ΕΛΛΗΝΙΚΗ ΔΗΜΟΚΡΑΤΙΑ
ΠΑΝΕΠΙΣΤΗΜΙΟ ΚΡΗΤΗΣ

ΕΝΤΑΤΙΚΗ ΙΑΤΡΙΚΗ

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Πανεπιστήμιο Κρήτης

Ευρωπαϊκή Ένωση
Ευρωπαϊκό Κοινωνικό Ταμείο

ΕΠΙΧΕΙΡΗΣΙΑΚΟ ΠΡΟΓΡΑΜΜΑ
ΕΚΠΑΙΔΕΥΣΗ ΚΑΙ ΔΙΑ ΒΙΟΥ ΜΑΘΗΣΗ
επένδυση στην κοινωνία της γνώσης
ΥΠΟΥΡΓΕΙΟ ΠΑΙΔΕΙΑΣ & ΘΡΗΣΚΕΥΜΑΤΩΝ, ΠΟΛΙΤΙΣΜΟΥ & ΑΘΛΗΤΙΣΜΟΥ
ΕΙΔΙΚΗ ΥΠΗΡΕΣΙΑ ΔΙΑΧΕΙΡΙΣΗΣ

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πρόγραμμα για την ανάπτυξη
ΕΥΡΩΠΑΪΚΟ ΚΟΙΝΩΝΙΚΟ ΤΑΜΕΙΟ

Με τη συγχρηματοδότηση της Ελλάδας και της Ευρωπαϊκής Ένωσης

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Με τη συγχρηματοδότηση της Ελλάδας και της Ευρωπαϊκής Ένωσης

Lesson overview

- Definitions
- Pathophysiology
- Diagnosis
- Early management
- Infection control
- Supportive therapies
- Diagnosis and management of organ-system dysfunction
- Late consequences of severe sepsis

Definitions and pathophysiology

Sepsis - History

- The term Sepsis was introduced by Hippocrates
- Sepsis was used to describe tissue breakdown associated with disease, foul smelling pus, and death
- In the mid 18th century Pasteur proved that the processes of sepsis was associated with infection

What is Sepsis

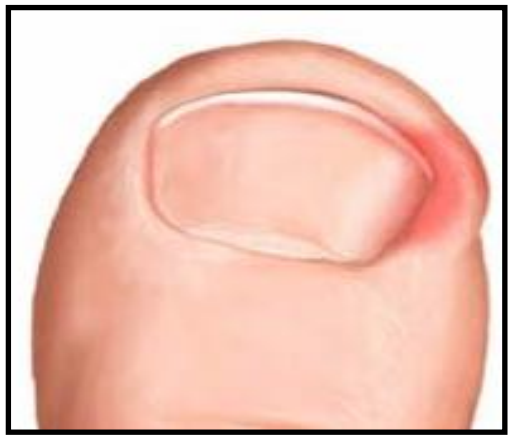
- Sepsis not a single disease, but rather a syndrome, that can result from several types of infections. It is associated with multiple organ-system dysfunction, and has a high mortality.

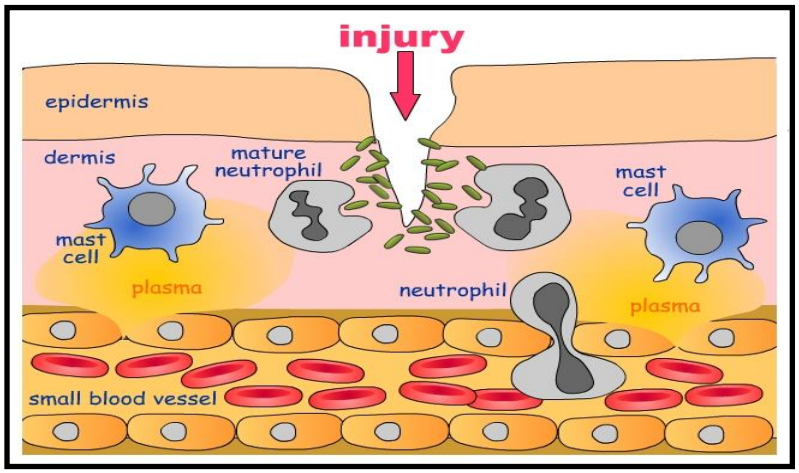
➢ **Sepsis** is defined as the syndrome of systemic inflammation when infection is the cause.

Infection

- Invasion of normally sterile host tissues by viable micro-organisms
- Infection both triggers and exacerbates the host response, and should always be sought and treated.

Inflammation and host response to injury



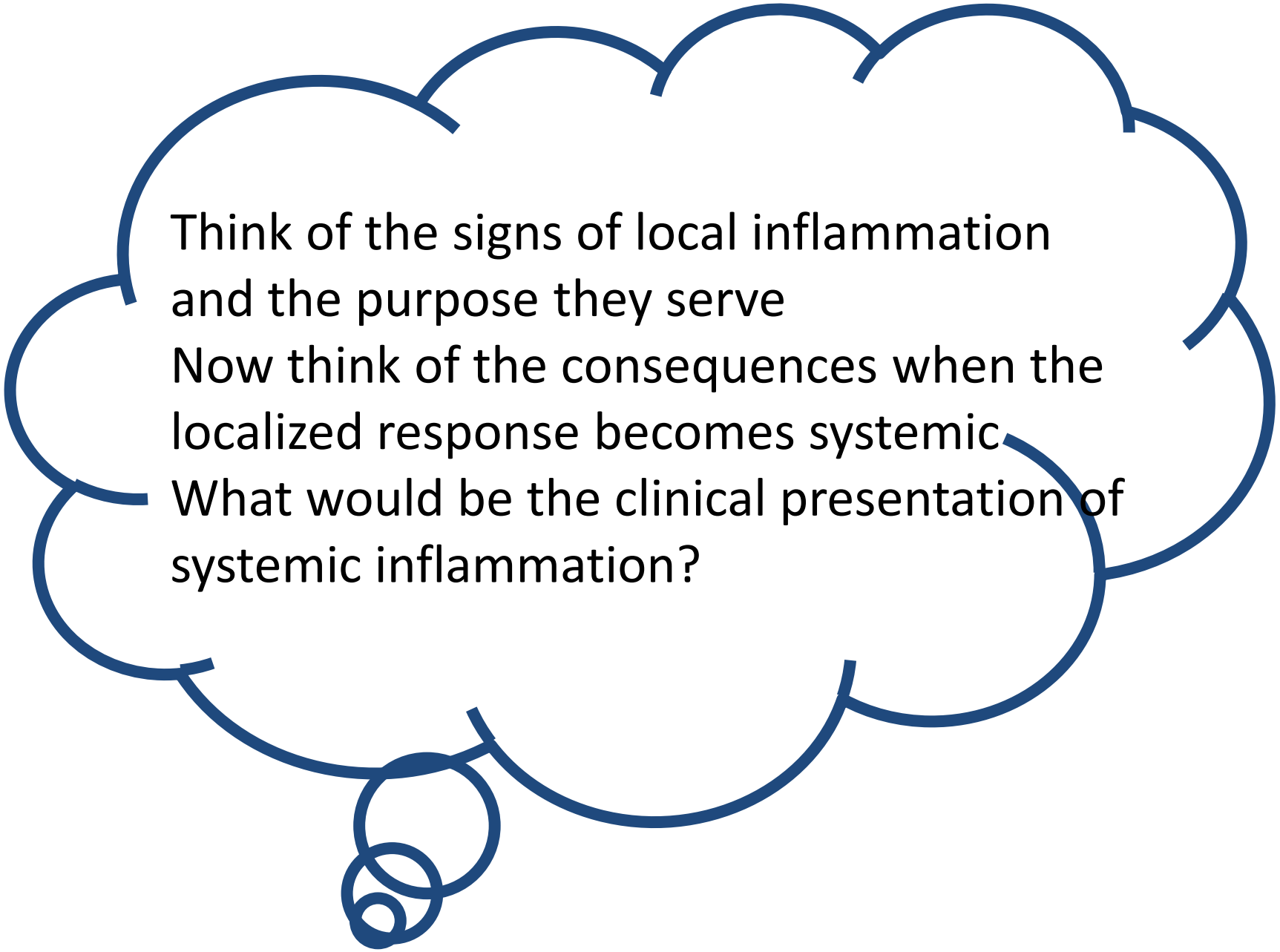


Inflammation

- Pain
- Heat
- Redness
- Swelling
- Loss of function

- Initiation of inflammation from resident cells recognizing pathogen-associated molecular patterns (PAMPs) or danger-associated molecular paterns (DAMPs)
- Activation and release inflammatory mediators
- Vasodilatation and increased permeability of the blood vessels to permit the migration of leukocytes
- Pathogen destruction
- Activation of wound healing

The danger model: a renewed sense of self Science. 2002


Think of the signs of local inflammation and the purpose they serve
Now think of the consequences when the localized response becomes systemic
What would be the clinical presentation of systemic inflammation?

Systemic inflammation

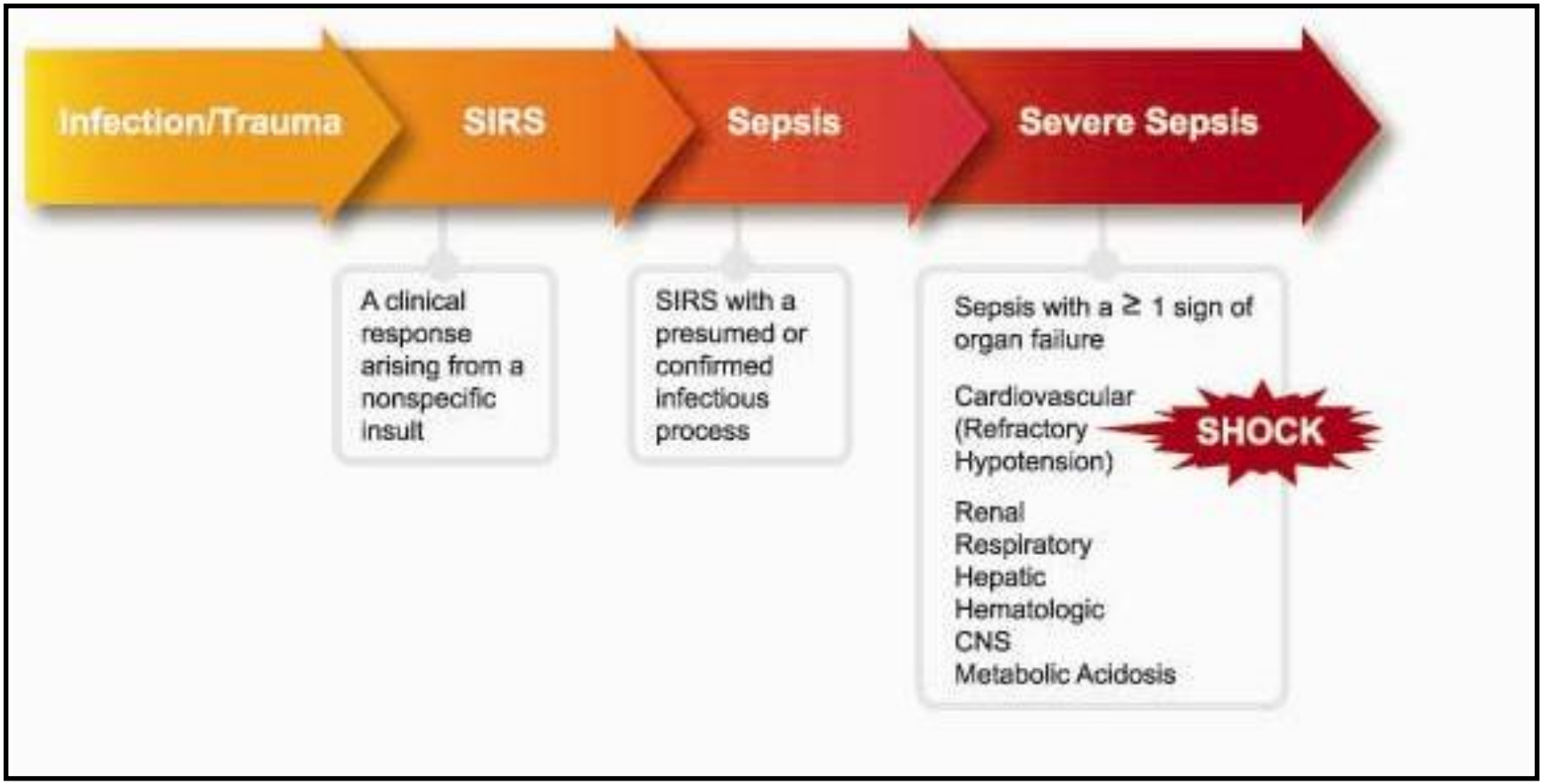
- Local initiation – spill-over
- Systemic release inflammatory mediators (fever)
- Systemic vasodilatation (hypotension)
- Increased vascular permeability (interstitial edema – tissue hypoxia and disfunction)

What is SIRS

- Systemic Inflammatory Response Syndrome is defined by the presence of ≥2 criteria as a result of inflammation

Criteria	Abnormally high or low	
Temperature	> 38° C	< 36° C
Heart Rate	> 90 bpm	
Respiratory Rate	> 20 breaths/min	PaCO2 < 32 mmHg
White Blood Cell Count	> 12,000 or > 10% bands	< 4,000 cells/mm3

Sepsis disease continuum



Diagnostic Criteria for Sepsis = Infection, documented or suspected, and some of the following:

- General variables
  - Fever (> 38.3°C) / Hypothermia (core temperature < 36°C)
  - Heart rate > 90/min or >2sd above the age normal
  - Tachypnea
- Inflammatory variables
  - WBC count > 12,000 /µL or < 4000/µL, or >10% immature forms
  - CRP or PCT >2sd normal

Diagnostic Criteria for Sepsis = Infection, documented or suspected, and some of the following:

- Hemodynamic variables -Tissue perfusion variables
  - Arterial hypotension (SBP< 90, MAP< 70 mm Hg, or ↓SBP>40 mm Hg
  - Significant edema or positive fluid balance (> 20 mL/kg over 24 hr)
  - Hyperlactatemia (> 1 mmol/L)
  - Decreased capillary refill or mottling
- Organ dysfunction variables
  - Arterial hypoxemia (Pao2/Fio2 < 300)
  - Acute oliguria (urine output < 0.5 mL/kg/hr for >2 hrs despite fluid resuscitation)
  - Creatinine increase > 0.5 mg/dL
  - Coagulation abnormalities (INR > 1.5 or aPTT > 60 s)
  - Thrombocytopenia (platelet count < 100,000 µL–1)
  - Altered mental status
  - Ileus (absent bowel sounds)
  - Hyperglycemia (glucose > 140 mg/dL) in the absence of diabetes
  - Hyperbilirubinemia (plasma total bilirubin > 4 mg/dL or 70 µmol/L)

