İSTANBUL
MEDENİYET ÜNİVERSİTESİ

EKMUD

SEPSİS YÖNETİMİNDE ZORLUKLAR VE ÇÖZÜMLER SEMPOZYUMU

SEPSİSDE ANTİMİKROBİYAL TEDAVİ NASIL OLMALI?

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İstanbul Medeniyet Üniversitesi Tıp Fakültesi
Enfeksiyon Hast. ve Klinik Mikr. AD
12 Nisan 2025

Sunum planı

- Antimikrobiyal tedavi yönetimi
  - Antimikrobiyal tedavi zamanlaması
  - Uygun antimikrobiyal seçimi
  - Biyobelirteçlerin rolü
  - Tedavi süresi

- Sepsis, enfeksiyona karşı düzensiz konak yanıtı nedeniyle oluşan yüksek mortalite ile seyreden tıbbi bir acil durumdur
- **Zamanında ve uygun antibiyotik** uygulaması tedavinin en önemli unsurudur.

The Surviving Sepsis Campaign Bundle: 2018 Update

Mitchell M. Levy, MD, MCCM[1]; Laura E. Evans, MD, MSc, FCCM[2]; Andrew Rhodes, MBBS, FRCA, FRCP, FFICM, MD (res)[3]

İlk 1 saatte yapılması gerekenler	**Öneri Gücü-Kanıt Düzeyi**
Laktat düzeyini ölç, başlangıçta >2mmol/L ise tekrar ölç	ZÖ- DKD
Antibiyotik vermeden önce kan kültürlerini al	**Bilinen en iyi uygulama**
Geniş spektrumlu antibiyotik başla	**GÖ-OKD**
Hipotansiyon var veya laktat düzeyi ≥4mmol/L ise hızlıca 30ml/kg kristalloid başla	GÖ-DKD
Hasta sıvı resüsitasyonu süresince veya resüsitasyon sonrasında hipotansif ise ≥65mmHg ortalama arter basıncı (MAP) değerine ulaşmak için vazopressör ver	GÖ-OKD

› Intensive Care Med. 2021 Nov;47(11):1181-1247. doi: 10.1007/s00134-021-06506-y. Epub 2021 Oct 2.

Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021

Laura Evans [1], Andrew Rhodes [2], Waleed Alhazzani [3], Massimo Antonelli [4],

- Sepsis ve septik şok tıbbi acil durumlardır ve tedavi ve resüsitasyona hemen başlanmalıdır

Antimikrobiyal Zamanlama

Surviving Sepsis Campaign 2021

	Şok var	Şok yok
Kesin veya yüksek olası sepsis	Antimikrobiyalleri hemen, ideal olarak kabulden sonra 1 saat içinde uygulayın	
Olası sepsis	Antimikrobiyalleri hemen, ideal olarak kabulden sonra 1 saat içinde uygulayın	Akut hastalığın enfeksiyöz ve enfeksiyöz olmayan nedenlerinin hızlı değerlendirilmesi* Enfeksiyon şüphesi devam ederse 3 saat içinde antimikrobiyalleri uygulayın

*Hızlı değerlendirme, öykü ve klinik muayeneyi, akut hastalığın hem enfeksiyöz hem de enfeksiyöz olmayan nedenlerine yönelik testleri ve sepsisi taklit edebilen akut durumlar için acil tedaviyi içerir. Mümkün olduğunda, hastanın başvurusunun enfeksiyöz bir nedeni olma olasılığına ilişkin bir karar verilebilmesi için başvurudan sonraki 3 saat içinde tamamlanmalı ve sepsis olasılığının yüksek olduğu düşünülüyorsa zamanında antimikrobiyal tedavi sağlanmalıdır.

Am J Respir Crit Care Med. 2017 Oct 1;196(7):856-863. doi: 10.1164/rccm.201609-1848O

The Timing of Early Antibiotics and Hospital Mortality in Sepsis

Vincent X Liu [1], Vikram Fielding-Singh [2], John D Greene [1], Jennifer M Baker [1], Theodore J Iwashyna [3] [4], Jay Bhattacharya [5], Gabriel J Escobar [1]

- 2010-2013 yılları arasında acil serviste tedavi edilen **35.000 sepsis hastası**
- Retrospektif
- **Ortalama antibiyotik verme süresi:** 2.1 saat (IQR: 1.4 - 3.1 saat)
- **Antibiyotik başlanmasındaki her 1 saatlik gecikme için ölüm olasılığı:**
  - **%9 artış** (OR: 1.09; %95 GA: 1.05-1.13)
- **1 saatlik gecikme ile mutlak ölüm artışı:**
  - Sepsis: **%0.3** (P = 0.04)
  - Şiddetli sepsis: **%0.4** (P = 0.02)
  - Septik şok: **%1.8** (P = 0.001)

Rationale: Prior sepsis studies evaluating antibiotic timing have shown mixed results.

Objectives: To evaluate the association between antibiotic timing and mortality among patients with sepsis receiving antibiotics within 6 hours of emergency department registration.

Methods: Retrospective study of 35,000 randomly selected inpatients with sepsis treated at 21 emergency departments between 2010 and 2013 in Northern California. The primary exposure was antibiotics given within 6 hours of emergency department registration. The primary outcome was adjusted in-hospital mortality. We used detailed physiologic data to quantify severity of illness within 1 hour of registration and logistic regression to estimate the odds of hospital mortality based on antibiotic timing and patient factors.

