



SEPSİS YÖNETİMİ



Doc. Dr. Devrim Bozkurt
EÜTF İç Hastalıkları ABD

- **Hippocrates.....Pasteur.....1992.....2003**

Enfeksiyona sistemik inflamatuvar yanıt

- Hipertermi $>38.3^{\circ}\text{C}$ or Hipotermi $<36^{\circ}\text{C}$
- Akut bilinç değişikliği
- Taşikardi >90 bpm
- Taşipne >20 bpm
- Lökositoz ($>12,000 \mu\text{L}^{-1}$) or Lökopeni ($<4,000 \mu\text{L}^{-1}$) or $>10\%$ bands
- Hiperglisemi (>120 mg/dl), diyabet yokluğunda!

- **Şiddetli Sepsis Sendromu**

Akut organ disfonksiyonu ile komplike

- | | |
|--|------------------------------|
| • Hipotansiyon ($<90/60$ or MAP <65) | Laktat >2 |
| • Kapiller refil ≥ 3 saniye | Kreatinin >2.0 mg/dl |
| • Dissemine intravasküler koagülasyon (DIC) | Platelet sayısı $<100,000$ |
| • AKI veya İdrar çıkışı <0.5 ml/kg/hr/2 saat | Bilirubin >2 or INR >1.5 |
| • Kardiyak disfonksiyon | Acute lung injury or ARDS |

- **Septik Şok**

(+) Hipotansiyon veya hiperlaktatemi ile komplike

- **Genel**

Ateş (>38.3 C)
Hipotermi
Taşikardi
Taşipne
Bilinç durumu
Ödem (20 ml/kg/gün)
Hiperglisemi (>120 mg/dL)

- **İnflamatuvar**

Lökositoz (12000/mm³)
Lökopeni (<4000/mm³)
>10% immatür PMNL
CRP
Procalcitonin

- **Hemodinamik Değişiklikler**

Arteriyel hipotansiyon
(SBP<90, >40 mmHg, MAP<70 mmHg.)
Miks venöz O₂ sat >70%
Kardiyak indeks artışı

- **Organ Disfonksiyonu**

Arteriyel hipoksemi
Akut oliguri (0.5 ml/kg/saat)
Kreatinin artışı (>0.5 mg/dl)
INR>1.5 veya aPTT>60
Paralitik ileus
Trombositopeni <100.000 mm³
Hiperbilirubinemi