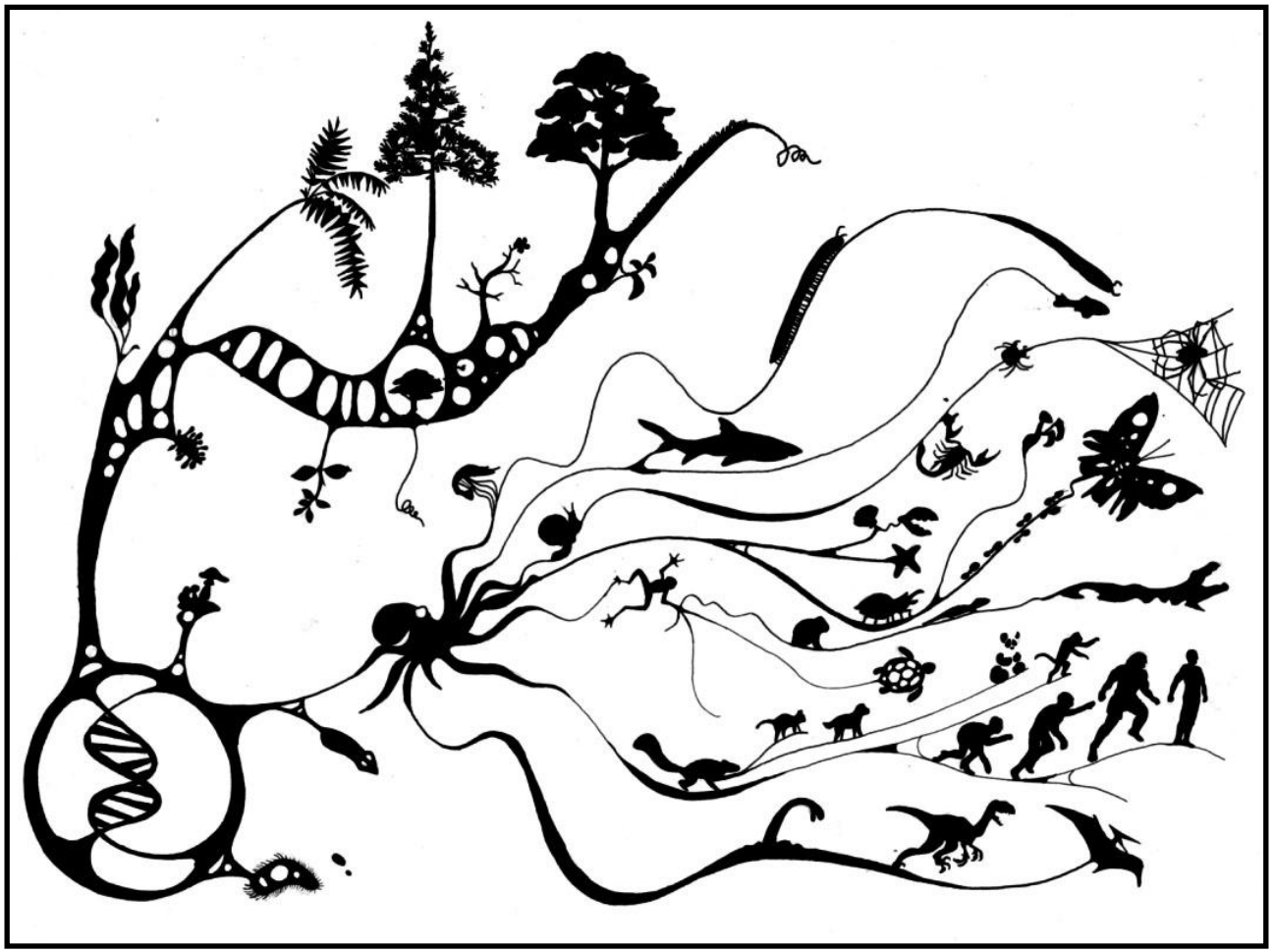
MODS

- Multiple organ dysfunction syndrome MODS
- MODS, much like sepsis, is not a disease but a syndrome characterized by dysfunction of ≥2 organ-systems of acute onset, as a result of severe sepsis or other severe injury

Definitions for organ-system dysfunction

- Sepsis-induced hypotension
- Lactate above upper limits laboratory normal
- Urine output < 0.5 mL/kg/hr >2 hrs despite fluid resuscitation
- PaO2/FiO2 < 250 or < 200 if pneumonia
- Creatinine > 2.0 mg/dL
- Bilirubin > 2 mg/dL
- Platelet count < 100,000 µL
- Coagulopathy (INR> 1.5)

Pathophysiology



Remember…our immune system function has been selected over years of evolution…

- **Mechanisms of tissue injury**
  - Uncontrolled growth of bacteria
  - Tissue damage by neutrophil enzymes
  - Reduced oxygen delivery – cellular dysfunction

- The biochemical processes of sepsis are enormously complex – the consequence of the coordinated interaction of hundreds of host-derived mediators including cytokines, complement, activation of coagulation, arachidonic acid metabolites, reactive oxygen and nitrogen species.

Vasodilation

- Under physiologic conditions helps bring immune cells at the site of injury
- Systemic vasodilation involving small arterioles and capillaries reflects the presence of mediators and the dysfunction of compensatory mechanisms
- Small amounts of NO, produced by eNOS normally regulate vascular tone
- Large amounts of NO, produced by iNOS can abnormally reduce vascular tone
- NO is not the only cause of systemic vasodilation – inhibition of NO synthesis did not improve sepsis outcome in patients

- Vasodilatation drastically increases the diameter of the vascular tree, reducing resistance, inducing relative hypovolemia and therefore lowers the effective blood pressure.

Nitric oxide
Μοριακή Ιατρική
VML 5.8

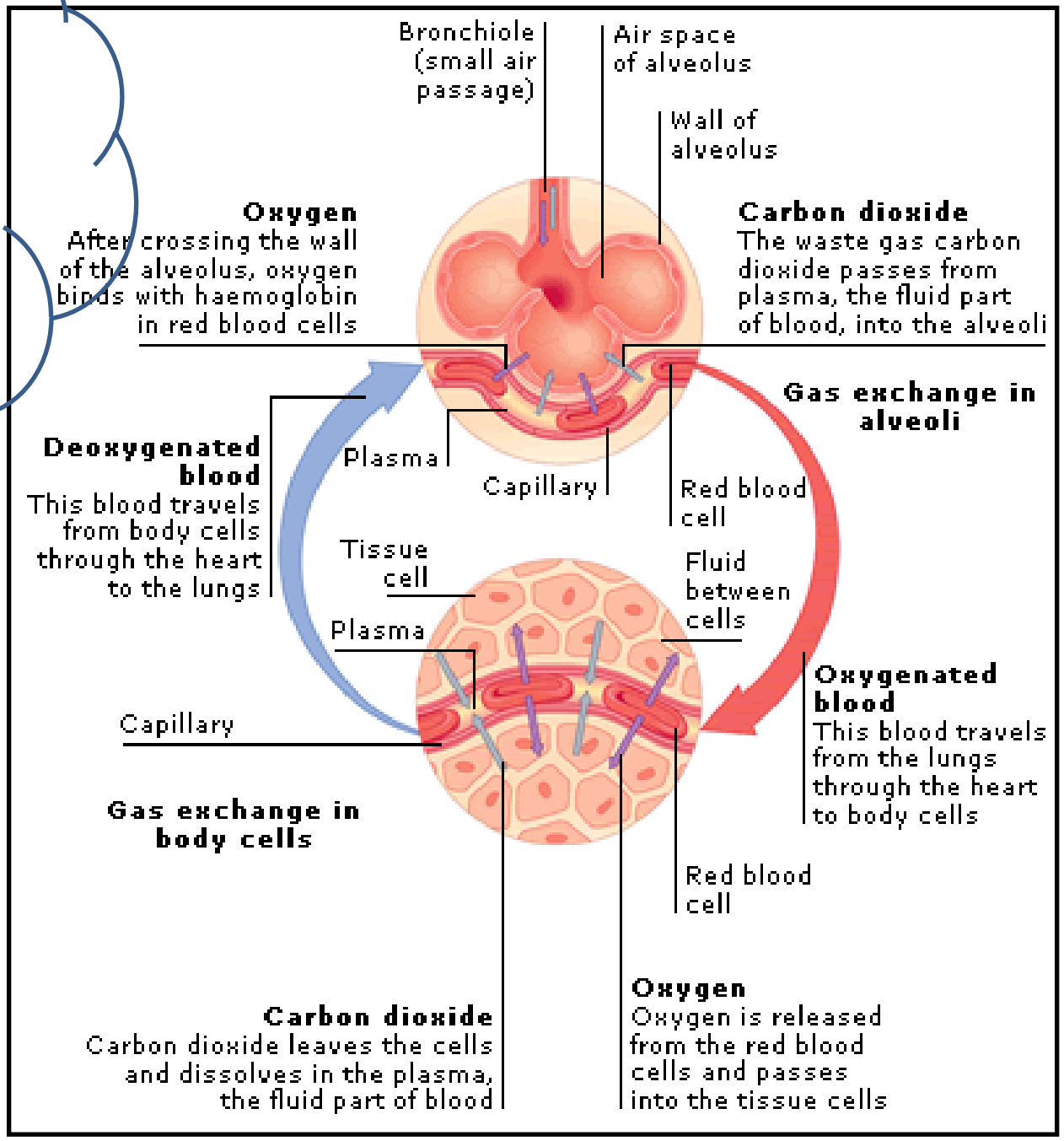
Loss of endothelial barrier function

- The response of endothelium to a local inflammatory stimulus includes expression of adhesion molecules and increase in permeability to facilitate the infiltration of immune cells at the area of injury so that the pathogen is cleared

- SIRS/Sepsis is associated with a diffuse activation of endothelium and increased vascular permeability. Loss of integrity of the endothelial barrier – a consequence of disruption of the endothelial tight junctions and loss of endothelial cells –results in loss of proteins and fluid into the interstitium.

- There are 2 main consequences: decrease of the effective intravascular volume – resulting in hypotension; and interstitial edema, which aggravates cellular hypoxia by increasing the distance between the erythrocyte in the capillary, and the adjacent cells, and so increasing the distance that oxygen must diffuse to reach the cell.

Think of the consequences of interstitial edema – Remember: oxygen diffusion is passive



Occlusion of capillaries

- SIRS/Sepsis is associated with activation of endothelium and coagulation cascade.
- Occlusion of capillaries by thrombi, activated leukocytes, and aggregates of erythrocytes, impairs perfusion. Oxygenated blood bypasses these occluded capillaries (shunt), failing to unload the oxygen and therefore increasing the local hypoxia

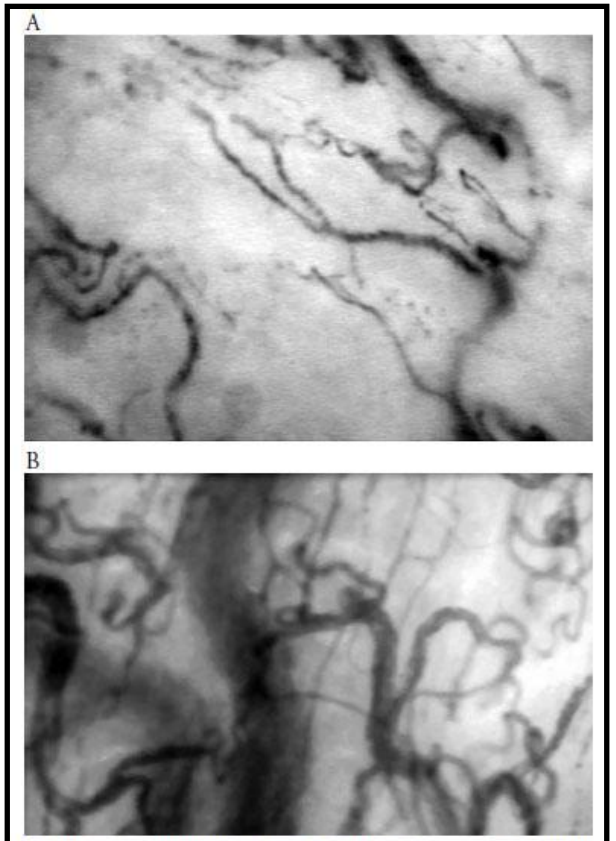
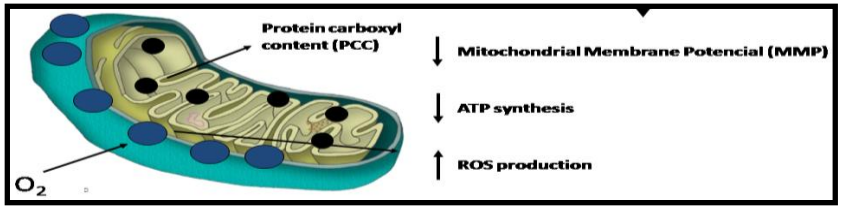


Figure 1 – Orthogonal polarization spectral imaging (OPS) of a patient admitted to the intensive Care Unit of Casa de Saúde São José: A) during septic shock; B) during recovery after shock just before extubation.

Mitochondrial dysfunction

- Sepsis-induced organ dysfunction has been suggested to be at least in part due to mitochondrial dysfunction as a result of oxidative stress and which results in failure of energy production.
- The pathogenesis of mitochondrial damage as a result of sepsis is probably a complex series of events.
- Both nitric oxide and ROS combined with the release of a variety of inflammatory mediators can act to directly or indirectly influence mitochondrial function and energy production.
- A self-amplifying cycle of ROS generation and mitochondrial damage occurs with mitochondrial dysfunction
- Mitochondrial dysfunction has been shown in animal models of sepsis

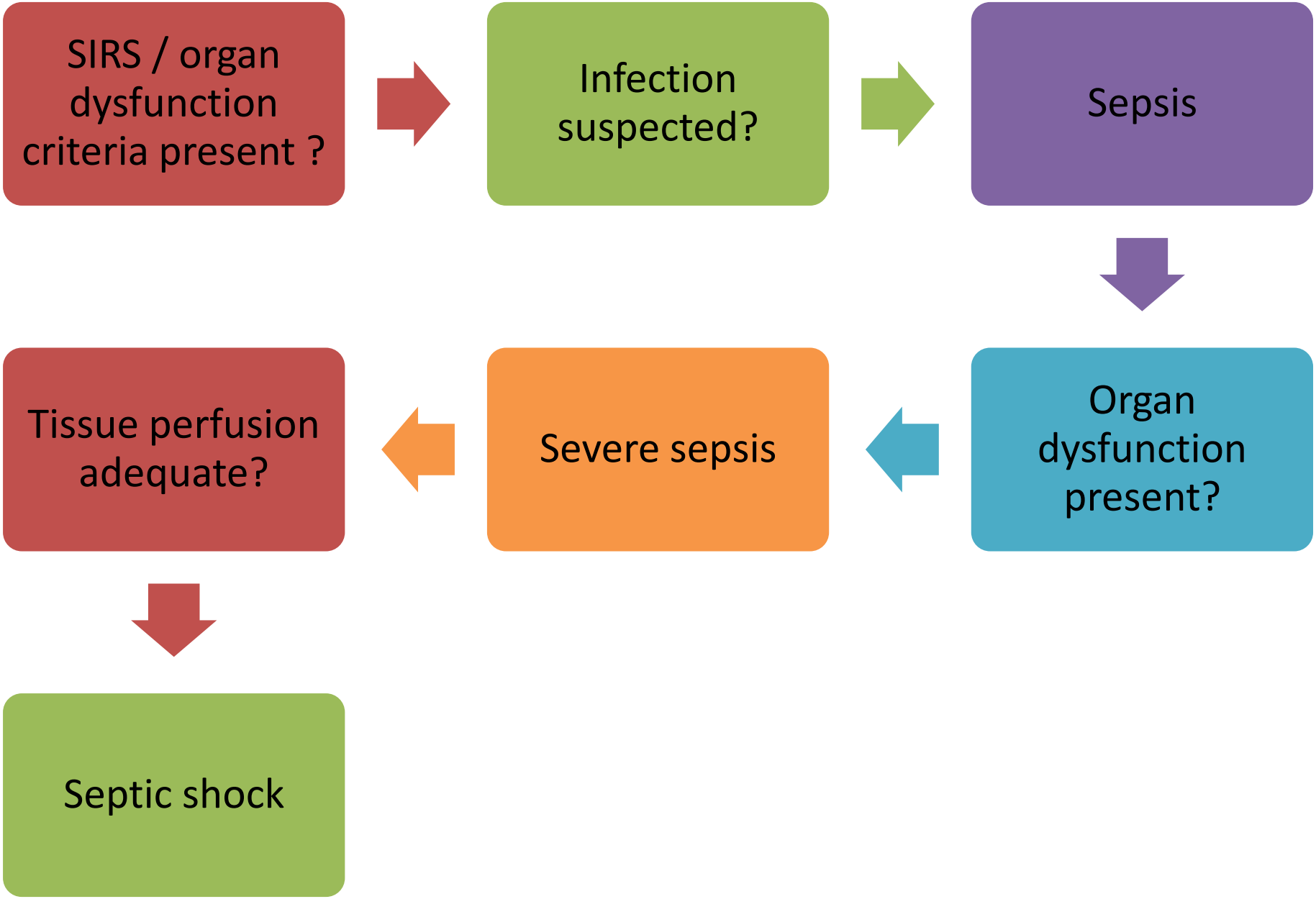


What is the pathologic basis for each of the following clinical features of severe sepsis or septic shock?

