	Moderate	Large
Milrinone	<0.3	0.4 -0.7	>0.7
Vasopressin	<0.03	0.03 -0.07	>0.07
Dopamine	<6	6 - 10	>10
Dobutamine	<6	6 - 10	>10
Epinephrine	<0.06	0.06 -0.15	>0.15
Norepinephrine	<0.11	0.11 -0.5	>05
Phenylephrine	<0.6	0.6 - 3	>3

https://www.researchgate.net/publication/23303398/figure/tbl1/AS:932288380538896@1599286279908/Denver-Postinjury-Multiple-Organ-Failure-Score.png

SCORING SYSTEMS IN MODS

- PIRO (Prediction, Infection, Response & Organ Dysfunction)
  - For use in emergency department when infection suspected
  - Various phenotypes (e.g. P2I1R1O1, etc.)

Focus of infection	Stage I (*n* = 431, 26%)	Stage II (*n* = 510, 31%)	Stage III (*n* = 601, 37%)	Stage IV (*n* = 96, 6%)
	Predicted hospital mortality rate 0–5%	Predicted hospital mortality rate 6–20%	Predicted hospital mortality rate 21–50%	Predicted hospital mortality rate 51–100%
	$P_{1\text{-}2}\ I_{1\text{-}2}\ R_1\ O_1$	$P_1\ I_2\ R_1\ O_2$		$P_{2\text{-}3}\ I_{1\text{-}2}\ R_2\ O_2$
	$P_1\ I_1\ R_1\ O_2$	$P_1\ I_{1\text{-}2}\ R_2\ O_2$	$P_3\ I_{1\text{-}2}\ R_2\ O_1$	
	$P_1\ I_{1\text{-}2}\ R_2\ O_1$	$P_2\ I_{1\text{-}2}\ R_1\ O_2$	$P_3\ I_{1\text{-}2}\ R_1\ O_2$	
	$P_2\ I_{1\text{-}2}\ R_1\ O_1$	$P_2\ I_{1\text{-}2}\ R_2\ O_1$		
		$P_3\ I_{1\text{-}2}\ R_1\ O_1$		

	Observed hospital mortality rate 3% (*n* = 14)	Observed hospital mortality rate 15% (*n* = 78)	Observed hospital mortality rate 24% (*n* = 145)	Observed hospital mortality rate 34% (*n* = 33)
Respiratory (*n* = 860, 52.5%)	3% (6/215)	19% (46/248)	26% (94/363)	44% (15/34)
Urinary (*n* = 332, 20.3%)	3% (2/66)	10% (11/111)	15% (21/136)	26% (5/19)
GI (*n* = 282, 17.5%)	3% (4/126)	12% (11/91)	29% (12/41)	28% (8/29)
Primary bacteraemia (*n* = 159, 9.7%)	8% (2/24)	17% (10/60)	30% (18/61)	36% (5/14)

Original cohort from 2013 https://annalsofintensivecare.springeropen.com/articles/10.1186/s13613-021-00966-7/tables/2

P score	Points	I score	Points	R score	Points	O score	Points
Age, years		*Type of infection*		*Altered temperature*		Hypotension	3
≤ 60	0	CAI	0	No	0	SOFA > 0	1
61–80	1	HCAI	1	Fever	− 1		
> 80	3	HAI	2	Hypothermia	1		
Male	1			Hyperglycemia	1		
Previous ATB	1			Tachypnea	1		
Chronic hepatic disease	4			*Severity of infection*			
Chronic hematologic disease	3			Infection or sepsis	0		
Cancer	3			Severe sepsis	1		
Atherosclerosis	1			Septic shock	4		
Karnovsky index < 70	2						
Total possible points	18		2		7		4
P1 (0–2 point)		I1 (0–1 point)		R1 (-1–3 points)		O1 (0 points)	
P2 (3–4 points)		I2 (2 points)		R2 (≥ 4 points)		O2 (≥ 1points)	
P3 (≥ 5 points)							

P-score predisposition score, *I score* insult/infection score, *R score* host response score, *O score* organ dysfunction score, *ATB* antibiotic therapy, *CAI* community-acquired infection, *HCAI* healthcare-associated infection, *HAI* hospital-acquired infection, *SOFA* sepsis-related organ failure assessment

https://annalsofintensivecare.springeropen.com/articles/10.1186/s13613-021-00966-7/tables/1