Measurements and main results: The median time to antibiotic administration was 2.1 hours (interquartile range, 1.4-3.1 h). The adjusted odds ratio for hospital mortality based on each hour of delay in antibiotics after registration was 1.09 (95% confidence interval [CI], 1.05-1.13) for each elapsed hour between registration and antibiotic administration. The increase in absolute mortality associated with an hour's delay in antibiotic administration was 0.3% (95% CI, 0.01-0.6%; P = 0.04) for sepsis, 0.4% (95% CI, 0.1-0.8%; P = 0.02) for severe sepsis, and 1.8% (95% CI, 0.8-3.0%; P = 0.001) for shock.

Conclusions: In a large, contemporary, and multicenter sample of patients with sepsis in the emergency department, hourly delays in antibiotic administration were associated with increased odds of hospital mortality even among patients who received antibiotics within 6 hours. The odds increased within each sepsis severity strata, and the increased odds of mortality were greatest in septic shock.

PLoS One. 2018 Sep 26;13(9):e0204608. doi: 10.1371/journal.pone.0204608. eCollection 2018.

Development and validation of a modified quick SOFA scale for risk assessment in sepsis syndrome.

Cag Y[1], Karabay O[2], Sipahi OR[3], Aksoy F[4], Durmus G[5], Batirel A[6], Ak O[6], Kocak-Tufan Z[7], Atilla A[8], Piskin N[9], Akbas T[10], Erol S[11], Ozturk-Engin D[11], Caskurlu H[1], Onal U[3], Erdogan H[12], Demirel A[13], Dogru A[1], Harman R[14], Hamidi AA[15], Karasu D[16], Korkmaz F[17], Korkmaz P[18], Civelek Eser F[19], Onem Y[20], Cesur S[10], Salmanoglu M[20], Erdem İ[21], Diktas H[22], Vahaboglu H[1].

Abstract

Sepsis is a severe clinical syndrome owing to its high mortality. Quick Sequential Organ Failure Assessment (qSOFA) score has been proposed for the prediction of fatal outcomes in sepsis syndrome in emergency departments. Due to the low predictive performance of the qSOFA score, we propose a modification to the score by adding age. We conducted a multicenter, retrospective cohort study among regional referral centers from various regions of the country. Participants recruited data of patients admitted to emergency departments and obtained a diagnosis of sepsis syndrome. Crude in-hospital mortality was the primary endpoint. A generalized mixed-effects model with random intercepts produced estimates for adverse outcomes. Model-based recursive partitioning demonstrated the effects and thresholds of significant covariates. Scores were internally validated. The H measure compared performances of scores. A total of 580 patients from 22 centers were included for further analysis. Stages of sepsis, age, time to antibiotics, and administration of carbapenem for empirical treatment were entered the final model. Among these, severe sepsis (OR, 4.40; CIs, 2.35-8.21), septic shock (OR, 8.78; CIs, 4.37-17.66), age (OR, 1.03; CIs, 1.02-1.05) and time to antibiotics (OR, 1.05; CIs, 1.01-1.10) were significantly associated with fatal outcomes. A decision tree demonstrated the thresholds for age. We modified the quick Sequential Organ Failure Assessment (mod-qSOFA) score by adding age (> 50 years old = one point) and compared this to the conventional score. H-measures for qSOFA and mod-qSOFA were found to be 0.11 and 0.14, respectively, whereas AUCs of both scores were 0.64. We propose the use of the modified qSOFA score for early risk assessment among sepsis patients for improved triage and management of this fatal syndrome.

PMID: 30256855 PMCID: PMC6157867 DOI: 10.1371/journal.pone.0204608

Free PMC Article

PLoS One. 2018 Sep 26;13(9):e0204608. doi: 10.1371/journal.pone.0204608. eCollection 2018.