- **Doku Perfüzyon**

Hiperlaktatemi
Kapiller dolgunluk

- **Şiddetli Sepsis**

Sepsis + Organ Disfonksiyonu

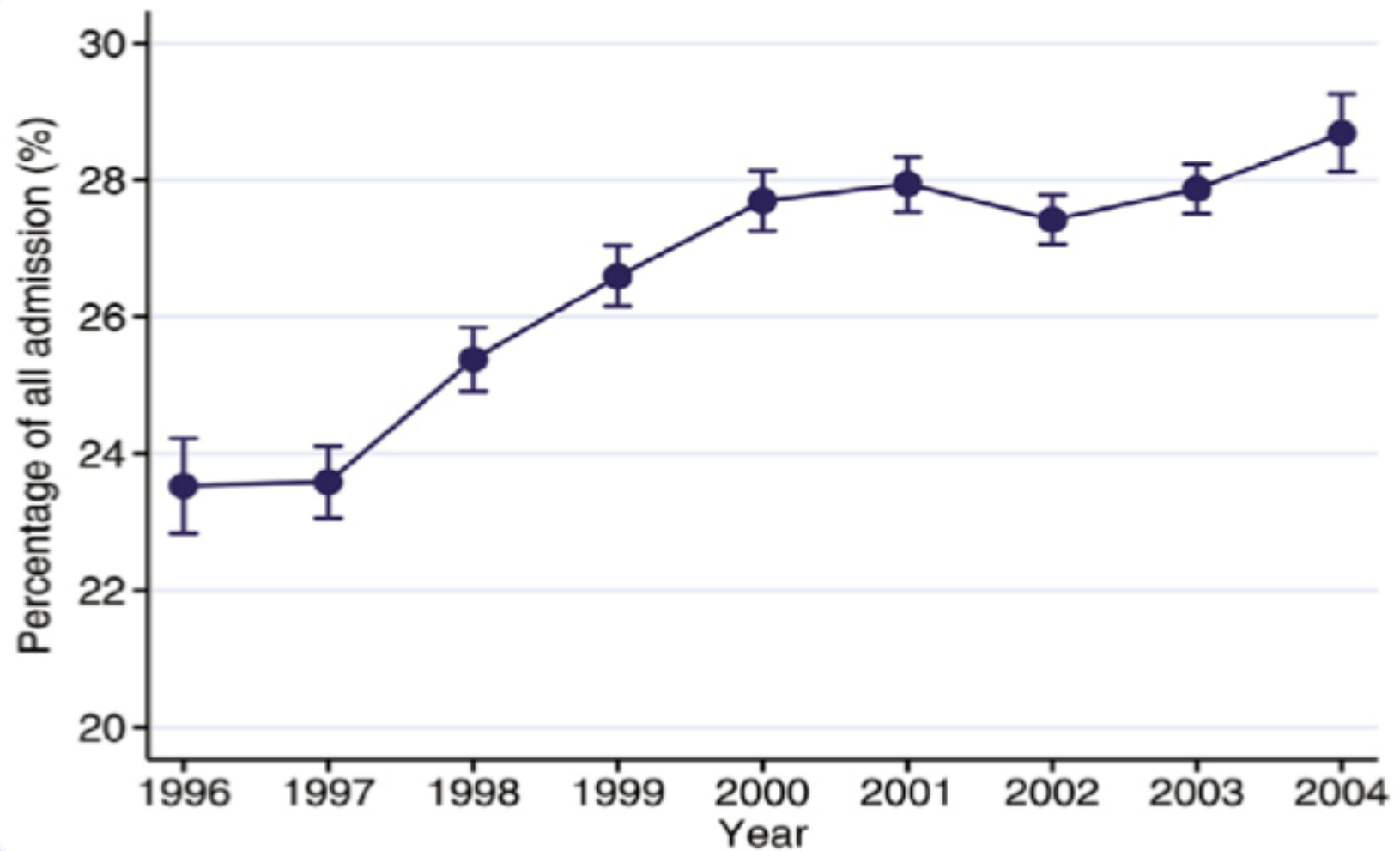
- **Septik Şok**

İv sıvı res. Refrakter hipotansiyon
veya Hiperlaktatemi

EPİDEMİYOLOJİ

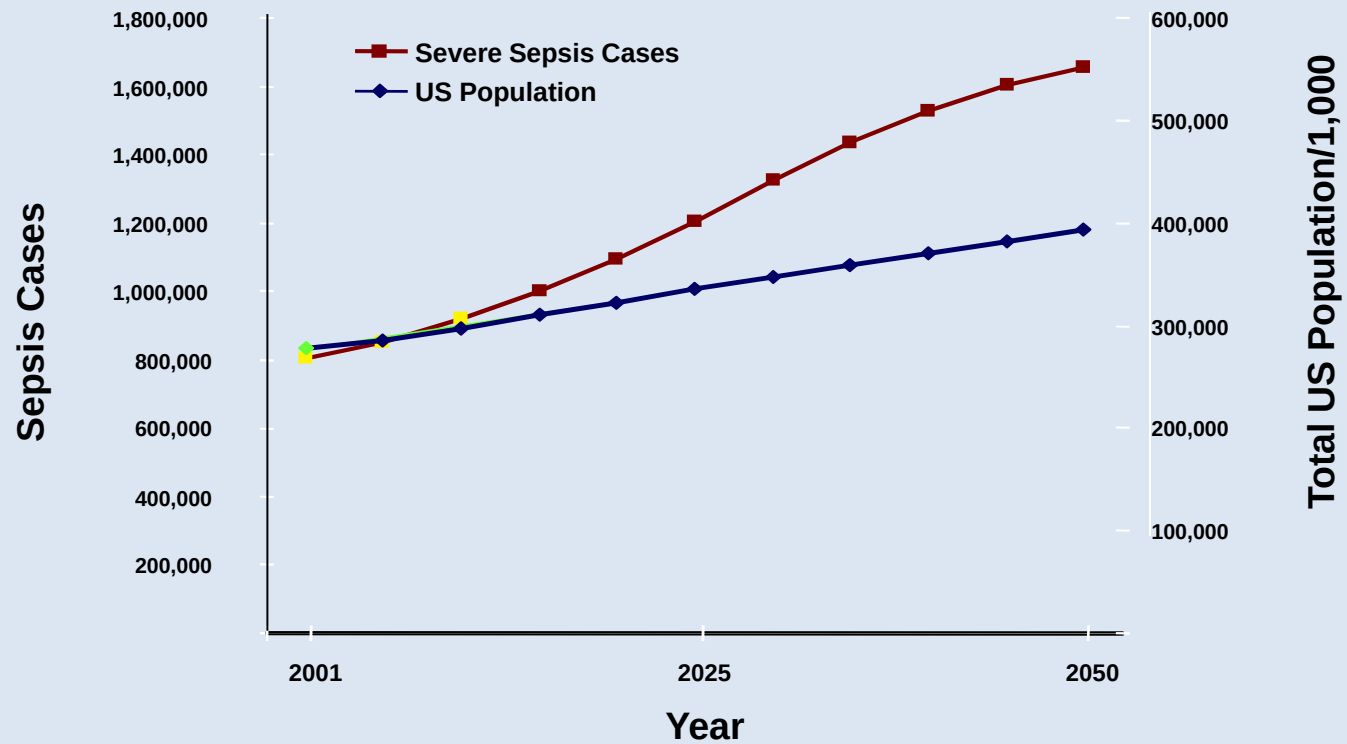
Önemli, çünkü.....

- Tüm hastane başvurularının %2'si $\approx$ yıllık 750.000
- 1/2'si YBU'nde tedavi görüyor
- Tüm YBÜ başvurularının %10'u
- Pnömoni-Intraabdominal-İdrar yolu enf.
- 1/3 hasta kültür (+) [Gram (-) 60%, Gram (+) 30%, Fungi 10%
- Erkekler, siyah ırk, yenidoğan ve yaşlılar kötü prognoz
- Genetik, virulans, komorbid hastalık, immün supresyon varlığı

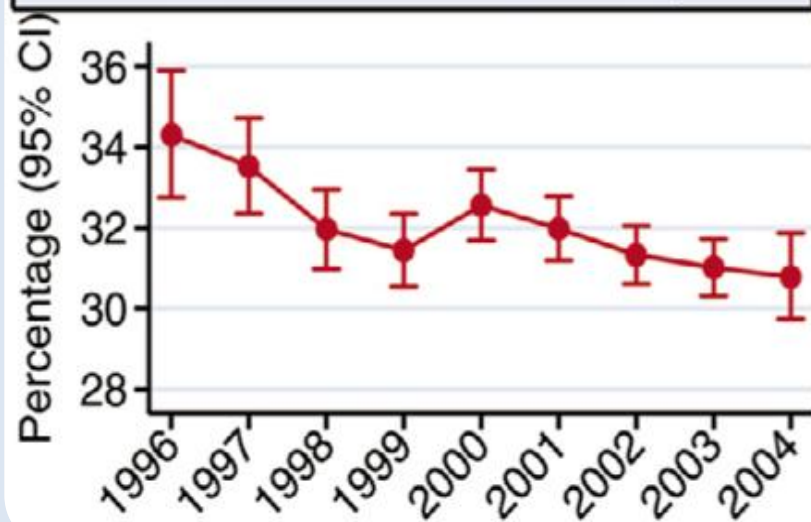


Martin, G. S., Mannino, D. M., Eaton, S., & Moss, M. (2003). The epidemiology of sepsis in the United States from 1979 through 2000. *New England Journal of Medicine*, 348(16), 1546–1554.