- Tachycardia
- Tachypnoea
- Pyrexia
- Leukocytosis
- Reduced systemic vascular resistance
- Increased mixed venous oxygen saturation

Diagnosis

- The early recognition of sepsis is not a diagnosis of a specific disease, but the recognition that a patient is ill and in danger of acute deterioration, and that immediate intervention is needed to:
  - Restore tissue perfusion
  - Determine the cause, and reverse or correct it
  - Institute appropriate physiologic support to prevent further tissue injury


SIRS / organ dysfunction criteria present ?
Infection suspected?
Sepsis
Organ dysfunction present?
Severe sepsis
Tissue perfusion adequate?
Septic shock

1+1=2

Obviously….

- You have to measure heart and respiratory rate, temperature and blood counts to diagnose SIRS
- You have to search for possible infection in patient with SIRS
- You have to evaluate organ system function to diagnose dysfunction
- You have to evaluate tissue perfusion (blood lactate) to find impairment

Clinical presentation of sepsis

- Fever – more severely ill patients or immuno-compromised patients may have low T
- Tachycardia – many patients are on b-blockers
- Tachypnoea - measure respiratory rate
- Infection site-specific symptoms and signs

❑**In severe sepsis:**

- Symptoms and signs of impaired perfusion and organ dysfunction
- Hypotension – not all hypotensive patients are septic

Symptoms and signs of impaired perfusion and organ dysfunction

- CNS: confusion, lethargy
- Respiratory: tachypnoea, hypoxemia
- Kidneys: reduced urine output - ↑ Ur, Cr (late)
- GI: reduced bowel movements
- Delayed capillary refill – increased blood lactate

Hemodynamic profile of severe sepsis

Vasodilatation/increased vascular permeability → increase unstressed volume → hypotension

→ tachycardia (+SIRS)

- Central Venous Pressure ↓
- Systemic Vascular Resistance ↓
- Cardiac output ⇳
    - See next

Cardiac output in septic shock

- CO=SV*HR
- HR is generally increased in sepsis
- SV depends on preload – afterload –contractility
- Afterload is reduced
- Preload is initially reduced, as a result of increase in unstressed volume, but can be restored with fluid resuscitation
- Contractility is sometimes impaired as a consequence of, mostly unknown, humoral mediators that directly act on myocardium

➢ Net Result: Cardiac output is usually increased after fluid resuscitation

- You learned that septic shock is characterized by cellular hypoxia
- Remember oxygen delivery formula – how is oxygen delivery compromised in septic patients?

Tissue hypoxia in sepsis

- Globally decreased DO2 due to ↓cardiac output
  - Inadequate fluid resuscitation
- Defects in local oxygen delivery
  - microvascular thrombosis
- Problems in oxygen diffusion
  - Peripheral vasodilatation resulting in an increased intravascular diameter
  - Increased capillary permeability with interstitial edema
- Defects in mitochondrial oxygen utilization

Early management

Resuscitation and haemodynamic support of the septic patient

- Recognition of inadequate tissue perfusion
  - Increased lactate
  - Organ dysfunction
- Cause: decreased effective blood volume
- Tx: increase total volume = give fluids

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Protocol-based fluid resuscitation

- Protocolized, quantitative resuscitation of patients with sepsis-induced tissue hypoperfusion (defined in this document as hypotension persisting after initial fluid challenge or blood lactate concentration ≥ 4 mmol/L). Goals during the first 6 hrs of resuscitation:
- a) Central venous pressure 8–12 mm Hg (12-15 on MV)
- b) Mean arterial pressure (MAP) ≥ 65 mm Hg
- c) Urine output ≥ 0.5 mL/kg/hr
- d) Central venous (superior vena cava) or mixed venous oxygen saturation 70% or 65%, respectively (grade 1C).
- In patients with elevated lactate levels targeting resuscitation to normalize lactate (grade 2C).

Fluid Therapy of Severe Sepsis

1. Crystalloids as the initial fluid of choice in the resuscitation of severe sepsis and septic shock (grade 1B).

2. Against the use of hydroxyethyl starches for fluid resuscitation of severe sepsis and septic shock (grade 1B).

3. Albumin in the fluid resuscitation of severe sepsis and septic shock when patients require substantial amounts of crystalloids (grade 2C).

4. Initial fluid challenge in patients with sepsis-induced tissue hypoperfusion with suspicion of hypovolemia to achieve a minimum of 30 mL/kg of crystalloids (a portion of this may be albumin equivalent). More rapid administration and greater amounts of fluid may be needed in some patients (grade 1C).

5. Fluid challenge technique be applied wherein fluid administration is continued as long as there is hemodynamic improvement either based on dynamic (eg, change in pulse pressure, stroke volume variation) or static (eg, arterial pressure, heart rate) variables (UG).

How do I give fluids to a septic patient

- I have indications of volume depletion
- I monitor heart rate, blood pressure, urine output, lactate, ± SvO2
- I give 30 ml/kg Ringer's lactate (RL)
- I continue giving fluid challenges of 500 ml RL as long as the patient remains volume depleted and volume responsive

Hemodynamic support

Vasopressors

1. Vasopressor therapy initially to target MAP of 65 mm Hg (1C).
2. Norepinephrine as the first choice vasopressor (1B).
3. Epinephrine when an additional agent is needed to maintain blood pressure (2B)
4. Vasopressin 0.03 units/minute can be added to norepinephrine (UG).
5. Low dose vasopressin is not recommended
6. Dopamine as an alternative vasopressor only in highly selected patients
7. Phenylephrine is not recommended except as salvage therapy (1C).
8. Low-dose dopamine should not be used for renal protection (1A).
9. All patients requiring vasopressors have an arterial catheter placed (UG).

Hemodynamic support

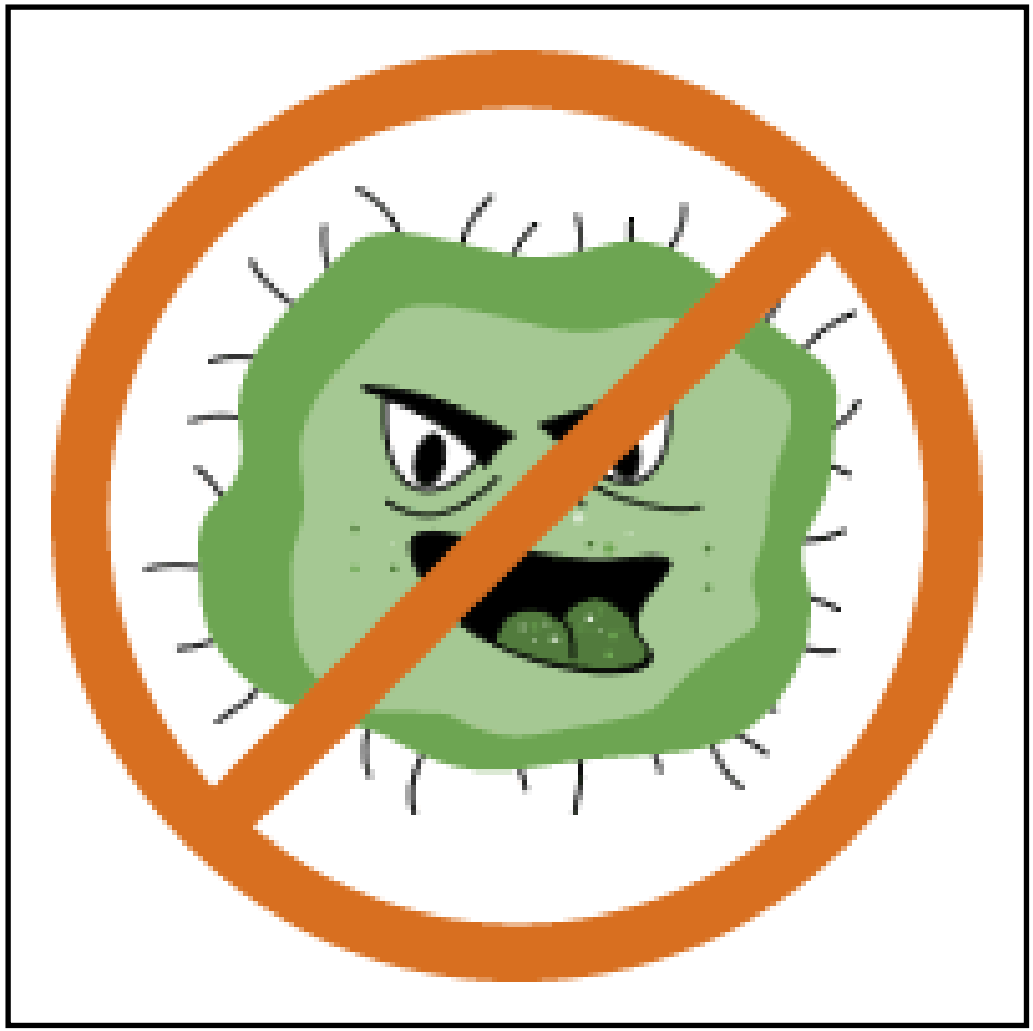
Inotropic Therapy

1. A trial of dobutamine infusion up to 20 μg/kg/min added to vasopressor (if in use) in the presence of (a) myocardial dysfunction or (b) ongoing signs of hypoperfusion, despite achieving adequate intravascular volume and adequate MAP (1C).
2. Not using a strategy to increase cardiac index to predetermined supranormal levels (1B).

How do I give pressors to a septic patient

- Administration of pressors should be given under continuous monitoring of BP in an ICU
- If BP<65mmHg I start norepinephrine (NE) while continue fluid resuscitation
- I use invasive hemodynamic monitoring on the patient who requires high doses of NE or inotropes
- I give dobutamine to the patient who needs high doses of NE (>0.5µg/kg/min) despite adequate fluid resuscitation, and has reduced cardiac contractility on U/S examination
- I consider vasopressin or epinephrine if the patient is not responding to very high doses of NE (>1.5µg/kg/min)

Infection control



Identification and control of the source of infection in 3 steps

Once resuscitation has been started, the next priority in the management of the septic patient is to diagnose and treat the cause of sepsis

- Obtain appropriate cultures
- Start empiric antibiotics
- Source control

Is the patient infected?

- In the patient presenting to the emergency department with an acute illness + SIRS criteria, history, physical examination and laboratory investigations usually allow establishing a diagnosis of infection.
- In hospitalized patients recognition of infection and source of infection is often more challenging. Several non-infectious causes of fever have to be considered. An increased white blood cell count is often present, however life-threatening infection can present with leukopenia. Overall, in hospitalized patients the discriminatory ability of leukocyte changes to differentiate infective and non-infective causes of fever is poor. Biomarkers such as C-reactive protein and procalcitonin (PCT) can be used to help diagnosis.
- When a diagnosis of infection cannot be confirmed a decision to treat with antibiotics is based on the probability that infection is the cause of the presenting clinical syndrome.

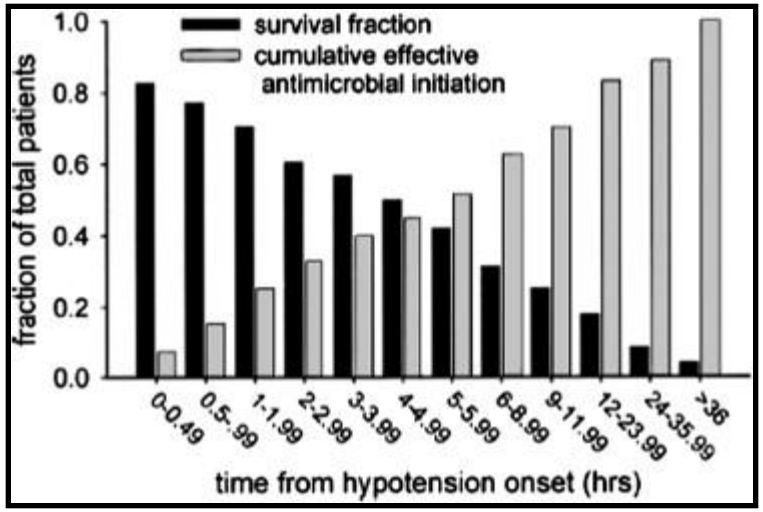
Confirmation of infection

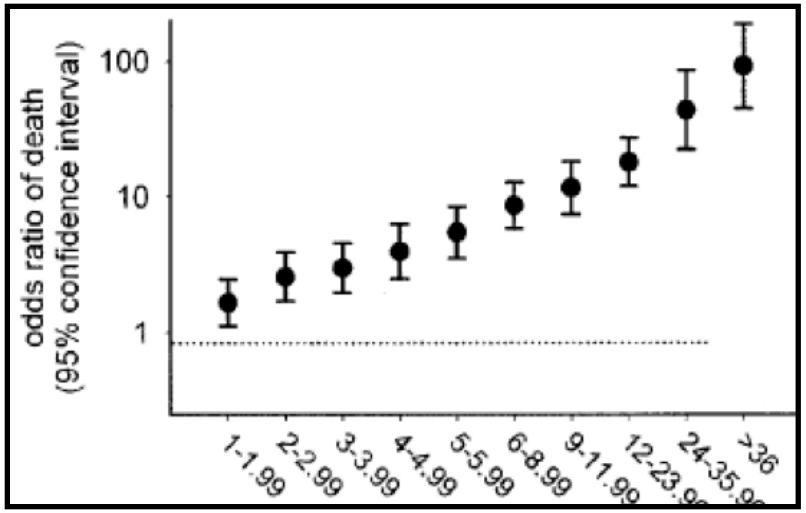
- Gold standard: culture evidence of tissue invasion
- Obtaining specimens prior to antibiotics maximize the diagnostic yield
- Positive blood cultures = systemic dissemination of micro-organism (positivity depends also on type of infection)
- Positive cultures of normally sterile tissue fluid =infection
- Positive Gram stain (particularly of CSF or urine samples) strongly suggests infection
- Positive sputum or urine cultures in intubated or catheterized patients may reflect colonization - use of quantitative culture techniques to improve reliability of culture data.