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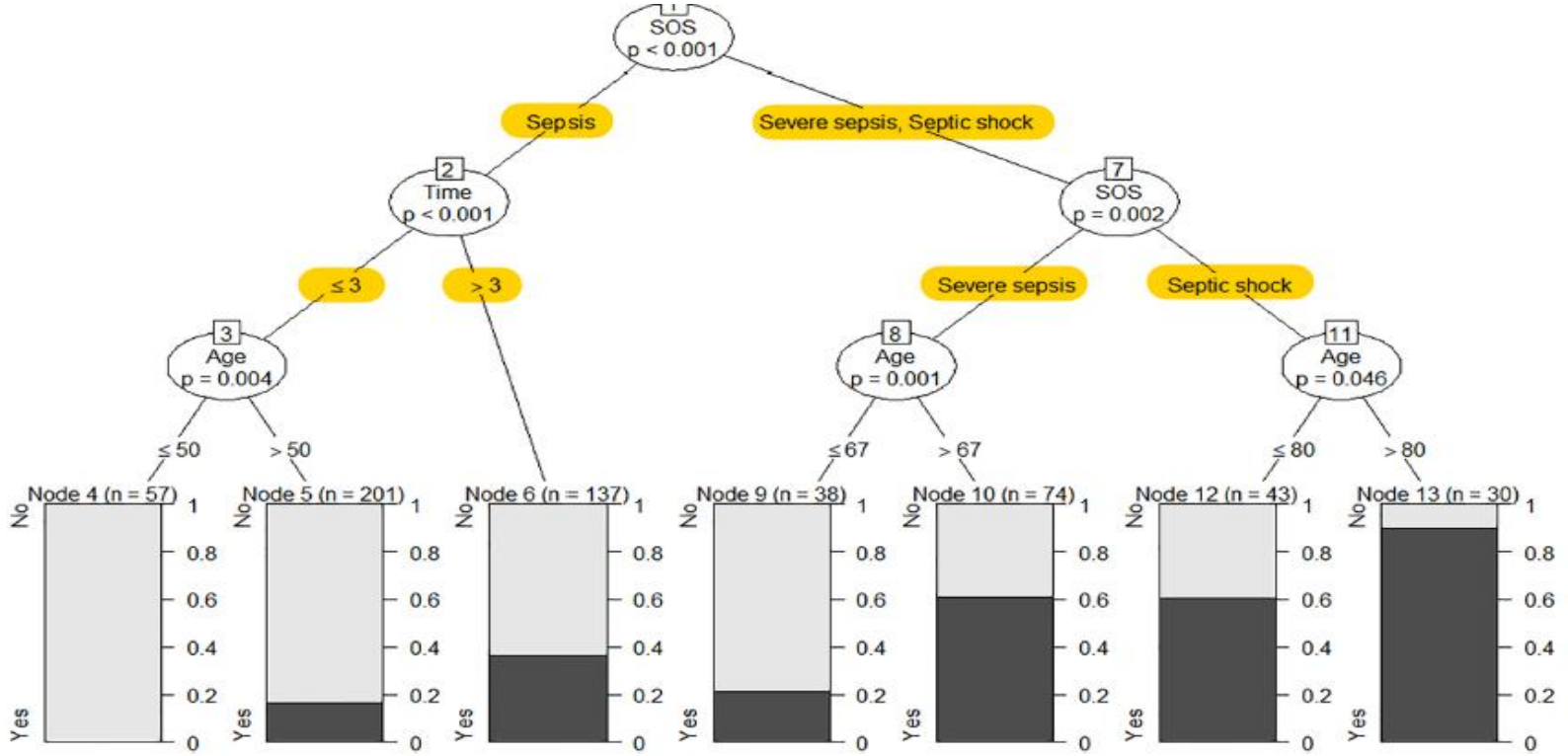


Fig 1. The model-based decision tree for fatal outcomes among patients with sepsis syndrome. The fatal outcome is first partitioned among stages of sepsis (SOS).

- **Ciddi sepsis ve septik şok gelişmemiş sepsis tanılı hastalarda**
- **Antibiyotik tedavisi ≤ 3 saatte başlanan ve ≤ 50 yaş mortlite yok**

Antibiyotik seçiminde

Hastanın

- Yaşı
- Kilosu
- Alerji öyküsü
- Klinik durumu
- Şüphelenilen veya mevcut enfeksiyon odağı
- İnvaziv cihaz varlığı
- Eşlik eden komorbid durumları (kronik böbrek yetmezliği, kronik karaciğer hastalığı, vb.),
- İmmunsupresyon durumu dikkate alınmalı

Uygun Ampirik Antimikrobiyal Tedavi -I

- Olası patojenlere karşı (**bakteriyel/fungal**) etkili bir veya daha fazla ilacı içermeli
- Gram (+), Gram (-), anaerob bakterileri kapsamalı (**geniş spektrum**)
- Çoklu ilaca dirençli **(MDR) patojenler** için risk varsa bu patojenleri kapsamalı

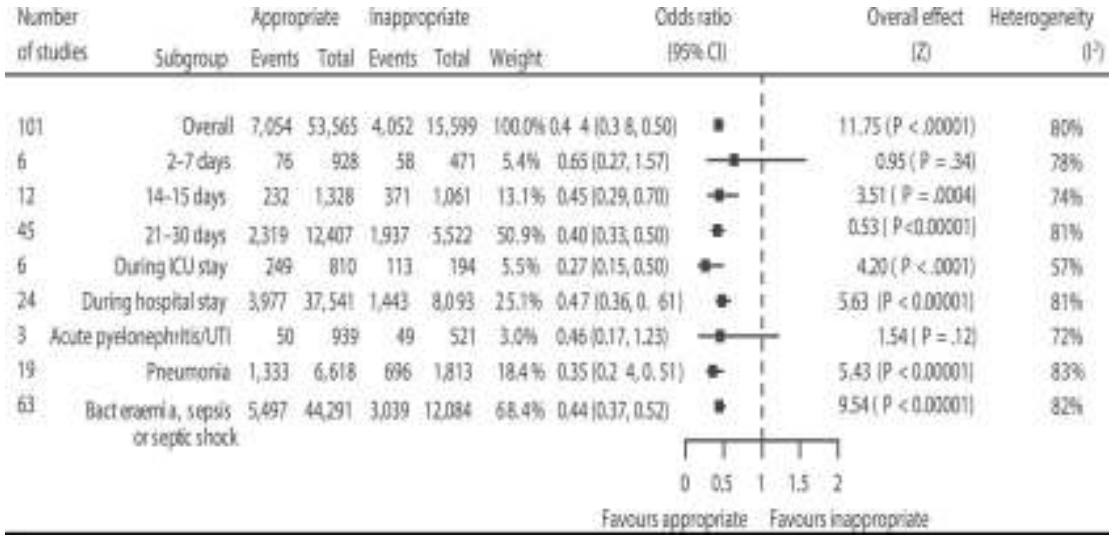
> Int J Antimicrob Agents. 2020 Dec;56(6):106184. doi: 10.1016/j.ijantimicag.2020.106184. Epub 2020 Oct 9.

