S E P S I S :
UPDATE GUIDELINE 2016: WHAT'S DIFFERENCES THAN GUIDELINE 2001 ?

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- Definitions
- Epidemiology
- Pathophysiology
- Treatment
- Future directions

Definitions

Systemic Inflammatory Response Syndrome (SIRS) :

- Systemic inflammatory response to various stresses.
- Meets 2 or more of the following criteria :
  - Temperature of >38 degree C/<36 degree C
  - Heart rate of more than 90 beats/min
  - RR >20 breaths/min or PaCo2 <32mmHg
  - WBC >12,000/mm3 or <4000/mm3

Older Definitions

SEPSIS :

- Evidence of SIRS accompanied by known or suspected infection.

Severe SEPSIS :

- Sepsis accompanied by hypoperfusion or organ dysfunction.
- Cardiovascular :
  - SBP<90 mmhg/MAP<70 for at least 1 hr despite adequate volume resuscitation or the use of vasopressors to achieve the same goals.
- Renal :
  - Urine output <0.5 ml/kg/hr or Acute Renal Failure.
- Pulmonary :
  - PaO2/FiO2 <250 if other organ dysfuncton is present or <200 if the lungs is the only dysfunctional organ.

Older Definitions

Severe SEPSIS (contd) :

- Gastrointestinal :
  - Hepatic dysfunction (hyperbilirubinemia,Elevated transaminases
- CNS :
  - Alteration in Mental status (delirium)
- Hematologic :
  - Platelet count of <80,000/mm3 or decreased by 50% over 3 days/DIC
- Metabolic :
  - PH<7.30 or base deficit >5.0 mmol/L
  - Plasma lactate >1.5 upper limit of normal.

Septic Shock :

- Severe Sepsis with persistent hypoperfusion or hypotension despite adequate fluid resuscitation

Consensus definitions

- 1991 - American College of Chest Physicians and the Society of Critical Care Medicine Consensus Conference.
- 2001 - Society of Critical Care Medicine, the European Society of Intensive Care Medicine, The American College of Chest Physicians, the American Thoracic Society and the Surgical Infection Society.
- 2016 - Society of Critical Care Medicine and the European Society of Intensive Care Medicine Redefinitions Task Force.

Sepsis 1

- Introduced the term “systemic inflammatory response syndrome” (SIRS).
- SIRS is considered to be present when patients have more than one of the following clinical findings:
  - Body temperature higher than 38°C or lower than36°C
  - Heart rate higher than 90/min
  - Hyperventilation evidenced by respiratory rate higher than 20/min or PaCO2lower than 32mmHg
  - White blood cell count higher than 12,000 cells/ µl or lower than 4,000/ µl

Sepsis 1

- Sepsis
  - SIRS plus infection
- Severe sepsis
  - sepsis associated with organ dysfunction, hypoperfusion or hypotension
- Septic shock
  - sepsis with arterial hypotension despite “adequate” fluid resuscitation

SIRS limitations

- SIRS lacks sensitivity for defining sepsis
  - 1 in 8 ICU patients with infection and organ dysfunction do not have 2 or more SIRS critieria
- SIRS not specific
  - 4 in 5 ICU patients without infection have ‘SIRS’ criteria
- Different sources of infection are associated with different mortality rates
- SIRS criteria do not account for the dynamic time-course of sepsis (e.g. rise and fall in white cell count over time, fluctuations in vital signs)

Sepsis 2

- Unchanged concepts of sepsis, severe sepsis, and septic shock
- Original SIRS overly sensitive and nonspecific -> increased complexity of scoring system.

Expanded SIRS criteria

Table 1 Diagnostic criteria for sepsis

Infection[a]
Documented or suspected *and* some of the following[b]:
General parameters
Fever (core temperature >38.3°C)
Hypothermia (core temperature <36°C
Heart rate >90 bpm or >2 SD above the normal value for age
Tachypnea: >30 bpm
Altered mental status
Significant edema or positive fluid balance (>20 ml/kg over 24 h)
Hyperglycemia (plasma glucose >110 mg/dl or 7.7 mM/l) in the absence of diabetes
Inflammatory parameters
Leukocytosis (white blood cell count >12,000/µl)
Leukopenia (white blood cell count <4,000/µl)
Normal white blood cell count with >10% immature forms
Plasma C reactive protein >2 SD above the normal value
Plasma procalcitonin >2 SD above the normal value
Hemodynamic parameters
Arterial hypotension[b] (systolic blood pressure <90 mmHg, mean arterial pressure <70, or a systolic blood pressure decrease >40 mmHg in adults or <2 SD below normal for age)
Mixed venous oxygen saturation >70%[b]
Cardiac index >3.5 l min^{-1} m^{-2}[c,d]
Organ dysfunction parameters
Arterial hypoxemia (PaO_2/FIO2 <300)
Acute oliguria (urine output <0.5 ml kg^{-1} h^{-1} or 45 mM/l for at least 2 h)
Creatinine increase ≥0.5 mg/dl
Coagulation abnormalities (international normalized ratio >1.5 or activated partial thromboplastin time >60 s)
Ileus (absent bowel sounds)
Thrombocytopenia (platelet count <100,000/µl)
Hyperbilirubinemia (plasma total bilirubin >4 mg/dl or 70 mmol/l)
Tissue perfusion parameters
Hyperlactatemia (>3 mmol/l)
Decreased capillary refill or mottling

[a] Defined as a pathological process induced by a micro-organism

[b] Values above 70% are normal in children (normally 75–80%) and should therefore not be used as a sign of sepsis in newborns or children

[c] Values of 3.5–5.5 are normal in children and should therefore not be used as a sign of sepsis in newborns or children

[d] Diagnostic criteria for sepsis in the pediatric population is signs and symptoms of inflammation plus infection with hyper- or hypothermia (rectal temperature >38.5°C or <35°C), tachycardia (may be absent in hypothermic patients) and at least one of the following indications of altered organ function: altered mental status, hypoxemia, elevated serum lactate level, and bounding pulses

Sepsis 3

- Sepsis is ’life-threatening organ dysfunction due to a dysregulated host response to infection.’
- Layperson definition ‘a life-threatening condition that arises when the body’s response to infection injures its own tissue.’
- ‘Severe sepsis’ no longer exists as a concept, there is simply ‘sepsis’ and ‘septic shock.’

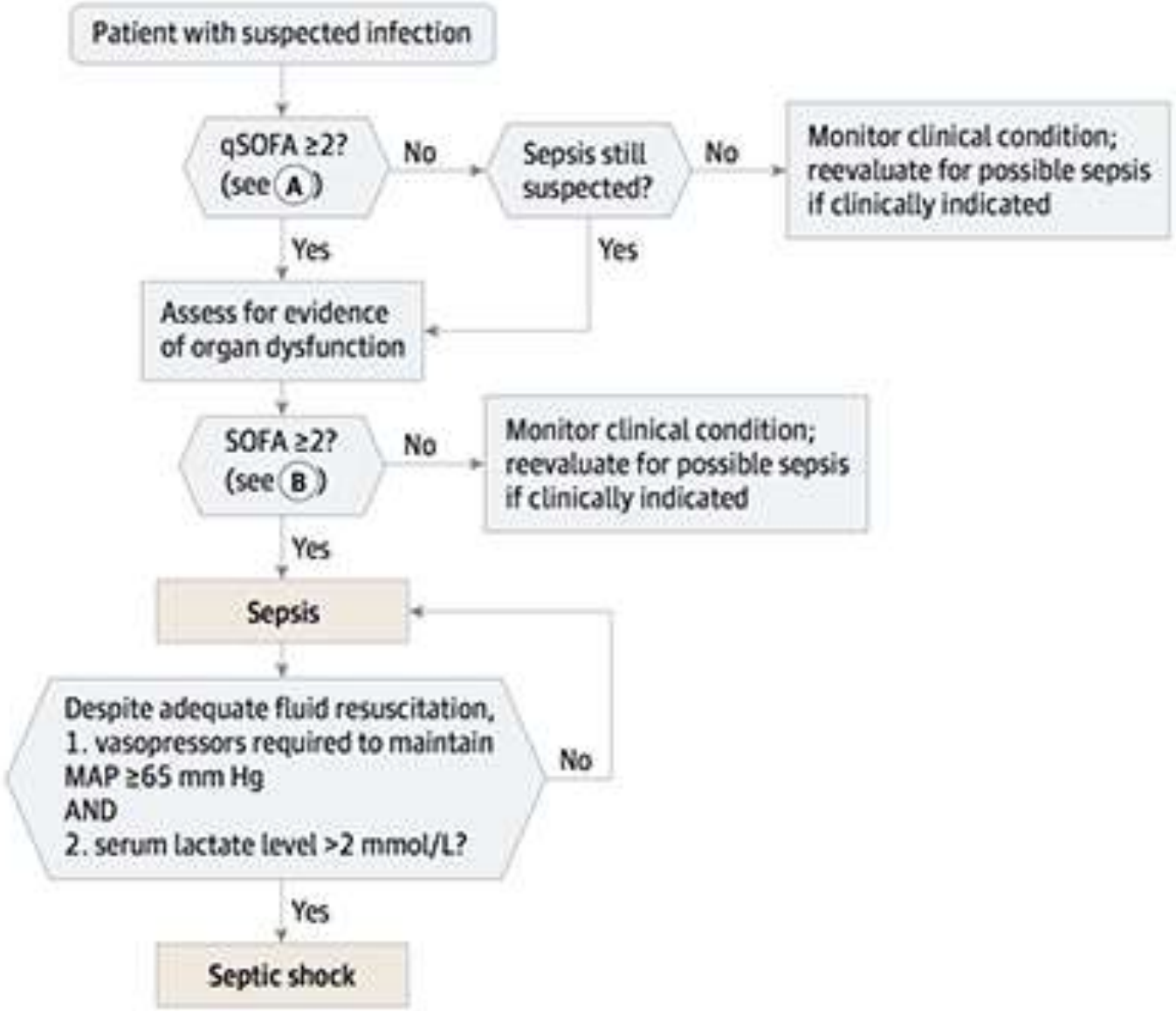
Sepsis

- Sepsis clinical criteria: organ dysfunction is defined as an increase of 2 points or more in the Sequential Organ Failure Assessment (SOFA) score
  - for patients with infections, an increase of 2 SOFA points gives an overall mortality rate of 10%
- Patients with suspected infection who are likely to have a prolonged ICU stay or to die in the hospital can be promptly identified at the bedside with qSOFA (“HAT”); i.e. 2 or more of:
  - **H**ypotension: SBP less than or equal to 100 mmHg
  - **A**ltered mental status (any GCS less than 15)
  - **T**achypnoea: RR greater than or equal to 22