SCORING SYSTEMS IN MODS

- Mortality prediction models (MPM-II and MPM0-III)
  - MPM-II (1993)
    - Assessment at 0, 24, 48 and 72 hours
    - Parameters
      - physiology (coma, HR>150, sBP<90)
      - chronic dg. (CKD, cirrhosis, metastases)
      - acute dg. (ARI, dysrhythmia, stroke, GIT bleeding, intracranial mass effect)
      - other factors (CPR, mechanical ventilation, emergency surgery)
    - Mortality overprediction (increases when criteria are not improving)
  - MPM0-III (2005)
    - 15 variables independent of diagnosis

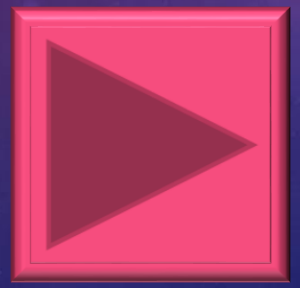
(Mortality Probability Models)

Variables (Help)	Values (1 if yes, 0 otherwise)	Beta
Medical or unscheduled surgery admission		0
Metastatic neoplasm		0
Cirrhosis		0
Chronic renal insufficiency		0
C.P.R. prior to admission		0
Coma (Glasgow 3-5) (Help)		0
Heart Rate > = 150		0
Systolic Blood Pressure < = 90 mmHg		0
Acute renal insufficiency		0
Cardiac dysrhythmia		0
Cerebrovascular incident		0
Gastrointestinal bleeding		0
Intracranial mass effect		0
Mechanical ventilation		0
Age	0	0.03057
Predicted Death rate :		Logit = 0
0 Compute Clear		Logit = Sum (values * beta) + age * 0.03057 -5.46836 Predicted death rate = $(e^{Logit}) / (1 + e^{Logit})$

https://f6publishing.blob.core.windows.net/664e9405-bb4d-437c-a4d5-60bd87208e7b/WJCCM-1-67-g005.jpg

SCORING SYSTEMS IN MODS

- SAPS II and III (Simplified Acute Physiology Score)
  - SAPS II (1993)
    - At ICU admission, better for disease group survival than individual prediction
    - Total 0 – 163 pts
    - Age
    - 12 physiological variables (incl. CVS, respiratory, renal, neurological, hematological, hepatic)
    - Type of admission (unscheduled surgery, scheduled surgery, medical)
    - Underlying disease variables (AIDS, metastases, hematologic malignancy)
  - SAPS III (2005)
    - See next slide



Age, years

<40	**0**
40-59	+5
60-69	+9
70-74	+13
75-79	+15
≥80	+18

Length of stay before ICU admission, days

<14 0	14-27 +6	≥28 +7

Intrahospital location before ICU admission

Emergency room	+5
Other ICU	+7
Other ward	+8

Use of major therapeutic options before ICU admission

Not all variables collected were included in the final data model, please see original article in "Evidence" for further information.

Other/none	**0**
Vasoactive drugs	+3

Planned or unplanned ICU admission

Planned	**0**
Unplanned	+3

Surgical status at ICU admission

Scheduled surgery	0
No surgery	+5
Emergency surgery	+6

Acute infection at ICU admission

Not all variables collected were included in the final data model, please see original article in "Evidence" for further information.

Other/none	**0**
Nosocomial	+4
Respiratory	+5

Glasgow Coma Scale/Score

Lowest within 1 hr of ICU admission

≥13 +1	7-12 +2	6 +7.5	5 +10	3-4 +15

Total bilirubin, mg/dL (μmol/L)

Highest within 1 hr of ICU admission

<2 mg/dL (<34.2 μmol/L)	+1
2-5.9 mg/dL (34.2-102.5 μmol/L)	+4
≥6 mg/dL (≥102.6 μmol/L)	+5

Body temperature, °C (°F)

Highest within 1 hr of ICU admission

≥35 °C (≥95 °F)	+1
<35 °C (<95 °F)	+7.5

Creatinine, mg/dL (μmol/L)

Highest within 1 hr of ICU admission

(3-4 μmol/L)	+15
(5 μmol/L)	+10
(6 μmol/L)	+7.5
<1.2 mg/dL (<106.1 μmol/L)	+1
1.2-1.9 mg/dL (106.1-176.7 μmol/L)	+2
2-3.4 mg/dL (176.8-309.3 μmol/L)	+7
≥3.5 mg/dL (≥309.4 μmol/L)	+8