Systematic review of the impact of appropriate versus inappropriate initial antibiotic therapy on outcomes of patients with severe bacterial infections

Matteo Bassetti [1], Jordi Rello [2], Francesco Blasi [3], Herman Goossens [4], Giovanni Sotgiu [5],

ABSTRACT

We investigated the impact of appropriate versus inappropriate initial antimicrobial therapy on the clinical outcomes of patients with severe bacterial infections as part of a systematic review and meta-analyses assessing the impact of delay in appropriate antimicrobial therapy. Literature searches of MEDLINE and Embase, conducted on 24 July 2018, identified studies published after 2007 reporting the impact of delay in appropriate antibiotic therapy for hospitalised adult patients with bacterial infections. Results were statistically pooled for outcomes including mortality, hospital length of stay (LOS) and treatment failure. Subgroup analyses were explored by site of infection where data permitted. Inclusion criteria were met by 145 studies, of which 114 reported data on the impact of appropriate versus inappropriate initial therapy. In the pooled analysis, rates of mortality were significantly in favour of appropriate therapy [odds ratio (OR)=0.44, 95% CI 0.38–0.50]. Across eight studies, LOS was shorter with appropriate therapy compared with inappropriate therapy [mean difference (MD) −2.54 days (95% CI −5.30 to 0.23)], but not significantly so. The incidence of treatment failure was significantly lower in patients who received appropriate therapy compared with patients who received inappropriate therapy (six studies: OR=0.33, 95% CI 0.16–0.66) as was mean hospital costs (four studies: MD −7.38 thousand US$ or Euros, 95% CI −14.14 to −0.62). Initiation of appropriate versus inappropriate antibiotics can reduce mortality, reduce treatment failure and decrease LOS, highlighting the importance of broad-spectrum empirical therapy and rapid diagnostics for early identification of the causative pathogen. [Study registration: PROSPERO: CRD42018104669]



Number of studies	Subgroup	Appropriate Events	Appropriate Total	Inappropriate Events	Inappropriate Total	Weight	Odds ratio (95% CI)	Overall effect (Z)	Heterogeneity (I^2)
101	Overall	7,054	53,565	4,052	15,599	100.0%	0.4 4 (0.3 8, 0.50)	11.75 (P < .00001)	80%
6	2-7 days	76	928	58	471	5.4%	0.65 (0.27, 1.57)	0.95 (P = .34)	78%
12	14-15 days	232	1,328	371	1,061	13.1%	0.45 (0.29, 0.70)	3.51 (P = .0004)	74%
45	21-30 days	2,319	12,407	1,937	5,522	50.9%	0.40 (0.33, 0.50)	0.53 (P<0.00001)	81%
6	During ICU stay	249	810	113	194	5.5%	0.27 (0.15, 0.50)	4.20 (P < .0001)	57%
24	During hospital stay	3,977	37,541	1,443	8,093	25.1%	0.47 (0.36, 0. 61)	5.63 (P < 0.00001)	81%
3	Acute pyelonephritis/UTI	50	939	49	521	3.0%	0.46 (0.17, 1.23)	1.54 (P = .12)	72%
19	Pneumonia	1,333	6,618	696	1,813	18.4%	0.35 (0.2 4, 0. 51)	5.43 (P < 0.00001)	83%
63	Bact eraemi a, sepsis or septic shock	5,497	44,291	3,039	12,084	68.4%	0.44 (0.37, 0.52)	9.54 (P < 0.00001)	82%

0 0.5 1 1.5 2

Favours appropriate Favours inappropriate

Bakteriyemi, sepsis ve septik şoklu hastalarda (63 çalışma; OR = 0,44, %95 CI 0,37-0,52) **uygun tedavi** kolunda ölüm oranları daha düşük.

Baykara et al. Critical Care (2018) 22:93
https://doi.org/10.1186/s13054-018-2013-1

Critical Care

RESEARCH Open Access

Epidemiology of sepsis in intensive care units in Turkey: a multicenter, point-prevalence study

Nur Baykara[1*], Halis Akalın[2], Mustafa Kemal Arslantaş[3], Volkan Hancı[4], Çiğdem Çağlayan[5], Fe
Kubilay Demirağ[7], Canan Baydemir[8], Necmettin Ünal[9] and Sepsis Study Group

- ***Acinetobacter spp.*** **(%37) en sık**
- **Karbapenem direnç oranları**
  - ***Acinetobacter spp.*** **(%74.9),**
  - ***Klebsiella spp.*****(%39.1),**
  - ***Pseudomonas spp.*** **(%26.5)**

Abstract

Background: The prevalence and mortality of sepsis are largely unknow
resistance. A national, multicenter, point-prevalence study was conducte
microorganisms, and outcome of sepsis in intensive care units (ICUs) in

Methods: A total of 132 ICUs from 94 hospitals participated. All patients (aged > 18 years) present at the participating ICUs or admitted for any duration within a 24-h period (08:00 on January 27, 2016 to 08:00 on January 28, 2016) were included. The presence of systemic inflammatory response syndrome (SIRS), severe sepsis, and septic shock were assessed and documented based on the consensus criteria of the American College of Chest Physicians and Society of Critical Care Medicine (SEPSIS-I) in infected patients. Patients with septic shock were also assessed using the SEPSIS-III definitions. Data regarding demographics, illness severity, comorbidities, microbiology, therapies, length of stay, and outcomes (dead/alive during 30 days) were recorded.

