SEPSİSDE GÜNCEL BİLGİLER

LÜTFİYE MÜLAZIMOĞLU
MARMARA ÜNİVERSİTESİ TIP FAKÜLTESİ

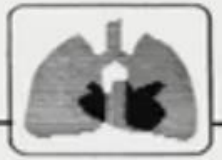
SEPSİS

- YBÜ ölümlerinin 1 numarası[1]
- Hastanedeki ölümlerin %30 ile %50 si sepsise atfediliyor[2]
- En yüksek hastane maliyeti[3]
- Sağkalanlarda yeniden yatışlar ve kognitif bozukluklar[4]
- Ve insidans giderek artıyor[5]

- 1 Minino et al, NCHS Data Brief 2012
- 2 Liu et al, JAMA 2014
- 3 Torio et al, HCUP SB 160, 2013
- 4 Winters et al, Crit Care Med 2010
- 5 Gaeiski et al, Crit Care Med 2013

tanımlar

History of Sepsis Definitions: "Sepsis-1"



accp/sccm consensus conference

1991

Definitions for Sepsis and Organ Failure and Guidelines for the Use of Innovative Therapies in Sepsis

aşağıdakilerden 2 veya daha fazla bulgunun varlığı =sistemik inflamatuvar yanıt =SIYS=SIRS

- Ateş >38ºC veya <35ºC
- Nabız>90 /min
- Solunum sayısı>20 /min veya PaCO2 <32 mmHg
- Beyaz küre >12,000 /mm^3, veya <4000 /mm^3, veya >%10 band oluşumu

Bone, et al.1992 Chest 101:1644-1655

SEPSİS


İNFEKSİYON
Sepsis
SİYS-
SIRS
TRAVMA
YANIK
PANKREATİT
SİSTEMİK İNFLAMATUVAR YANIT SENDROMU

tanımlar

History of Sepsis Definitions: "Sepsis-1"

accp/sccm consensus conference — 1991

Definitions for Sepsis and Organ Failure and Guidelines for the Use of Innovative Therapies in Sepsis

"SEPSIS-2" - 2001 Consensus Conference SCCM/ESICM/ACCP/ATS/SIS

- Expanded list of possible diagnostic criteria, but otherwise no significant change to this framework

Table 1. Diagnostic criteria for sepsis

TABLE 2. Severe Sepsis

Severe sepsis definition = sepsis-induced tissue hypoperfusion or organ dysfunction (any of the following thought to be due to the infection)
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 Pao_2/Fio_2 < 250 in the absence of pneumonia as infection source
Acute lung injury with Pao_2/Fio_2 < 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)

Adapted from Levy MM, Fink MP, Marshall JC, et al: 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Crit Care Med* 2003; 31: 1250–1256.

SEPSİS

- 2014

- Enfeksiyona karşı kuralsız/düzensiz konak cevabı sebebi ile hayatı tehdit edici organ disfonksiyonu

JAMA The Journal of the American Medical Association

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February 23, 2016, Vol 315, No. 8 >

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Special Communication | February 23, 2016

CARING FOR THE CRITICALLY ILL PATIENT

The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) FREE

Mervyn Singer, MD, FRCP[1]; Clifford S. Deutschman, MD, MS[2]; Christopher Warren Seymour, MD, MSc[3]; Manu Shankar-Hari, MSc, MD, FFICM[4]; Djillali Annane, MD, PhD[5]; Michael Bauer, MD[6]; Rinaldo Bellomo, MD[7]; Gordon R. Bernard, MD[8]; Jean-Daniel Chiche, MD, PhD[9]; Craig M. Coopersmith, MD[10]; Richard S. Hotchkiss, MD[11]; Mitchell M. Levy, MD[12]; John C. Marshall, MD[13]; Greg S. Martin, MD, MSc[14]; Steven M. Opal, MD[12]; Gordon D. Rubenfeld, MD, MS[15,16]; Tom van der Poll, MD, PhD[17]; Jean-Louis Vincent, MD, PhD[18]; Derek C. Angus, MD, MPH[19,20]

- Sepsis: enfeksiyona kuralsız/düzensiz konak yanıtı nedeni ile yaşamı tehdit eden organ disfonksiyonu: qSOFAda 2 veya üstü skor
- Septik şok: hipovolemi olmaksızın dolaşımsal, hücesel ve metabolik anormallikler ile giden ve ortalama arter basıncını 65 mm Hg veya üstünde tutmak için vasopressor kullanımı gerektiren durumdur ve laktat seviyesi 2 mmol/L (>18 mg/dL) üzerindedir. Mortalite %40 ın üzerindedir.

- **SEPSİS**
  - AĞIR/CİDDİ SEPSİS TANIMI YOK
- **SEPTİK ŞOK**

qSOFA (Quick SOFA Score) for Sepsis Identification

Predicts poor outcome in infection patients; initial step in suspected sepsis evaluation

Note: The qSOFA was introduced in February 2016 as a way to initially evaluate for poor outcome in infected patients by the Sepsis-3 group as an evolving definition and understanding of sepsis, moving away from the previous SIRS criteria-based definitions.