Septic Shock

- Septic shock is ‘a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality.’
- Septic shock clinical criteria: Sepsis and (despite adequate volume resuscitation) both of:
  - Persistent hypotension requiring vasopressors to maintain MAP greater than or equal to 65 mm Hg, and
  - Lactate greater than or equal to 2 mmol/L
- With these criteria, hospital mortality is in excess of 40%

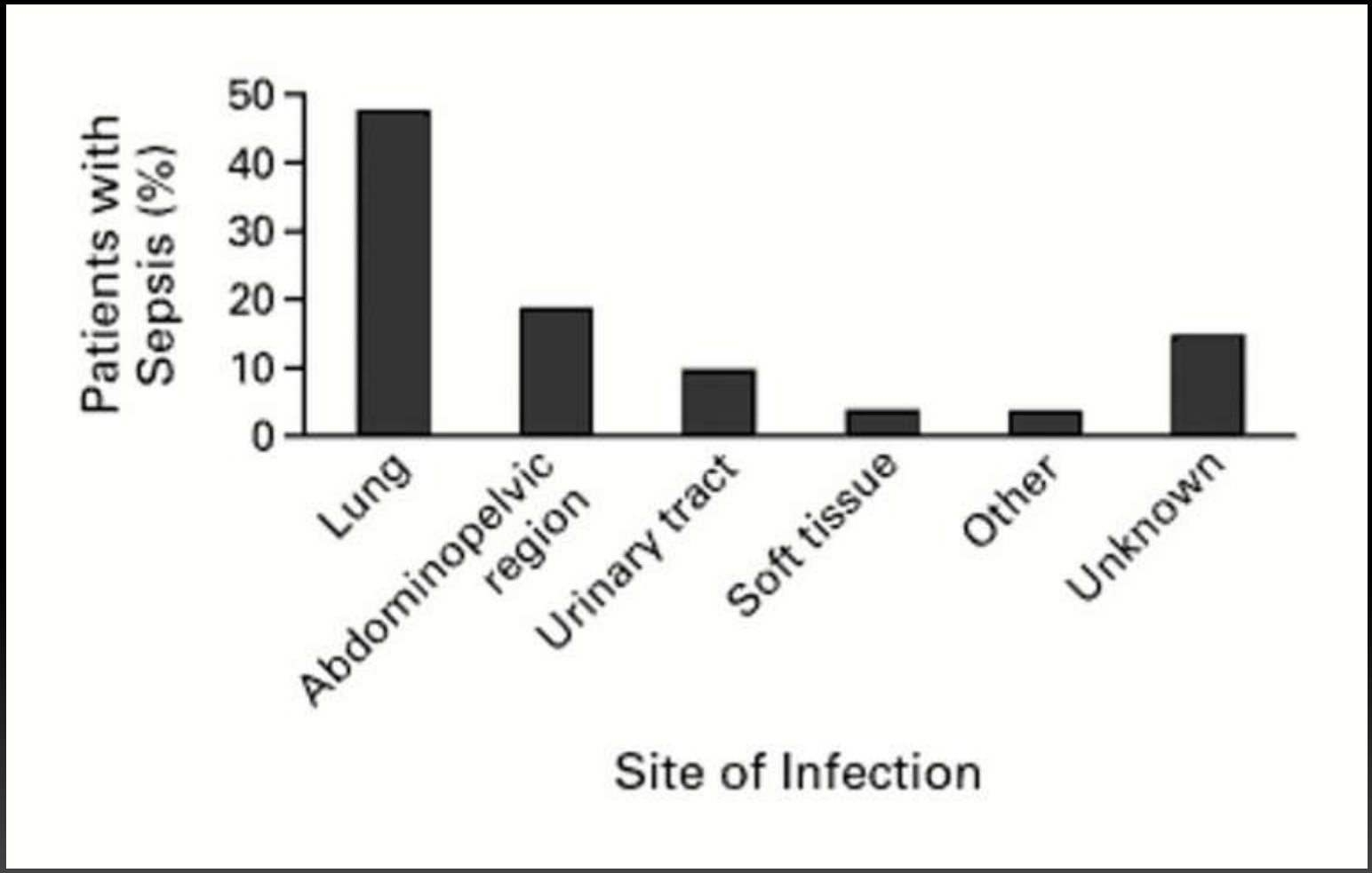
Figure. Operationalization of Clinical Criteria Identifying Patients With Sepsis and Septic Shock



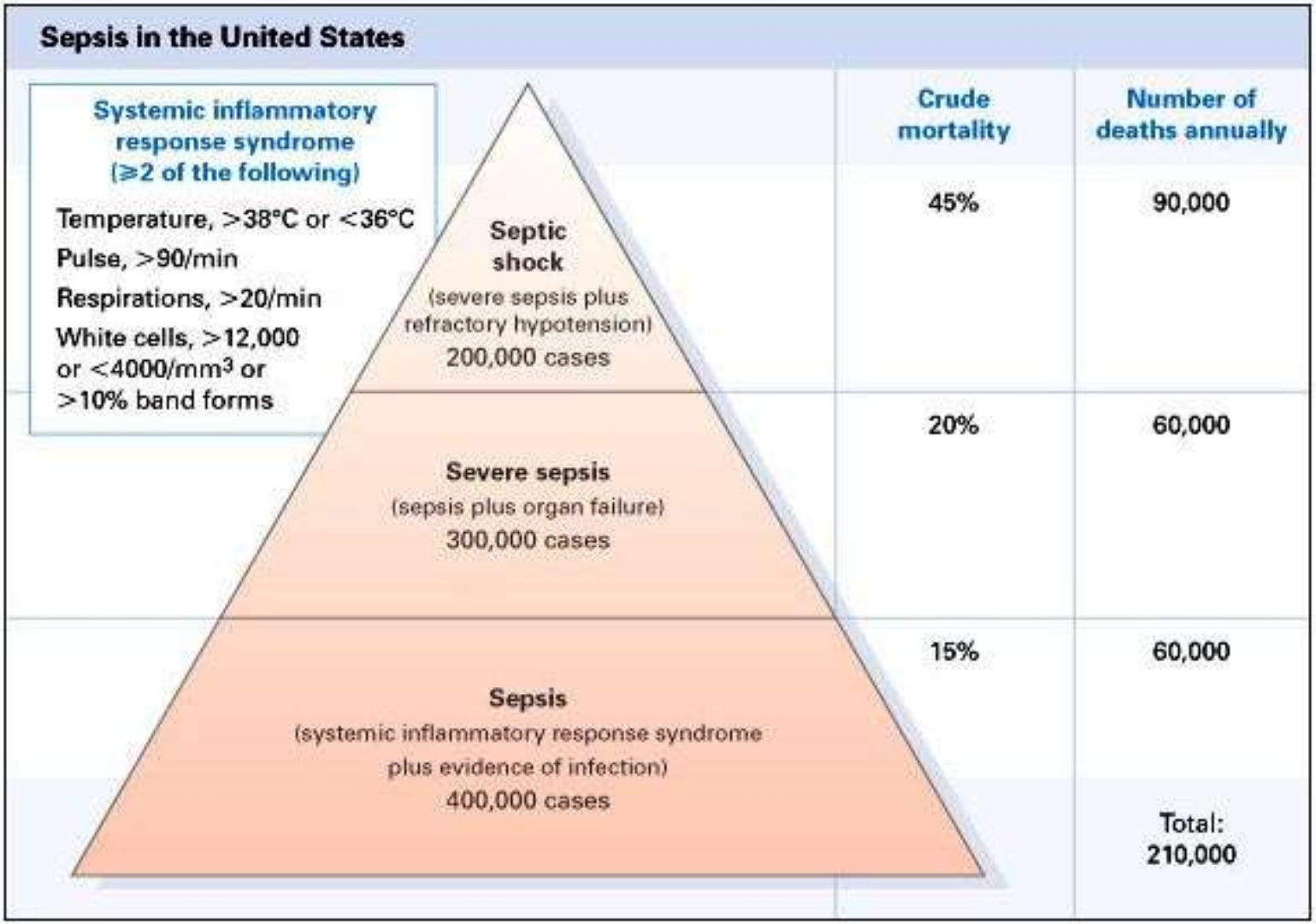
Epidemiology

- Current estimates suggest that over 750,000 cases of Sepsis are diagnosed annually, resulting in more than 200,000 deaths.
- The incidence rate for Sepsis has been increasing over the past two decades, driving an increase in the number of deaths despite a decline in case-fatality rates.
- Sepsis is the tenth leading cause of death in the United States and accounts for more than 17 billion dollars in direct healthcare expenditures.
- Risk factors include age > 65 years, male, non-whites.
- A primary site of infection cannot be established in 10% of patients with severe Sepsis/SIRS.

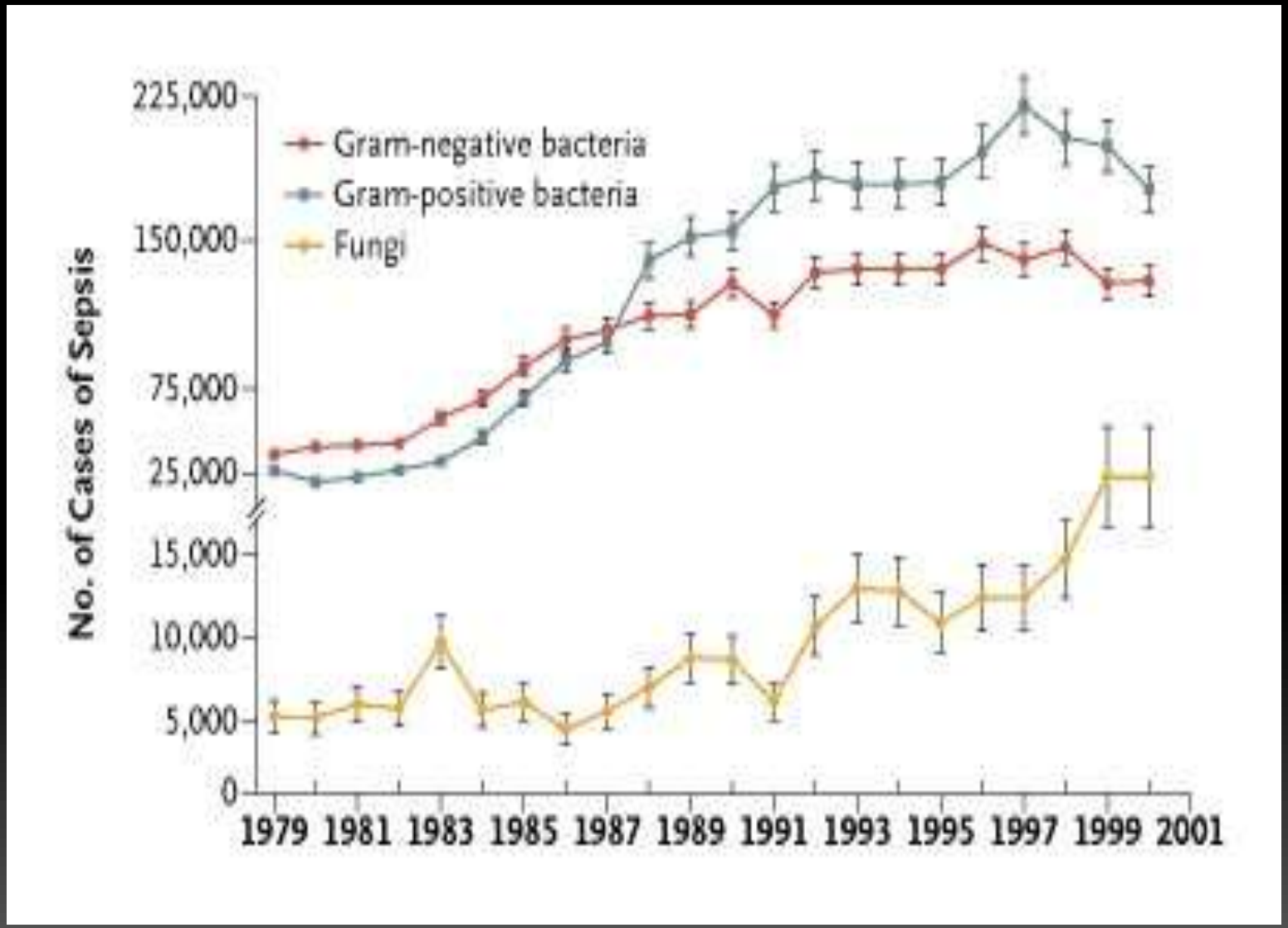
Epidemiology:



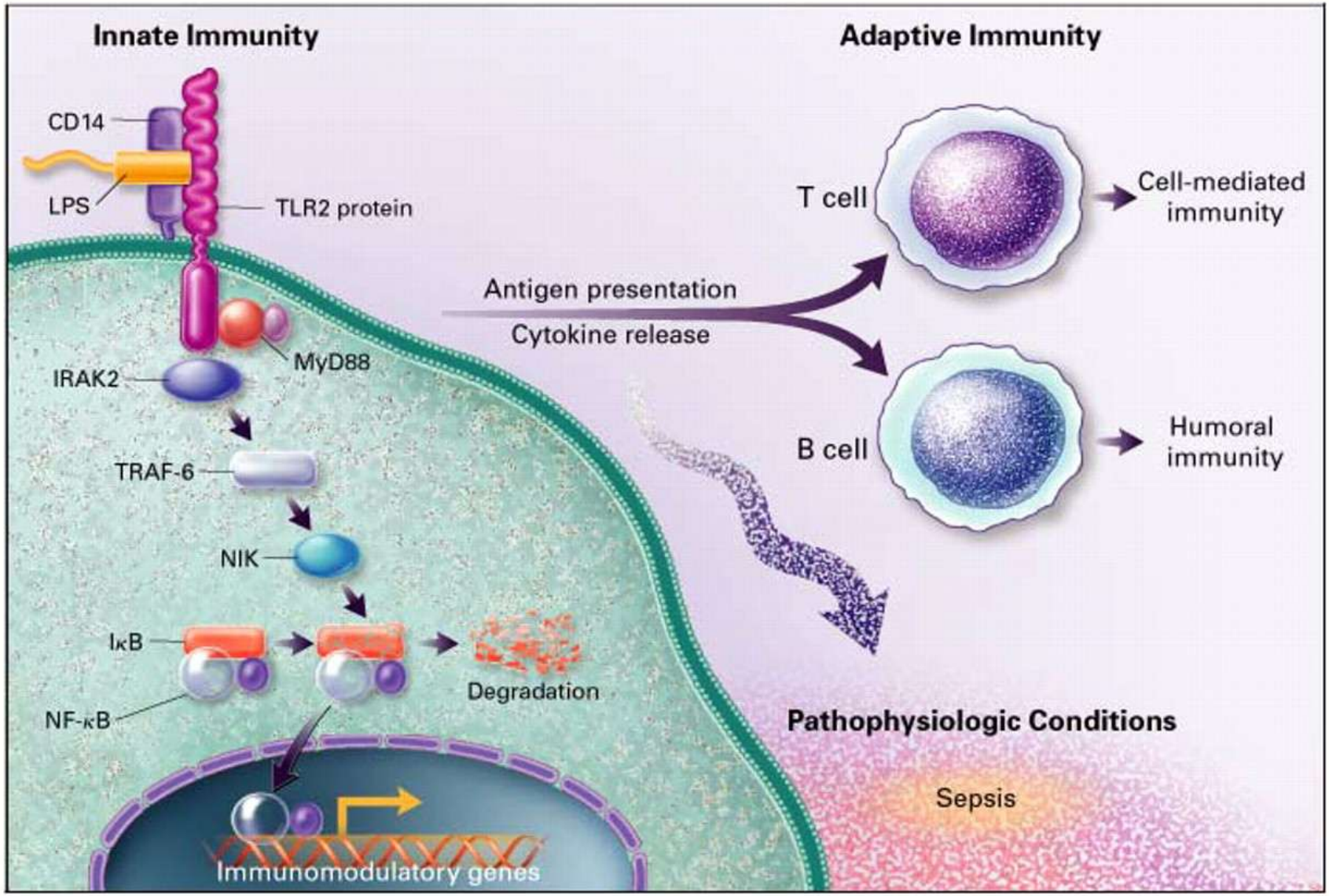
Epidemiology : Mortality rate



Epidemiology : Causative organism



Pathophysiology of Sepsis

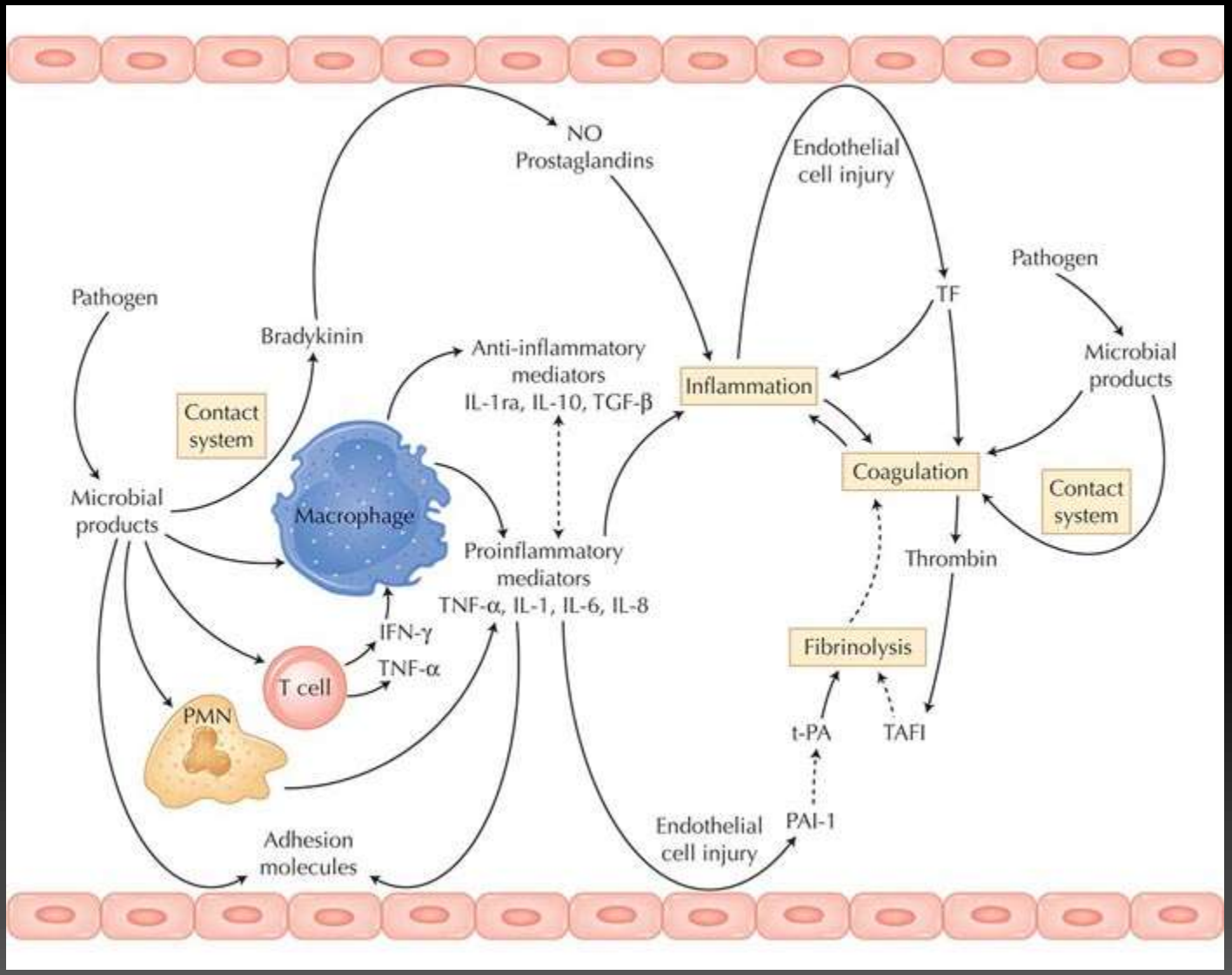


Pathophysiology of Sepsis

Disorder Due to Uncontrolled Inflammation?

- Increased inflammatory mediators like IL-1, TNF, IL-6.
- Based on animal studies.
- In a study in children with meningococcemia, TNF levels directly correlated with mortality.
- Clinical trials involving TNF anagonist, antiendotoxin antibodies, IL-1 receptor antagonists, corticosteroids failed to show any benefits.
- Patients with RA treated with TNF antagonist develop infectious complications.