Results: Of the 1499 patients included in the analysis, 237 (15.8%) had infection without SIRS, 163 (10.8%) had infection with SIRS, 260 (17.3%) had severe sepsis without shock, and 203 (13.5%) had septic shock. The mortality rates were higher in patients with severe sepsis (55.7%) and septic shock (70.4%) than those with infection alone (24.8%) and infection + SIRS (31.2%) ($p < 0.001$). According to SEPSIS-III, 104 (6.9%) patients had septic shock (mortality rate, 75.9%). The respiratory system (71.6%) was the most common site of infection, and *Acinetobacter* spp. (33.7%) were the most common isolated pathogen. Approximately, 74.9%, 39.1%, and 26.5% of *Acinetobacter*, *Klebsiella*, and *Pseudomonas* spp. isolates, respectively, were carbapenem-resistant, which was not associated with a higher mortality risk. Age, acute physiology and chronic health evaluation II score at ICU admission, sequential organ failure assessment score on study day, solid organ malignancy, presence of severe sepsis or shock, *Candida spp.* infection, renal replacement treatment, and a nurse-to-patient ratio of 1:4 (compared with a nurse-to-patient ratio of 1:2) were independent predictors of mortality in infected patients.

Conclusions: A high prevalence of sepsis and an unacceptably high mortality rate were observed in Turkish ICUs. Although the prevalence of carbapenem resistance was high in Turkish ICUs, it was not associated with a higher risk for mortality.

Antimikrobiyal direnci öngörme

Genel risk faktörleri

- Son 1 yılda bilinen bir mikroorganizma ile enfeksiyon veya kolonizasyon
- Son üç aydaki antibiyotik kullanımı
- Hastaneye yatışı
- YBÜ yatışı
- Lokal epidemiyolojik veriler
- İmmun yetmezlik durumu dikkate alınmalı

- **MRSA için ilave olarak**
- Santral venöz kateter veya intravasküler cihaz varlığı
- Hemodiyaliz veya peritoneal diyaliz
- IV ilaç bağımlısı olmak
- **Candida için ilave olarak**
- TPN
- Yakın zamanda cerrahi (özellikle gastrointestinal ya da hepatobilier)

Uygun Ampirik Antimikrobiyal Tedavi -II

Surviving Sepsis Campaign 2021

- Metisiline dirençli *S. aureus* (MRSA) açısından yüksek risk varsa MRSA etkili antibiyotiklerin ampirik kullanımı önerilir.
  - En İyi Uygulama bildirimi
- Fungal enfeksiyon riski yüksek ise ampirik antifungal tedavi önerilir.
  - Zayıf öneri, düşük kalite kanıt
- MDR organizmalar için yüksek risk mevcutsa ampirik çift Gram-negatif etkili antimikrobiyal önerilir.
  - Zayıf öneri, çok düşük kanıt kalitesi
- Antiviral ajanların kullanımı konusunda herhangi bir öneri yok

Antibiyotiklerin Kombine Kullanımı

Cochrane Database Syst Rev. 2014 Jan 7;(1):CD003344. doi: 10.1002/14651858.CD003344.pub3.

Beta lactam antibiotic monotherapy versus beta lactam-aminoglycoside antibiotic combination therapy for sepsis.

Paul M[1], Lador A, Grozinsky-Glasberg S, Leibovici L.

Metaanalizde sepsiste beta-laktam ve aminoglikozid kombinasyon tedavisinin beta-laktam monoterapisine üstünlüğü gösterilememiş, monoterapi azalmış nefrotoksisiteyle ilişkili

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, May 2010, p. 1742–1748 Vol. 54, No. 5
0066-4804/10/$12.00 doi:10.1128/AAC.01365-09

Empiric Combination Antibiotic Therapy Is Associated with Improved Outcome against Sepsis Due to Gram-Negative Bacteria: a Retrospective Analysis[▽]

Scott T. Micek,[1] Emily C. Welch,[1] Junaid Khan,[2] Mubashir Pervez,[2] Joshua A. Doherty,[3] Richard M. Reichley,[3] and Marin H. Kollef[2]*

Pseudomonas spp. **ve** ***Acinetobacter spp*****. gibi ÇİD Gram negatif etkenlere bağlı sepsis ve septik şokta beta laktam antibiyotikler ve aminoglikozidlerin kombine tedavisi artmış sağkalım oranları ile ilişkili**

Crit Care Med. 2010 Sep;38(9):1773-85. doi: 10.1097/CCM.0b013e3181eb3ccd.

Early combination antibiotic therapy yields improved survival compared with monotherapy in septic shock: a propensity-matched analysis.

Kumar A[1], Zarychanski R, Light B, Parrillo J, Maki D, Simon D, Laporta D, Lapinsky S, Ellis P, Mirzanejad Y, Martinka G, Keenan S, Wood G, Arabi Y, Feinstein D, Kumar A, Dodek P, Kravetsky L, Doucette S; Cooperative Antimicrobial Therapy of Septic Shock (CATSS) Database Research Group.