❖ Confirmation of infection comes at least 2 days later

Empiric antibiotic therapy

- In all cases of presumed infections empiric antibiotic therapy should be started immediately
- Choice of antibiotics based on guidelines and knowledge of local resistance patterns
- Delays in initiating therapy when severe sepsis or septic shock is present is associated with increased risk of death
- De-escalation of antibiotics based on culture results





Source control

- Source control : measures to stop ongoing microbial contamination and to restore optimal anatomy
- The least invasive approach for source control is preferred
- **Drainage** is the creation of a controlled connection between a closed cavity and an epithelial surface
- **Debridement** is the mechanical removal of infected non-viable tissue, typically by surgical resection

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- Diagnosis

1. Cultures as clinically appropriate before antimicrobial therapy if no significant delay (> 45 mins) in the start of antimicrobial(s) (1C) - At least 2 sets of blood cultures
2. Imaging studies performed to confirm a potential source of infection (UG).

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- Antimicrobial Therapy

1. Administration of effective iv antimicrobials within the 1st hour of recognition of severe sepsis or septic shock (grade 1B) as the goal of therapy.

2a. Initial empiric anti-infective therapy of one or more drugs that have activity against all likely pathogens (bacterial and/or fungal or viral) and that penetrate in adequate concentrations into tissues presumed to be the source of sepsis (1B).

2b. Antimicrobial regimen should be reassessed daily for potential deescalation (1B).

3. Use of low procalcitonin levels or similar biomarkers to assist the clinician in the discontinuation of empiric antibiotics in patients who initially appeared septic, but have no subsequent evidence of infection (grade 2C).

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4a. Combination empirical therapy for neutropenic patients with severe sepsis (grade 2B) and for multidrugresistant bacterial pathogens

4b. Empiric combination therapy should not be administered for more than 3–5 days. De-escalation to the most appropriate single therapy should be performed as soon as the susceptibility profile is known (grade 2B).

5. Duration of therapy typically 7–10 days; longer courses may be appropriate in patients who have a slow clinical response, undrainable foci of infection, bacteremia with S. aureus; some fungal and viral infections or immunologic deficiencies (grade 2C).

6. Antiviral therapy initiated as early as possible in patients with severe sepsis or septic shock of viral origin (grade 2C).

7. Antimicrobial agents should not be used in patients with severe inflammatory states determined to be of noninfectious cause (UG).

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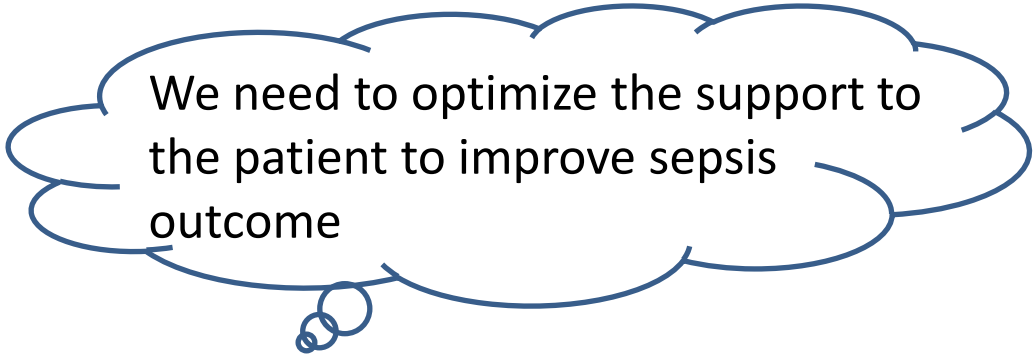
E. Source Control

1. A specific anatomical diagnosis of infection requiring consideration for emergent source control be sought and diagnosed or excluded as rapidly as possible, and intervention be undertaken for source control within the first 12 hr after the diagnosis is made, if feasible (grade 1C).
2. When infected peripancreatic necrosis is identified as a potential source of infection, definitive intervention is best delayed until adequate demarcation of viable and nonviable tissues has occurred (grade 2B).
3. When source control in a severely septic patient is required, the effective intervention associated with the least physiologic insult should be used (eg, percutaneous rather than surgical drainage of an abscess) (UG).
4. If intravascular access devices are a possible source of severe sepsis or septic shock, they should be removed promptly after other vascular access has been established (UG).

Supportive therapies

ADJUNCTIVE THERAPY FOR SEPSIS



- Corticosteroids
- Glucose control
- Blood products
- Mechanical Ventilation
- Sedation, analgesia, and neuromuscular blockers
- Renal replacement therapy
- Nutrition
- DVT prophylaxis
- Stress ulcer prophylaxis

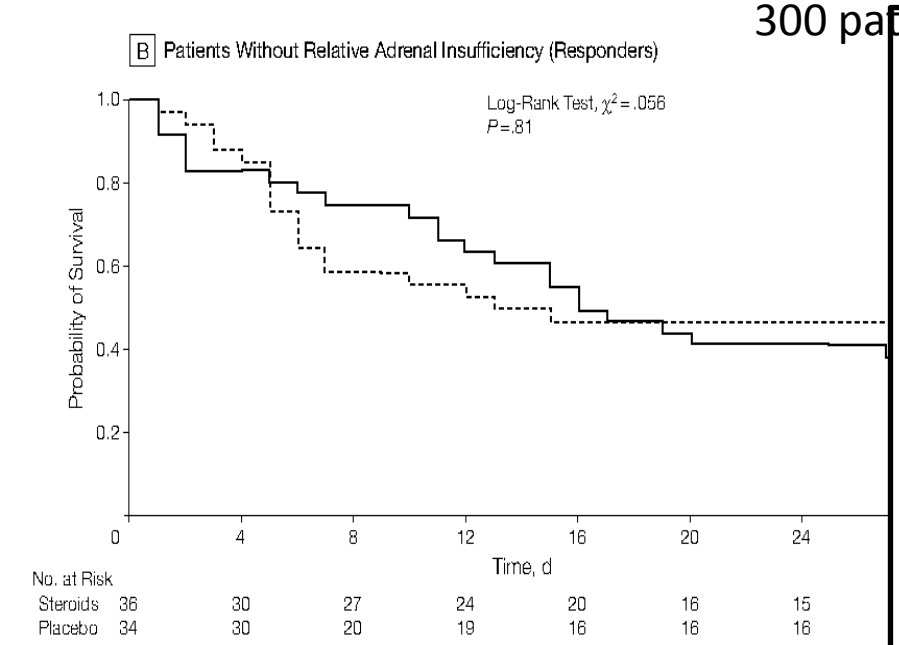
Corticosteroids

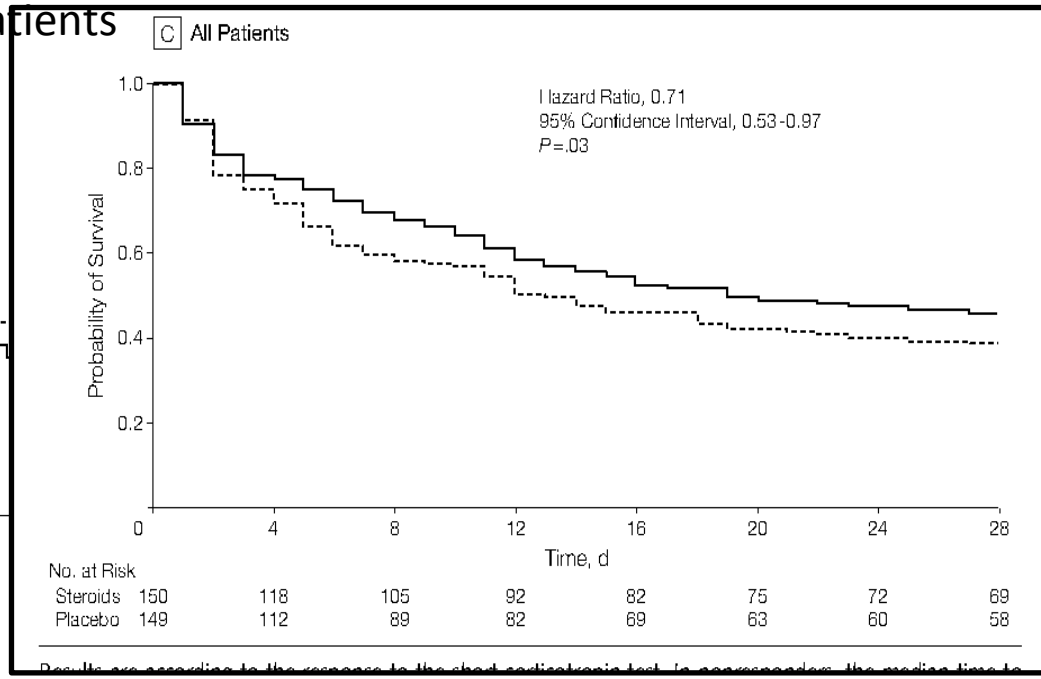
- Guidelines: Do not use hydrocortisone to treat adult septic shock patients if adequate fluid resuscitation and vasopressor therapy are able to restore hemodynamic stability. In case this is not achievable, we suggest intravenous hydrocortisone alone at a dose of 200 mg per day (grade 2C).
- One study showed that hydrocortisone 200-300 mg/d reduced mortality in corticotropin unresponsive patients with septic shock who require fluids and vasopressor support
- A larger, multi-centre study (CORTICUS) showed only that hydrocortisone hastened the reversal of shock in those in whom shock was reversed. Hydrocortisone did not improve survival in patients with septic shock, either overall or in patients who did not have a response to corticotropin.
- The mechanism of action is thought to be via improving catecholamine receptor responsiveness to exogenous catecholamines.

➢ **Septic shock may be associated with relative adrenal insufficiency, but hydrocortisone supplementation can be considered in fluid <u>and</u> pressor – non responding patients**

Effect of Treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock - Annane et al. JAMA 2002

300 patients





ICU mortality 55-60%

The NEW ENGLAND JOURNAL of MEDICINE

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Hydrocortisone Therapy for Patients with Septic Shock

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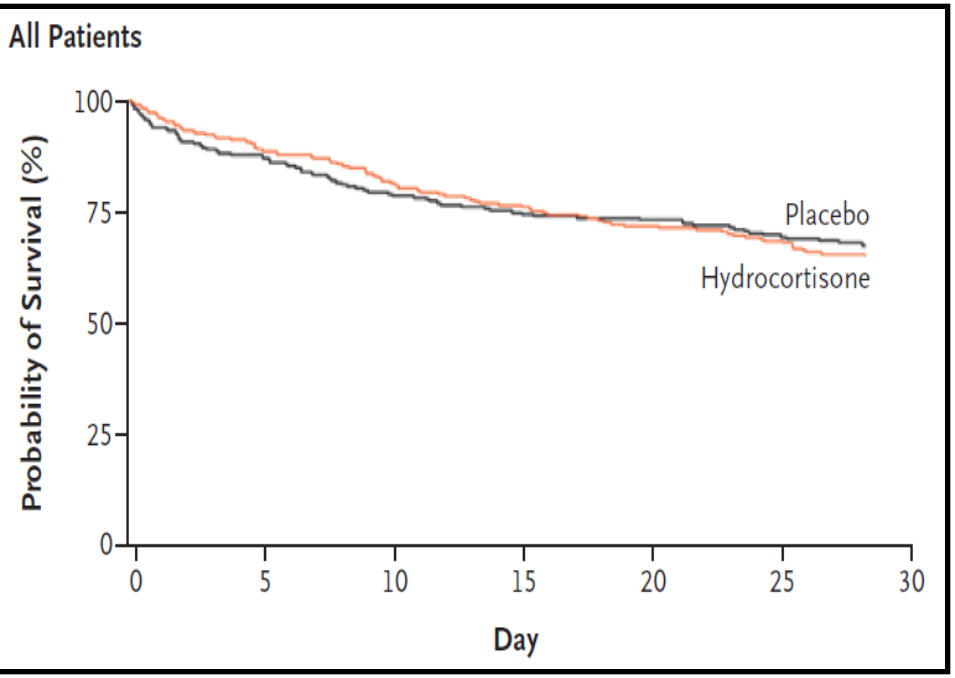


500 patients
40% mortality

- median time until reversal of shock was shorter in the hydrocortisone group than in the placebo group: 3.3 days (95% CI, 2.9 to 3.9) versus 5.8 days (95% CI, 5.2 to 6.9)

- In the hydrocortisone group, there was an increased incidence of infections, including new episodes of sepsis or septic shock, OR 1.37 (95% CI, 1.05 to 1.79)
- Neuromuscular weakness was rarely reported

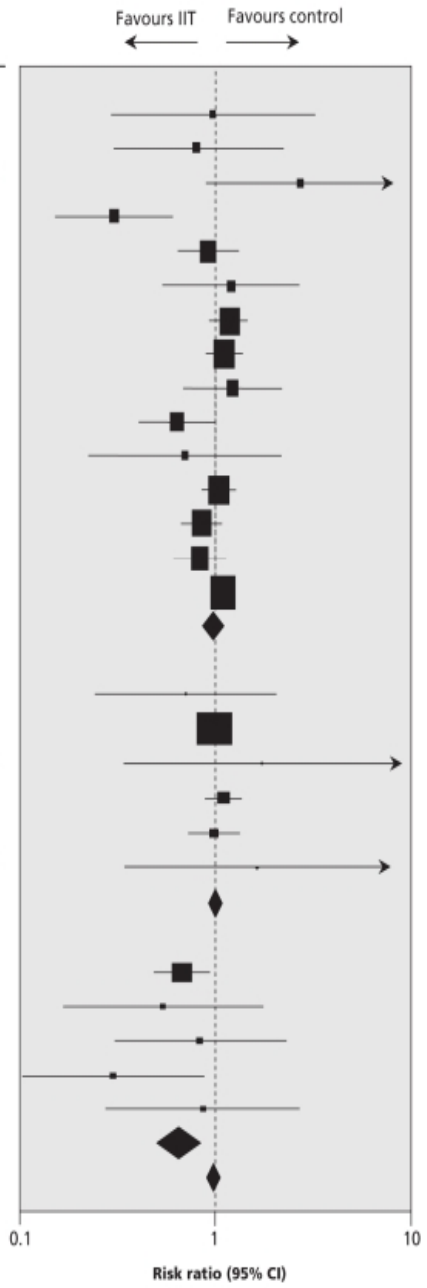
Glucose control

- Glucose control has been shown to reduce morbidity and mortality in ICU patients in some studies. Yet there is a significant risk of hypoglycaemia, reported even during the conduct of rigorous clinical trials. Glucose levels should be maintained <150 mg/dl