Pathogenesis of Sepsis

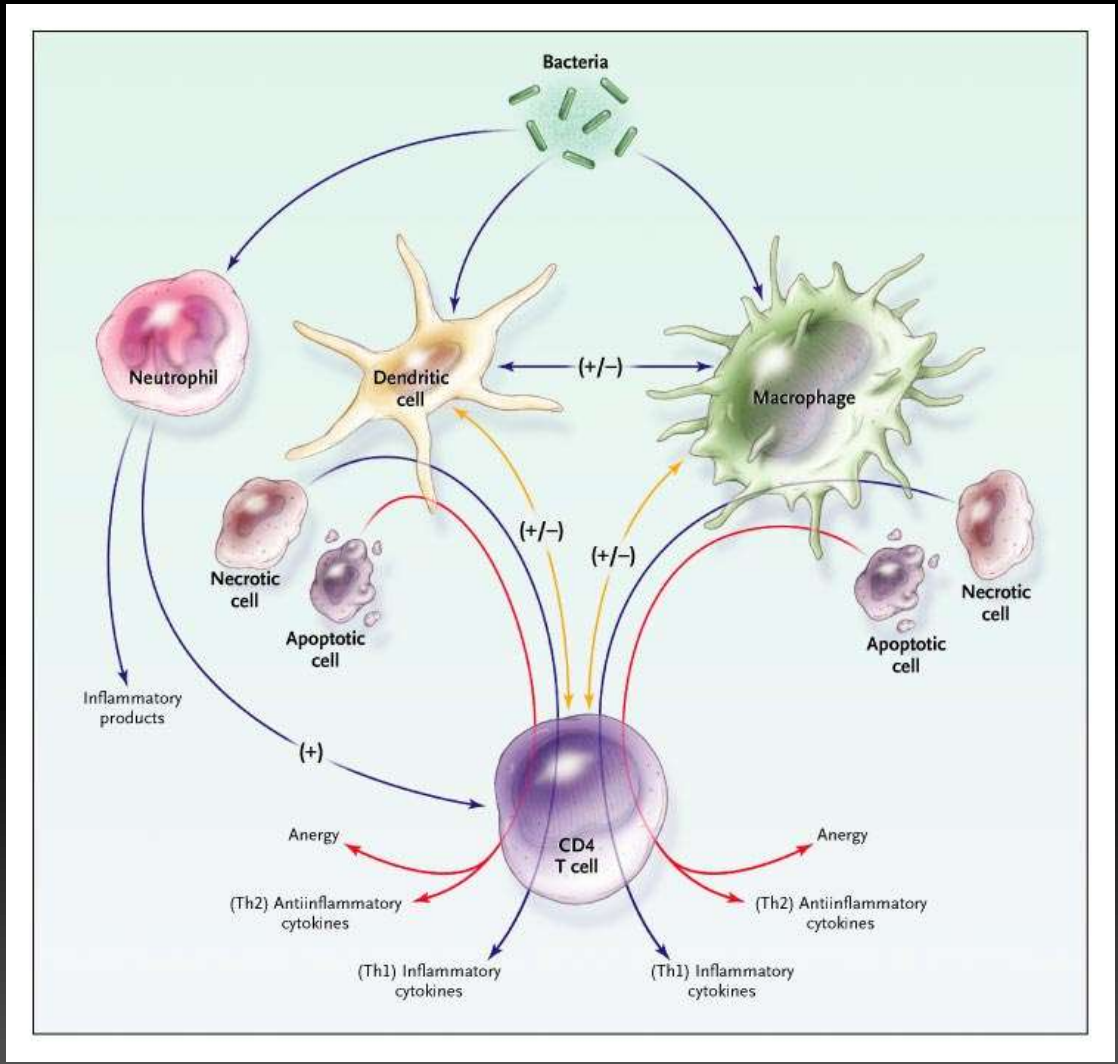


Pathophysiology of Sepsis

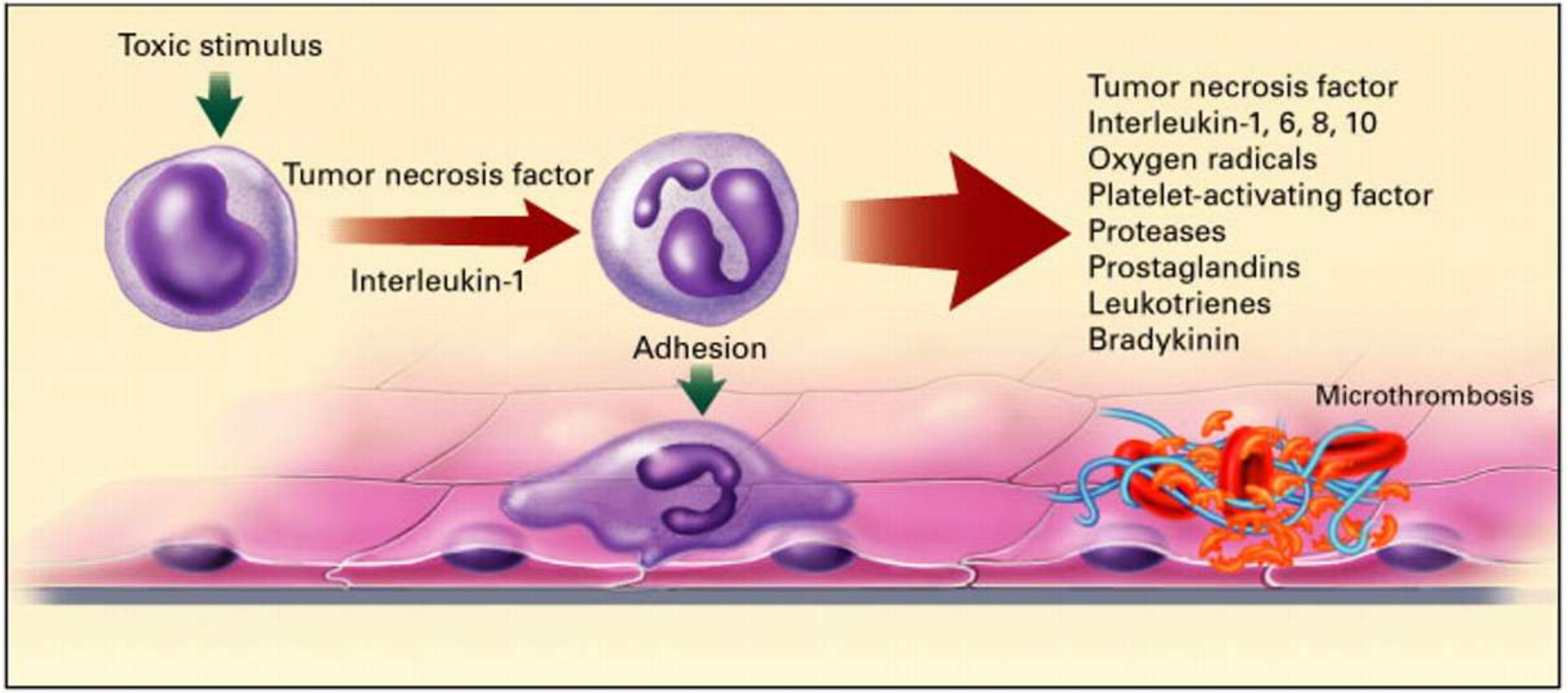
Failure of Immune System to Eliminate Microorganism?

- Shift from inflammatory (ThI) to antiinflammatory response (Th2).
- Anergy.
- Apotosis of B cells, T cells, Dendritic cells.
- Loss of macrophage expression of MHC Class I and co-stimulatory molecules.
- Immunosuppressive effect of apoptotic cells.

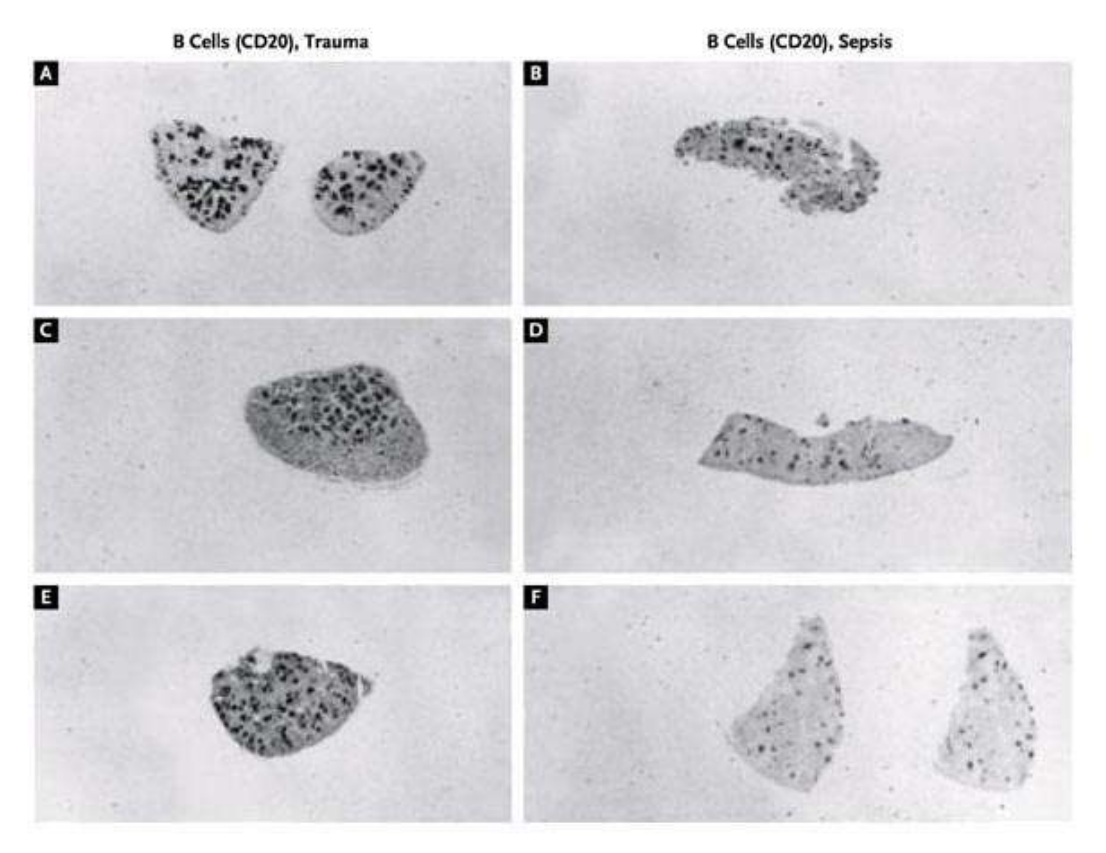
Pathogenesis of Sepsis



Pathogenesis of Sepsis



Pathogenesis of Sepsis



The dark stained regions are concentrations of B cells in lymphoid follicles that are visible to the naked eye. The patients with Sepsis have dramatically smaller and fewer lymphoid follicles than the patients with trauma.

Pathogenesis of Sepsis

Factors that influence Immune Response :

- Genetic factors, polymorphisms in cytokine genes, TLR4 mutations, MBP.
- Type of organism, virulence, size of inoculum.
- Host Factors :
  - Age, Nutritional status, Coexisting illness, COPD, CHF, Cancer, DM, Immunodeficiency.
- Therapeutic efforts to modify the host immune response in critical illness will require a more thorough understanding of the cytokine milieu and the factors that determine their production.