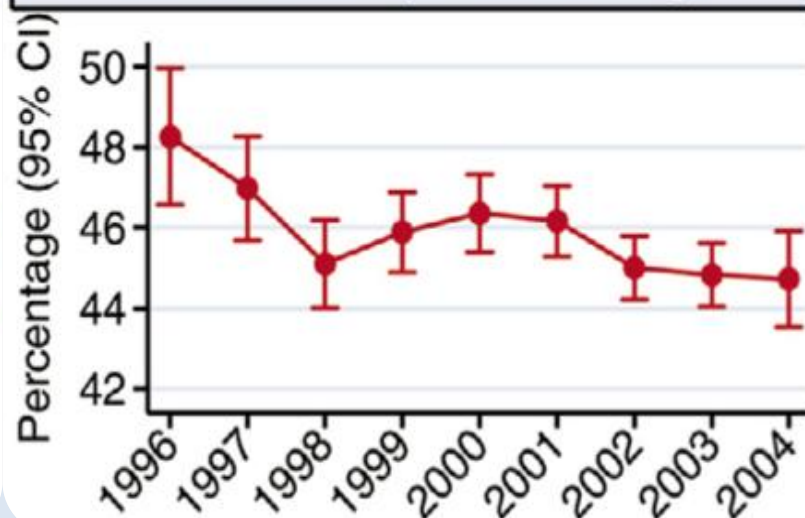
Future



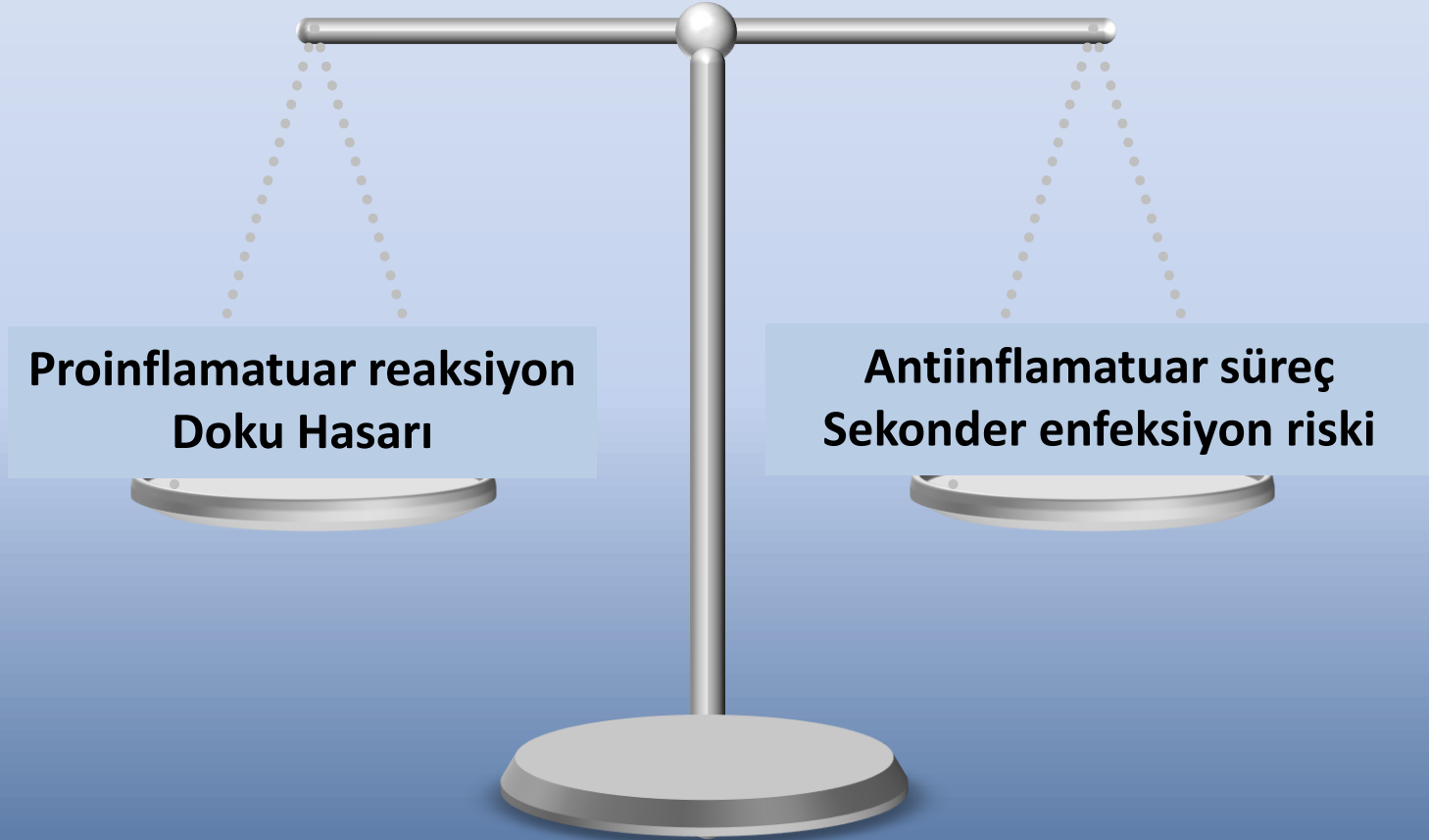
Critical care unit mortality



Ultimate hospital mortality



PATOFİZYOLOJİ

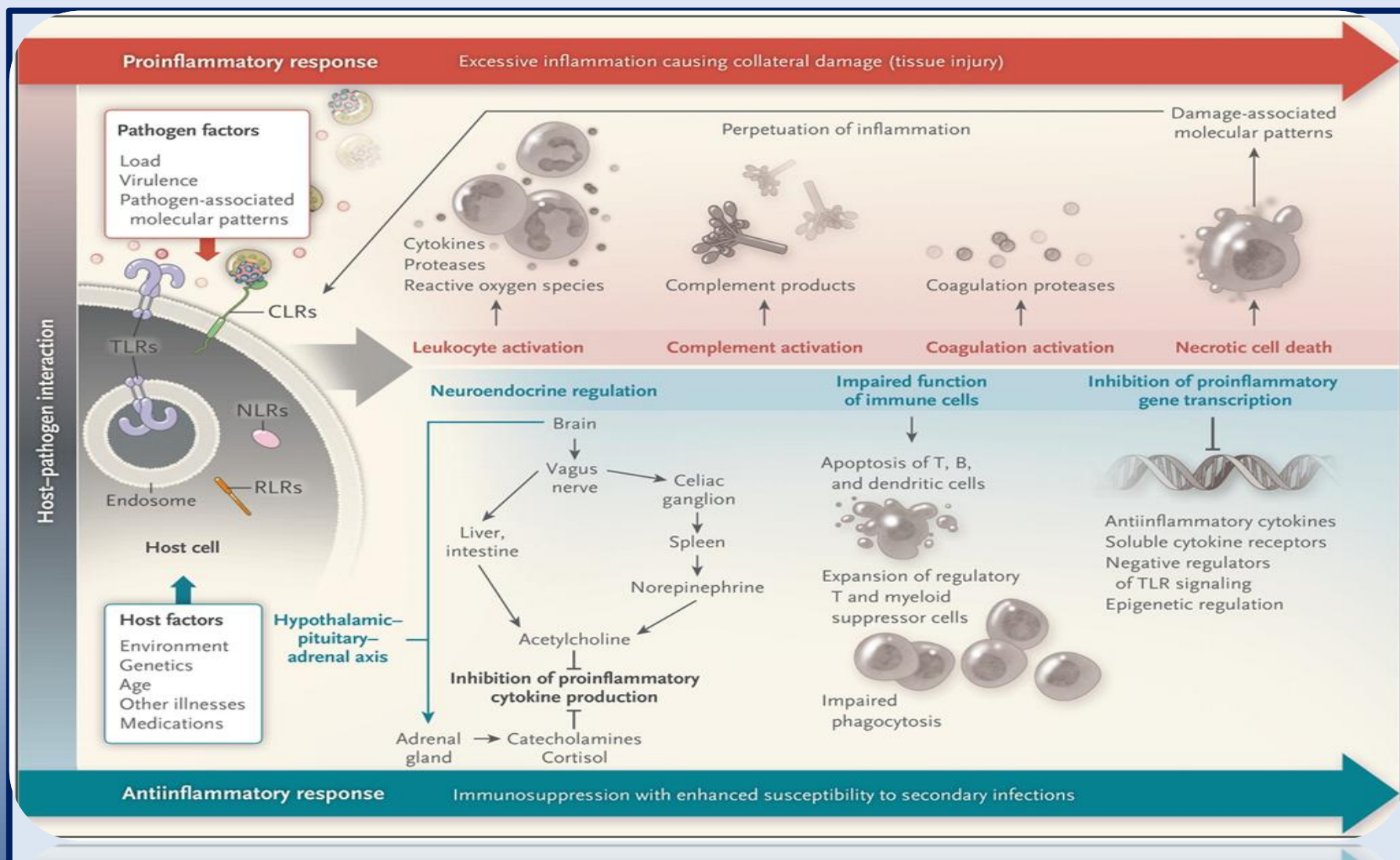


İmmün sistem hücrelerindeki Durum Tanıma (*Pattern Recognition*) Reseptörleri:

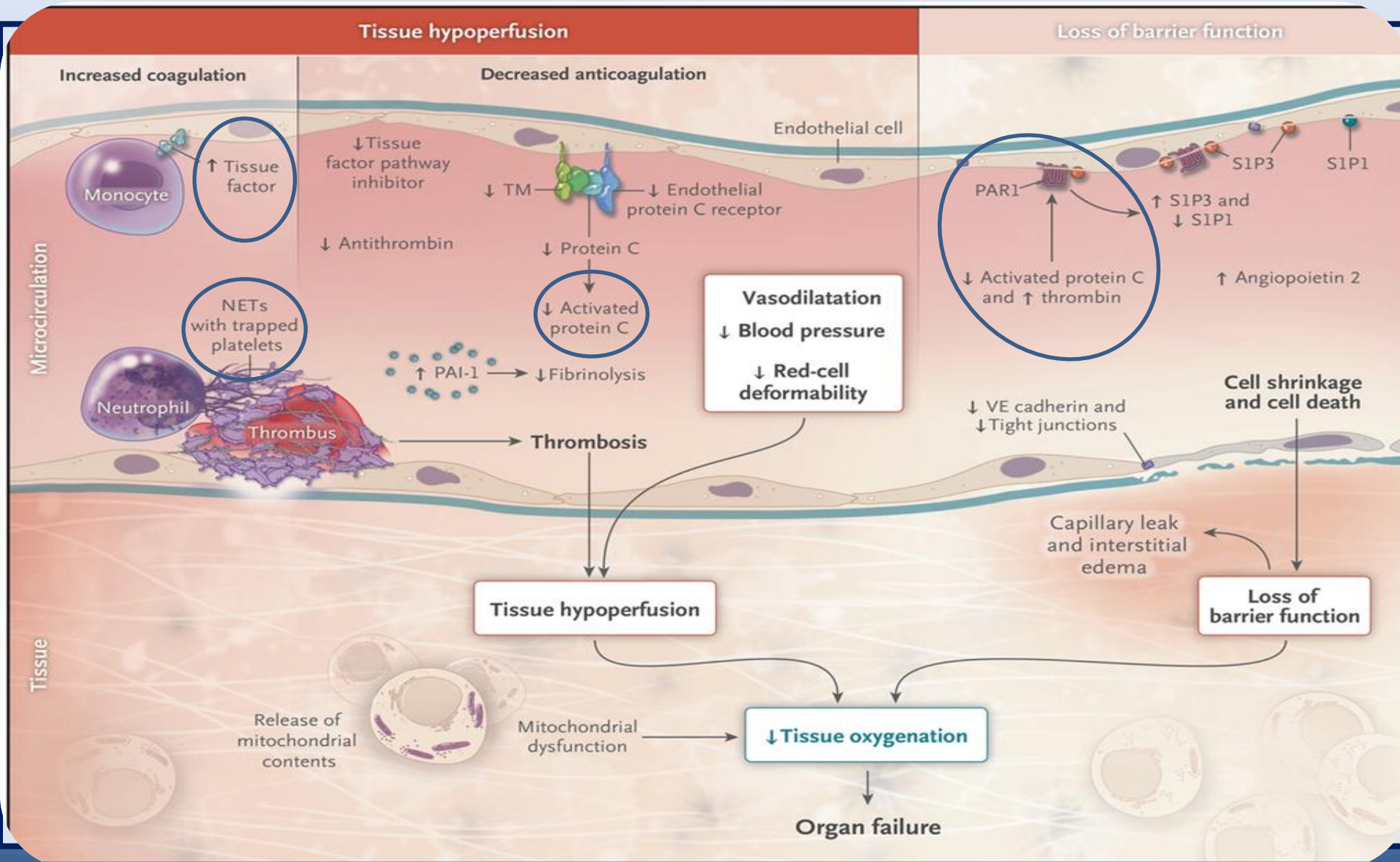
- ❖ Toll-benzeri-Reseptörler (**TLRs**)
- ❖ C tipi Lektin Reseptörler (**CLRs**)
- ❖ Retinoik asit Gen-1 Reseptör (**RLRs**)
- ❖ Nükleotid bağlayıcı oligomerizasyon Reseptör (**NLRs**)

Ajan patojene ait moleküler substratlar Alarminler

- ❖ 1.Hasarlı hücrelerden salınan endojen moleküller
- ❖ 2.Protein B1
- ❖ 3.S100 proteini
- ❖ 4.Ekstrasellüler RNA, DNA ve histon



Severe Sepsis and Septic Shock Derek C. Angus, M.D., M.P.H., and Tom van der Poll, M.D., Ph.D.
N Engl J Med 2013; 369:840-85



Organ failure

TEDAVİ

R. P. Dellinger
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Djillali Annane
Herwig Gerlach
Steven M. Opal
Jonathan E. Sevransky
Charles L. Sprung
Ivor S. Douglas
Roman Jaeschke
Tiffany M. Osborn
Mark E. Nunnally
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Ruth M. Kleinpell
Derek C. Angus
Clifford S. Deutschman
Flavia R. Machado
Gordon D. Rubenfeld
Steven Webb
Richard J. Beale
Jean-Louis Vincent
Rui Moreno

The Surviving Sepsis Campaign Guidelines Committee
including The Pediatric Subgroup*

Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock, 2012

SURVIVING SEPSIS CAMPAIGN CARE BUNDLES

TO BE COMPLETED WITHIN 3 HOURS:

- 1) Measure lactate level
- 2) Obtain blood cultures prior to administration of antibiotics
- 3) Administer broad spectrum antibiotics
- 4) Administer 30 mL/kg crystalloid for hypotension or lactate ≥ 4 mmol/L

TO BE COMPLETED WITHIN 6 HOURS:

- 5) Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation) to maintain a mean arterial pressure (MAP) ≥ 65 mm Hg
- 6) In the event of persistent arterial hypotension despite volume resuscitation (septic shock) or initial lactate ≥ 4 mmol/L (36 mg/dL):
 - Measure central venous pressure (CVP)*
 - Measure central venous oxygen saturation (ScvO₂)*
- 7) Remeasure lactate if initial lactate was elevated*

*Targets for quantitative resuscitation included in the guidelines are CVP of ≥ 8 mm Hg, ScvO₂ of $\geq 70\%$, and normalization of lactate.



We recommend crystalloids be used as the initial fluid of choice in the resuscitation of severe sepsis and septic shock (grade 1B).

We recommend against the use of hydroxyethyl starches (HES) for fluid resuscitation of severe sepsis and septic shock (grade 1B). (This recommendation is based on the results of the VISEP, CRYSTMAS, 6S, and CHEST trials. The results of the recently completed CRYSTAL trial were not considered.)

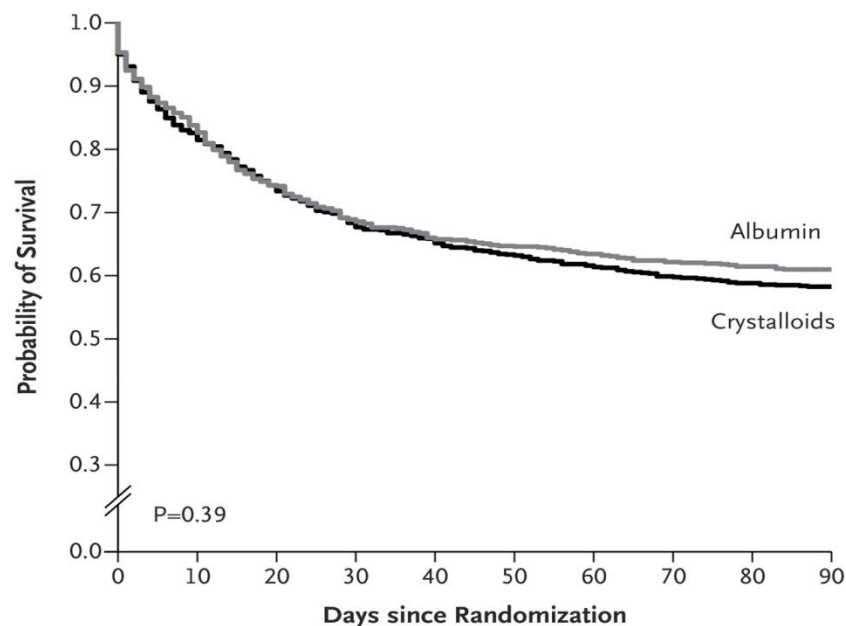
We suggest the use of albumin in the fluid resuscitation of severe sepsis and septic shock when patients require substantial amounts of crystalloids (grade 2C).