Septik şokta erken başlanan kombinasyon tedavisi azalmış mortaliteyle ilişkili

Uygun Antimikrobiyal Tedavi-III

- Muhtemel enfeksiyon odağına **yeterli konsantrasyonlarda** ulaşabilmeli
  - Lipofilik antibiyotikler (örn. kinolonlar) tüm dokularda yüksek konsantrasyona erişir
  - Hidrofilik antibiyotikler (örn. aminoglikozitler) dokulara iyi nüfuz edemez
- **Sidal serum seviyelerine** ulaşmak için **doğru dozda, optimum zamanda ve parenteral** olarak uygulanmalı

De Backer D, et al. Intensive Care Med. 2019.
Stijn I. Blot, et al. Advanced Drug Delivery Reviews. 2014

Antimikrobiyallerin Fizikokimyasal ve Farmakokinetik Özellikleri

Antimicrobial	Hydrophilic	Lipophilic	Highly Protein Bound (>70%)	Hepatic Metabolism	Renal Elimination
Amikacin	√				√
Azithromycin		√		√	
Aztreonam	√				√
Cefazolin			√		√
Cefepime	√				√
Ceftazidime	√				√
Ceftriaxone	√		√		
Ciprofloxacin					√
Clindamycin		√	√	√	
Daptomycin	√		√		√
Doripenem	√				√
Doxycycline		√	√	√	
Ertapenem	√		√		√
Gentamicin	√				√
Levofloxacin					√
Linezolid		√			
Meropenem	√				√
Metronidazole		√		√	
Minocycline		√	√	√	
Nafcillin			√	√	
Oxacillin			√	√	
Piperacillin-tazobactam	√				√
Tigecycline		√	√	√	
Tobramycin	√				√
Vancomycin	√				√

Phe K, J Infect Dis. 2020

Kritik Hastalarda Antibiyotik Farmakokinetiği

Patofizyolojik Değişiklikler:

- Kapiller kaçak, hipoalbüminemi, agresif sıvı replasmanı → **Artmış dağılım hacmi**
- Hiperdinamik dolaşım
- Böbrek ve karaciğer fonksiyonlarındaki değişkenlik

Organ Destek Uygulamaları:

- RRT (Renal replasman tedavisi)
- ECMO (Ekstrakorporeal membran oksijenizasyon)

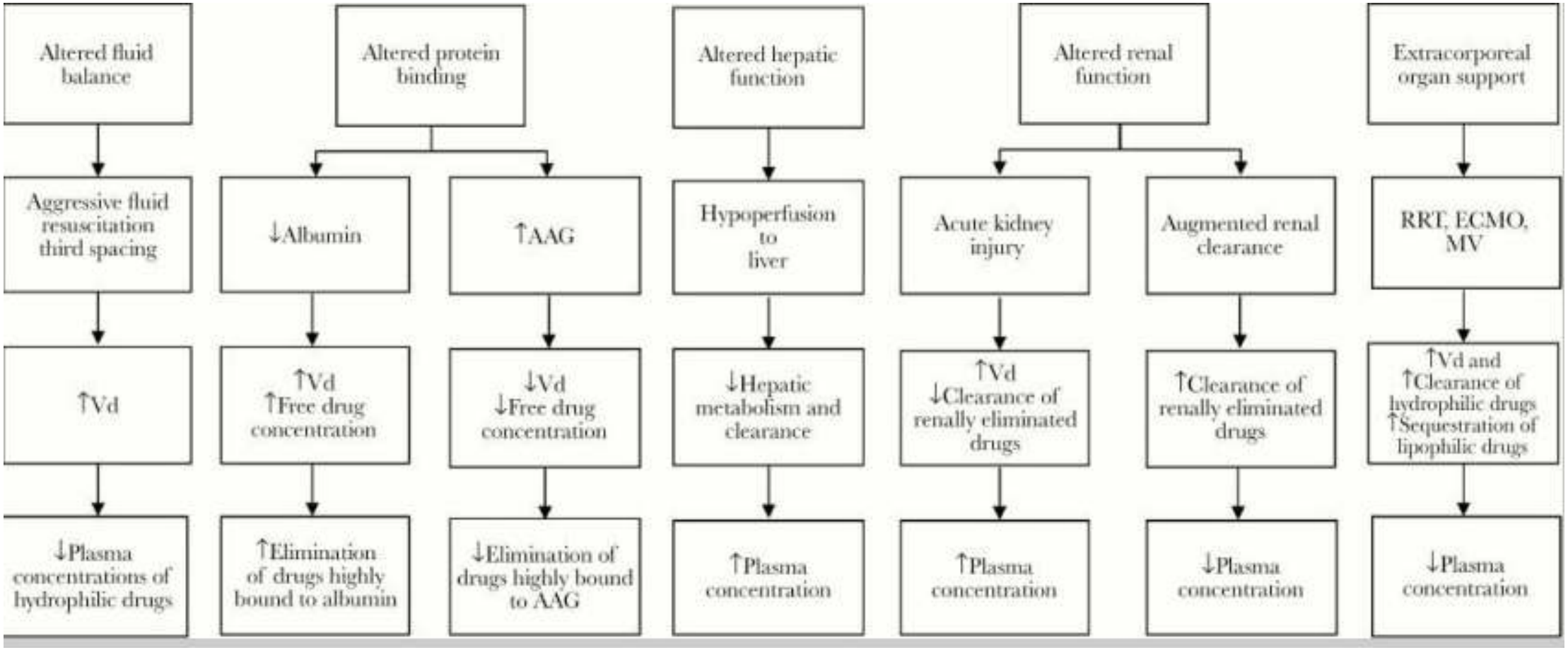
Phe K, J Infect Dis. 2020
De Backer D, et al. Intensive Care Med. 2019.
Stijn I. Blot, et al. Advanced Drug Delivery Reviews. 2014