Multiple Organ Dysfunction Syndrome (MODS)

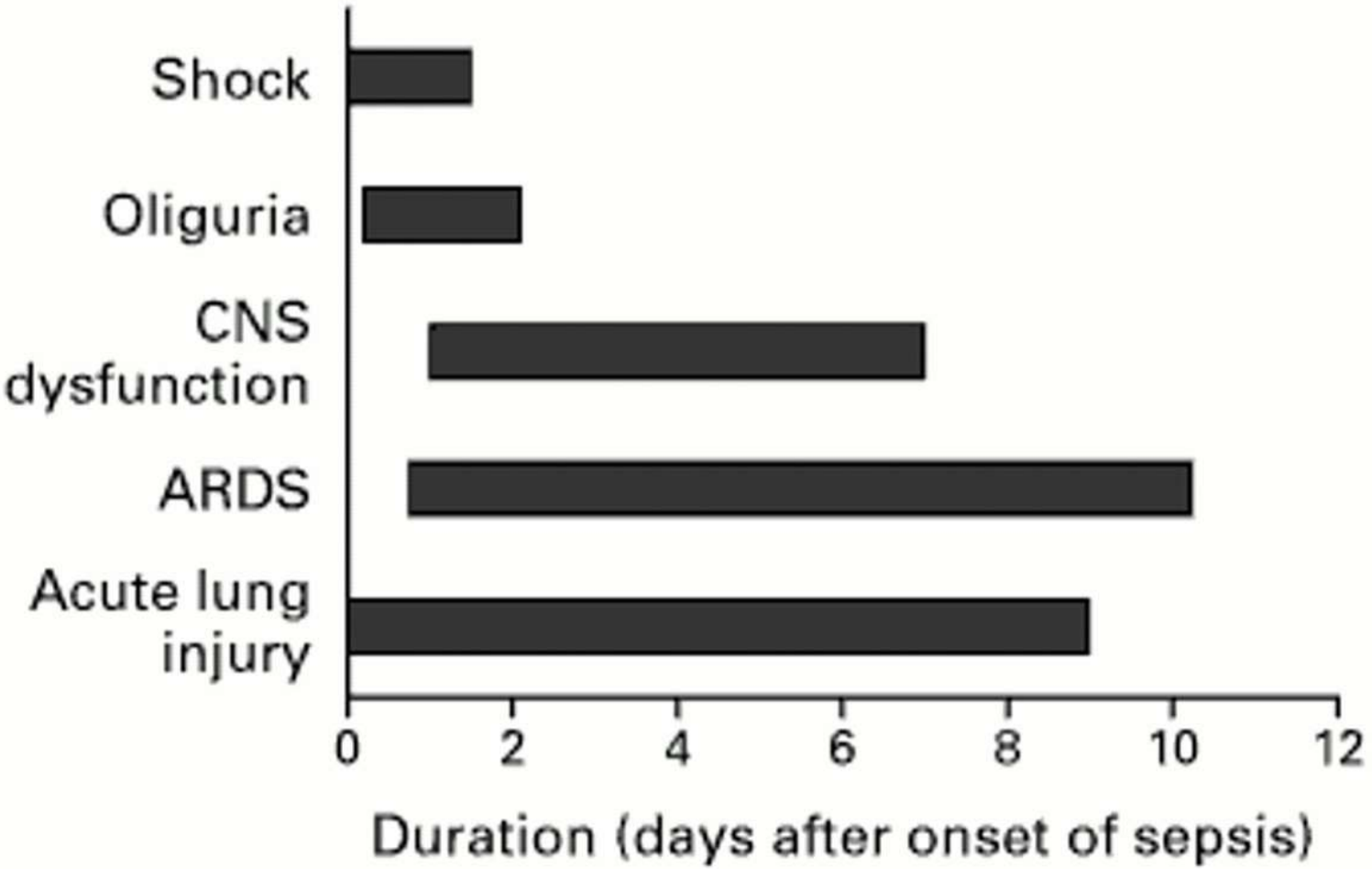
- MODS occurs late and is the most common cause of death in patients with Sepsis.
- Lactic acidosis led investigators to think that this is due to tissue ischaemia.
- Minimal cell death in postmortem samples taken from the failed organs of patients with Sepsis.
- Recovery from Sepsis is associated with near complete recovery of organ function, even in organs whose cells have poor regenerative capacity.
- Increased tissue oxygen tensions in various organs (muscle, gut, bladder) in animals and patients with Sepsis.

MODS : Possible Explanations

Late acting mediators of Sepsis

- HMGB1 (high mobility group box 1) was identified as a late-acting, cytokine-like mediator of inflammation and lethality in an animal model of endotoxemia and Sepsis.
- Neutralizing antibodies against HMGB1 confer significant protection against LPS- or Sepsis-induced mortality.
- It is elevated in late phase of Sepsis, suggesting that this may play a role in pathogenesis of MODS.
- Ethyl pyruvate and certain cholinergic agonists, which inhibits HMGB1 are therapeutic in various animal models of Sepsis even when given well after the onset of symptoms.
- Increased levels of MIF (Macrophage migration inhibitory factor) have been demonstrated in both the plasma and alveoli of patients with ARDS, suggesting that it may play a role in the pathogenesis of Sepsis induced organ dysfunction.

MODS


Shock
Oliguria
CNS dysfunction
ARDS
Acute lung injury
0
2
4
6
8
10
12
Duration (days after onset of sepsis)

Management of Sepsis and Septic Shock

- Initial Resuscitation: Fluid therapy, vasoactive agents
- Prompt administration of broad-spectrum antibiotics.
- Aggressive supportive care in intensive care units/ mechanical ventilation.
- Steroids
- Tight glycemic control.
- Activated protein C.

CONFERENCE REPORTS AND EXPERT PANEL

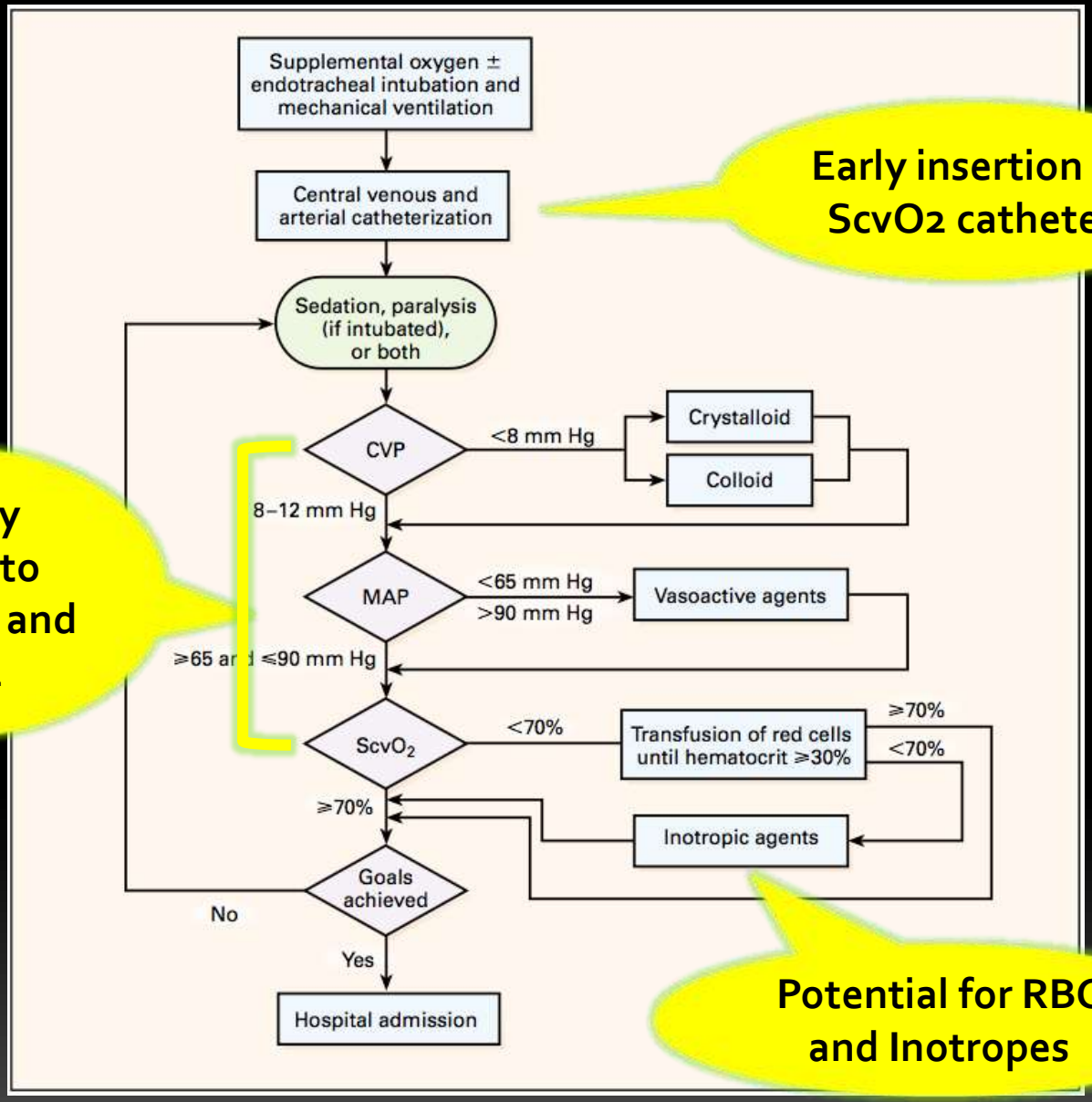
Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016

Andrew Rhodes[1*], Laura E. Evans[2], Waleed Alhazzani[3], Mitchell M. Levy[4], Massimo Antonelli[5], Ricard Ferrer[6], Anand Kumar[7], Jonathan E. Sevransky[8], Charles L. Sprung[9], Mark E. Nunnally[2], Bram Rochwerg[3], Gordon D. Rubenfeld[10], Derek C. Angus[11], Djillali Annane[12], Richard J. Beale[13], Geoffrey J. Bellinghan[14], Gordon R. Bernard[15], Jean-Daniel Chiche[16], Craig Coopersmith[8], Daniel P. De Backer[17], Craig J. French[18], Seitaro Fujishima[19], Herwig Gerlach[20], Jorge Luis Hidalgo[21], Steven M. Hollenberg[22], Alan E. Jones[23], Dilip R. Karnad[24], Ruth M. Kleinpell[25], Younsuk Koh[26], Thiago Costa Lisboa[27], Flavia R. Machado[28], John J. Marini[29], John C. Marshall[30], John E. Mazuski[31], Lauralyn A. McIntyre[32], Anthony S. McLean[33], Sangeeta Mehta[34], Rui P. Moreno[35], John Myburgh[36], Paolo Navalesi[37], Osamu Nishida[38], Tiffany M. Osborn[31], Anders Perner[39], Colleen M. Plunkett[25], Marco Ranieri[40], Christa A. Schorr[22], Maureen A. Seckel[41], Christopher W. Seymour[42], Lisa Shieh[43], Khalid A. Shukri[44], Steven Q. Simpson[45], Mervyn Singer[46], B. Taylor Thompson[47], Sean R. Townsend[48], Thomas Van der Poll[49], Jean-Louis Vincent[50], W. Joost Wiersinga[49], Janice L. Zimmerman[51] and R. Phillip Dellinger[22]