New/Worsened Altered Mentation

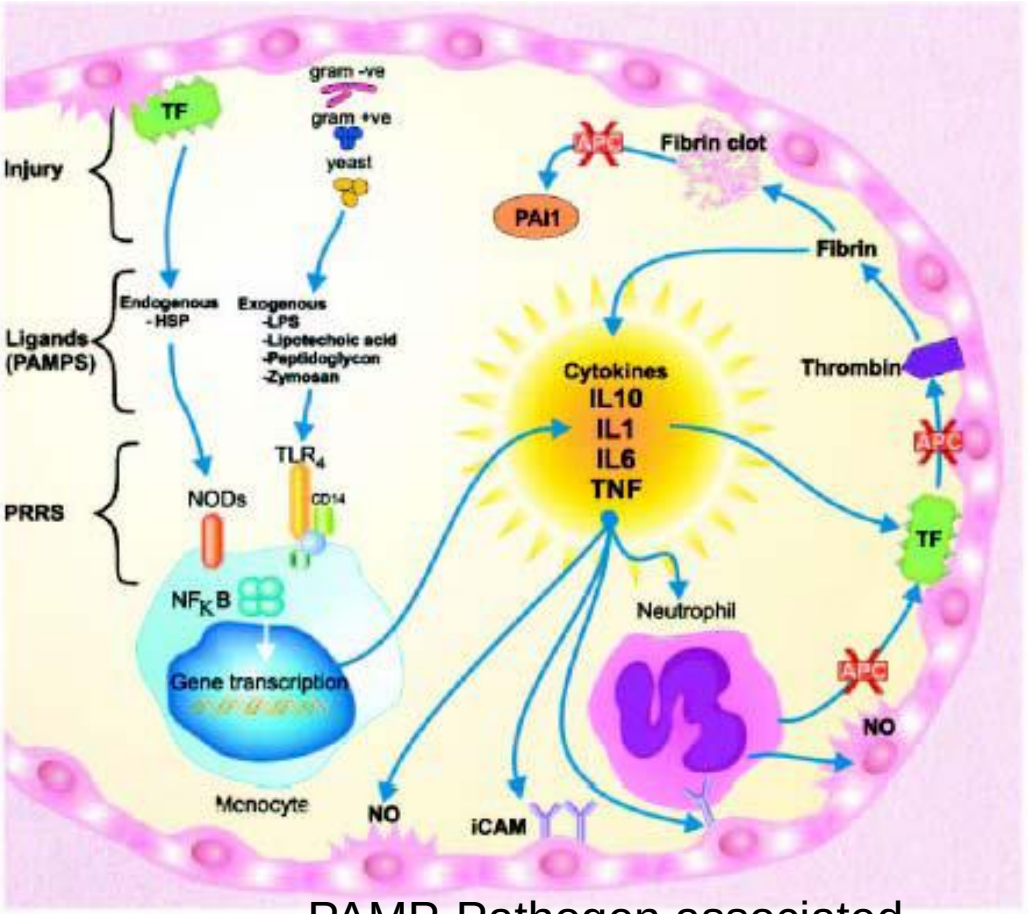
YES

RR ≥ 22

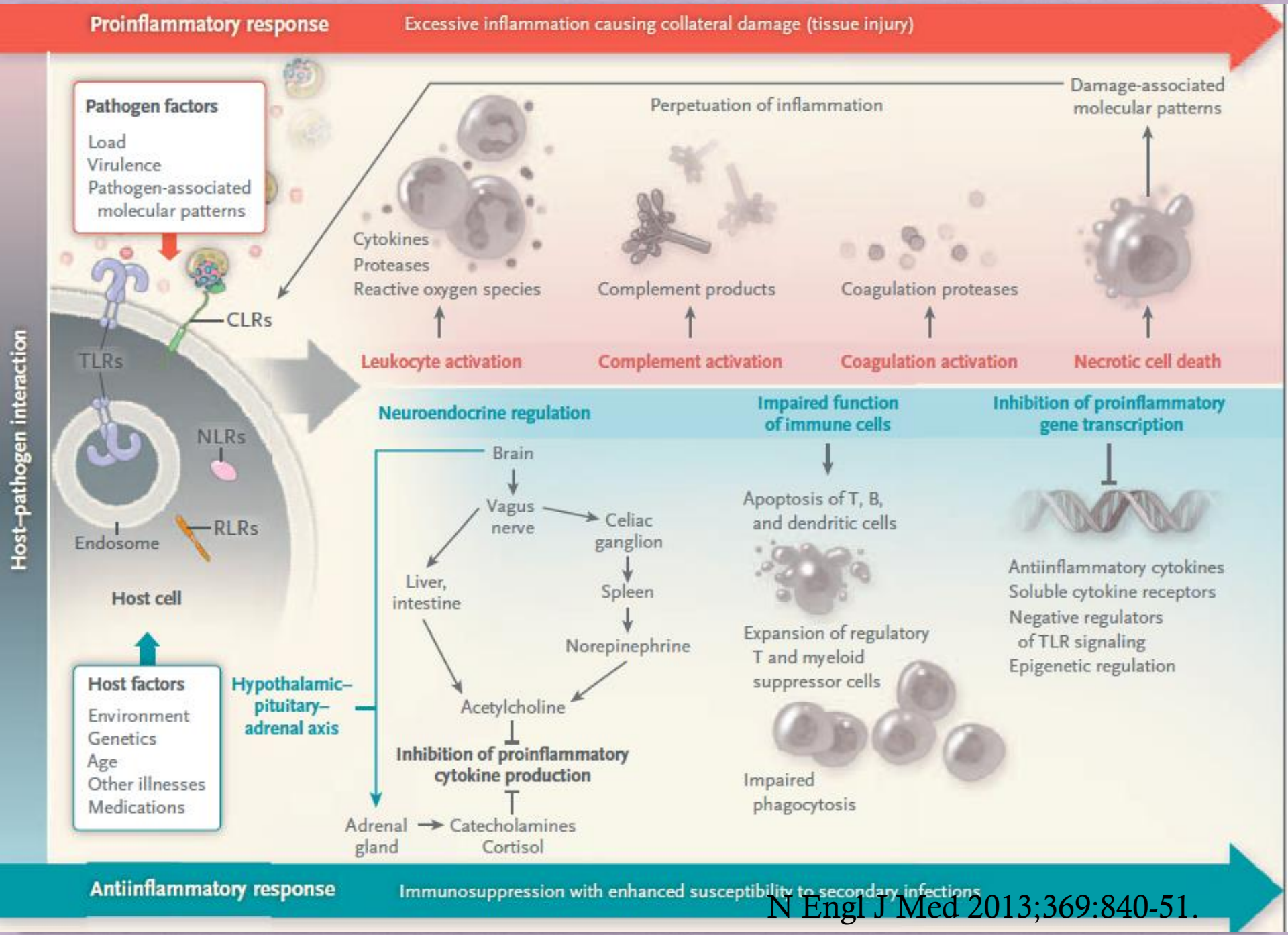
YES

Systolic BP ≤ 100

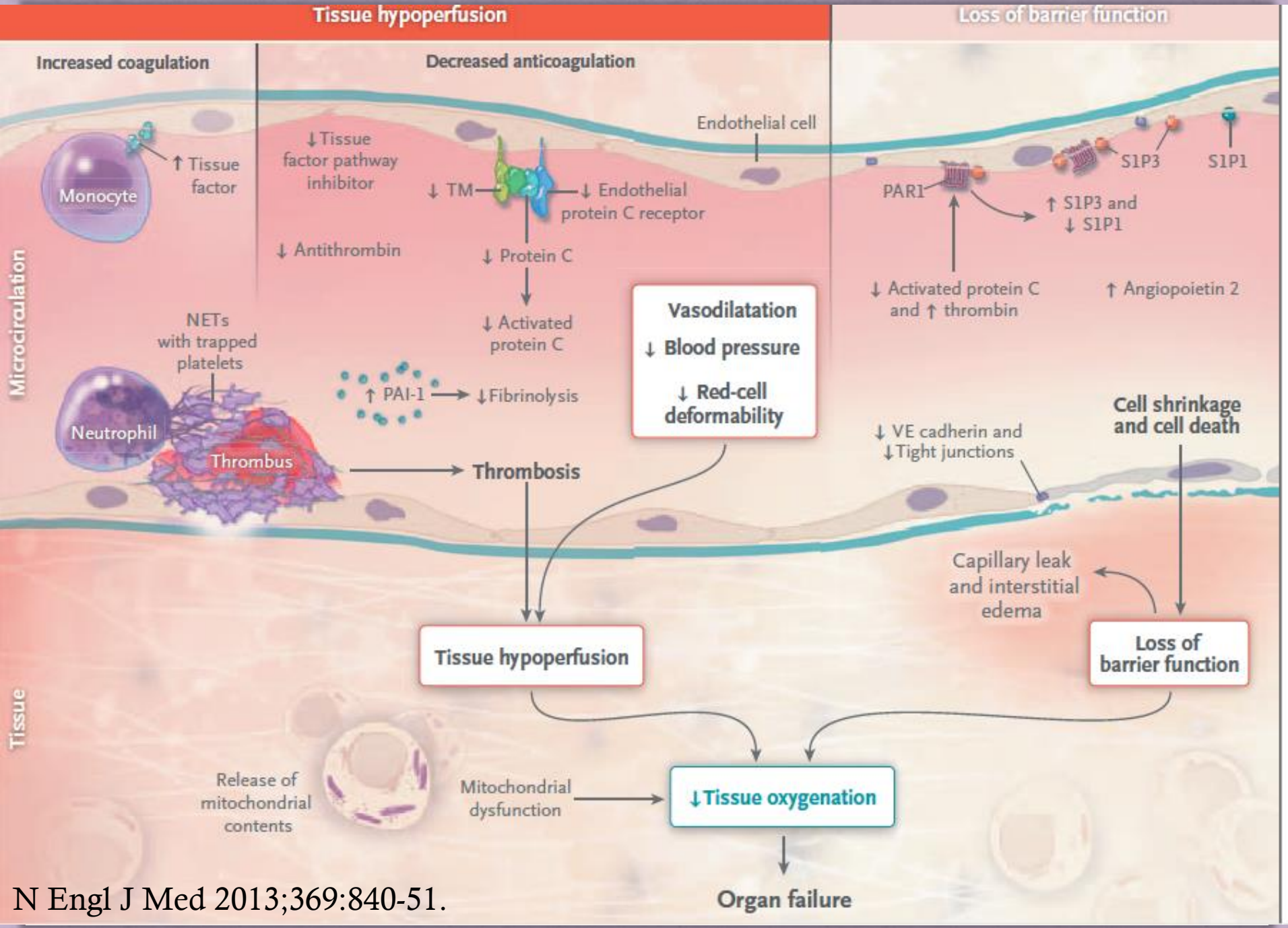
YES



PAMP-Pathogen associated molecular pattern
TLR-Toll like receptor



N Engl J Med 2013;369:840-51.



N Engl J Med 2013;369:840-51.

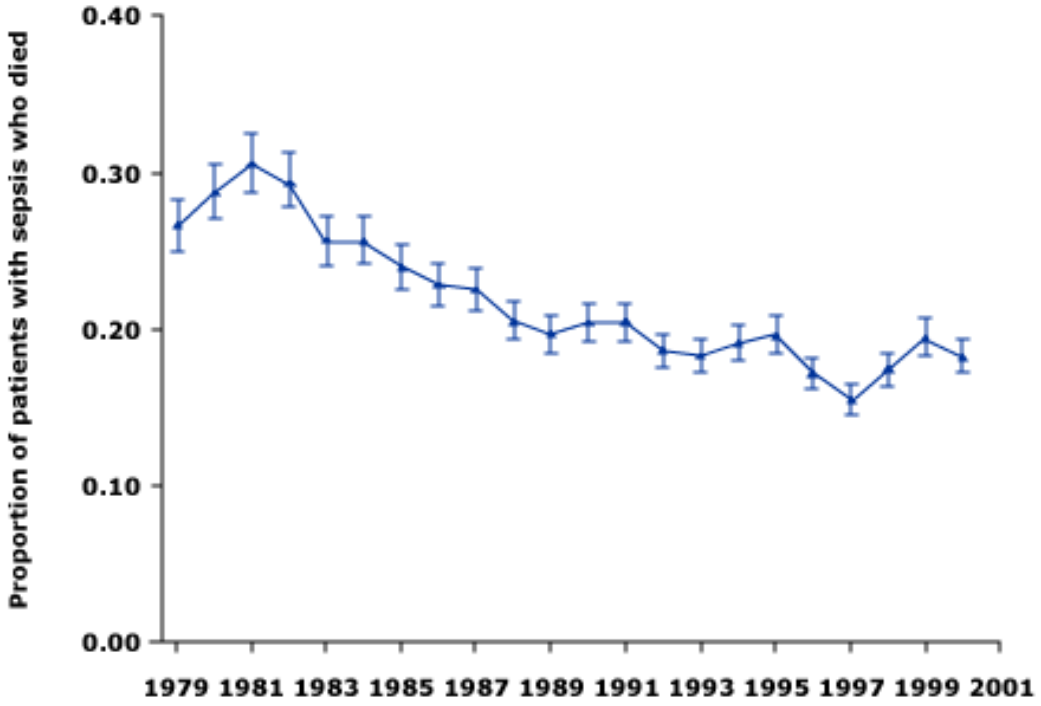
Sepsis azalmıyor-artıyor; çünkü:

- Uzayan ömür, onkolojik vakalarda, immunsupresif tedavilerde, invaziv girişimlerde artış

- Dirençli mikroorganizmalarda artış

Angus DC et al. 2001. Crit Care Med 29:1303-1310.
Balk RA. 2000. Crit Care Clin 16(2):179-191

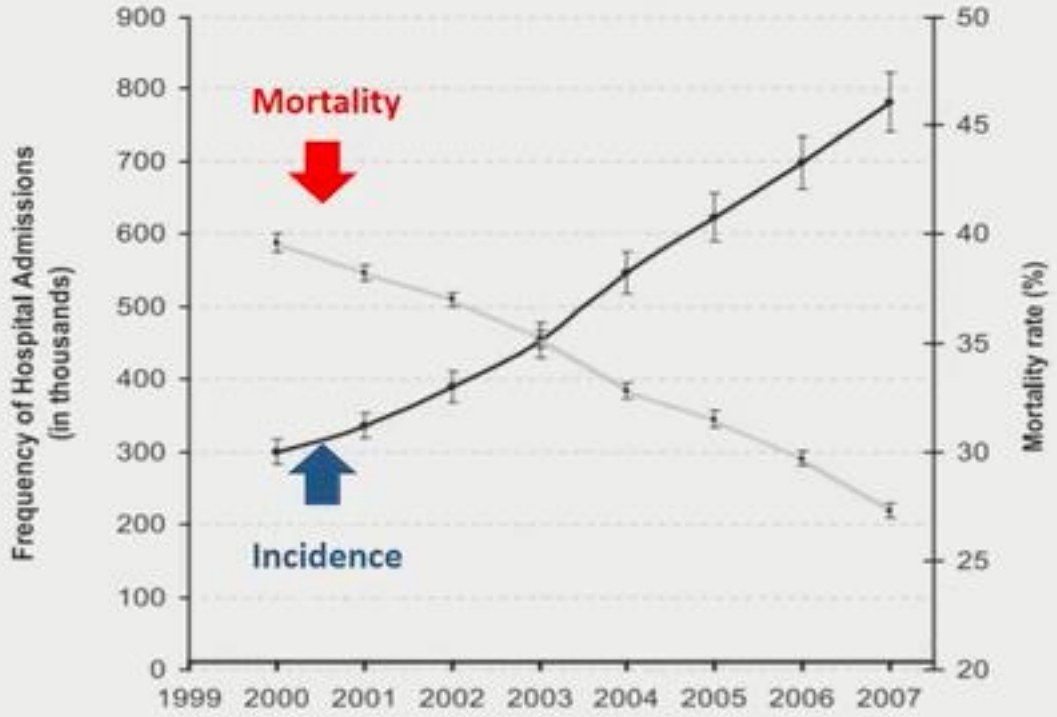
Overall in-hospital mortality rate among patients hospitalized for sepsis, 1979-2000



Mortality averaged 28 percent during the first six years of the study and 18 percent during the last six years. The I bar represent the standard error. Martin, GS, Mannino, DM, Eaton, S, Moss, M. The epidemiology of sepsis in the United States from 1979 through 2000. N Engl Med 2003; 348:1546.

Declining Mortality Rates

Positive Impact of Treatment Initiatives, Dissemination of Evidence-Based Guidelines, and Overall Better Care ?