Heart rate, beats/min

Highest within 1 hr of ICU admission

<120	+1
120-159	+5
≥160	+7

Leukocytes, G/L

Highest within 1 hr of ICU admission

<15 +1	≥15 +2

pH

Lowest within 1 hr of ICU admission

>7.25 +1	≤7.25 +3

Platelets, G/L

Lowest within 1 hr of ICU admission

≥100	+1
50-99	+5
20-49	+8
<20	+13

Systolic blood pressure, mm Hg

Lowest within 1 hr of ICU admission

≥120	+1
70-119	+3
40-69	+8
<40	+12

Oxygenation

PaO_2, FiO_2 refer to arterial oxygen pressure (lowest), inspiratory oxygen concentration and MV refers to ventilatory support and mechanical ventilation

PaO_2≥60 and no MV	+1
PaO_2<60 and no MV	+5
PaO_2/FiO_2≥100 and MV	+7
PaO_2/FiO_2<100 and MV	+11

Comorbidities

Cancer therapy

Chemotherapy, immunosuppression, radiotherapy, steroid treatment

No 0	Yes +3

Chronic HF (NYHA IV)

No 0	Yes +6

Haematological cancer

No 0	Yes +6

Cirrhosis

No 0	Yes +8

AIDS

No 0	Yes +8

Metastatic cancer

No 0	Yes +11

Reason(s) for ICU admission

If both reasons are present, only the worse value (-4) is scored; select "Neurologic: seizures"

Neither	**0**
Cardiovascular: rhythm disturbances	-5
Neurologic: seizures	-4

Cardiovascular: hypovolemic hemorrhagic shock, hypovolemic non-hemorrhagic shock

No 0	Yes +3

Digestive: acute abdomen, other

No 0	Yes +3

Neurologic: focal neurologic deficit

No 0	Yes +7

Digestive: severe pancreatitis

No 0	Yes +9

Neurologic: intracranial mass effect

No 0	Yes +10

Variable	Age restriction				Score appointed
	Neonate	Infant	Child	Adolescent	
SBP (mmHg)	40-55	45-65	55-75	65-85	3
	<40	<45	<55	<65	7
Temperature	All ages		<33°C or>40°C		3
Mental status	All ages		Stupor or coma (GCS<8)		5
	Neonate	**Infant**	**Child**	**Adolescent**	
Heart rate	215-225	215-225	185-205	145-155	3
	>225	>225	>205	>155	4
Pupillary reflex	All ages=one pupil fixed		Pupil>3 mm		7
	All ages=both fixed		pupil>3 mm		11
Acidosis pH	All ages=pH: 7.0-7.28 or total CO_2 (mEq/L): 5-16.9				2
	All ages=pH: <7.0 or total CO_2: <5				6
pH	All ages=7.48-7.55				2
	All ages≥7.55				3
PCO_2 (mmHg)	All ages=50.0-75.0				1
	All ages≥75.0				3
Total CO_2 (mmol/L)	All ages≥34.0				4
Arterial PaO_2 (mmHg)	All ages=42.0-49.9				3
	All ages=42.0				6
Glucose	All ages>11.0 mmol/L (200 mg/dl)				2
Potassium	All ages>6.9 mmol/L				3
	Neonate	**Infant**	**Child**	**Adolescent**	
Creatinine (μmol/L)	>75	>80	>80	>115	2
White blood cells	All ages≤3000 cells/mm^3				4
	Neonate		All other ages		
Prothrombin time (PT)	PT>22.0 s		PT>22.0 s		3
Partial thromboplastin time (PTT)	PTT>85.0 s		PTT>57.0 s		3
Platelets (cells/mm^3)	All ages=100,000-200,000				2
	50,000-99,999				4
	<50,000				5

SCORING SYSTEMS IN MODS

PRISM III (1996) & IV (2013) score

- PRISM III
  - 17 variables, 26 ranges
- PRISM IV
  - + Age
  - + Admission source
  - + CPR in previous 24 hrs
  - + Cancer
  - + Low-risk systems of primary dysfunction
  - + Neurologic variable (subscore from PRISM III)
  - + Non-neurologic variable (subscore from PRISM III)