Albumin Replacement in Patients with Severe Sepsis or Septic Shock

Pietro Caironi, M.D., Gianni Tognoni, M.D., Serge Masson, Ph.D., Roberto Fumagalli, M.D., Antonio Pesenti, M.D., Marilena Romero, Ph.D., Caterina Fanizza, M.Stat., Luisa Caspani, M.D., Stefano Faenza, M.D., Giacomo Grasselli, M.D., Gaetano Iapichino, M.D., Massimo Antonelli, M.D., Vieri Parrini, M.D., Gilberto Fiore, M.D., Roberto Latini, M.D., and Luciano Gattinoni, M.D. for the ALBIOS Study Investigators
N Engl J Med 2014; 370:1412-1421 [April 10, 2014](#) DOI: 10.1056/NEJMoa1305727

In conclusion, the **use of albumin** in addition to crystalloids to correct hypoalbuminemia, as compared with the use of crystalloids alone, in patients with severe sepsis during their stay in the ICU **did not provide a survival benefit at 28 or 90 days**, despite improvements in hemodynamic variables.

The clinical benefit of albumin that was seen in the post hoc analysis of the subgroup of patients with septic shock warrants further confirmation.



No. at Risk										
Albumin	903	733	647	597	567	556	545	535	529	523
Crystalloids	907	729	652	598	676	551	538	521	511	504

We recommend norepinephrine as the first-choice vasopressor (grade 1B).

We suggest epinephrine (added to and potentially substituted for norepinephrine) when an additional agent is needed to maintain adequate blood pressure (grade 2B).

Vasopressin (up to 0.03 U/min) can be added to norepinephrine with the intent of raising MAP to target or decreasing norepinephrine dosage (UG).

Low-dose vasopressin is not recommended as the single initial vasopressor for treatment of sepsis-induced hypotension, and vasopressin doses higher than 0.03–0.04 U/min should be reserved for salvage therapy (failure to achieve an adequate MAP with other vasopressor agents) (UG).

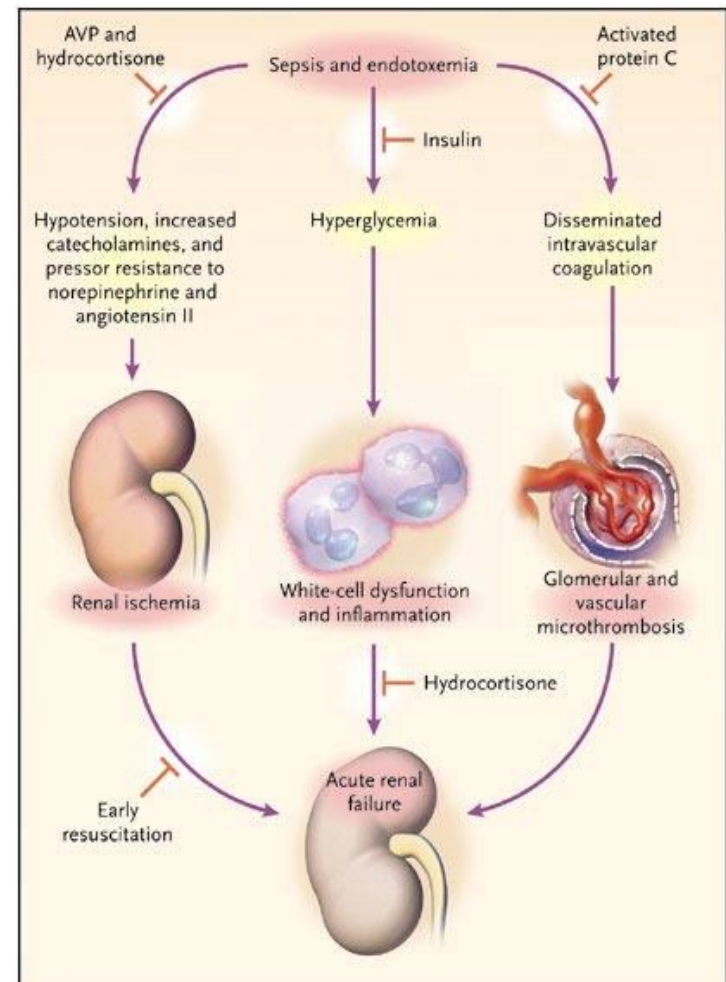
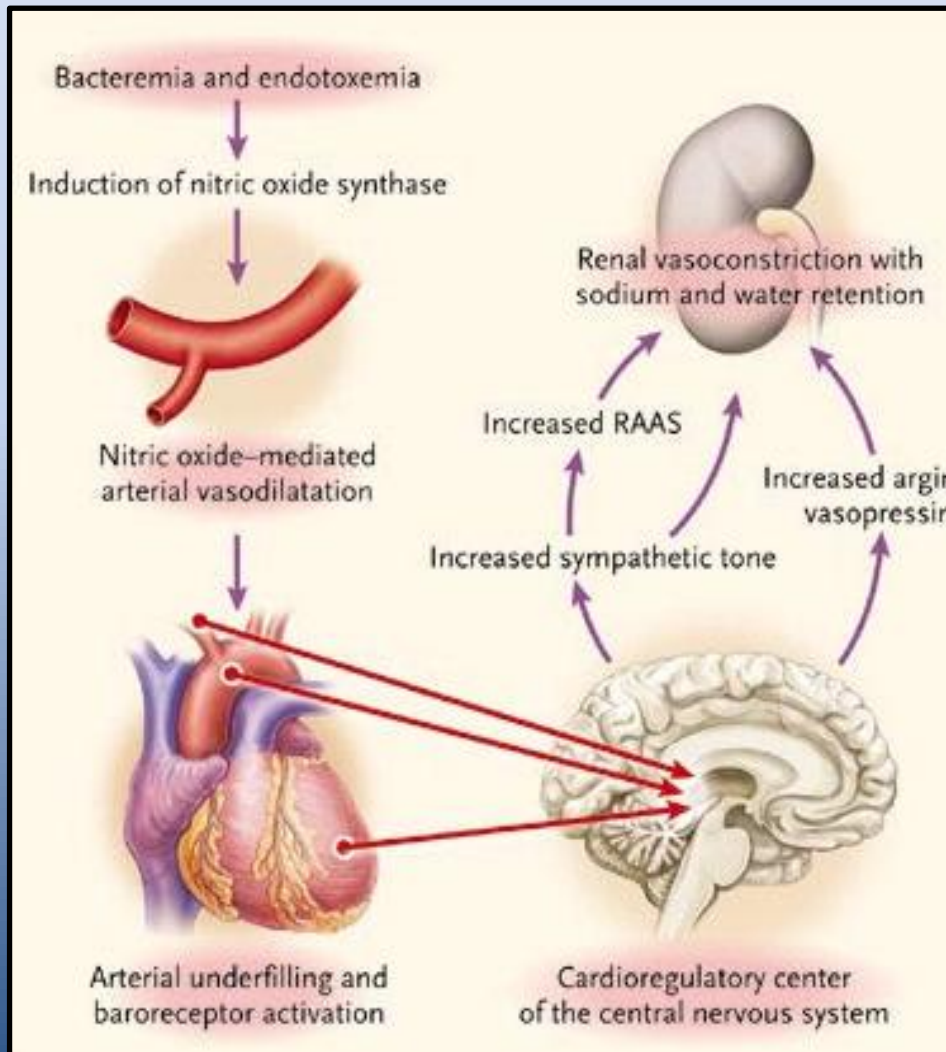
We suggest dopamine as an alternative vasopressor agent to norepinephrine only in highly selected patients (e.g., patients with low risk of tachyarrhythmias and absolute or relative bradycardia) (grade 2C).