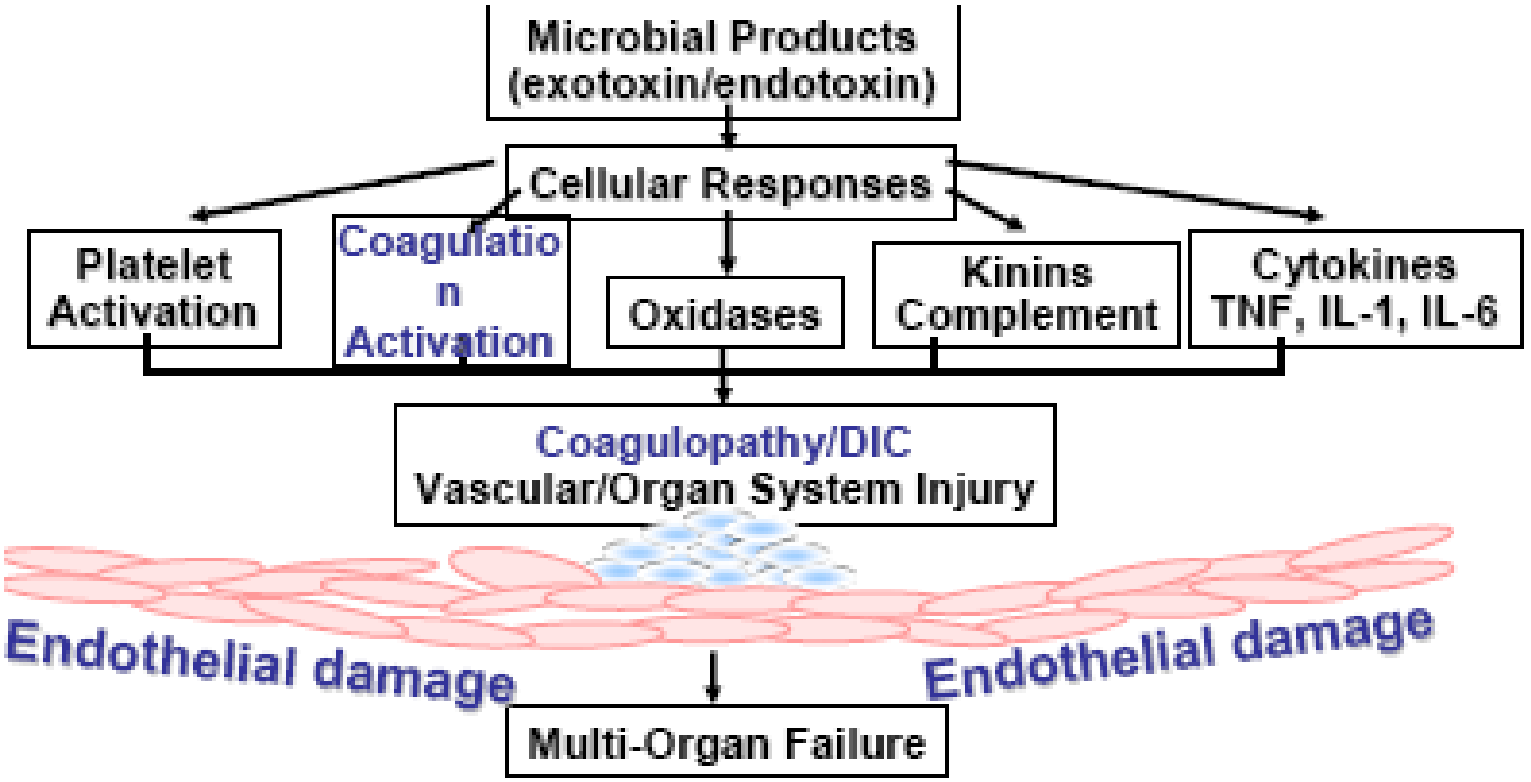


Kumar et al, Chest 2011

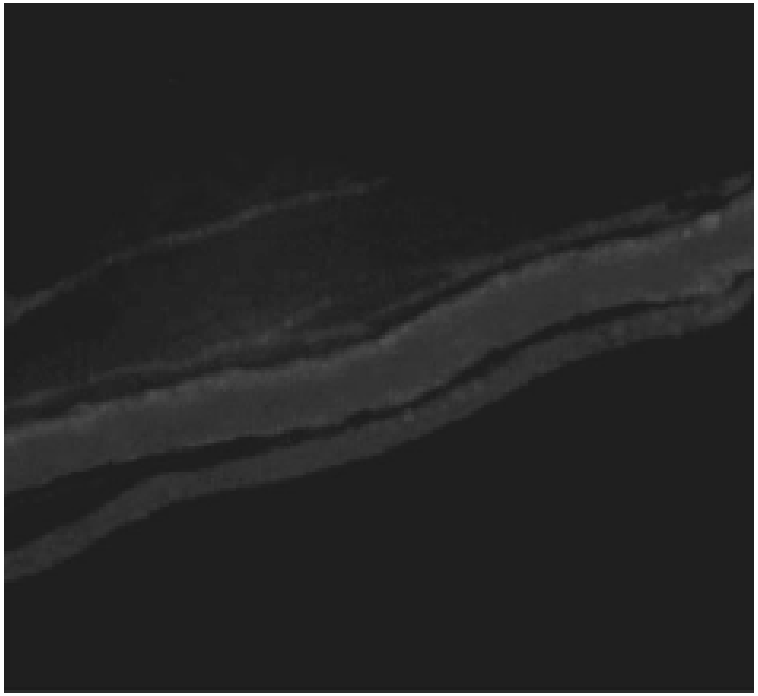
mortalite

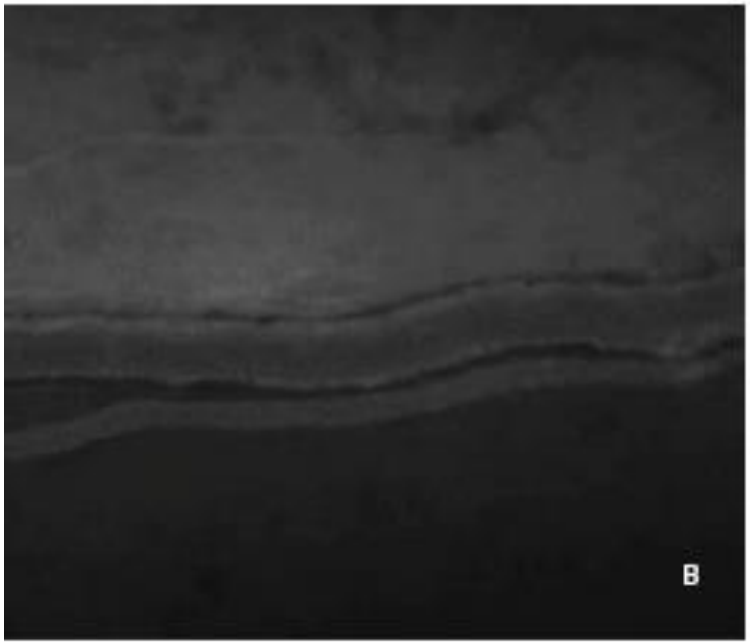
- Myokard infarktüsünü takiben
- Ağır sepsis 2.sırada
  - Vaka-fatalite oranı:%28

- Angus DC et al. 2001. Crit Care Med 29:1303-1310.


Microbial Products
(exotoxin/endotoxin)
Cellular Responses
Platelet Activation
Coagulation Activation
Oxidases
Kinins Complement
Cytokines TNF, IL-1, IL-6
Coagulopathy/DIC
Vascular/Organ System Injury
Endothelial damage
Endothelial damage
Multi-Organ Failure

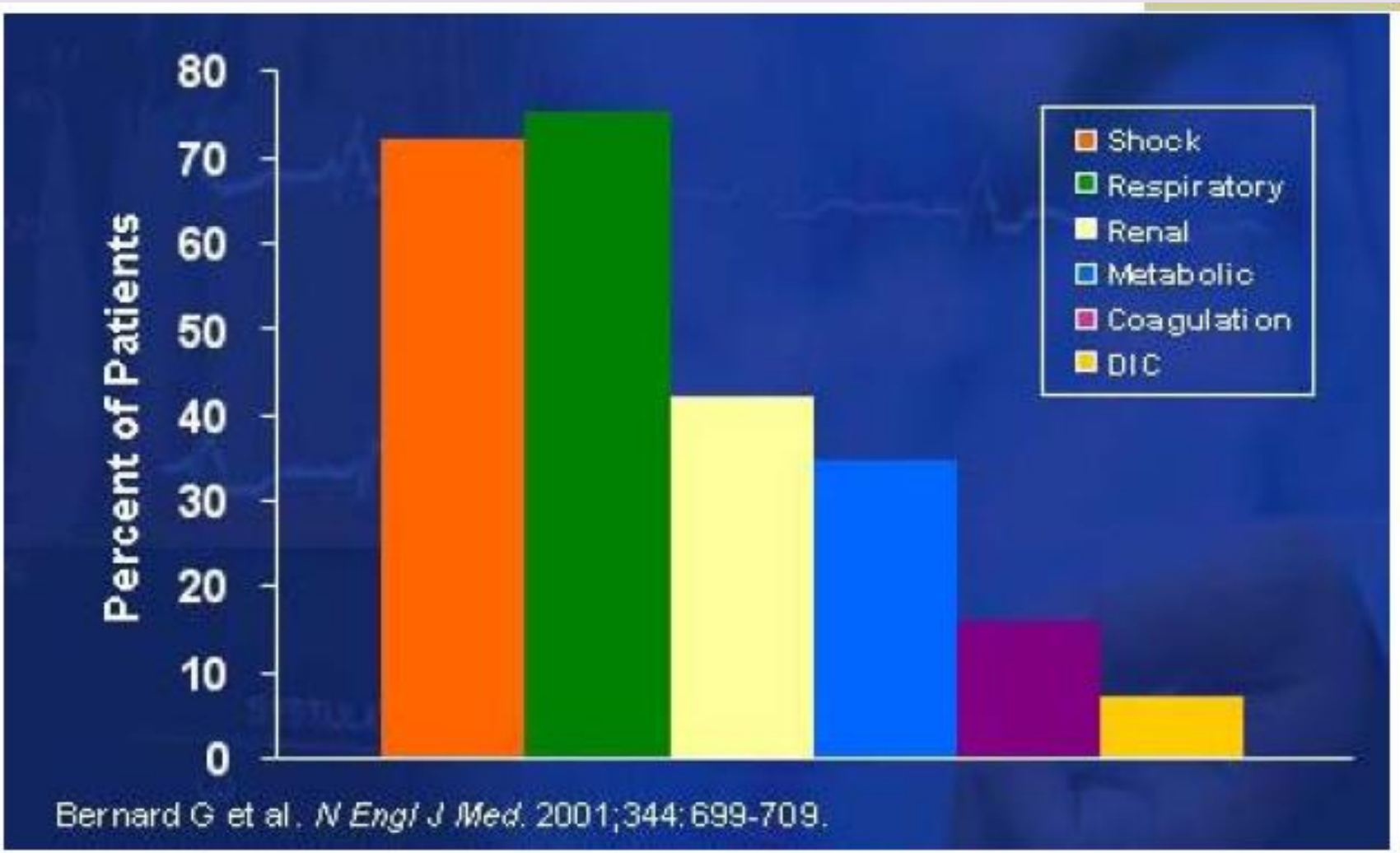
McGown.British Journal of Anaesthesia 98 (2): 163–75 (2007).





tal microscopy (IVM) images of rat mesenteric

Tanı esnasında organ disfonksiyonu



Doğru tanı için-şüphe-qSOFA

- MİKROBİYOLOJİ • BİYOBELİRTEÇLER
- DİRENÇ

biyobelirteç>100

- **Tanı / ayırıcı tanı desteği**
- **Seyirde destek / monitorizasyon**
- **Evrelemeye yardımcı**
- **Prognoz öngörücü**
- **Antibiyotik yönetiminde destek**
- **Hızlı**
- **Kolay ulaşılabilir**
- **Ucuz**

- Duyarlı-hastalık varlığında gerçek pozitif
- Özgül-hastalık yokluğunda gerçek negatif
- Pozitif/negatif öngörü değeri yüksek olmalı

Larsen FF, Petersen JA. Eur J Intern Med. 2017 Sep 28
Esposito S et al, J Global Antimic Res 2017

- -C-reaktif protein;

- -Prokalsitonin
- -Pentraksin 3
- -Plazma chitotriosidase
- -Presepsin
- -Interleukin-27
- -Hepsidin
- -Makrofaj migrasyon inhibitor faktör
- Monosit kemoatraktan protein 1 -MCP-1

- -İmmatür granulosit sayımı;
- -plazma hücreden muaf DNA saptanması
- -CD64
- -CD14
- -Soluble urokinaz tip plazminojen aktivator reseptor (suPAR)

C-Reaktif Protein

- **Karaciğerde sentezlenir**
- **Inflamasyon/infeksiyon**
- **Düzey hastalık ciddiyeti ile korele değil**
- **Yavaş yükselir**
- **Erken tanı için uygun değil**
- **Ciddi hasta için uygun değil**

Lelubre et al,
Biomed Res Int. 2013

Prokalsitonin-pct

- **Normalde Paratiroid bezinin C hücrelerinde sentezlenir**
- **Nöroendokrin akciğer-intestin**
- **Kalsitoninin 116 amino asidli prekürsörüdür**
- **Sepsisi takip eden 2-4 saat içinde yükselmeye başlar**
- **Yüksek negatif prediktif değer**
- **Kinetik izlem**
- **Deeskalasyon desteği -0.5 ng/ml altı**
- **Kardiyojenik şok, pankreatit,rabdomyoliz, otoimmunhastalıklar da yükselir**
- **Ö/D %70-80**