2012 Recommendation for Initial Resuscitation.

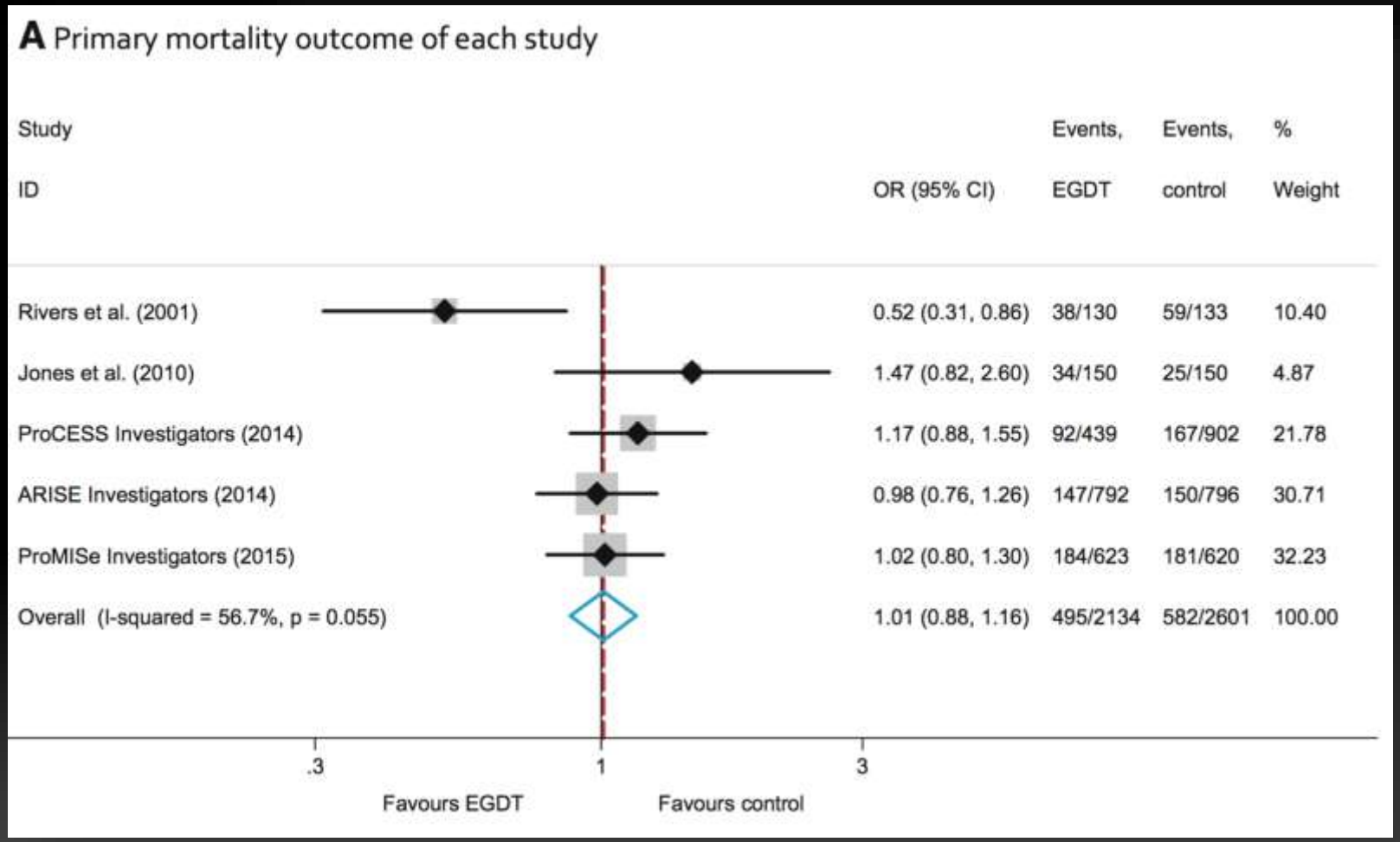
We recommend the protocolized, quantitative resuscitation of patients with sepsis- induced tissue hypoperfusion. During the first 6 hours of resuscitation, the goals of initial resuscitation should include all of the following as a part of a treatment protocol:

a) CVP 8–12 mm Hg
b) MAP ≥ 65 mm Hg
c) Urine output ≥ 0.5 mL/kg/hr
d) Scv02 ≥ 70%.



N Engl J Med, Vol. 345, No. 19 · November 8, 2001

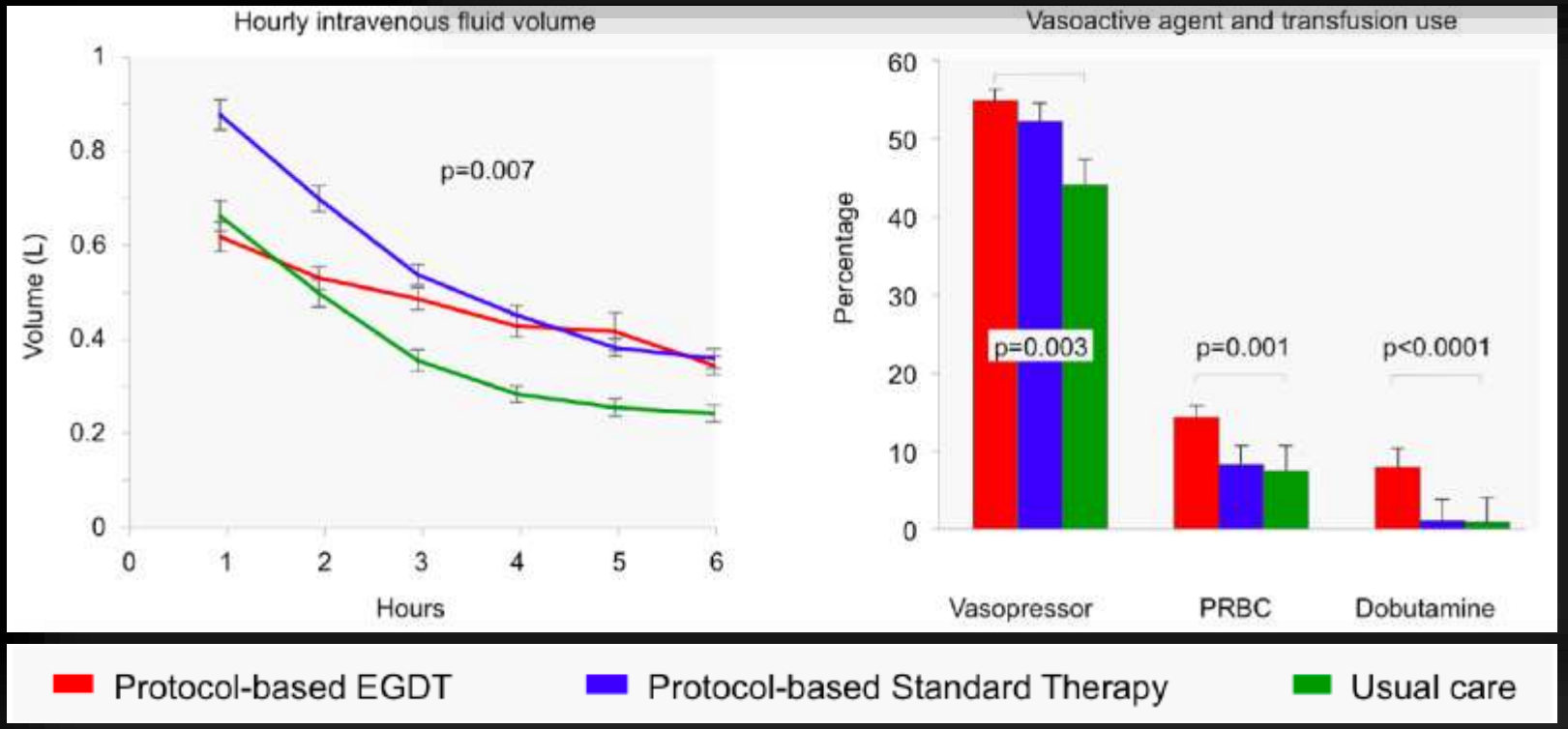
A systematic review and meta-analysis of early goal-directed therapy for septic shock: the ARISE, ProCESS and ProMISe Investigators



Intensive Care Med (2015) 41:1549–1560
DOI 10.1007/s00134-015-3822-1

A Randomized Trial of Protocol-Based Care for Early Septic Shock

The ProCESS Investigators*



Intravenous Fluids	
EGDT	2.8 L
Usual Care	2.3 L

Intravenous Antibiotics	
EGDT	97.5%
Usual Care	96.9%

DOI: 10.1056/NEJMoa1401602

Caveats / Limitations of ProCESS, ARISE & Promise

- The overall management of sepsis has changed…
  - In all three studies patients had early antibiotics, > 30ml/kg of intravenous fluid prior to randomization.
- We need therefore to be very careful about over interpreting the results in areas where this paradgim is not valid.

The River's work was useful….

- As it provided us a construct on how to understand resuscitation:
  - Start early- (give antibiotics)
  - Correct hypovolaemia
  - Restore perfusion pressure
  - And in some cases a little more may be required..!
- These concepts are as important today as they ever were.

Sepsis and septic shock are medical emergencies and we recommend that treatment and resuscitation begin immediately.

Best Practice Statement

Source Control

- **We recommend that a specific anatomic diagnosis of infection requiring emergent source control be identified or excluded as rapidly as possible in patients with sepsis or septic shock, and that any required source control intervention be implemented as soon as medically and logistically practical after the diagnosis is made.**

(Best Practice Statement).

Antibiotics

- **We recommend that administration of IV antimicrobials be initiated as soon as possible after recognition and within 1 h for both sepsis and septic shock.**

(strong recommendation, moderate quality of evidence).

- **We recommend empiric broad-spectrum therapy with one or more antimicrobials to cover all likely pathogens.**

(strong recommendation, moderate quality of evidence).