Phenylephrine is not recommended in the treatment of septic shock except in the following circumstances: (a) norepinephrine is associated with serious arrhythmias, (b) cardiac output is known to be high and blood pressure persistently low, or (c) as salvage therapy when combined inotrope/vasopressor drugs and low-dose vasopressin have failed to achieve the MAP target (grade 1C).

Adjuan Tedaviler

- Dobutamin !!!
- Düşük doz dopamin tedavisi ?
- Hidrokortizon !!!
- IVIG ?
- Plazmaferez ?
- Hb (hedef 7-9 g/dL, Kanama, KAH, MI)
- Trombosit (hedef >10,000 Kanama riski >20,000, Cerrahi >50,000)
- TDP ? Aktif Kanama, İnvaziv pro
- Antitrombin ?
- Aktive Protein C ?
- Bikarbonat (pH>7,15) ?
- DVT profilaksisi !!!
- Stres ülser Profilaksi !!!
- Beslenme iv Glukoz+Enteral

SEPSİS ve BÖBREK



Viewpoint

A proposed algorithm for initiation of renal replacement therapy in adult critically ill patients

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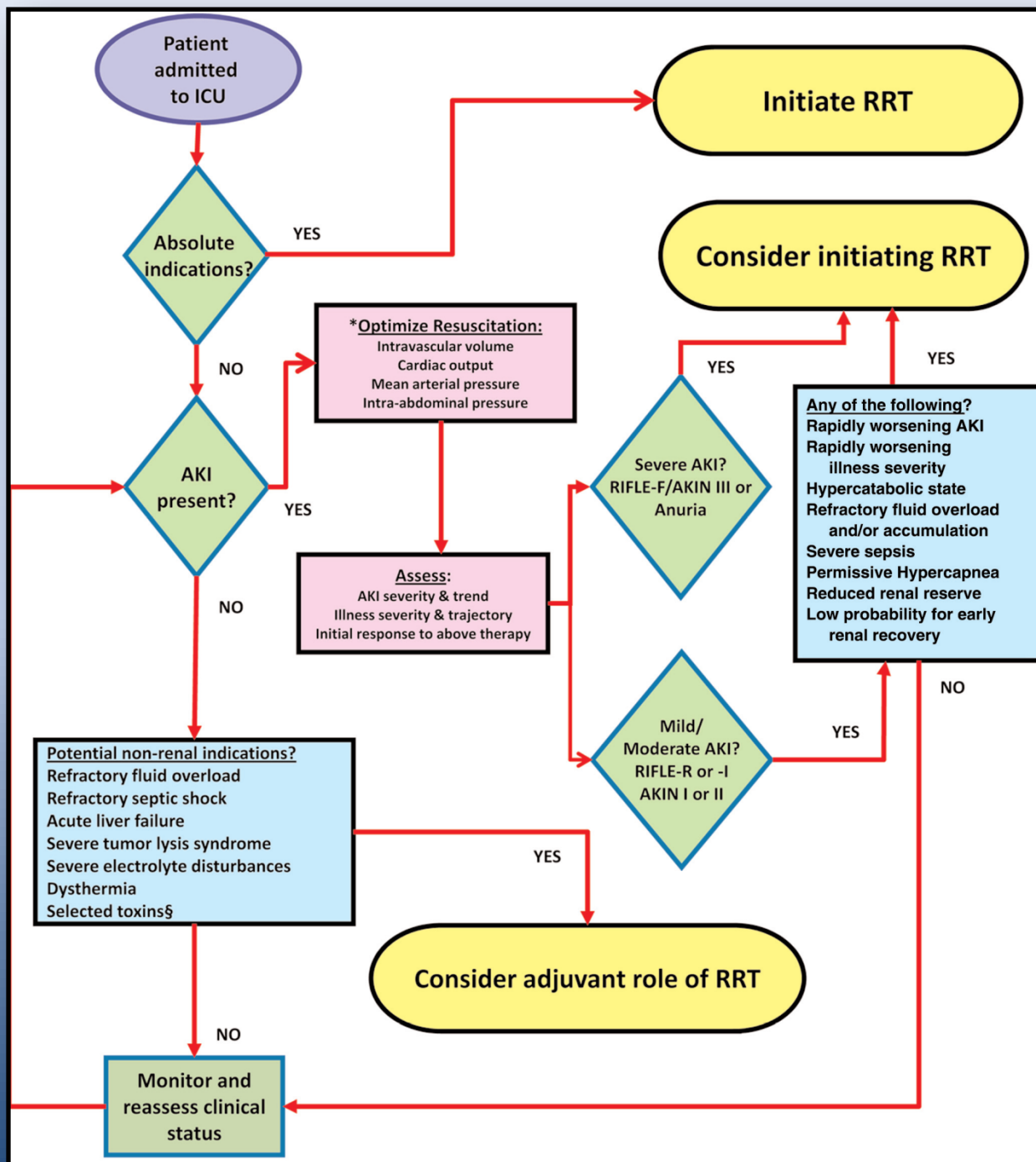
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Critical Care 2009, **13**:317 (doi:10.1186/cc8037)

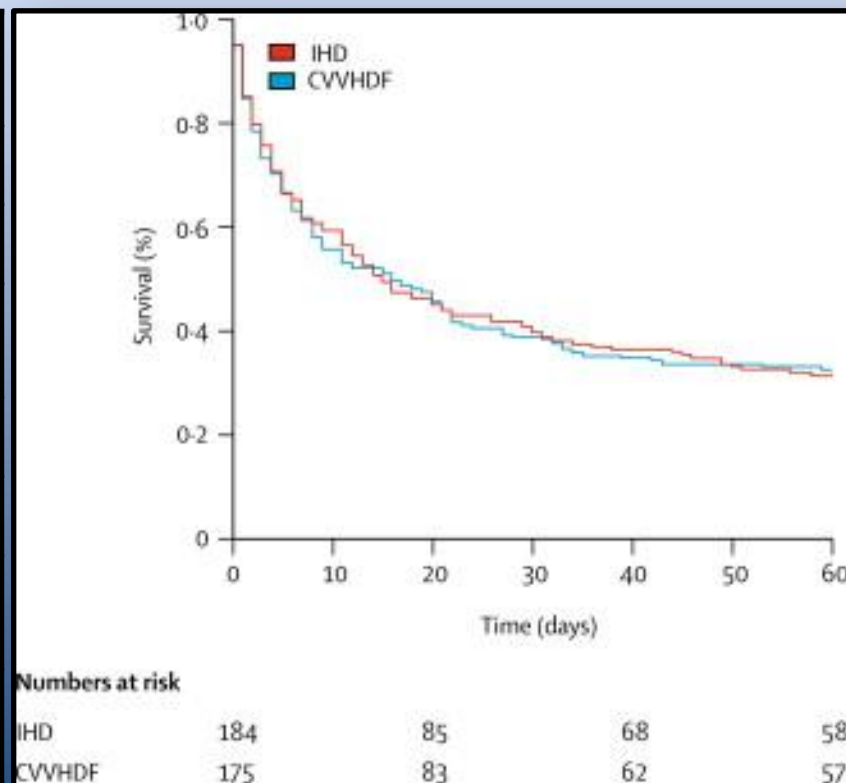


THE LANCET

Continuous venovenous haemodiafiltration versus intermittent haemodialysis for acute renal failure in patients with multiple-organ dysfunction syndrome: a multicentre randomised trial