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DISSEMINATED INTRAVASCULAR COAGULOPATHY

DIC- DISSEMINATED INTRAVASCULAR COAGULOPATHY

- Thrombohemorrhagic disorder characterised by an excessive activation of a coagulation system and formation of thrombi
- Acute, subacute, chronic form

- Occurs as a complication of many disorders, not a primary disease
  - 50% cases: obstetrics (amniotic fluid embolism, retained dead fetus, placenta tissue embolism)
  - 33% carcinomatosis
  - Rest- massive trauma, massive burns, sepsis, systemic inflammation

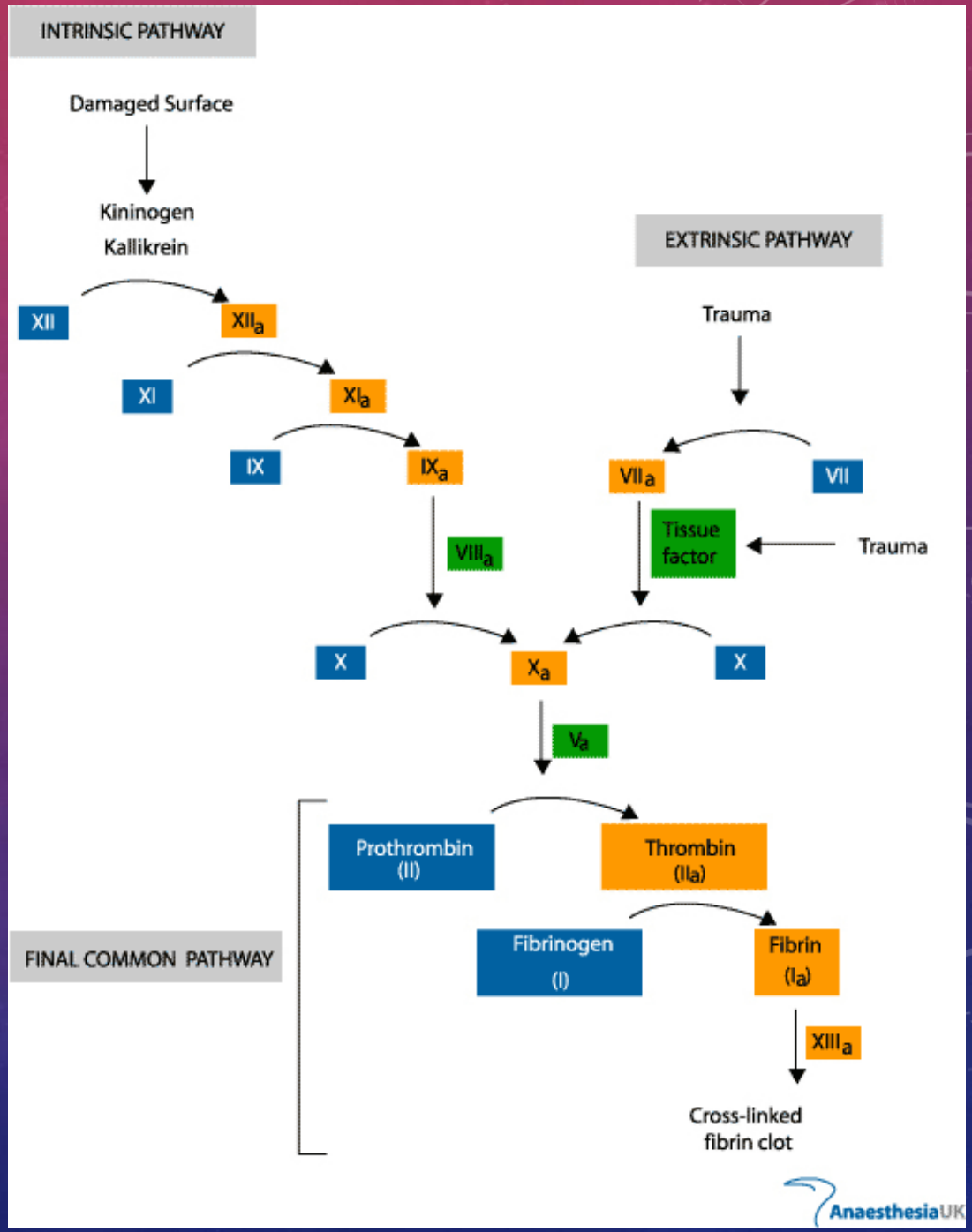
DIC- DISSEMINATED INTRAVASCULAR COAGULOPATHY

- Normally - coagulation is a local process
- DIC - systemic coagulation (at more places at same time), that leads to consumption and thus depletion of coagulation factors and platelets - **consumption coagulopathy,** with secondary fibrinolysis. Bleeding, thrombi!