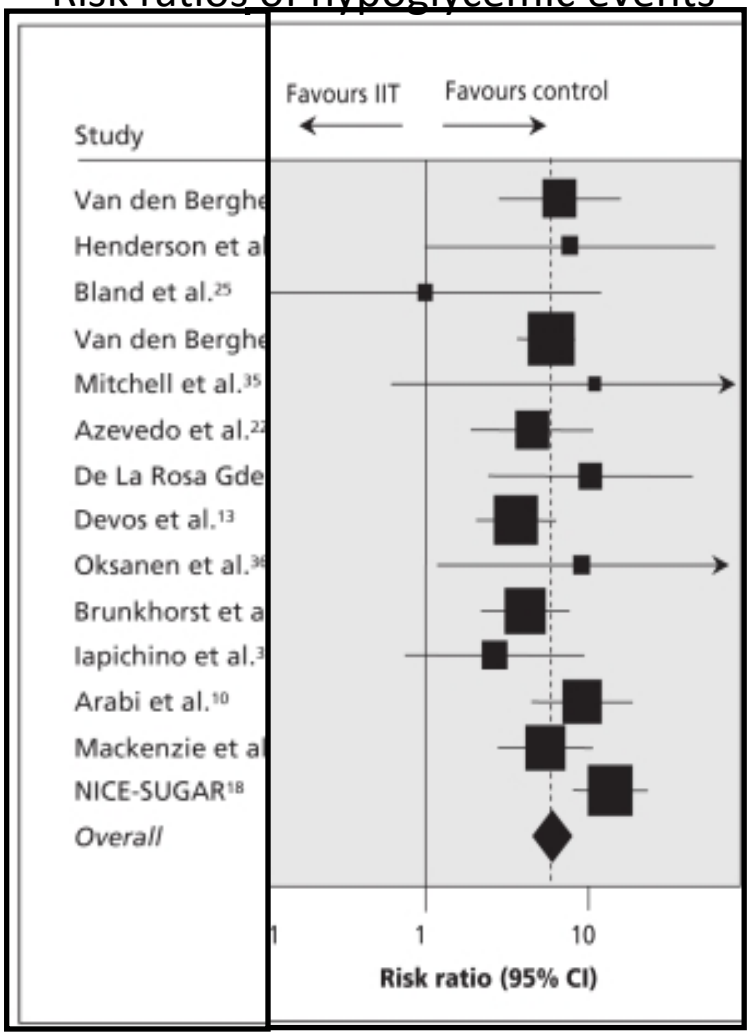
- Clear adherence to a well thought through protocol, well-trained nursing/medical involvement and supervision, regular blood testing and routine administration of glucose containing solutions (to avoid inadvertent hypoglycaemia) must be considered mandatory when patients are receiving insulin. Hourly glucose testing should be performed until the levels have stabilised and thereafter four hourly testing is acceptable. Point-of-care testing has been shown to overestimate glucose levels and must be used with caution.

Intensive insulin therapy and mortality among critically ill patients: a meta-analysis including NICE-SUGAR study data

Study	No. deaths / total no. patients: IIT	Control	Risk ratio (95% CI)
Mixed ICU			
Yu et al.[39]	4/28	4/27	0.96 (0.27–3.47)
Henderson et al.[31]	5/32	7/35	0.78 (0.28–2.22)
Mitchell et al.[35]	9/35	3/35	3.00 (0.89–10.16)
Wang et al.[38]	7/58	26/58	0.27 (0.13–0.57)
Azevedo et al.[22]	38/168	42/169	0.91 (0.62–1.34)
McMullin et al.[34]	6/11	4/9	1.23 (0.49–3.04)
Devos et al.[13]	107/550	89/551	1.20 (0.93–1.55)
Brunkhorst et al.[11]	98/247	102/288	1.12 (0.90–1.39)
Iapichino et al.[32]	15/45	12/45	1.25 (0.66–2.36)
He et al.[30]	16/58	29/64	0.61 (0.37–1.00)
Zhang et al.[40]	4/168	6/170	0.67 (0.19–2.35)
De La Rosa Gdel et al.[12]	102/254	96/250	1.05 (0.84–1.30)
Arabi et al.[10]	72/266	83/257	0.84 (0.64–1.09)
Mackenzie et al.[33]	39/121	47/119	0.82 (0.58–1.15)
NICE-SUGAR[18]	829/3010	751/3012	1.10 (1.01–1.20)
All mixed ICU patients	1351/5051	1301/5089	0.99 (0.87–1.12)
Medical ICU			
Bland et al.[25]	1/5	2/5	0.50 (0.06–3.91)
Van den Berghe et al.[9]	214/595	228/605	0.95 (0.82–1.11)
Walters et al.[37]	1/13	0/12	2.79 (0.12–62.48)
Farah et al.[27]	22/41	22/48	1.17 (0.77–1.78)
Oksanen et al.[36]	13/39	18/51	0.94 (0.53–1.68)
Bruno et al.[26]	2/31	0/15	2.50 (0.13–49.05)
All medical ICU patients	253/724	270/736	1.00 (0.78–1.28)
Surgical ICU			
Van den Berghe et al.[8]	55/765	85/783	0.66 (0.48–0.92)
Grey et al.[28]	4/34	6/27	0.53 (0.17–1.69)
Bilotta et al.[24]	6/40	7/38	0.81 (0.30–2.20)
He et al.[29]	7/150	6/38	0.30 (0.11–0.83)
Bilotta et al.[23]	5/48	6/49	0.85 (0.28–2.60)
All surgical ICU patients	77/1037	110/935	0.63 (0.44–0.91)
All ICU patients	1681/6812	1681/6760	0.93 (0.83–1.04)

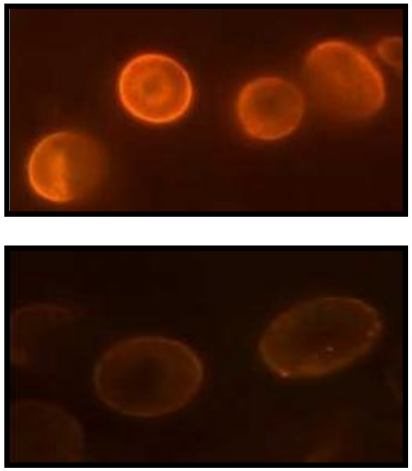


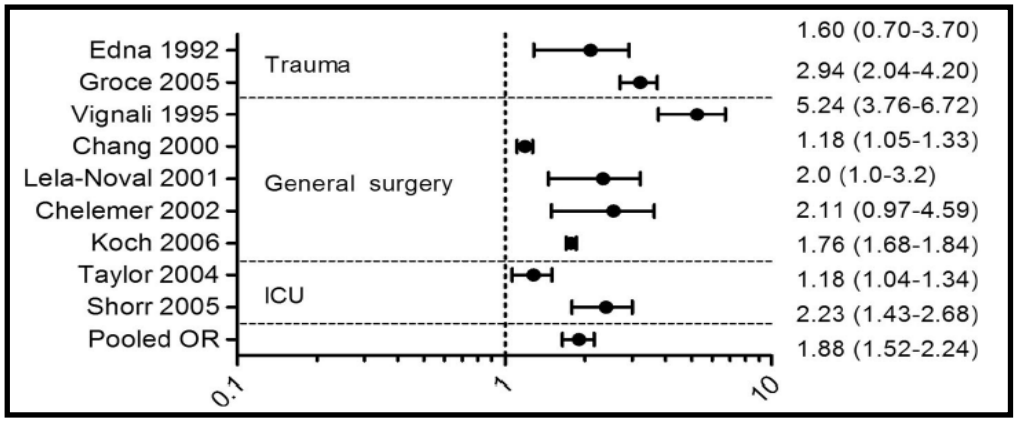
Risk ratios of hypoglycemic events



Blood products

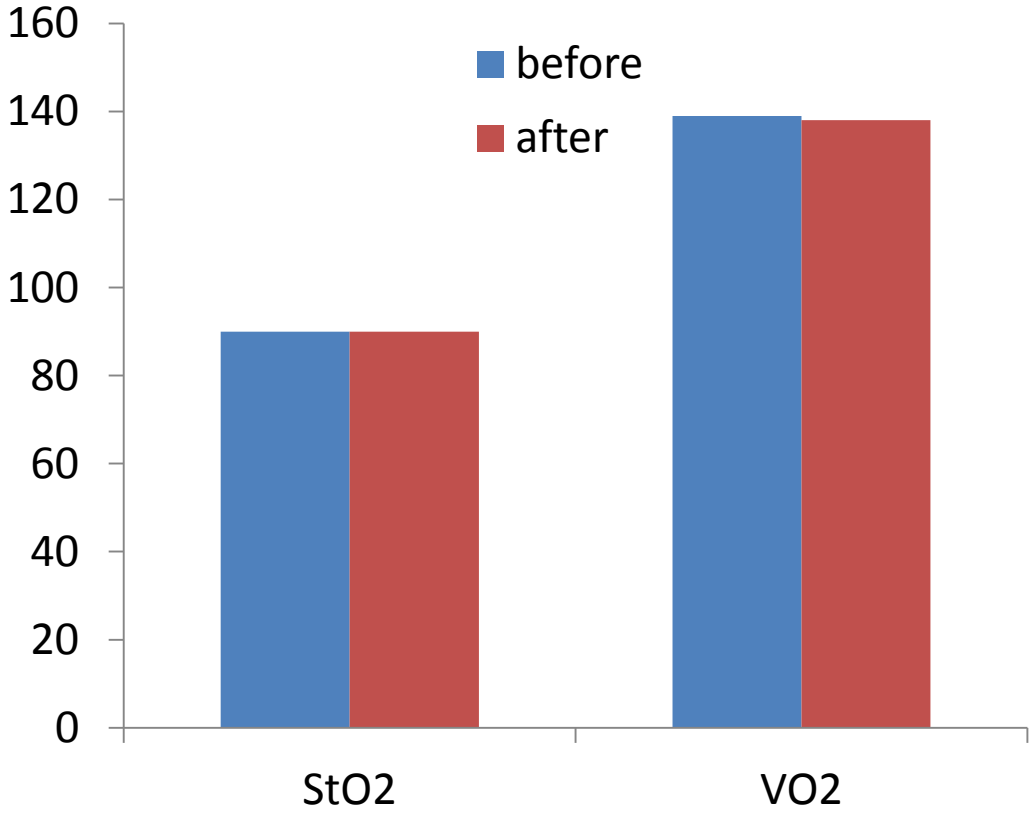
- Transfusion of blood products is associated with complications and should be restricted to absolutely necessary
- Red blood cells: Hb 7-9 g/dl
- Platelets : <5 x 109/l to prevent spontaneous bleeding; >50 x 109/l prior to surgery
- Fresh frozen plasma: for bleeding patients or prior to surgery when abnormal laboratory tests suggest their use





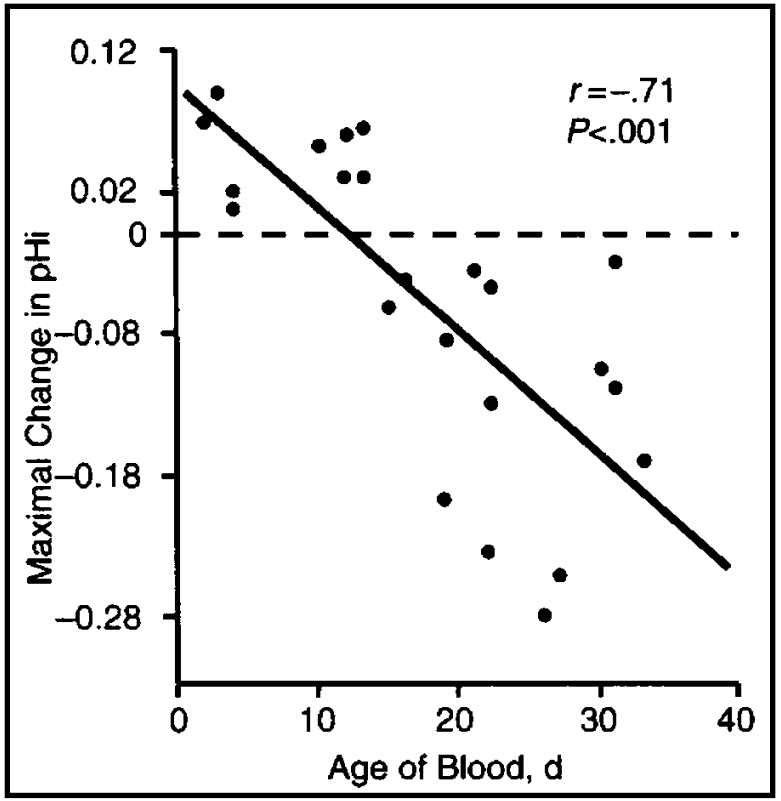
Crit Care Med 2008 Vol. 36, No. 9

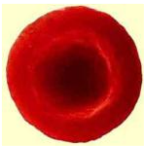
RBC transfusion and Oxygen delivery



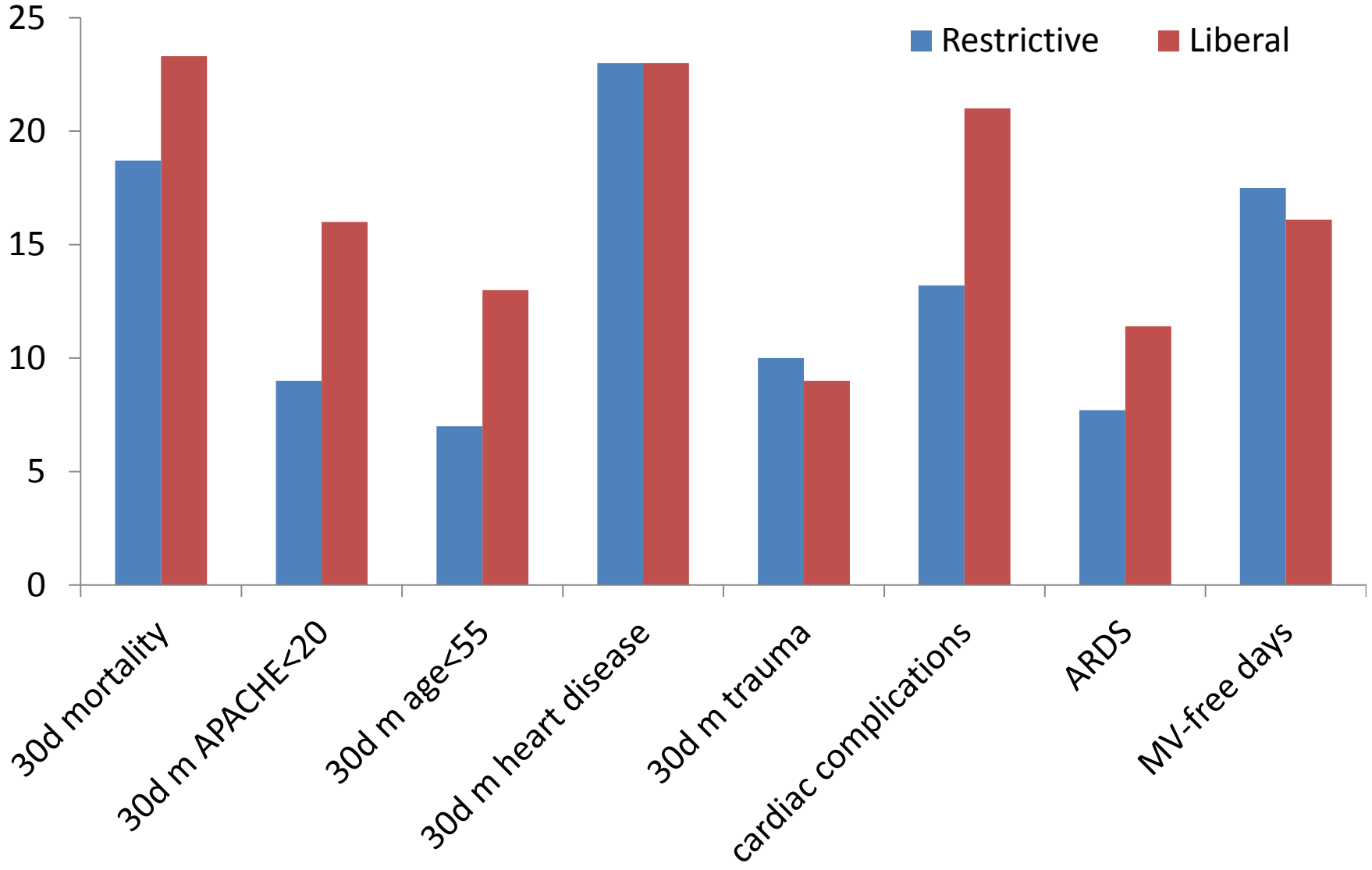
Tissue oxygenation measured by Near-infrared spectroscopy
Creteur Crit Care 2009