Vinsonneau et al, Lancet, 368, 379-385, 2006

	IHD	CVVHD	P
Survival			
Day 28	41.8%	38.9%	0.65
Day 60 (1ary EP)	32.5%	32.6%	0.98
Day 90	27.2%	28.5%	0.95
RRT duration (d)	11	11	0.84
Length ICU stay (d)	20	19	0.73
Length hosp stay (d)	30	32	0.66



THE SHARF STUDY

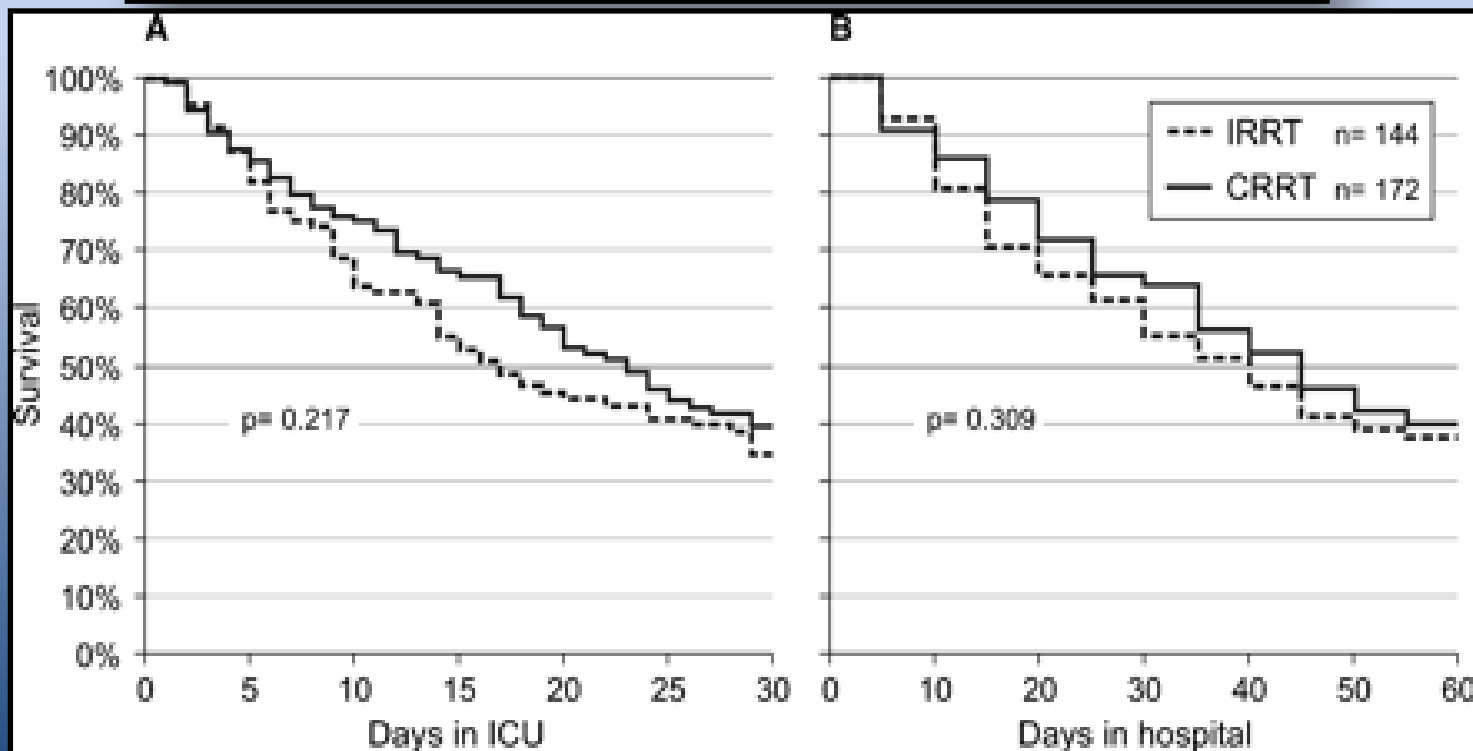


Original Article

Intermittent versus continuous renal replacement therapy for acute kidney injury patients admitted to the intensive care unit: results of a randomized clinical trial

Robert L. Lins¹, Monique M. Elseviers², Patricia Van der Niepen³, Eric Hoste⁴, Manu L. Malbrain⁵, Pierre Damas⁶ and Jacques Devriendt⁷ for the SHARF investigators

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Continuous versus intermittent renal replacement therapy for critically ill patients with acute kidney injury: A meta-analysis

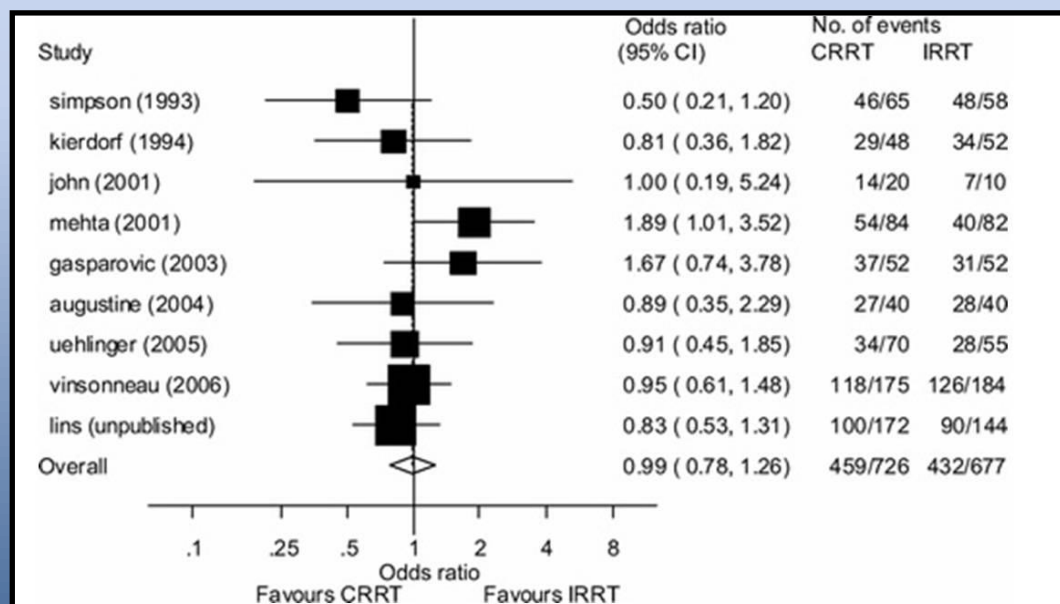
Bagshaw, Sean M. MD, MSc; Berthiaume, Luc R. MD; Delaney, Anthony MBBS, MSc; Bellomo, Rinaldo MD



Wolters Kluwer | Lippincott
Health Williams & Wilkins

Critical Care Medicine
OFFICIAL JOURNAL OF THE SOCIETY OF CRITICAL CARE MEDICINE

Bagshaw et al, Crit Care Med, 36: 610-617; 2008



Forrest plot of pooled odds ratios for mortality from nine randomized trials. CI, confidence interval; CRRT, continuous renal replacement therapy; IRRT, intermittent renal replacement therapy.