- Combination of
  - **coagulation defect** (low fibrinogen and other plasma coagulation factors) and of
  - **primary hemostasis defect** (thrombocytopenia)
  - Intensive activation of **fibrinolysis** (D-dimer)

COAGULATION CASCADE

- Excessive activation of a coagulation system or insufficient function of anticoagulant system has a key role in DIC



https://www.researchgate.net/profile/Sebastien-Le-Yaouanq/publication/277033524/figure/fig12/AS:669484671045647@1536628992399/Cascade-de-la-coagulation-sanguine-source-wwwfrcacouk.ppm

PATHOPHYSIOLOGY

- DIC starts by activation of a coagulation cascade (exposure of tissue factor or activation of other procoagulants)
- Tissue factor activates factor VII. Tissue factor is normally not present in circulation !

- Systemic coagulation -> microthrombi -> obliteration of small vessels -> **tissue ischemia**
- Consumption of coagulation factors -> **bleeding**
  - Can be a massive bleeding- **hemorrhagic, hypovolemic shock !**

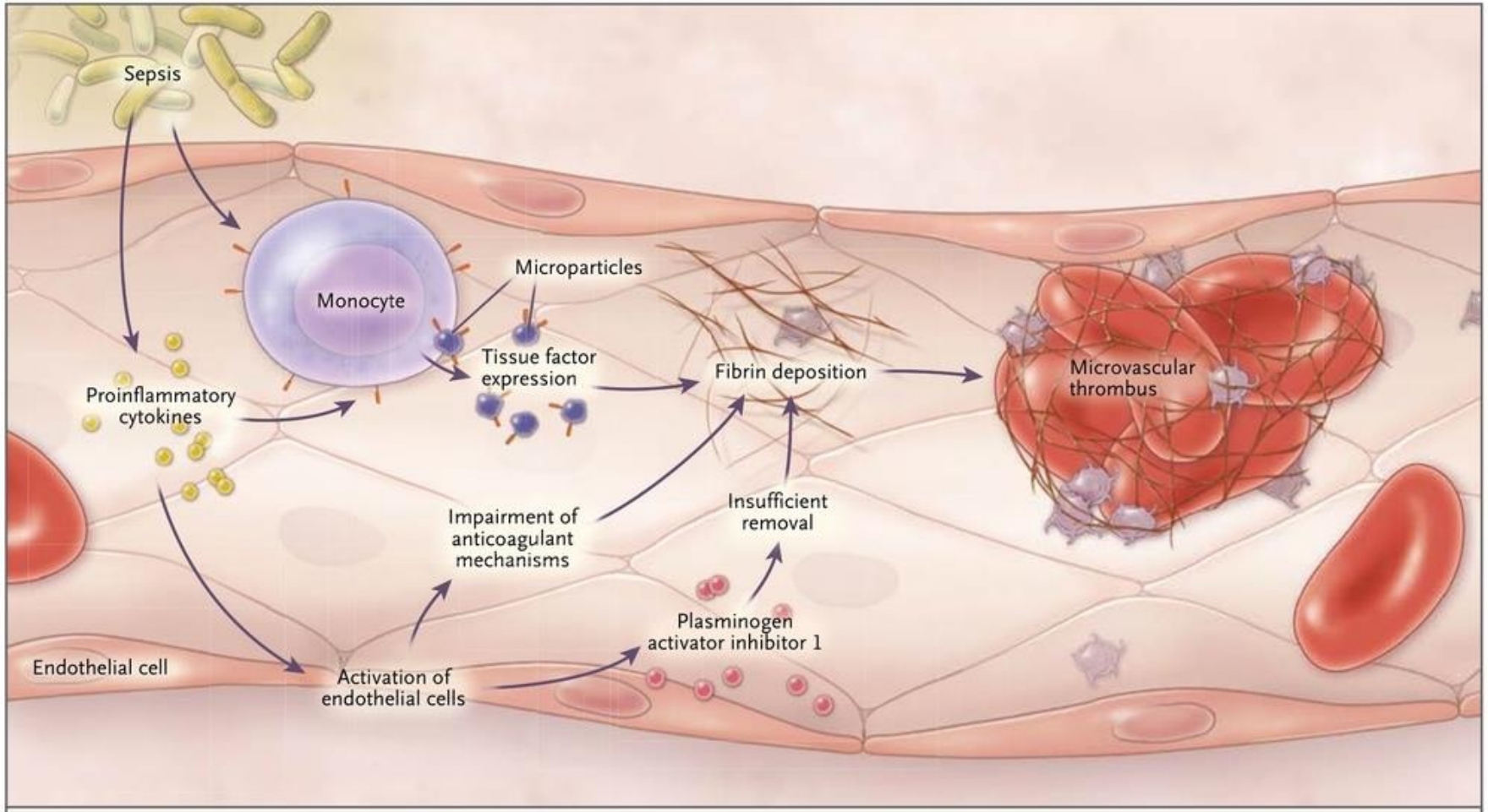
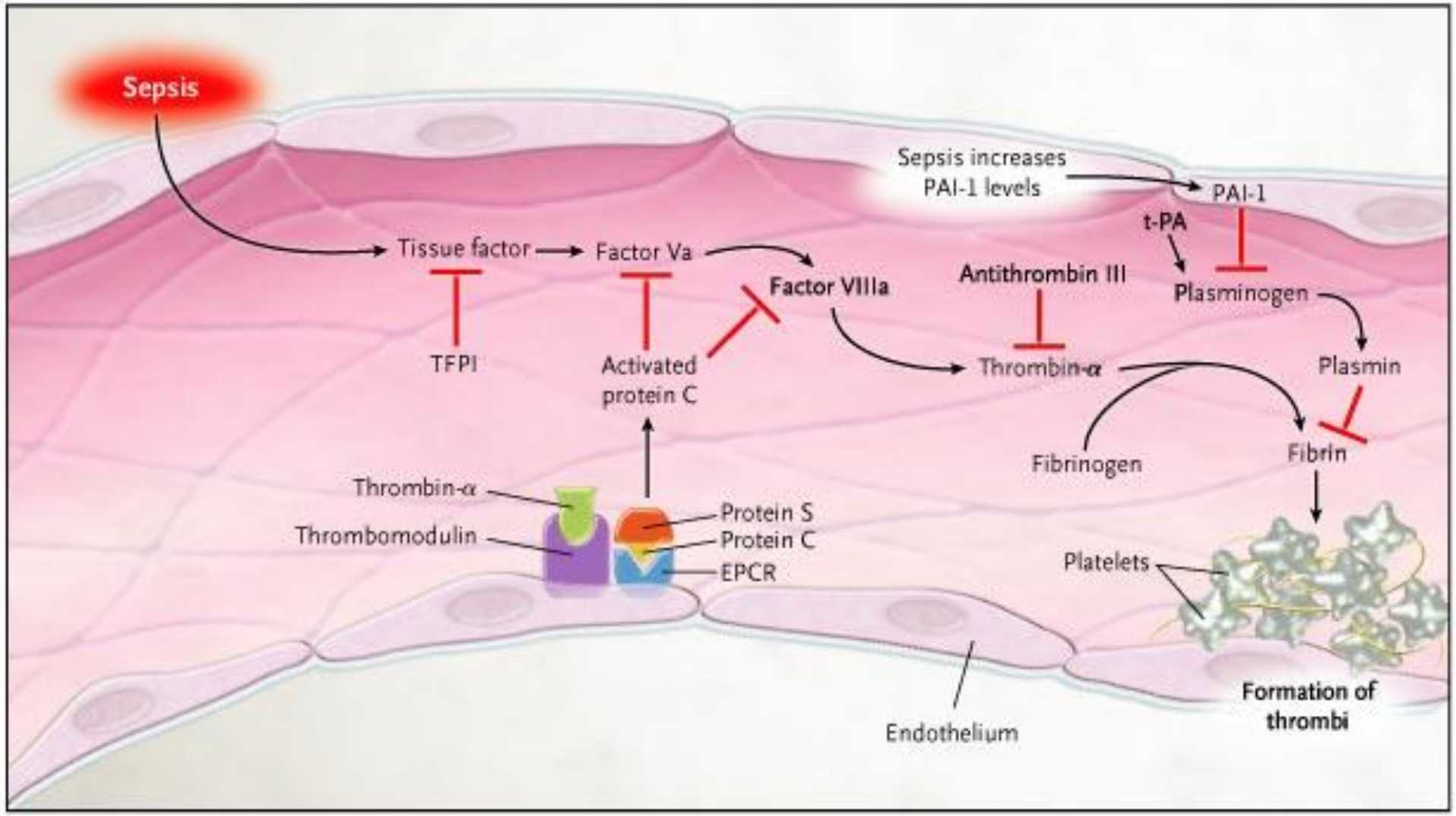