- **Westwood et al, Health Technol Assess 2015**

Pro-Adrenomedullin

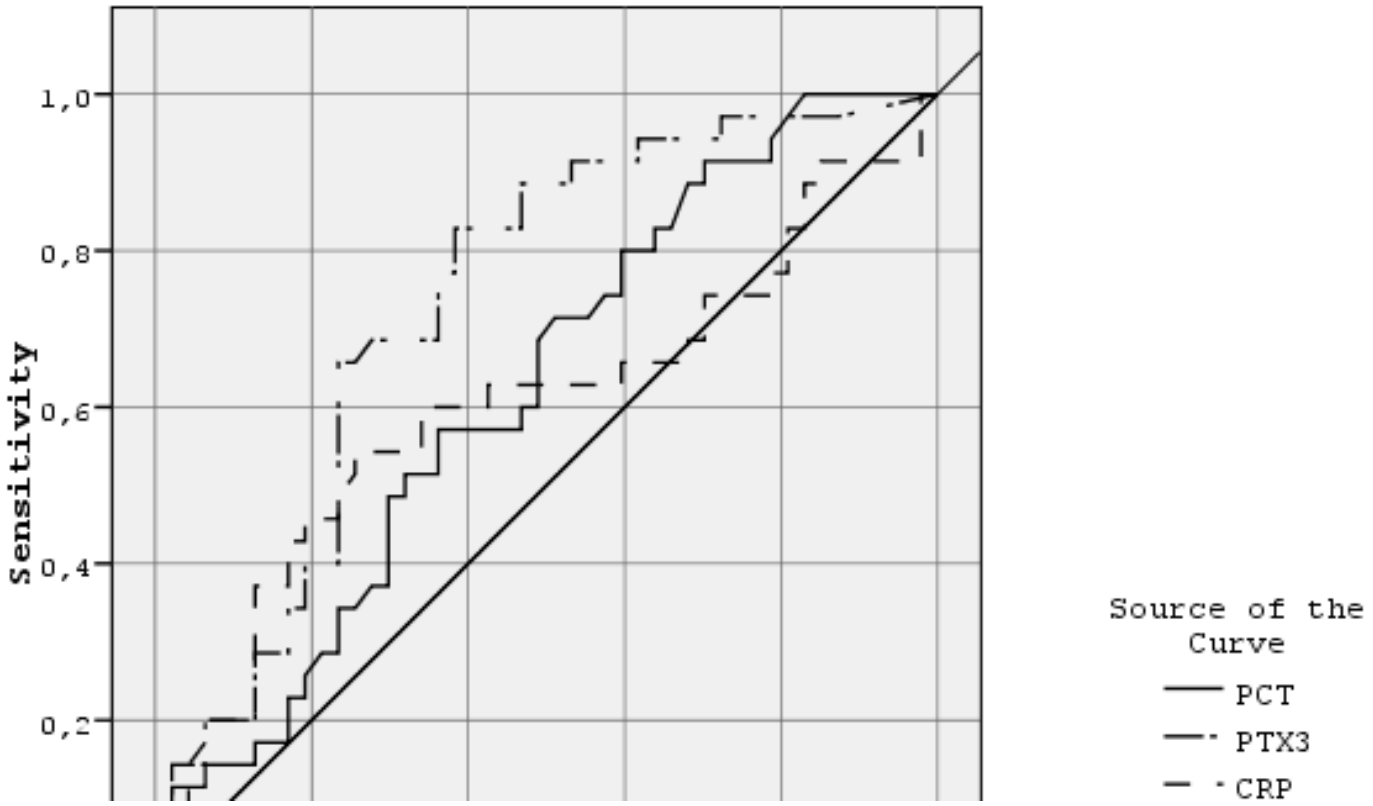
- Sepsis ve septik şoklu hastaların plazmasında
- Adrenomedullin degradasyon ürünü
- Hastalık ciddiyetini belirlemede umut vadediyor→YBU yatışı regulasyonu
- Dolayısı ile tedavi yönetimi

- Carlyn CJ et al, Diagn Microbiol Infect Dis 2017

Pentraxin 3

- **Pentraxin 3 bir patern tanıma reseptorü**
- **Bakteriyal, fungal ve viral ligandları tanır**
- **Akciğer epiteli, alveolar duvar PTX3 üretebilir**
- **tedavi monitorizasyonunda kullanılabilir**

- **Bilgin&Mülazımoğlu**


Sensitivity
1,0
0,8
0,6
0,4
0,2
Source of the Curve
PCT
PTX3
CRP

Research

Open Access

Use of plasma C-reactive protein, procalcitonin, neutrophils, macrophage migration inhibitory factor, soluble urokinase-type plasminogen activator receptor, and soluble triggering receptor expressed on myeloid cells-1 in combination to diagnose infections: a prospective study

Kristian Kofoed[1,2], Ove Andersen[1,2], Gitte Kronborg[2], Michael Tvede[3], Janne Petersen[1], Jesper Eugen-Olsen[1] and Klaus Larsen[1]

[1]Clinical Research Unit, Copenhagen University Hospital, Hvidovre, Kettegaard Allé 30, DK-2650 Hvidovre, Denmark
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Corresponding author: Kristian Kofoed, kristian.kofoed@hvh.regionh.dk

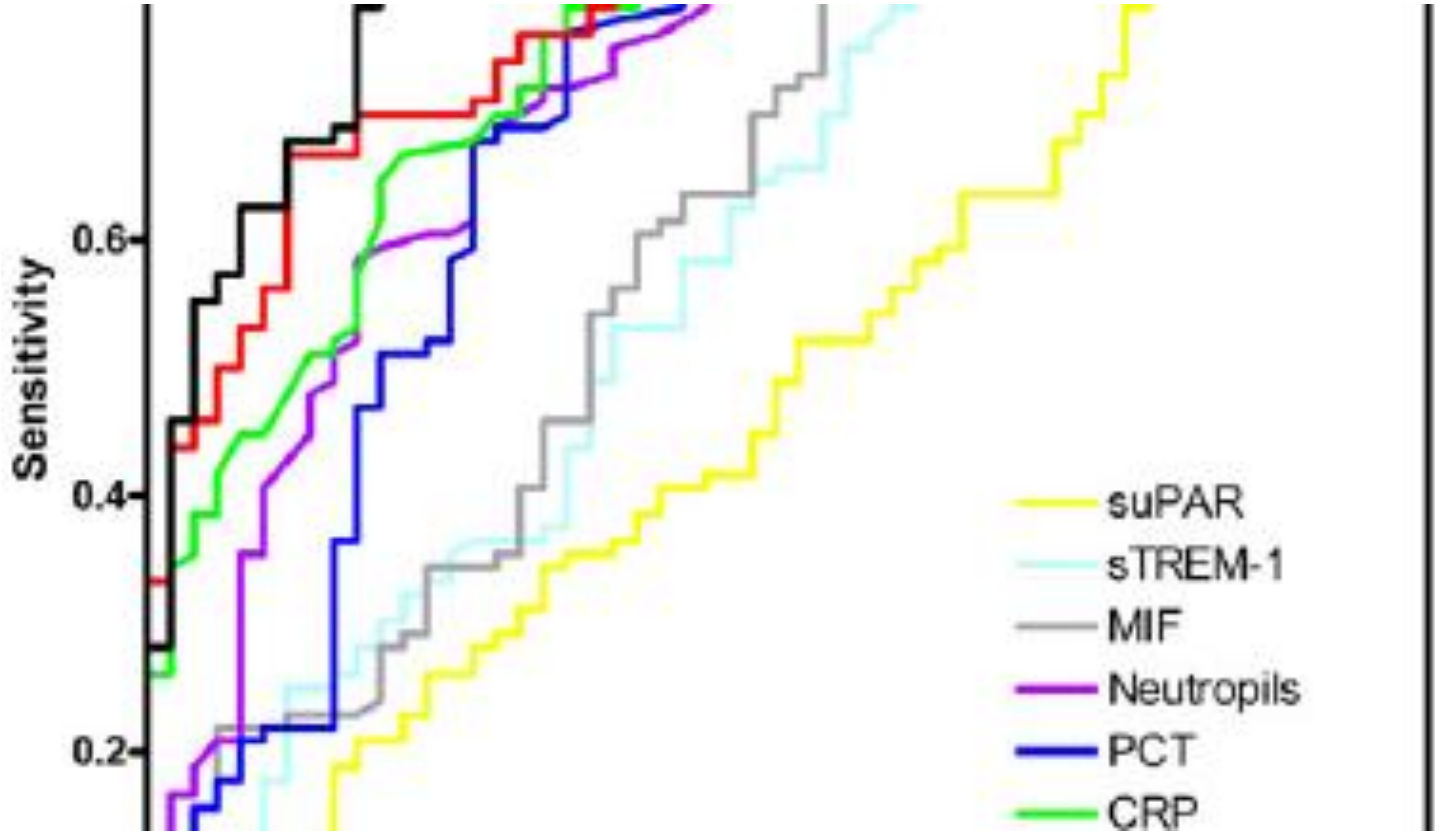
Received: 1 Dec 2006 Revisions requested: 31 Jan 2007 Revisions received: 21 Feb 2007 Accepted: 16 Mar 2007 Published: 16 Mar 2007