Sonuçta

- Antibiyotik düzeylerinde büyük dalgalanmalar görülebilir
- Serbest ilaç konsantrasyonları terapötik düzeyin altına düşebilir
- Standart dozlar yetersiz kalabilir
- Başlangıçta terapötik kan seviyesine daha hızlı ulaşmak için **yükleme dozu** gerekir.
    - beta-laktamlar, aminoglikozitler, glikopeptitler, kolistin
    - Sonraki dozlar, ilaç klirensine göre ayarlanmalıdır.

Phe K, J Infect Dis. 2020
De Backer D, et al. Intensive Care Med. 2019.
Stijn I. Blot, et al. Advanced Drug Delivery Reviews. 2014

Fizyolojik değişiklikler ve antimikrobiyal farmakokinetik üzerindeki etkileri



AAG, α1-asit glikoprotein; Vd, dağılım hacmi.

Phe K, J Infect Dis. 2020

Multicenter Study > Crit Care. 2010;14(4):R126. doi: 10.1186/cc9091. Epub 2010 Jul 1.

Insufficient β-lactam concentrations in the early phase of severe sepsis and septic shock

Fabio Silvio Taccone [1], Pierre-François Laterre, Thierry Dugernier, Herbert Spapen,

- Antibiyotiklerin serum konsantrasyonları, uygulamadan önce ve uygulamadan 1, 1,5, 4,5 ve 6 veya 8 saat sonra HPLC ile belirlendi.
- Hedef PK profiline ulaşan hasta sayısı meropenem için 12/16 (%75), seftazidim için 5/18 (%28), sefepim için 3/19 (%16) ve piperasilin-tazobaktam için 12/27 (%44).
- Piperasilin-tazobaktam, seftazidim ve sefepim için standart dozaj rejimleri, şiddetli sepsis ve septik şokun erken evresinde daha az duyarlı patojenleri ampirik olarak kapsamak için yetersiz olabilir.

Methods: Open, prospective, multicenter study in four Belgian intensive care units. All consecutive patients with a diagnosis of severe sepsis or septic shock, in whom treatment with the study drugs was indicated, were included. Serum concentrations of the antibiotics were determined by high-pressure liquid chromatography (HPLC) before and 1, 1.5, 4.5 and 6 or 8 hours after administration.

Results: 80 patients were treated with piperacillin-tazobactam (n = 27), ceftazidime (n = 18), cefepime (n = 19) or meropenem (n = 16). Serum concentrations remained above 4 times the minimal inhibitory concentration (T > 4 × MIC), corresponding to the clinical breakpoint for Pseudomonas aeruginosa defined by the European Committee on Antimicrobial Susceptibility Testing (EUCAST), for 57% of the dosage interval for meropenem (target MIC = 8 μg/mL), 45% for ceftazidime (MIC = 32 μg/mL), 34% for cefepime (MIC = 32 μg/mL), and 33% for piperacillin-tazobactam (MIC = 64 μg/mL). The number of patients who attained the target PK profile was 12/16 for meropenem (75%), 5/18 for ceftazidime (28%), 3/19 (16%) for cefepime, and 12/27 (44%) for piperacillin-tazobactam.

Conclusions: Serum concentrations of the antibiotic after the first dose were acceptable only for meropenem. Standard dosage regimens for piperacillin-tazobactam, ceftazidime and cefepime may, therefore, be insufficient to empirically cover less susceptible pathogens in the early phase of severe sepsis and septic shock.

Table 4 Probability of target T >4 × MIC attainment for various MICs

From: Insufficient β-lactam concentrations in the early phase of severe sepsis and septic shock

		Adequate PK N (%)			
MIC (μg/mL)	Target concentration (μg/mL)	meropenem (n = 16)	ceftazidime (n = 18)	cefepime (n = 19)	piperacillin-tazobactam (n = 27)
32	128	0	0	0	1 (4)
16	64	0	0	1 (5)	**12 (44)**
8	32	0	**5 (28)**	**3 (16)**	15 (56)
4	16	3 (18)	14 (78)	7 (36)	21 (78)
2	8	**12 (75)**	18 (100)	15 (79)	25 (93)
1	4	15 (94)	18 (100)	17 (90)	27 (100)
0.5	2	16 (100)	18 (100)	19 (100)	27 (100)

Data are expressed as counts (percentage). In bold: MIC corresponding to European Committee on Antimicrobial Susceptibility Testing (EUCAST) clinical breakpoints for *Pseudomonas aeruginosa*.
MIC, minimal inhibitory concentration; PK, pharmacokinetics.