Figure 2. Pathogenesis of Disseminated Intravascular Coagulation in Sepsis.

Through the generation of proinflammatory cytokines and the activation of monocytes, bacteria cause the up-regulation of tissue factor as well as the release of microparticles expressing tissue factor, thus leading to the activation of coagulation. Proinflammatory cytokines also cause the activation of endothelial cells, a process that impairs anticoagulant mechanisms and down-regulates fibrinolysis by generating increased amounts of plasminogen activator inhibitor.

Hunt BJ. Bleeding and coagulopathies in critical care. N Engl J Med. 2014 Feb 27;370(9):847-59. doi: 10.1056/NEJMra1208626. PMID: 24571757.



Russell JA. Management of sepsis. N Engl J Med. 2006 Oct 19;355(16):1699-713. doi: 10.1056/NEJMra043632. Erratum in: N Engl J Med. 2006 Nov 23;355(21):2267. PMID: 17050894

PATHOPHYSIOLOGY

- **Pathological presence of a tissue factor in a circulation - sources**
  - Cells from different tissues - during birth, large trauma, operation, tumor cells
  - Pathological cellular forms - myelo- and lymphoproliferative processes (tissue factor in their cell membrane)
  - Activated endothelia and monocytes - by endotoxin, systemic inflammation; expressing of tissue factor on cell surface
  - Cytoplasmatic tissue factor released from hemolysed erythrocytes

  - Mucus from adenocarcinomas directly activate f. X.
  - TNF-alfa: induces endothelial cells to express tissue factor and to decrease thrombomodulin, implicated in DIC occuring with sepsis

DIC TYPES

Type**	Intervention
Bleeding	Blood transfusion Synthetis protease inhibitors Antifibrinolytic therapy
Massive bleeding	
Organ failure	Natural protease inhibitors*
Non-symptomatic	Heparin

* antifibrinolytics treatment in organ failure not recommended strongly
** underlying cause treatment priority, except of massive bleeding type

DIC STAGES

1. Hypercoagulative
    - Consumption of platelets and coagulation factors
    - Microcirculation obstruction
    - Ischemic damage to tissues
2. Hypocoagulative & Fibrinolytic
    - Insufficient amount of platelets and coagulation factors
    - Fibrinolysis finishing the chain of a disaster
        - Bleeding and insufficient clotting

CLINICAL FEATURES

- Bleeding
  - gingival, GIT bleeding, hematuria, epistaxis, hematomas, bleeding of surgical and puncture wounds, brain bleeding, internal organ bleeding, joints
- Microthrombi and microemboli
  - peripheral acrocyanosis, pregangrenous changes, organ impairment (lungs, kidney, liver)
- Result
  - Microangiopathic hemolytic anaemia, dyspnoea, cyanosis, respiratory failure, convulsions, coma, oliguria, acute renal failure, sudden or progressive circulatory failure, shock

CLINICAL FEATURES

- Onset
  - Acute, fulminant: e.g. endotoxic, shock, amniotic fluid embolism
    - Dominated by a bleeding diathesis
  - Chronic, insidious: e.g. carcinomatosis, dead fetus retention
    - Dominated by thrombotic complications

LABORATORY FINDINGS

- Low fibrinogen
- Low coagulation factors
- Thrombocytopenia
- Increased FDP (fibrin degradation products): D- dimer

  D- dimer :

  - norm: 0-0,5 ug/ml FEU
  - > 4 ug/ml FEU: compatible with DIC, but not diagnostic
  - >8ug/ml FEU: strongly suggestive of DIC
- PT, PTT - prolonged

marek.brenisin@gmail.com
marek.brenisin@upjs.sk