Critical Care 2007, 11:R38 (doi:10.1186/cc5723)

Table 3

Accuracy of the six inflammatory markers and the combined three-marker and three-marker tests in diagnosing bacterial infection in SIRS patients

Biomarker	Sensitivity (95% CI)[a]	Specificity (95% CI)[a]	AUC (95% CI)	Specificity = 0.7	Specificity = 0.8	Positive predictive value[b]	Negative predictive value[b]
				Sensitivity (95% CI)	Sensitivity (95% CI)		
CRP	0.86 (0.78–0.93)	0.60 (0.46–0.73)	0.81 (0.73–0.86)	0.72 (0.62–0.81)	0.67 (0.56–0.76)	0.79	0.73
PCT	0.80 (0.71–0.88)	0.58 (0.44–0.71)	0.72 (0.63–0.79)	0.69 (0.58–0.78)	0.51 (0.41–0.61)	0.80	0.63
Neutrophil count	0.74 (0.64–0.82)	0.64 (0.50–0.76)	0.74 (0.66–0.81)	0.70 (0.60–0.79)	0.59 (0.49–0.69)	0.82	0.57
MIF	0.80 (0.71–0.88)	0.47 (0.34–0.61)	0.63 (0.53–0.72)	0.41 (0.31–0.51)	0.29 (0.20–0.39)	0.73	0.58
sTREM-1	0.82 (0.73–0.89)	0.40 (0.27–0.54)	0.61 (0.52–0.71)	0.36 (0.27–0.47)	0.32 (0.23–0.43)	0.71	0.56
suPAR	0.35 (0.26–0.46)	0.67 (0.53–0.79)	0.50 (0.40–0.60)	0.31 (0.22–0.42)	0.23 (0.15–0.33)	0.65	0.37
3-marker[c]	0.67 (0.56–0.76)	0.89 (0.78–0.96)	0.84 (0.71–0.91)	0.76 (0.66–0.84)	0.70 (0.60–0.79)	0.91	0.60
6-marker[d]	0.88 (0.79–0.93)	0.78 (0.65–0.88)	0.88 (0.81–0.92)	0.89 (0.80–0.94)	0.84 (0.76–0.91)	0.88	0.78


Sensitivity
0.6
0.4
0.2
suPAR
sTREM-1
MIF
Neutropils
PCT
CRP

sonuç/yorum

Mevcut biyobelirteçler sepsisde tanıdan ziyade hastalık ve tedavi izleminde ve hastalık ciddiyetini belirlemede faydalıdır

Erken tanı desteği ve diğer enflamatuvar –yanık- gibi durumlardan ayırtedici olması açısından:

İmmatür granulosit sayımı;

plazma hücreden muaf DNA saptanması

yöntemlere ihtiyaç vardır

Hampson et al, Ann Surg. 2017

Arneth et al, J Clin LAnal, 2014

Ancak SEPSİS

- BİR İNFEKSİYON HASTALIĞIDIR/ erken doğru tedavi hayat kurtarıcıdır
- TÜM BU DESTEKLER İLE BİRLİKTE
  - MİKROBİYOLOJİK TANI
  - ASLOLANDIR.

.

Clinical Infectious Diseases

MAJOR ARTICLE

The Effect of Molecular Rapid Diagnostic Testing on Clinical Outcomes in Bloodstream Infections: A Systematic Review and Meta-analysis

Tristan T. Timbrook,[1,4] Jacob B. Morton,[1,4] Kevin W. McConeghy,[2] Aisling R. Caffrey,[1,2,4] Eleftherios Mylonakis,[3] and Kerry L. LaPlante[1,2,4]

[1]Rhode Island Infectious Diseases Research Program, Providence Veterans Affairs Medical Center, [2]Center of Innovation in Long Term Services and Supports, Providence Veterans Affairs Medical Center, [3]Infectious Diseases Division, Warren Alpert Medical School of Brown University, Providence, and [4]College of Pharmacy, University of Rhode Island, Kingston