Oxygen consumption measured by indirect calorimetry
Marik JAMA 1993



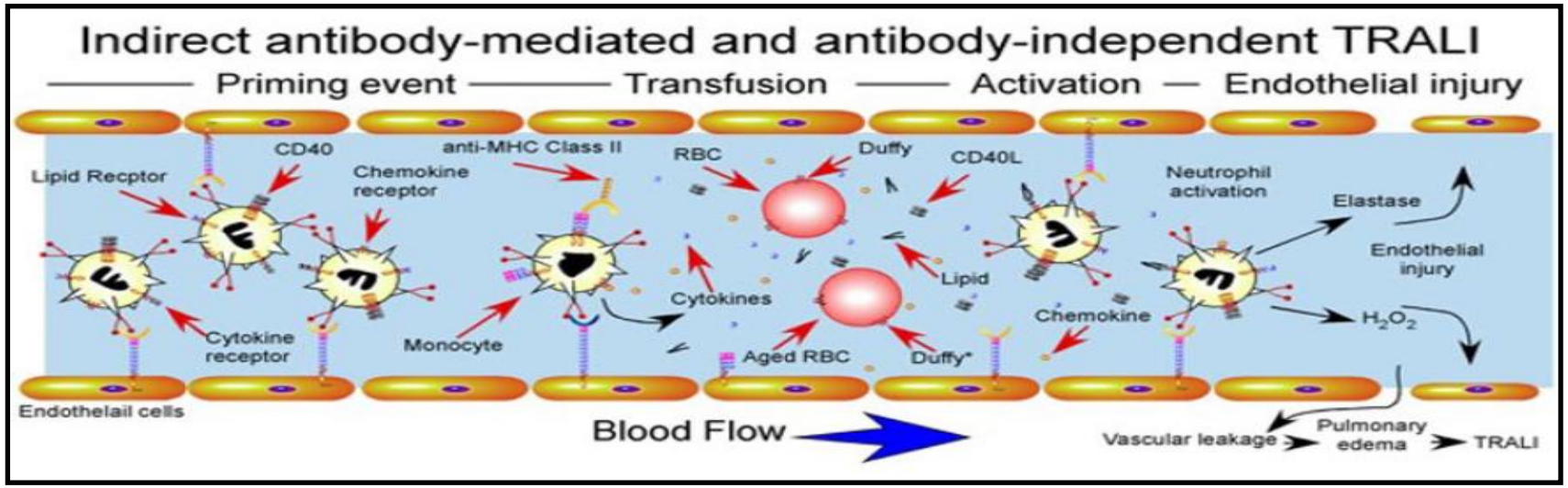


The TRICC trial - NEJM 1999



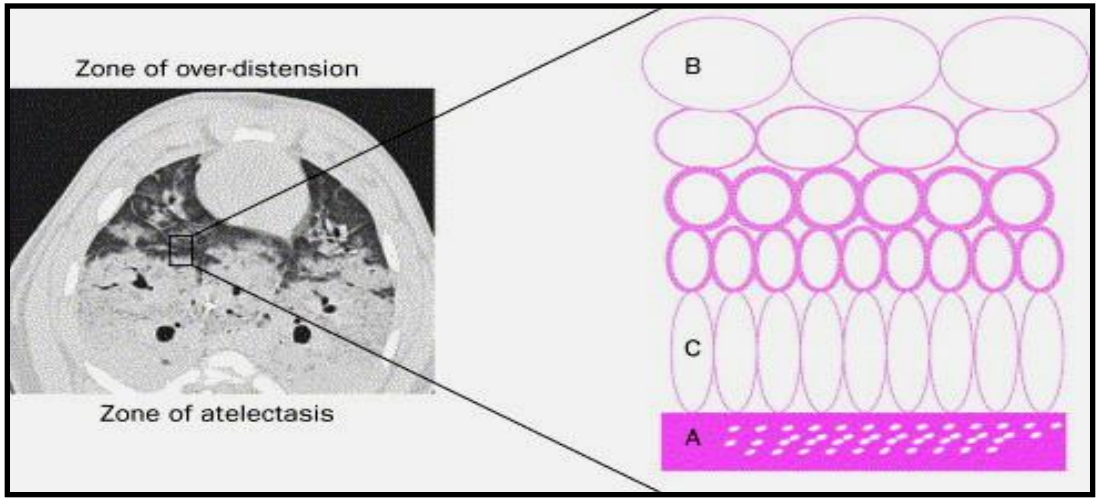
TRALI

- Transfusion-related acute lung injury: ARDS developing within 6h of transfusion of blood products
- Immunologic mechanisms – antibodies against HLA and neutrophils in donor plasma, as well as primed recepeint neutrophils are involved in the pathogenesis
- Plasma from multiparous women is the major risk factor for TRALI
- Components at risk for inducing TRALI are plasma>PLTs>RBCs

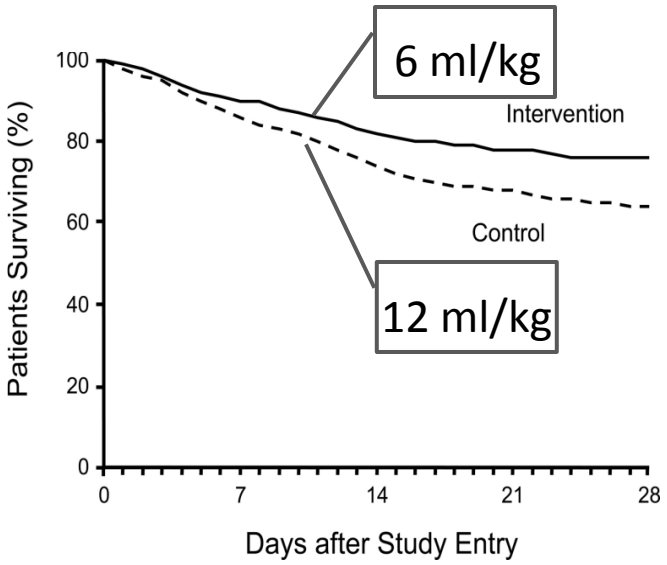


Mechanical Ventilation

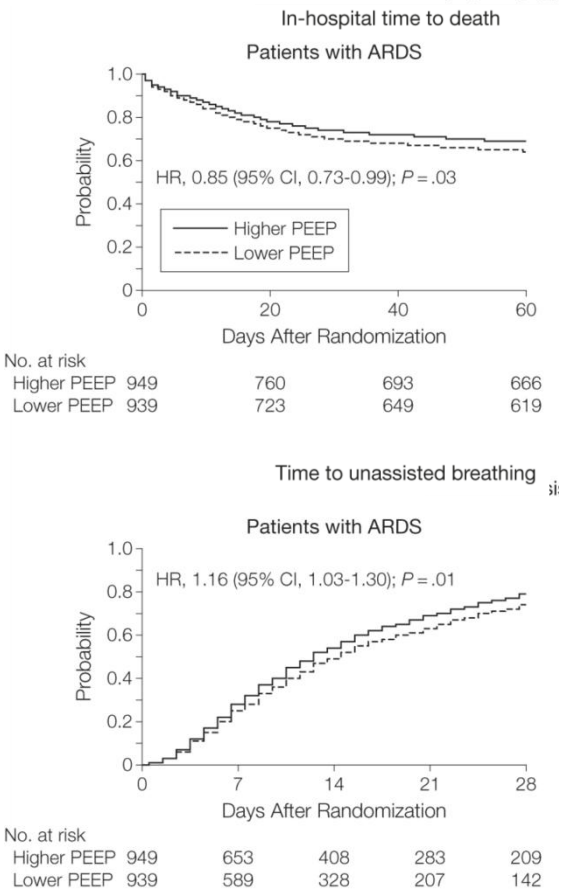
- The principles of mechanical ventilation in septic patients are:
  - Avoid over-distention of the lung
  - Prevent cyclic opening of alveoli
  - Promote early spontaneous breathing

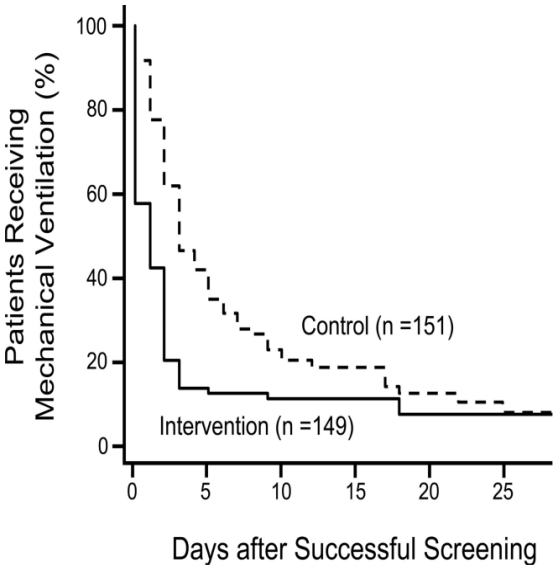


MV studies



The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome.
N Engl J Med 2000; 342, 1301-1308





Ely EW, Baker AM, Dunagan DP, Effect on the duration of mechanical ventilation of identifying patients capable of breathing spontaneously.
N Engl J Med 1996; 335, 1864

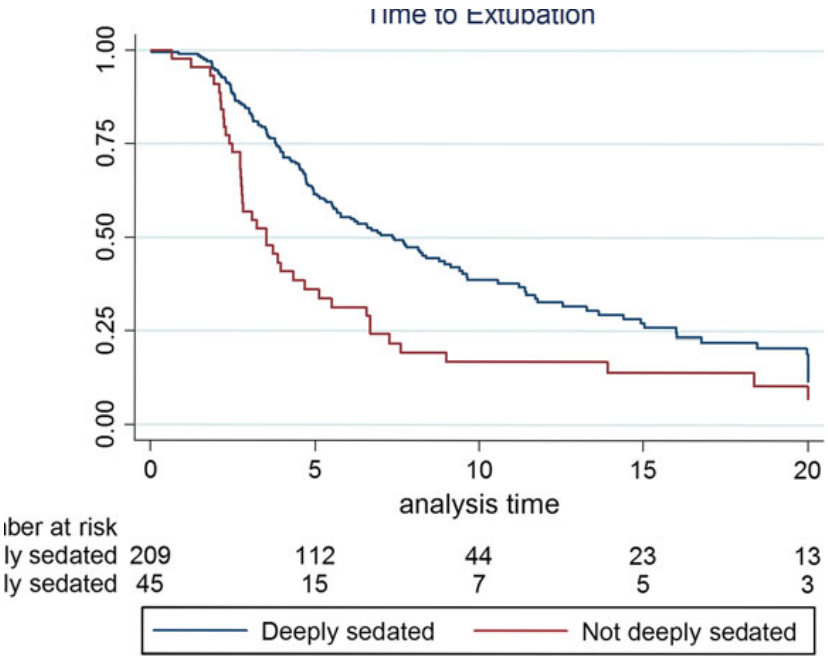
Higher vs Lower Positive End-Expiratory Pressure in Patients With Acute Lung Injury and Acute Respiratory Distress Syndrome: Systematic Review and Meta-analysis

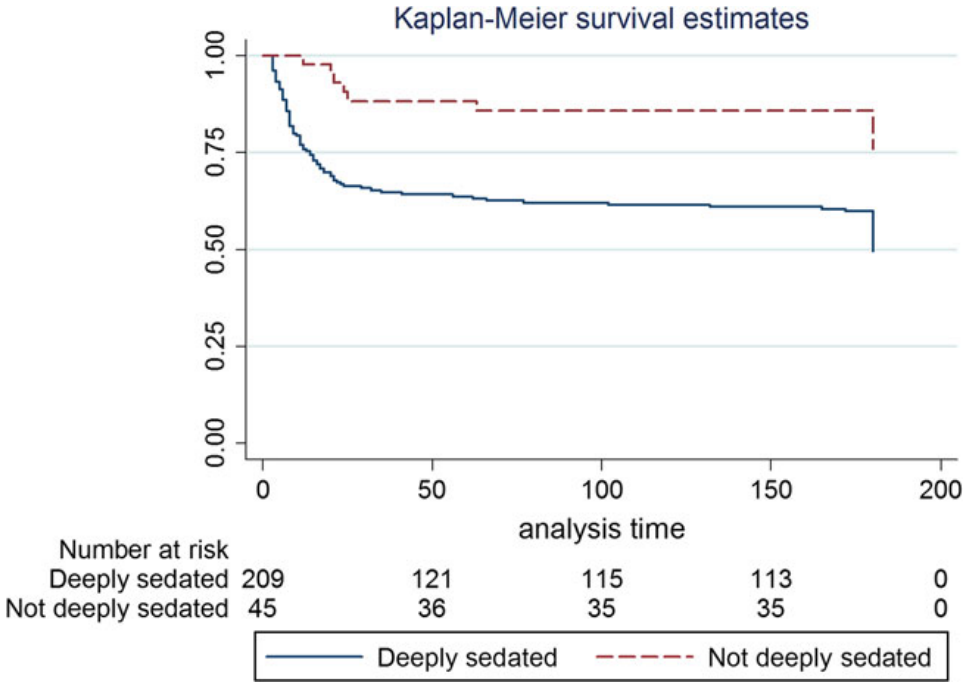
JAMA. 2010;303(9):865-873.