Initial Resuscitation

- **We recommend that in the resuscitation from sepsis-induced hypoperfusion, at least 30ml/kg of intravenous crystalloid fluid be given within the first 3 hours.**

(Strong recommendation; low quality of evidence)

- **We recommend that following initial fluid resuscitation, additional fluids be guided by frequent reassessment of hemodynamic status.**

(Best Practice Statement)

Fluid Therapy

- **We recommend crystalloids as the fluid of choice for initial resuscitation and subsequent intravascular volume replacement in patients with sepsis and septic shock**

(Strong recommendation, moderate quality of evidence).

- **We suggest using albumin in addition to crystalloids when patients require substantial amounts of crystalloids**

(weak recommendation, low quality of evidence).

High versus Low Blood-Pressure Target in Patients with Septic Shock

We recommend an initial target mean arterial pressure of 65 mmHg in patients with septic shock requiring vasopressors. (Strong recommendation; moderate quality of evidence)

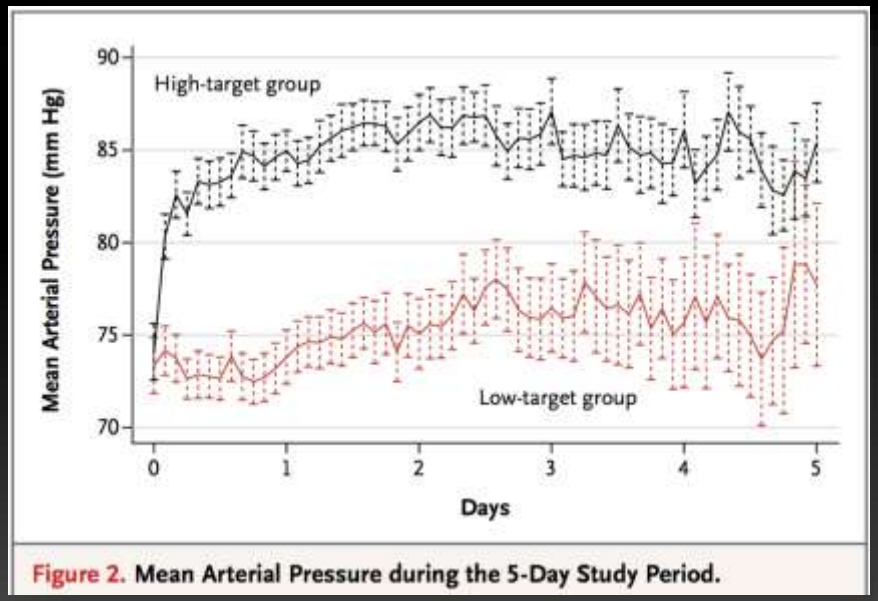


Figure 2. Mean Arterial Pressure during the 5-Day Study Period.

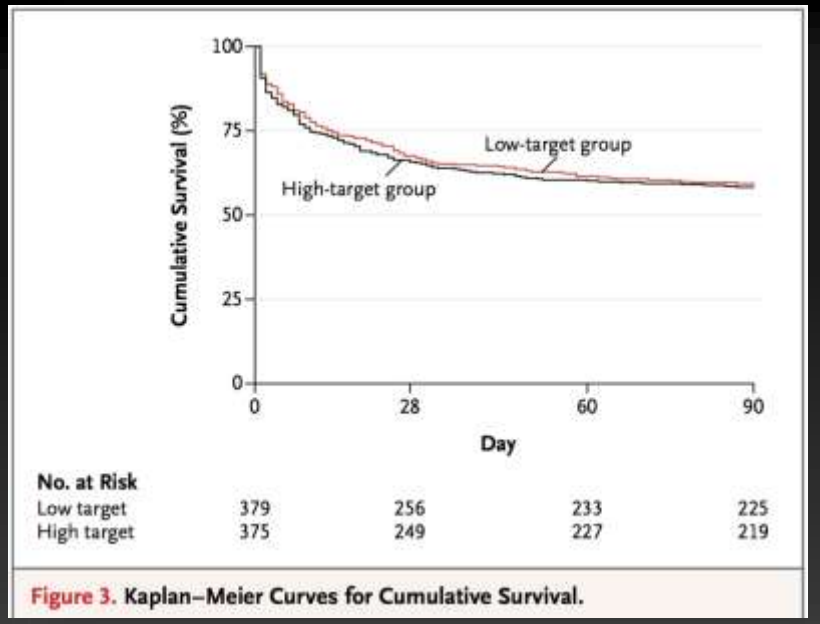


Figure 3. Kaplan–Meier Curves for Cumulative Survival.

DOI: 10.1056/NEJMoa1312173

Vasoactive agents

- **We recommend norepinephrine as the first choice vasopressor**

(strong recommendation, moderate quality of evidence).

- **We suggest adding either vasopressin (up to 0.03 U/min) or epinephrine to norepinephrine with the intent of raising MAP to target, or adding vasopressin (up to 0.03 U/min) to decrease norepinephrine dosage.**

(weak recommendation, low quality of evidence)

TABLE 2. DRUGS COMMONLY USED FOR CIRCULATORY SUPPORT.

DRUG	PHARMACOLOGIC ROLE	CLINICAL EFFECT	USUAL DOSE RANGE
Epinephrine	Alpha- and beta-adrenergic agonist	Chronotropism, inotropism, vasoconstriction	5 to 20 μg/min
Norepinephrine	Alpha- and beta-adrenergic agonist*	Chronotropism, inotropism, vasoconstriction	5 to 20 μg/min
Dopamine	Dopamine and beta-adrenergic agonist, progressive alpha-adrenergic effect with increasing doses	Chronotropism, inotropism, vasoconstriction	2 to 20 μg/kg of body weight/min
Dobutamine	Beta-adrenergic agonist	Chronotropism, inotropism, vasodilation	5 to 15 μg/kg/min
Phenylephrine	Alpha-adrenergic agonist	Vasoconstriction	2 to 20 μg/min

*The alpha-adrenergic effect is greater than the beta-adrenergic effect.

If shock is not resolving quickly…..

- **We recommend further hemodynamic assessment (such as assessing cardiac function) to determine the type of shock if the clinical examination does not lead to a clear diagnosis.**

(Best Practice Statement)

- **We suggest that dynamic over static variables be used to predict fluid responsiveness, where available.**

(Weak recommendation; low quality of evidence)

Lactate can help guide resuscitation

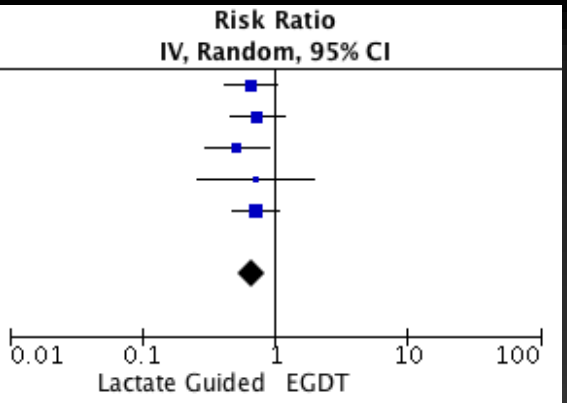
- **We suggest guiding resuscitation to normalize lactate in patients with elevated lactate levels as a marker of tissue hypoperfusion.**

(Weak recommendation; low quality of evidence)

Study or Subgroup	Lactate Guided Events	Lactate Guided Total	Standard Events	Standard Total	Weight	Risk Ratio IV, Random, 95% CI	Year
Jansen, 2010	20	68	30	67	24.9%	0.66 [0.42, 1.03]	2010
Jones, 2010	25	150	34	150	23.8%	0.74 [0.46, 1.17]	2010
Tian, 2012	14	43	12	19	16.9%	0.52 [0.30, 0.89]	2012
Yu, 2013	5	25	7	25	5.1%	0.71 [0.26, 1.95]	2013
Lyu 2015	20	50	28	50	29.2%	0.71 [0.47, 1.09]	2015
Total (95% CI)		**336**		**311**	**100.0%**	**0.67 [0.53, 0.84]**	
Total events	84		111				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.14$, df = 4 (P = 0.89); $I^2 = 0\%$

Test for overall effect: Z = 3.51 (P = 0.0004)



Summary

- Start resuscitation early with source control, intravenous fluids and antibiotics.
- Frequent assessment of the patients' volume status is crucial throughout the resuscitation period.
- We suggest guiding resuscitation to normalize lactate in patients with elevated lactate levels as a marker of tissue hypoperfusion.

SCREENING FOR SEPSIS AND PERFORMANCE IMPROVEMENT

1. **We recommend that hospitals and hospital systems have a performance improvement program for sepsis including sepsis screening for acutely ill, high-risk patients. (BPS)**

Sepsis Performance Improvement

- Performance improvement efforts for sepsis are associated with improved patient outcomes
- A recent meta-analysis of 50 observational studies:
  - Performance improvement programs associated with a significant increase in compliance with the SSC bundles and a reduction in mortality (OR 0.66; 95% CI 0.61-0.72).

Diagnosis

- 1. We recommend that appropriate routine microbiologic cultures (including blood) be obtained before starting antimicrobial therapy in patients with suspected sepsis and septic shock if doing so results in no substantial delay in the start of antimicrobials. (BPS)
  - Remarks: Appropriate routine microbiologic cultures always include at least two sets of blood cultures (aerobic and anaerobic).

Antibiotics

- **We suggest empiric combination therapy (using at least two antibiotics of different antimicrobial classes) aimed at the most likely bacterial pathogen(s) for the initial management of septic shock.**
  - **(Weak recommendation; low quality of evidence)**

Choice of Antibiotics

If pseudomonas is an unlikely pathogen, combine vancomycin with one of the following:

- Cephalosporin, 3rd or 4th generation (e.g., ceftriaxone, cefotaxime, or cefepime).
- Beta-lactam/beta-lactamase inhibitor (e.g., ampicillin-sulbactam).
- Fluroquinolones (eg., Levofloxacin, gatifloxacin, moxifloxacin.)

If pseudomonas is suspected, combine vancomycin with two of the following :

- Antipseudomonal cephalosporin (e.g., cefepime, ceftazidime, or cefoperazone).
- Antipseudomonal carbapenem (eg, imipenem, meropenem).
- Antipseudomonal beta-lactam/beta-lactamase inhibitor (e.g., pipercillin-tazobactam,ticarcillin-clavulanate).
- Aminoglycoside (e.g., gentamicin, amikacin, tobramycin).
- Fluoroquinolone with good anti-pseudomonal activity (e.g., ciprofloxacin).
- Monobactam (e.g., aztreonam).