The New England Journal of Medicine

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NUMBER 5



DAILY HEMODIALYSIS AND THE OUTCOME OF ACUTE RENAL FAILURE

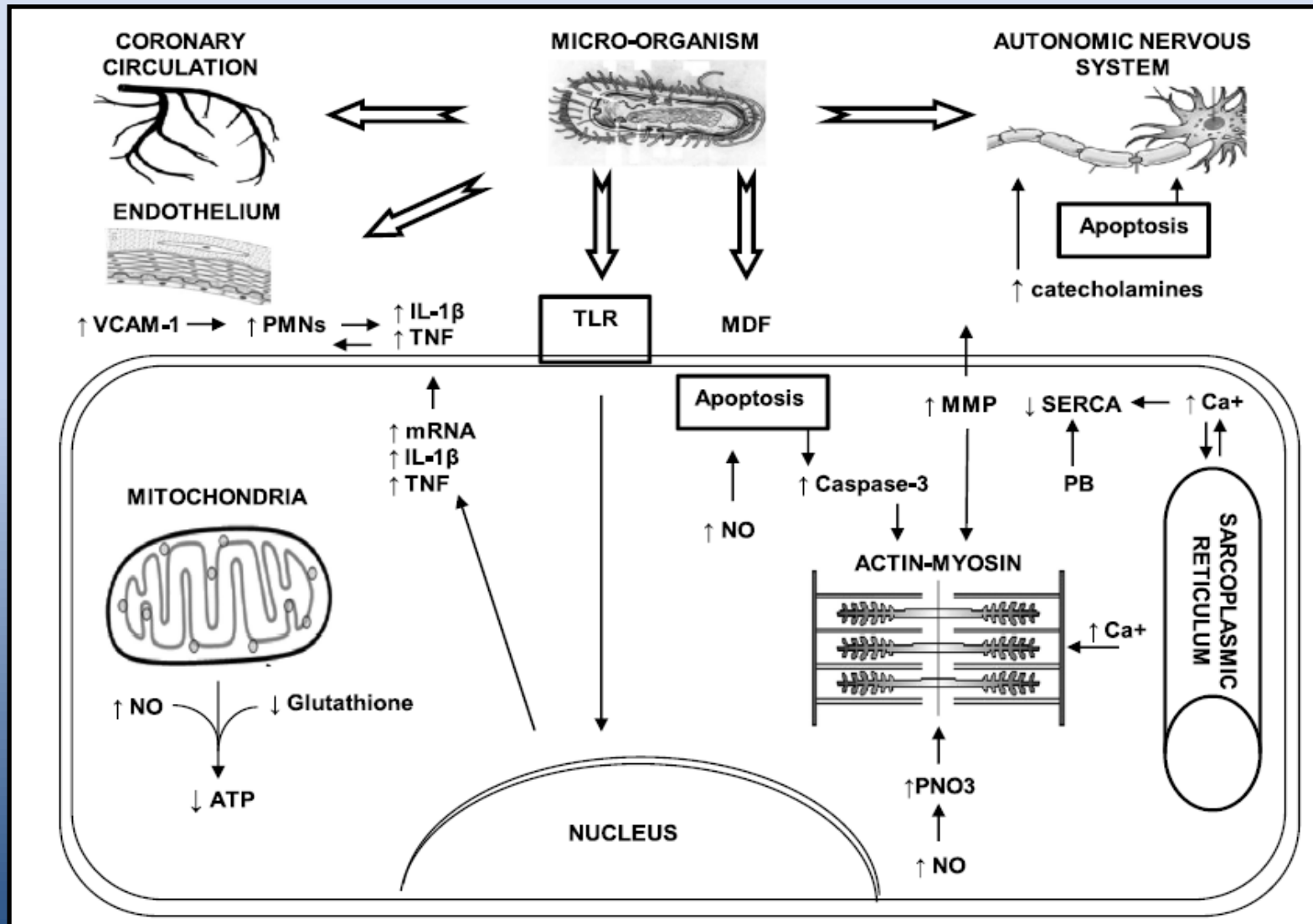
OUTCOMES ACCORDING TO TREATMENT GROUP.*

	ALTERNATE- DAY HEMODIALYSIS (N=80)	DAILY HEMODIALYSIS (N=80)	P VALUE
Mortality — no. (%)†	37 (46)	22 (28)	0.01
Resolution of acute renal failure — days	16±6	9±2	0.001

*Plus-minus values are means ±SD.

†Mortality was calculated according to the intention to treat.

SEPSİS ve KALP



- ilk 6 saat **EGDT** temel.
- Enfeksiyöz ajan eradikasyonu
- Volüm kontrolü (Kardiyo-Renal Sendrom)
- Statin
- **Levosimendan**

- Kardiyak kronotrop etki yapmadan inotrop etki
- O2 tüketimi artışı minimal, miyokardiyal iskemi riski az
- Diyastolik disfonksiyon düzelmesi, lokal vd etkiyle doku perfüzyon iyileşmesi.
- Anti inflamatuvar anti-sitokin etki

Morelli A, De Castro S, Teboul JL, Singer M, Rocco M, Conti G, De Luca L, et al. Effects of levosimendan on systemic and regional hemodynamics in septic myocardial depression. **Intensive Care Med.** 2005;**31(5):638-644.**

Nanas JN, Papazoglou PP, Terrovitis JV, Kanakakis J, Dalianis A, Tsolakis E, Tsagalou EP, et al. Hemodynamic effects of levosimendan added to dobutamine in patients with decompensated advanced heart failure refractory to dobutamine alone. **Am J Cardiol.** 2004;**94(10):1329-1332.**

Erbayun K, Tok D, Vatansever S, Ok G, Turkoz E, Aydede H, Erhan Y, et al. Levosimendan up-regulates transforming growth factor-beta and smad signaling in the aorta in the early stage of sepsis. **Ulus Travma Acil Cerrahi Derg.** 2010;**16(4):293-299.**

Andrea Morelli
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Leonardo De Luca
Emanuele Di Angelantonio
Alessandra Orecchioni
Natesa G. Pandian
Paolo Pietropaoli

Effects of levosimendan on systemic and regional hemodynamics in septic myocardial depression

Biochimie xxx (2014) 1–8



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Biochimie

journal homepage: www.elsevier.com/locate/biochi



Research paper

Effects of levosimendan on mitochondrial function in patients with septic shock: A randomized trial

Alessandra Torraco^{a,1}, Rosalba Carrozzo^{a,1}, Fiorella Piemonte^a, Anna Pastore^b,
Giulia Tozzi^a, Daniela Verrigni^a, Marco Assenza^c, Alessandra Orecchioni^d,
Annalia D'Egidio^d, Elisa Marraffa^d, Giovanni Landoni^e, Enrico Bertini^a, Andrea Morelli^{d,*}

Effects of levosimendan on right ventricular afterload in patients with acute respiratory distress syndrome: A pilot study*

Andrea Morelli, MD; Jean-Louis Teboul, MD, PhD; Salvatore Maurizio Maggiore, MD, PhD;
Antoine Vieillard-Baron, MD; Monica Rocco, MD; Giorgio Conti, MD; Andrea De Gaetano, MD, PhD;
Umberto Picchini, Dr in statistics; Alessandra Orecchioni, MD; Iacopo Carbone, MD; Luigi Tritapepe, MD;
Paolo Pietropaoli, MD; Martin Westphal, MD