Sedation, Analgesia & N/M blocking

- The targets of S/A/NMBA are to provide patient comfort and facilitate patient-ventilator interaction
- Adequate analgesia should be provided to all patients, at all times. Opioids are the most commonly used agents in the ICU.
- Sedation is not always necessary for patients to tolerate the endotracheal tube. When administered sedation should be titrated to pre-specified end-points, using a sedation scale. Short acting agents and daily interruption are recommended
- A short (<48h) course of NMBA can be used in patients with severe ARDS to facilitate protective mechanical ventilation

Sedation studies





Sedation depth and long-term mortality in mechanically ventilated critically ill adults: a prospective longitudinal multicentre cohort study Intensive Care Med. 2013 Jan 24

Renal Replacement Therapy

- Acute kidney injury is a common complication of severe sepsis and septic shock
- RRT does not prevent further kidney injury
- RRT is recommended to treat increases in Ur, K, acidosis associated with renal failure, and to facilitate fluid balance management
- Continuous and intermittent RRT are equally effective. Continuous RRT facilitates better fluid managment

Nutrition

- Early enteral nutrition is to cover patient requirements is the goal for every ICU patient because
  - Energy and protein deficits induce muscle loss and immunodeficiency
  - Enteral feeding promotes intestinal mucosal integrity and prevents bacterial translocation
- Full enteral feeding is usually not feasible in early sepsis due to GI dysfunction
- Early institution of parenteral feeding has not been proven effective in improving patient outcome and has been associated with higher infection rate
- Immune-enhancing nutrition formulas have not been proven effective in improving patient outcome

DVT & stress ulcer prophylaxis

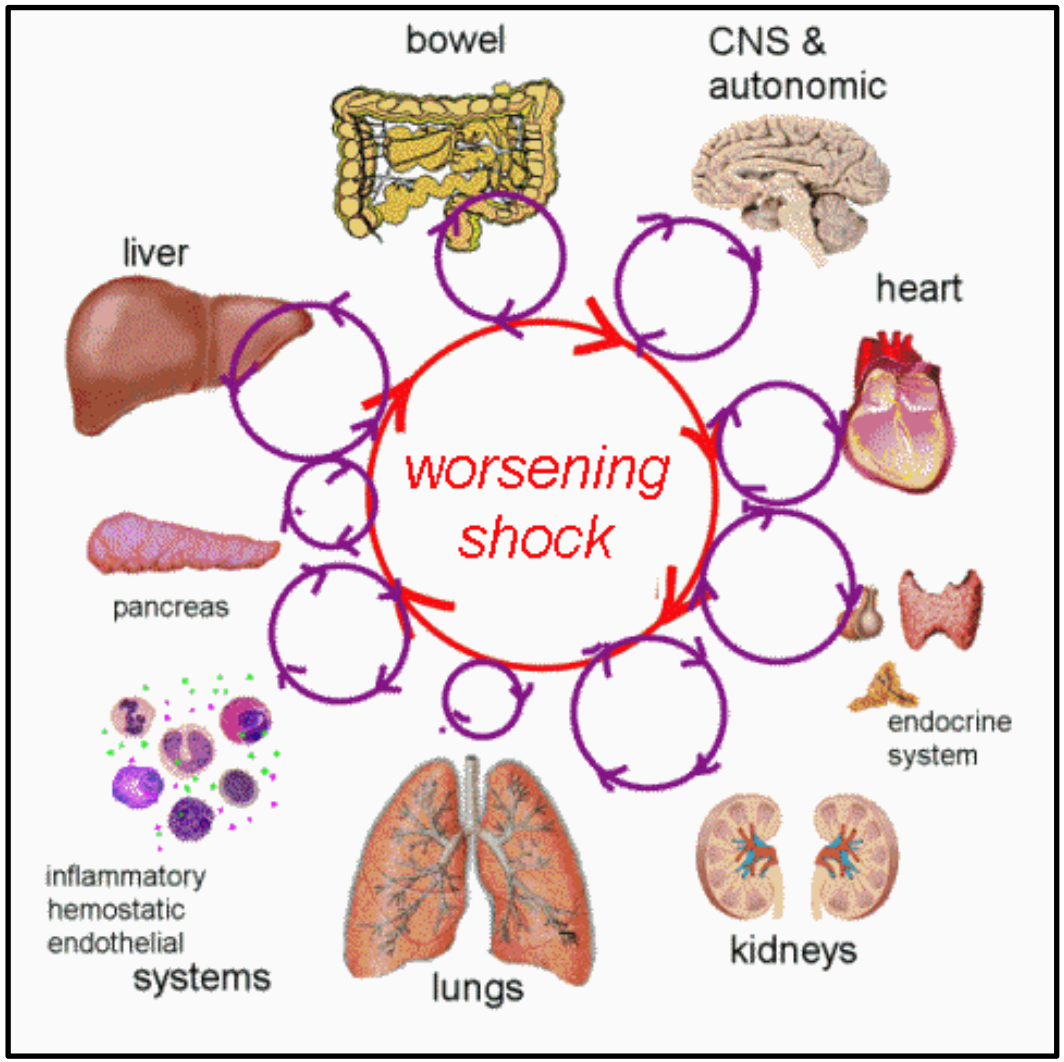
- ICU patients are bedridden and at risk for the development of deep vein thrombosis (DVT) and pulmonary embolus (PE), therefore prophylaxis is recommended. LMWH is preferred as easier to use. LMWH is renally excreted and may accumulate in patients with severe renal dysfunction. A dosage reduction/monitoring of anti-xa has been recommended in patients with creatinine clearance of <30 ml/minute.

- Upper gastrointestinal bleeds occur less frequently in ICU patients who receive prophylaxis for stress ulcers but there is no evidence of a reduction in mortality from this therapy. Histamine-2 (H2) receptor antagonists and proton pump inhibitors are similarly effective.

What not…
therapies proven ineffective

- Bicarbonates to correct metabolic acidosis
- Activated protein C
- Immunoglobulins
- Sellinium
- Immunomodulating nutrition
- Antithrombin
- Erythropoietin

Organ-system dysfunction



MANAGEMENT OF ORGAN DYSFUNCTION IN ICU

- Acute multiple organ dysfunction can complicate the course of septic shock, but also of any type of shock.
- Organ dysfunction is the result of uncontrolled systemic inflammatory response and hypo-perfusion
- Organ dysfunction can be induced and exacerbated by the provided medical treatments

➢ Management of shock-induced organ dysfunction

➢ Minimize treatment-induced organ dysfunction

Definitions for organ-system dysfunction

- Sepsis-induced hypotension
- Lactate above upper limits laboratory normal
- Urine output < 0.5 mL/kg/hr for more than 2 hrs despite adequate fluid resuscitation
- Acute lung injury with Pao2/Fio2 < 250 in the absence of pneumonia as infection source
- Acute lung injury with Pao2/Fio2 < 200 in the presence of pneumonia as infection source
- Creatinine > 2.0 mg/dL (176.8 µmol/L)
- Bilirubin > 2 mg/dL (34.2 µmol/L)
- Platelet count < 100,000 µL
- Coagulopathy (international normalized ratio > 1.5)

Sofa score

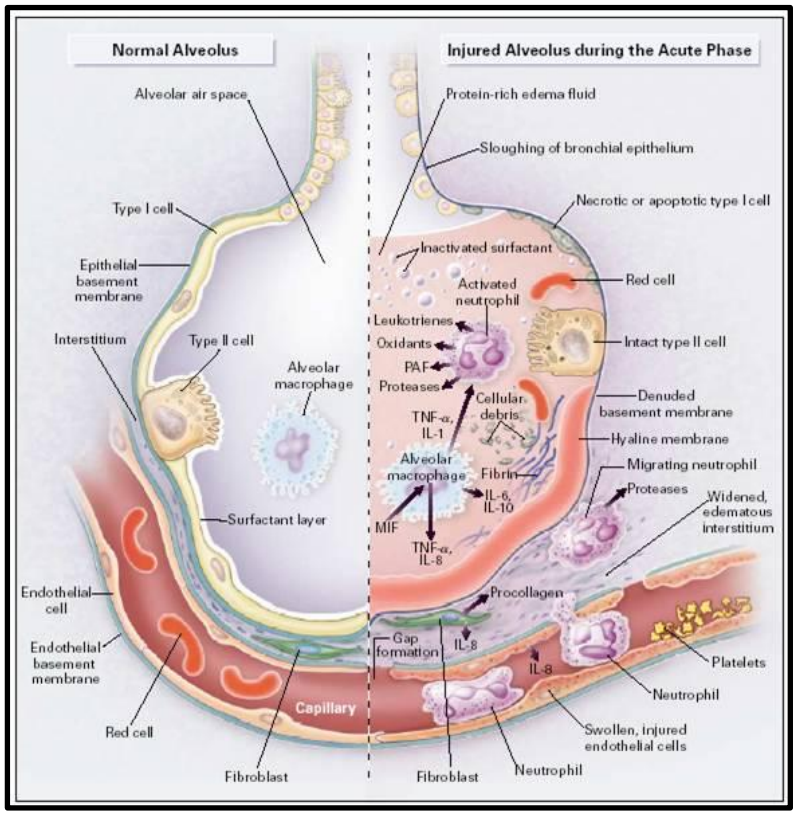
SOFA score	0	1	2	3	4
Respirationa PaO_2/FIO_2 (mm Hg) SaO_2/FIO_2	>400	<400 221–301	<300 142–220	<200 67–141	<100 <67
Coagulation Platelets $10^3/mm^3$	>150	<150	<100	<50	<20
Liver Bilirubin (mg/dL)	<1.2	1.2–1.9	2.0–5.9	6.0–11.9	>12.0
Cardiovascular[b] Hypotension	No hypotension	MAP <70	Dopamine </=5 or dobutamine (any)	Dopamine >5 or norepinephrine </=0.1	Dopamine >15 or norepinephrine >0.1
CNS Glasgow Coma Score	15	13–14	10–12	6–9	<6
Renal Creatinine (mg/dL) or urine output (mL/d)	<1.2	1.2–1.9	2.0–3.4	3.5–4.9 or <500	>5.0 or <200

Cardiovascular dysfunction

- Characteristics
  - Peripheral vasodilatation
  - Increased capillary permeability
  - Micro-vascular occlusion
  - Myocardial depression
- Treatment
  - Goal directed fluid resuscitation
  - Inotropes
  - Cautious use of blood products
- Prevention – mimimization of edema
  - Goal-directed fluid resuscitation
  - Cautious removal of excess volume after resuscitation

Respiratory dysfunction

- Definition of ARDS
  - Acute onset = within one week
  - bilateral opacities not fully explained by effusions, lobar/lung collapse, or nodules
  - respiratory failure not fully explained by cardiac failure or fluid overload
  - Hypoxemia while receiving a minimum level of PEEP of 5 cm H2O or higher
  - Severity PaO2 /FiO2:
    - Mild ≤ 300
    - Moderate ≤ 200
    - Severe ≤ 100



- Respiratory dysfunction initially results from the systemic inflammatory response that leads to increased capillary permeability with interstitial edema and exudation of protein-rich fluid into the alveolar space. Gas exchange is compromised leading to hypoxemia and tachypnea. Lung compliance is reduced.
- Additional insults include ventilator-induced lung injury (VILI) and ventilator-associated pneumonia (VAP).

VILI - VAP

- VILI: as several alveoli become filled with edematous fluid, the air (tidal volume) provided by the ventilator in each breath is distributed to less lung units than normally. This can cause abnormal stretch of lung cells, resulting in production of pro-inflammatory cytokines and oxidative molecules, further damaging the lung. Additionally this inflammatory response can “spill-over” inducing systemic inflammation and distal organ injury.
- Protective lung ventilation strategies, consistent of low tidal volumes (6-8 ml/kg) and higher levels of PEEP, reduce not only pulmonary, but also distant organ injury, and improve survival.
- Goal directed fluid resuscitation can minimize interstitial and therefore pulmonary edema

- VAP: intubation overrides normal upper respiratory system barriers to infection. Ventilated patients are at risk of developing pneumonia, caused by often multidrug resistant, bacteria
- Strategies to reduce VAP include elevation of the head of the bed, hand hygiene and efforts to minimize days on mechanical ventilation

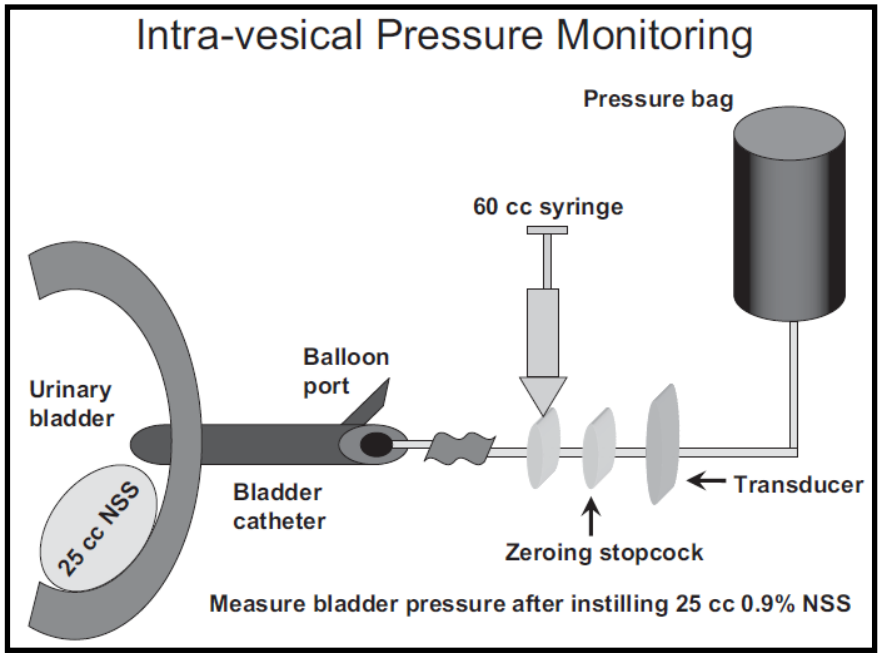
Renal dysfunction

- Renal dysfunction, histologicaly characterized by acute tubular necrosis, commonly results from hypo-perfusion, and so early resuscitation is the key to minimizing subsequent renal dysfunction.
- Abdominal compartment syndrome, which sometimes occurs in patients with abdominal pathology, can also compromise renal perfusion.
- Finally, nephrotoxic medications can contribute to the evolution of acute tubular dysfunction and acute kidney injury (AKI).
- AKI classification

	Cr fold-change from baseline	Urine output
Stage I	1,5-2	≤0.5ml/kg/h for >6h
Stage II	2-3	≤0.5ml/kg/h for >12h
Stage III	≥3 or RRT	≤0.3ml/kg/h for 24h or anuria for 12h

Abdominal hypertension and compartment syndrome

- AH: sustained ↑ IAP >12mmHg
- Grade I: 12-15
- Grade II: 16-20
- Grade III: 21-25
- Grade IV: >25
- ACS: sustained IAP>20+organ dysfunction
  - Respiratory
  - Kidney
  - Hypotension
  - Metabolic acidosis
  - Coagulopathy/liver dysfunction