Clinical Infectious Diseases® 2017;64(1):15–23

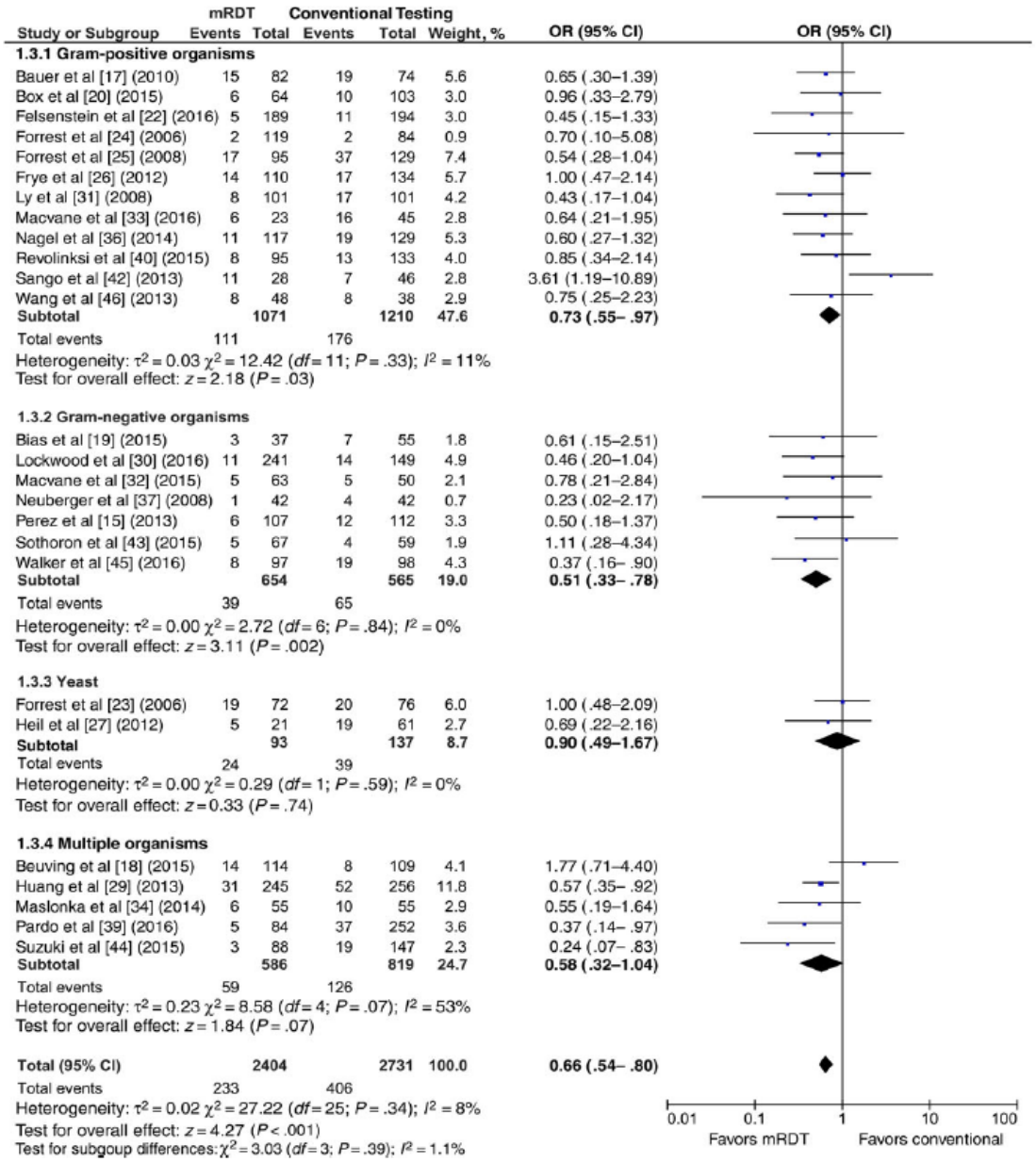
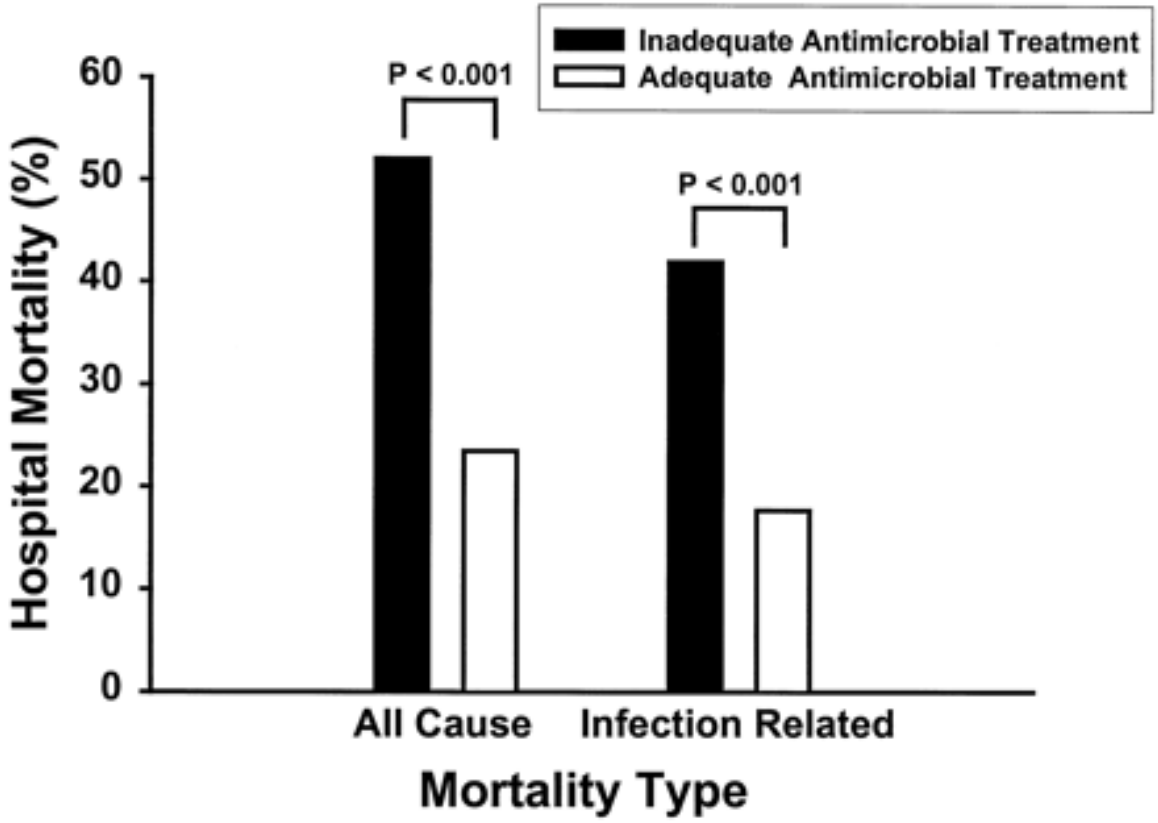
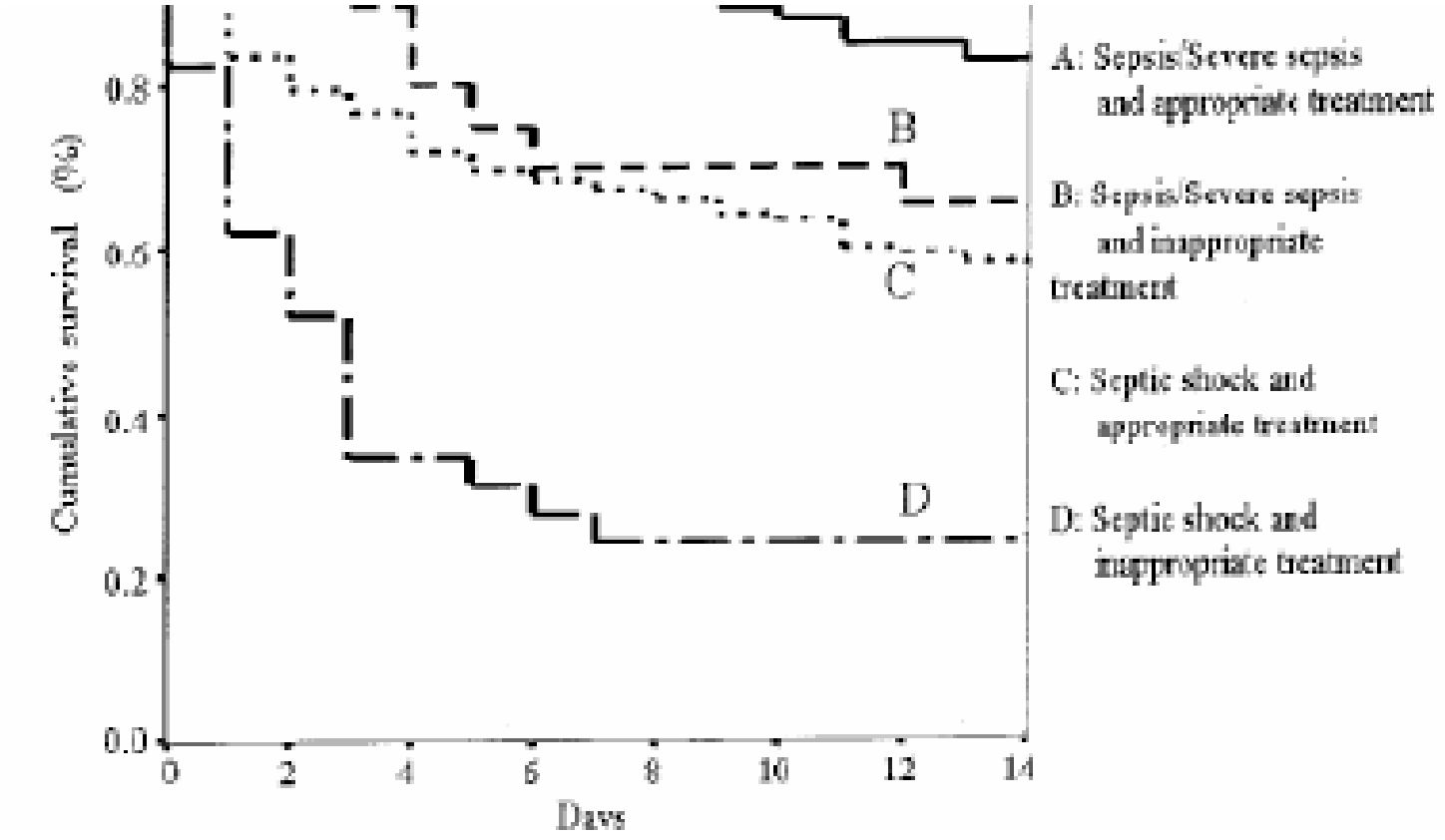


Figure 3. Mortality with molecular rapid diagnostic testing (mRDT) versus conventional testing by organism type in bloodstream infection. Odds ratios (ORs) were determined with the Mantel-Haenszel random-effects method. Abbreviation: CI, confidence interval.


Inadequate Antimicrobial Treatment
Adequate Antimicrobial Treatment
P < 0.001
P < 0.001
Hospital Mortality (%)
60
50
40
30
20
10
0
All Cause
Infection Related
Mortality Type

;115:462-474


Cumulative survival (%)
0.0
0.2
0.4
0.6
0.8
0
2
4
6
8
10
12
14
Days
A
B
C
D
A: Sepsis/Severe sepsis and appropriate treatment
B: Sepsis/Severe sepsis and inappropriate treatment
C: Septic shock and appropriate treatment
D: Septic shock and inappropriate treatment

Antimikrobiyal tedavi

- Sepsis ve septik şokda -tanıdan-tanımlamadan-itibaren 1 saat içinde başlanmış olmalı (kan kültürü alarak)
- Parenteral olarak verilmeli-maksimum dozda verilmeli-farmakokinetik ve dinamik parametreler gözönünde bulundurulmalı
- Odağın olası patojenlerini kapsamalı
- Olası infeksiyon odağına penetrasyonu iyi olmalı
- Toplum veya çalıştığınız birimin direnç paternine uygun olmalı

Erken ve yeterli, hedefe yönelik antimikrobiyal tedavi-İlk1 saat içinde-

- hastalığın nerede geliştiği,
- son 90 gün içerisinde 2 gün veya daha uzun hastane yatış öyküsü,
- son 90 gün içerisinde antibiyotik kullanım öyküsü,

Erken ve yeterli, hedefe yönelik antimikrobiyal tedavi-2

- sağlıkla ilişkili hizmet alıp almaması-diyaliz; yara bakımı gibi,
- immunsupresif hastalık veya immunsupresif tedavi durumu
- lokal direnç paternleri
- özel durum-özel mikroorganizma ilişkisi

Erken Hedefe Kilitlenmiş Tedavi (tanıdan itibaren 6 saat içinde)

- CVP 8-12 mmHg
- Ortalama arteriel basınç (MAP) ≥65 mmHg
- SKB ≥90 mmHg
- SvO2 ≥ 70%
- İdrar çıkışı 0.5mL/kg/hr

Glukoz kontrolü

- Glukoz düzeyi 180 mg/dL yi geçmedikçe insülin tedavisi gündeme gelmemelidir.
- NICE-SUGAR çalışması glukoz düzeyinin 150 mg/dL civarında tutulmasının faydalı olacağını göstermektedir.