Evaluation of Common Sources of Sepsis†

Suspected site	Symptoms/signs	Microbiologic evaluation
Upper respiratory tract	Pharyngeal inflammation plus exudate ± swelling and lymph-adenopathy	Throat swab for aerobic culture
Lower respiratory tract	Productive cough, pleuritic chest pain, consolidative auscultatory findings	Sputum of good quality, quantitative culture of protected brush or bronchoalveolar lavage
Urinary tract	Fever, urgency, dysuria, loin pain	Urine microscopy >50 WBC/hpf plus: - midstream urine >100,000 cfu/mL - catheter urine >100,000 cfu/mL - Suprapubic aspirate >1000 cfu/mL
Wound or burn	Inflammation, edema, erythema, discharge of pus	Gram stain and culture of draining pus, wound culture not reliable
Skin/soft tissue	Erythema, edema, lymphangitis	Culture blister fluid or draining pus; role of tissue aspirates not proven
Central nervous system	Signs of meningeal irritation	CSF microscopy, protein, glucose, culture, bacterial antigen test
Gastrointestinal	Abdominal pain, distension, diarrhea, and vomiting	Stool culture for Salmonella, Shigella, and Campylobacter
Intraabdominal	Specific abdominal symptoms/signs	Aerobic and anaerobic culture of percutaneously or surgically drained abdominal fluid collections
Peritoneal dialysis (PD) infections	Cloudy PD fluid, abdominal pain, fever	Cell count and culture of PD fluid
Genital tract	Low abdominal pain, vaginal discharge	Endocervical and high vaginal swabs onto selective media

†Adapted from Cohen, J, Microbiologic requirements for studies of sepsis. In: Sibbald, WJ, Vincent, JL (eds), Clinical Trials for the Treatment of Sepsis, Springer-Verlag, Berlin, 1995, p 73.

Antibiotics

- We suggest that combination therapy not be routinely used for on-going treatment of most other serious infections, including bacteremia and sepsis without shock.
  - (Weak recommendation; low quality of evidence).

- We recommend against combination therapy for the routine treatment of neutropenic sepsis/bacteremia.
  - (Strong recommendation; moderate quality of evidence).

Antimicrobial Therapy
Antibiotic Stewardship

- We recommend that empiric antimicrobial therapy be narrowed once pathogen identification and sensitivities are established and/or adequate clinical improvement is noted.
  - (BPS)
- We suggest that an antimicrobial treatment duration of 7-10 days is adequate for most serious infections associated with sepsis and septic shock.
  - (Weak recommendation; low quality of evidence)
- We recommend daily assessment for de-escalation of antimicrobial therapy in patients with sepsis and septic shock.
  - (BPS)
- We suggest that measurement of procalcitonin levels can be used to support shortening the duration of antimicrobial therapy in sepsis patients.
  - (Weak recommendation; low quality of evidence)

CORTICOSTEROIDS

1. We suggest against using intravenous hydrocortisone to treat septic shock patients if adequate fluid resuscitation and vasopressor therapy are able to restore hemodynamic stability. If this is not achievable, we suggest intravenous hydrocortisone at a dose of 200 mg per day.

   (Weak recommendation; low quality of evidence)

Mechanical Ventilation

- We suggest using higher PEEP over lower PEEP in adult patients with sepsis-induced moderate to severe ARDS.
  - Weak recommendation; moderate quality of evidence
- We recommend using prone over supine position in adult patients with sepsis-induced ARDS and a PaO_2/FIO_2 ratio <150.
  - (Strong recommendation; moderate quality of evidence)

Mechanical Ventilation

- We recommend against the use of HFOV in adult patients with sepsis-induced ARDS.
  - (Strong recommendation; moderate quality of evidence)
- We recommend against the use of beta-2 agonists for the treatment of patients with sepsis- induced ARDS without bronchospasm.
  - (Strong recommendation; moderate quality of evidence)

Mechanical Ventilation

- We suggest using lower tidal volumes over higher tidal volumes in adult patients with sepsis-induced respiratory failure without ARDS.
  - (Weak recommendation; low quality of evidence)

GLUCOSE CONTROL

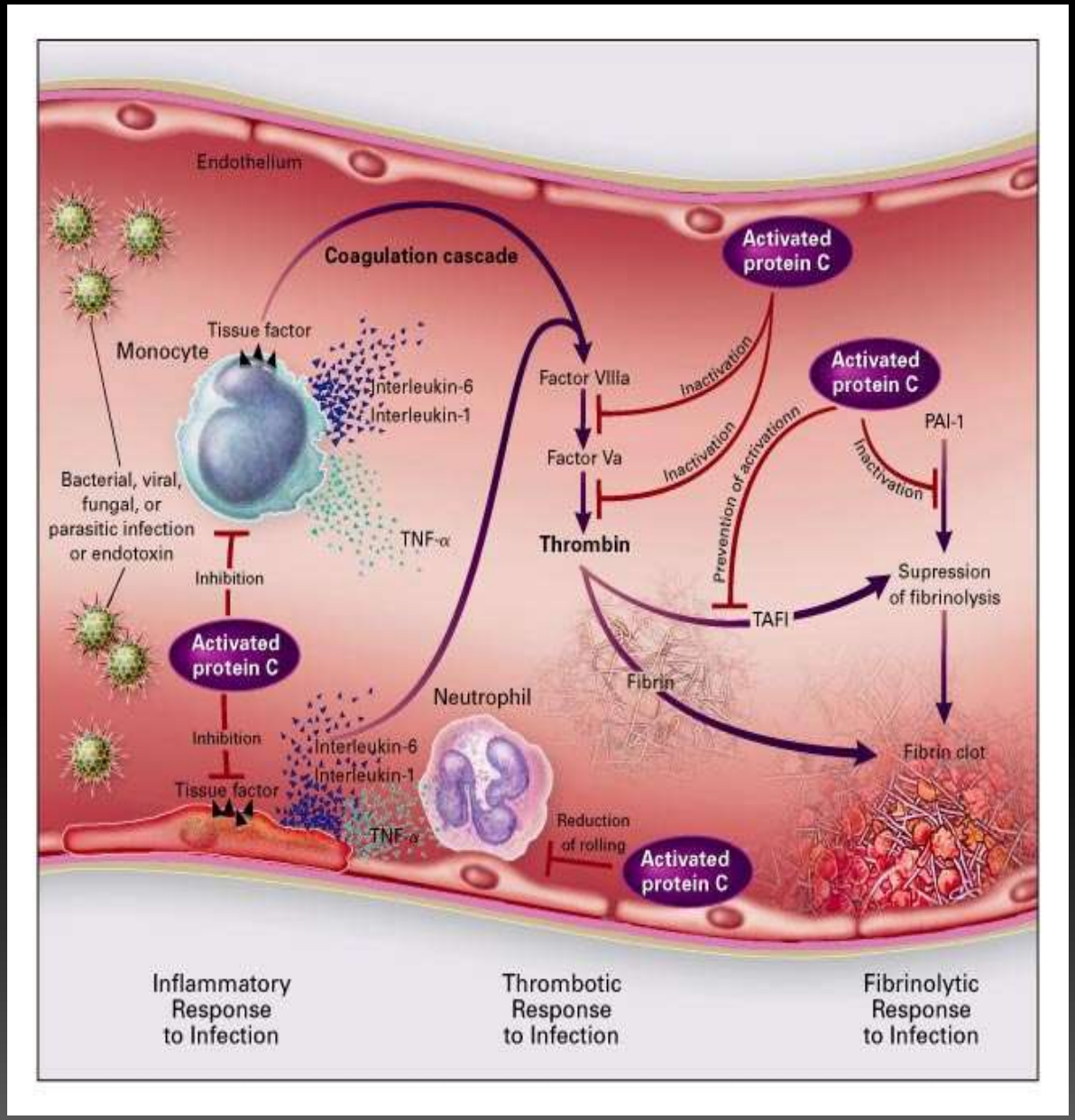
1. We recommend a protocolized approach to blood glucose management in ICU patients with sepsis, commencing insulin dosing when 2 consecutive blood glucose levels are >180 mg/dL. This approach should target an upper blood glucose level ≤180 mg/dL rather than an upper target blood glucose ≤110 mg/dL. (Strong recommendation; high quality of evidence)
2. We recommend that blood glucose values be monitored every 1 to 2 hrs until glucose values and insulin infusion rates are stable, then every 4 hrs thereafter in patients receiving insulin infusions. (BPS)

GLUCOSE CONTROL

3. We recommend that glucose levels obtained with point-of-care testing of capillary blood be interpreted with caution, as such measurements may not accurately estimate arterial blood or plasma glucose values. (BPS)

4. We suggest the use of arterial blood rather than capillary blood for point of care testing using glucose meters if patients have arterial catheters. (Weak recommendation; low quality of evidence)

Activated Protein C



Activated Protein C

- Mechanism of action:
  - antithrombotic, antiinflammatory, profibrinolytic.
- PROWESS Trial:
  - 1690 randomly assigned to placebo or DAA, 28-day mortality rate was significantly lower in the drotrecogin-treated group (24.7% vs. 30.8%).

- In 2001, FDA approved the use of drotrecogin alfa (activated DAA) for the treatment of severe Sepsis.
- DAA produced the largest benefit in the sickest subgroups, with an absolute mortality reduction of 7.4% in patients with more than one organ dysfunction and 13% ($P = 0.0002$) in patients with APACHE II scores totaling more than 24.

- The treatment was effective regardless of age, severity of illness, the number of dysfunctional organs or systems, the site of infection (pulmonary or extrapulmonary), and the type of infecting organism (gram-positive, gram-negative, or mixed).

Activated Protein C

Drawbacks:

- Change in study protocol, drug preparations, APACHE scoring.
- Increased risk of bleeding **including** fatal intracranial hemorrhage, in patients receiving DAA.
- The study excluded these groups of patients :
  - Higher risk of bleeding, INR > 3.0, hypercoagulable states.
  - Chronic liver disease, pancreatitis.
  - Chronic renal failure who were dependent on dialysis.
  - Recent surgery, organ-transplant recipients, HIV with CD4 < 50 cells.
  - Patients with thrombocytopenia (defined as a platelet count of less than 30,000 per cubic mm).
  - Those who had taken acetylsalicylic acid at a dose of > 650 mg per day within three days before the study.
  - Age <18 years, weight > 135 kg.
- Many patients with severe Sepsis meet one or more of these criteria.
- Further studies will be needed to assess the safety of activated protein C in these groups of patients.

Conclusions…

- The incidence of Sepsis is increasing.
- Possible contributing factors :
  - Use of antibiotics leading to microbial resistance
  - More invasive procedures
  - Increasing use of immunosuppressants.
- There have been new insights into the pathogenesis of Sepsis which could be potential therapeutic targets in the future.
- Treatment of Sepsis includes early institution of antibiotics, volume resuscitation, tight glycemic control, steroids protein C when indicated.

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