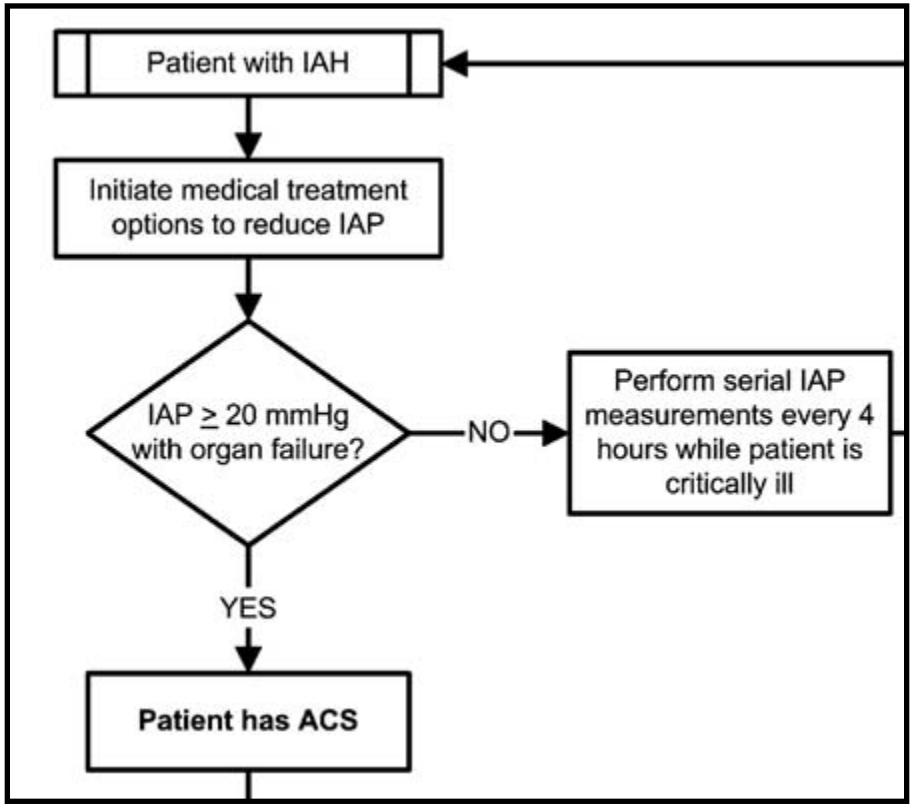
Risk Factors for IAH / ACS

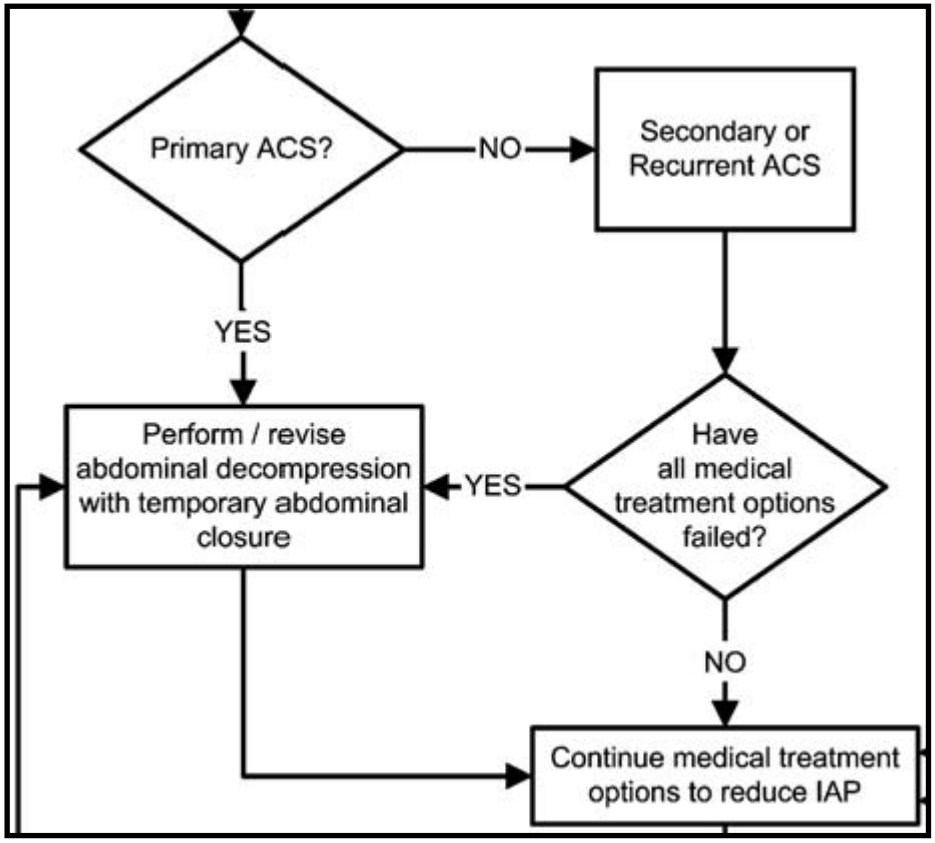
1. Diminished abdominal wall compliance
   - Acute respiratory failure, especially with elevated intrathoracic pressure
   - Abdominal surgery with primary fascial closure
   - Major trauma / burns
   - Prone positioning

2. Increased intra-luminal contents
   - Gastroparesis
   - Ileus
   - Colonic pseudo-obstruction

3. Increased abdominal contents
   - Hemoperitoneum / pneumoperitoneum
   - Ascites / liver dysfunction

4. Capillary leak / fluid resuscitation
   - Acidosis (pH < 7.2)
   - Hypotension
   - Hypothermia (core temperature < 33°C)
   - Polytransfusion (>10 units of blood / 24 hours)
   - Massive fluid resuscitation (> 5 L / 24 hours)
   - Oliguria
   - Sepsis
   - Major trauma / burns
   - Damage control laparotomy





Medical Treatment Options to Reduce IAP

1. Improve abdominal wall compliance
   - Sedation / analgesia
   - Neuromuscular blockade
   - Body positioning

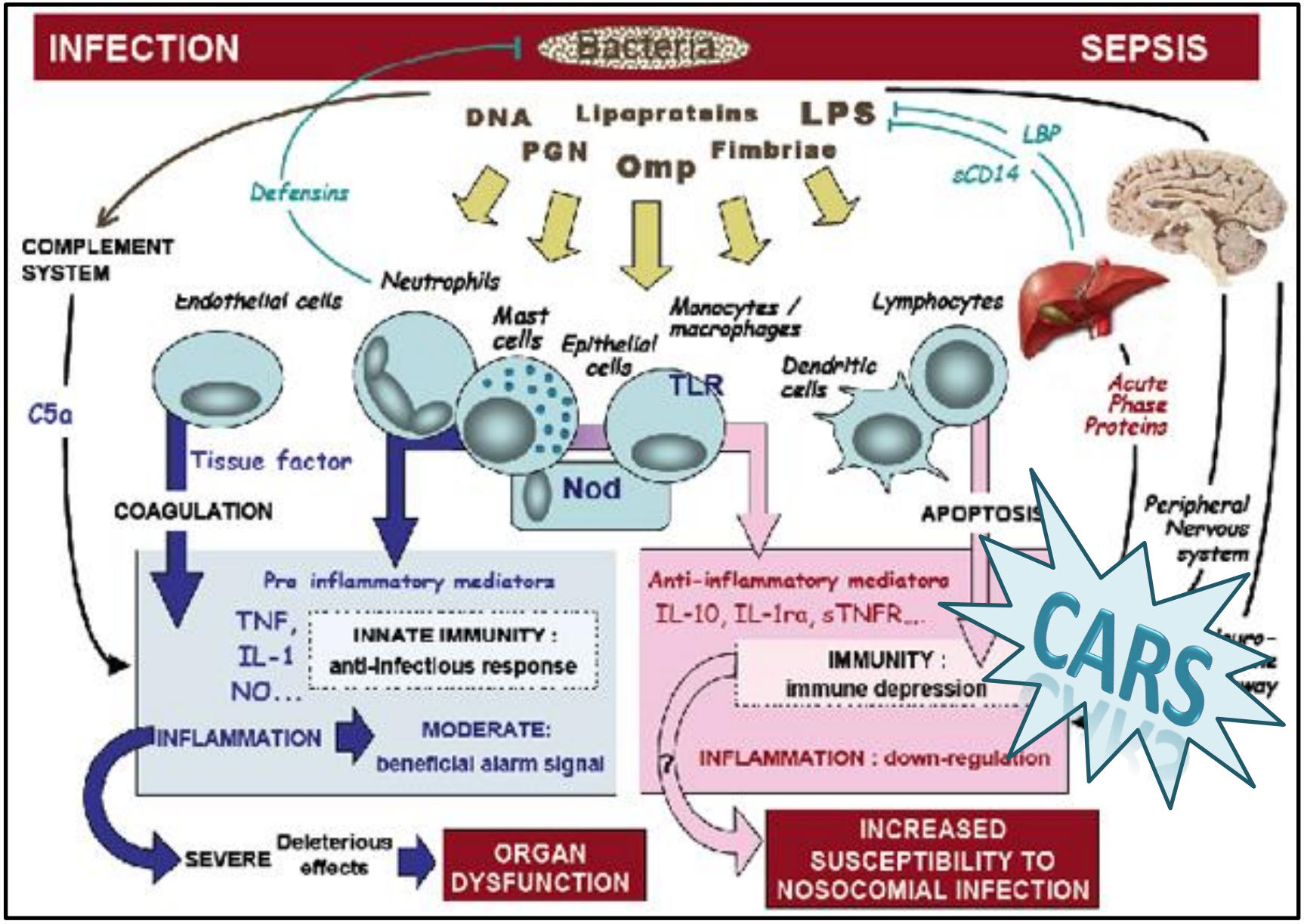
2. Evacuate intra-luminal contents
   - Nasogastric decompression
   - Rectal decompression / enemas
   - Gastro-/colo-prokinetic agents

3. Evacuate abdominal fluid collections
   - Percutaneous decompression

4. Correct positive fluid balance
   - Fluid restriction
   - Diuretics
   - Colloids
   - Hemodialysis / ultrafiltration

Hematologic, Hepatic, and neurologic dysfunction

- Hematologic
  - DIC –abnormal activation of coagulation
  - Lymphocytopenia - apoptosis
  - Thrombocytopenia - peripheral distruction, bone marrow suppression (d/d from drug-induced)
- Hepatic
  - Hyperbilirubinemia (d/d from drug-induced)
- Neurologic
  - Reduced level of consciousness
  - Delirium: acute and fluctuating disturbance of consciousness and cognition


INFECTION
Bacteria
SEPSIS
DNA
Lipoproteins
LPS
PGN
Omp
Fimbriae
LBP
sCD14
Defensins
COMPLEMENT SYSTEM
Neutrophils
Endothelial cells
Mast cells
Epithelial cells
Monocytes / macrophages
Lymphocytes
Dendritic cells
TLR
Nod
C5a
Tissue factor
COAGULATION
APOPTOSIS
Acute Phase Proteins
Peripheral Nervous system
Pro inflammatory mediators
TNF, IL-1 NO...
INNATE IMMUNITY : anti-infectious response
INFLAMMATION
MODERATE: beneficial alarm signal
SEVERE
Deleterious effects
ORGAN DYSFUNCTION
Anti-inflammatory mediators
IL-10, IL-1ra, sTNFR...
IMMUNITY : immune depression
INFLAMMATION : down-regulation
CARS
INCREASED SUSCEPTIBILITY TO NOSOCOMIAL INFECTION

ICU- aquired infections
Central venous Catheter-related infections and VAP

- Presence of catheters/tubes susceptible to colonization by micro-organisms that produce biofilms
- Antibiotic-resistant microorganisms (use of broad-spectrum antibiotics)
- Altered endogenous flora due to antibiotics and stress-ulcer prophylaxis
- Immunosupression (CARS)
- Insufficient hand hygiene

Organ dysfunction and clinical futility

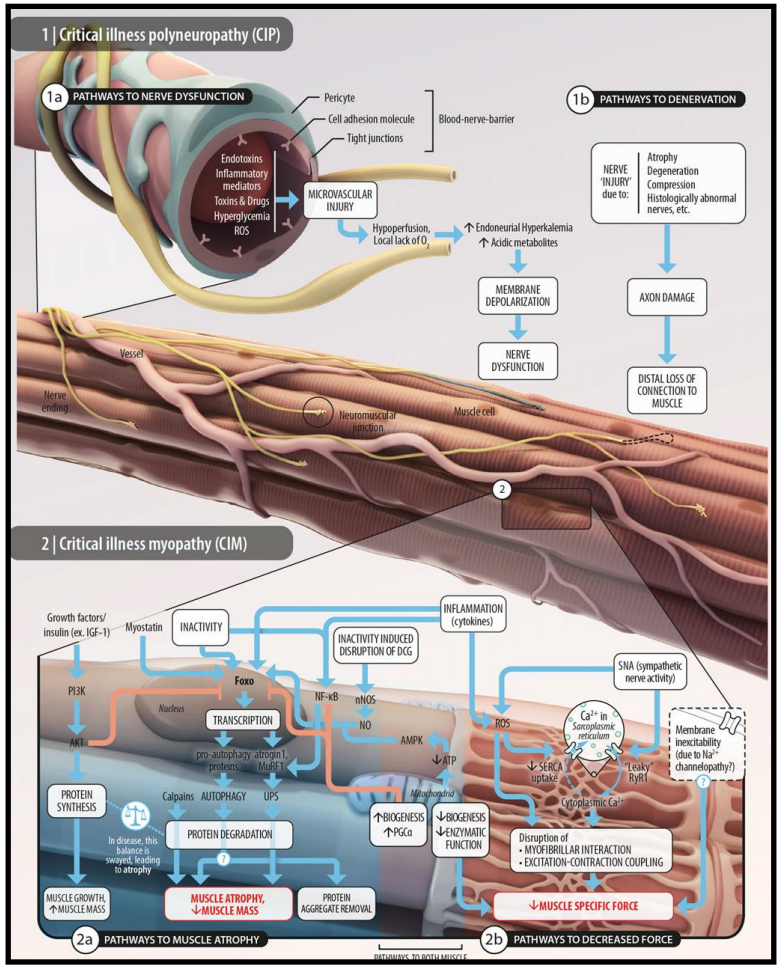
- Although increasing severity or number of organ-system dysfunction is associated with worse clinical outcome, nor the presence or the number of organ dysfunction can indicate termination of support. Rather, the decision is affected by the reversibility and the time course of organ dysfunction. The presence of treatable disease, co-morbidities, predicted quality of life, and patient preferences all influence the decision for maintaining or withholding aggressive life support.

- Predicted mortality based on scoring systems such as APACHE II is not used to guide choices on life support

Late consequences of severe sepsis

Critical illness polyneuropathy CIP-myopathy CIM

- CIP is a distal axonal sensory-motor polyneuropathy affecting both limb and respiratory muscles
- Most patient with severe sepsis develop some degree of CIP / sepsis is the most common cause of CIP
- No specific treatment available
- Skeletal muscle dysfunction in the critically ill derives from a variable combination of decreased muscle mass and impaired contractility
- The muscle atrophy of CIM demonstrates a remarkably preferential loss of myosin relative to actin
- CIP and CIM significantly contribute to ICU-acquired weakness and adversely affect patients quality of life
- Early mobilization and physiotherapy in ICU is currently the only available therapy



Post-traumatic stress disorder Cognitive dysfunction

- Critical illness is associated with nonspecific brain injury and neuropsychiatric impairments.
- About 2/3 of patients present post-traumatic stress disorder and/or cognitive impairment during the first year after discharge
- New cognitive impairments acquired during critical illness affect memory, executive functioning, and attention, and adversely affect survivors' daily functioning, ability to return to work, and quality of life
- Early rehabilitation appears as a promising intervention to improve health-related quality of life of ICU-survivors

CONCLUSION

- The key to a successful management of sepsis/SIRS, is
  - **early** recognition,
  - **early** aggressive and targeted resuscitation,
  - **early** appropriate antibiotic therapy and source control
- Adjunctive therapies can improve the clinical course and survival. Minimizing potential adverse effects of treatment is critical.
- Multidisciplinary collaboration is important to clinical management.

- Definitions
- Pathophysiology
- Diagnosis
- Early management
- Infection control
- Supportive therapies
- Diagnosis and management of organ-system dysfunction
- Late consequences of severe sepsis

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