1) Griesdale DE, de Souza RJ, van Dam RM, Heyland DK, Cook DJ, Malhotra A, Dhaliwal R, Henderson WR, Chittock DR, Finfer S, Talmor D. Intensive insulin therapy and mortality among critically ill patients: a meta-analysis including NICE-SUGAR study data. CMAJ. 2009 Apr 14;180(8):799-800.
2) NICE-SUGAR Study Investigators, Finfer S, Chittock DR, Su SY, Blair D, Foster D, Dhingra V, Bellomo R, Cook D, Dodek P, Henderson WR, Hébert PC, Heritier S, Heyland DK, McArthur C, McDonald E, Mitchell I, Myburgh JA, Norton R, Potter J, Robinson BG, Ronco JJ. Intensive versus conventional glucose control in critically ill patients. N Engl J Med. 2009 Mar 26;360(13):1283-97. Epub 2009 Mar 24
3) Wiener RS, Wiener DC, Larson RJ. Benefits and risks of tight glucose control in critically ill adults: A meta-analysis. JAMA 2008;300:933–44

Glukokortikoid

- Septik şokda çalışmalar adrenal yetmezlik olabileceğini gösterdiğinden bu durumu bertaraf etmek için 50mg hidrokortizon veya eşdeğeri (örn.10 mg metilprednizolon) her 6 saatte bir toplam 5-7 gün süreyle uygulanabilir; ancak bu konu henüz tartışmalıdır.

Sprung CL, Annane D, Keh D, Moreno R, Singer M, Freivogel K, Weiss YG, Benbenishty J, Kalenka A, Forst H, Laterre PF, Reinhart K, Cuthbertson BH, Payen D, Briegel J; CORTICUS Study Group.Hydrocortisone therapy for patients with septic shock.N Engl J Med. 2008;10;358(2):111-24

Sentetik glukokortikoidlerin eşdeğer dozları

		Glukokortikoid etki	Minerolokortikoid etki
Hidrokortizon	(20 mg)	1	1
Prednisone	(5 mg)	4	0.7
Methylprednisolone	(4 mg)	5	0.5
Dexamethasone	(0.5 mg)	30	0
Bethametasone	(0.6 mg)	25-50	0

Adjunctive Glucocorticoid Therapy in Patients with Septic Shock

B. Venkatesh, S. Finfer, J. Cohen, D. Rajbhandari, Y. Arabi, R. Bellomo, L. Billot, M. Correa, P. Glass, M. Harward, C. Joyce, Q. Li, C. McArthur, A. Perner, A. Rhodes, K. Thompson, S. Webb, and J. Myburgh, for the ADRENAL Trial Investigators and the Australian–New Zealand Intensive Care Society Clinical Trials Group*

ABSTRACT

BACKGROUND

Whether hydrocortisone reduces mortality among patients with septic shock is unclear.

METHODS

We randomly assigned patients with septic shock who were undergoing mechanical ventilation to receive hydrocortisone (at a dose of 200 mg per day) or placebo for 7 days or until death or discharge from the intensive care unit (ICU), whichever came first. The primary outcome was death from any cause at 90 days.

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*A full list of investigators in the ADRENAL

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2018, at NEJM.org.
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CONCLUSIONS

Among patients with septic shock undergoing mechanical ventilation, a continuous infusion of hydrocortisone did not result in lower 90-day mortality than placebo. (Funded by the National Health and Medical Research Council of Australia and others; ADRENAL ClinicalTrials.gov number, NCT01448109.)

Commentary

Do statins have a role in preventing or treating sepsis?

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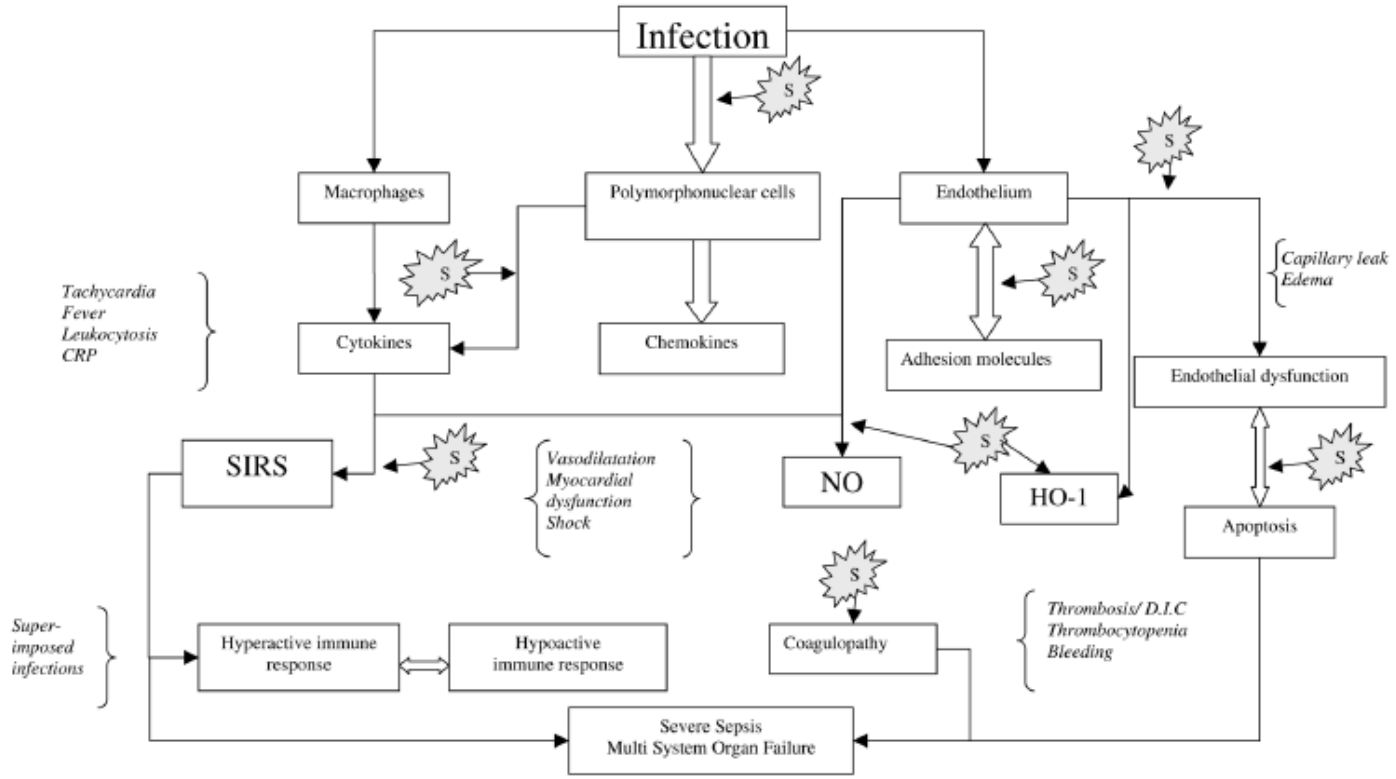
Infection
S
Macrophages
Polymorphonuclear cells
Endothelium
S
S
S
Tachycardia
Fever
Leukocytosis
CRP
Cytokines
Chemokines
Adhesion molecules
Capillary leak
Edema
Endothelial dysfunction
SIRS
S
Vasodilatation
Myocardial
dysfunction
Shock
NO
S
HO-1
S
Apoptosis
S
Super-
imposed
infections
Hyperactive immune
response
Hypoactive
immune response
Coagulopathy
Thrombosis/ D.I.C
Thrombocytopenia
Bleeding
Severe Sepsis
Multi System Organ Failure

TABLE 7. Randomized controlled trials of immunotherapy in sepsis and septic shock[a]

Type of trial	No. of trials	Total no. of patients	Mortality (%) in patients receiving:	
			Placebo	Therapy
Anti-endotoxin	4	2,010	35	35
Anti-IL-1R	3	1,898	35	31
Anti-bradykinin	2	755	36	39
Anti-PAF	2	870	50	45
Anti-TNF	8	4,132	41	40
Soluble TNF-R	2	688	38	40
NSAIDS	3	514	40	37
Steroids	9	1,267	35	39
Activated protein C	1	1,690	31	25
All studies	33	13,824	38	37

Comparing the Outcomes of Adults with *Enterobacteriaceae* Bacteremia Receiving Short-Course versus Prolonged-Course Antibiotic Therapy

Darunee Chotiprasitsakul, Jennifer H. Han, Anna T. Conley, Sara E. Cosgrove, Anthony D. Harris, Ebbing Lautenbach, and Pranita D. Tamma

Clinical Infectious Diseases (in press)

Disclosure: All authors have nothing to declare on this study

Dikkatiniz için teşekkür ederim.