Study Protocol | Open access | Published: 21 March 2025

Standard versus double dosing of beta-lactam antibiotics in critically ill patients with sepsis: The BULLSEYE study protocol for a multicenter randomized controlled trial

M. M. B. Horstink ✉, D. R. Geel, C. A. den Uil, P. E. Deetman, H. Endeman, A. Abdulla, T. M. Bosch, W. J. R. Rietdijk, F. W. Thielen, J. J. Haringman, P. van Vliet, T. A. Rijpstra, C. Bethlehem, A. Beishuizen, A. E. Muller & B. C. P. Koch on behalf of The BULLSEYE investigators

BMC Infectious Diseases **25**, Article number: 392 (2025) | Cite this article

Uygun Antimikrobiyal Tedavi-IV

- Farmakokinetik/farmakodinamik (PK/PD) prensiplere ve spesifik ilaç özelliklerine dayalı olarak antimikrobiyallerin dozlama stratejilerinin optimize edilmesi önerilir.
  - En İyi Uygulama Bildirimi
- İlk bolustan sonra **uzun süreli beta-laktam infüzyonu** önerilmekte.
  - Zayıf öneri, orta kalitede kanıt

Surviving Sepsis Campaign 2021

- Beta-laktamlar (zamana bağlı antibiyotikler) için : **Yüksek günlük dozlar, sürekli veya uzun infüzyonlar**
- Aminoglikozitler ve kinolonlar gibi konsantrasyona bağlı antibiyotikler için: **Uzun aralıklı yüksek günlük dozlar**
- Terapötik ilaç monitorizasyonu, özellikle aminoglikozidler ve vankomisin gibi dar terapötik indeksli ilaçlar için kullanılabilir

Stijn I. Blot, et al. Advanced Drug Delivery Reviews. 2014
Roberts JA, et al. Crit Care Med. 2008

Meta-Analysis > JAMA. 2024 Aug 27;332(8):638-648. doi: 10.1001/jama.2024.9803.

Prolonged vs Intermittent Infusions of β-Lactam Antibiotics in Adults With Sepsis or Septic Shock: A Systematic Review and Meta-Analysis

Mohd H Abdul-Aziz [1], Naomi E Hammond [2 3], Stephen J Brett [4], Menino O Cotta [1],

- **17 RK çalışma**
- **9014 ciddi sepsis/septik şok hastası**

Primer Sonuç: 90 günlük tüm nedenlere bağlı mortalite

- **Uzun süreli β-laktam infüzyonu**, **intermittan infüzyona** göre:
  - **%14 daha düşük ölüm oranı** (RR: 0.86; %95 CI: 0.72-0.98)
  - **%99.1 olasılıkla daha düşük mortalite ile ilişkili**
- **YBÜ mortalitesi:** %16 azalma (RR: 0.84; %95 CI : 0.70-0.97)
- **Klinik kür oranı:** %16 artış (RR: 1.16; %95 CI: 1.07-1.31)

Study selection: Randomized clinical trials comparing prolonged (continuous or extended) and intermittent infusions of β-lactam antibiotics in critically ill adults with sepsis or septic shock.

Data extraction and synthesis: Data extraction and risk of bias were assessed independently by 2 reviewers. Certainty of evidence was evaluated with the Grading of Recommendations Assessment, Development and Evaluation approach. A bayesian framework was used as the primary analysis approach and a frequentist framework as the secondary approach.

Main outcomes and measures: The primary outcome was all-cause 90-day mortality. Secondary outcomes included intensive care unit (ICU) mortality and clinical cure.

Results: From 18 eligible randomized clinical trials that included 9108 critically ill adults with sepsis or septic shock (median age, 54 years; IQR, 48-57; 5961 men [65%]), 17 trials (9014 participants) contributed data to the primary outcome. The pooled estimated risk ratio for all-cause 90-day mortality for prolonged infusions of β-lactam antibiotics compared with intermittent infusions was 0.86 (95% credible interval, 0.72-0.98; I2 = 21.5%; high certainty), with a 99.1% posterior probability that prolonged infusions were associated with lower 90-day mortality. Prolonged infusion of β-lactam antibiotics was associated with a reduced risk of intensive care unit mortality (risk ratio, 0.84; 95% credible interval, 0.70-0.97; high certainty) and an increase in clinical cure (risk ratio, 1.16; 95% credible interval, 1.07-1.31; moderate certainty).

Conclusions and relevance: Among adults in the intensive care unit who had sepsis or septic shock, the use of prolonged β-lactam antibiotic infusions was associated with a reduced risk of 90-day mortality compared with intermittent infusions. The current evidence presents a high degree of certainty for clinicians to consider prolonged infusions as a standard of care in the management of sepsis and septic shock.

Antibiyotik Başlanmasında ve Sonlandırılmasında Biyobelirteçlerin Rolü

- Antibiyotik yönetiminde en yaygın kullanılanlar C-reaktif protein (CRP) ve prokalsitonindir.
- Biyobelirteçler, antibiyotik tedavisine ne zaman başlanacağını belirlemektense tedavi süresini yönlendirmek için daha değerlidir.

- Antimikrobiyallere ne zaman **başlanacağına karar vermek için**; prokalsitonin kullanılması **önerilmez**.
  - Zayıf öneri, çok düşük kanıt kalitesi
- Yeterli kaynak kontrolü yapılan ve optimal tedavi süresinin belirsiz olan yetişkinlerde **antimikrobiyal tedavinin sonlandırılmasında** prokalsitonin ve klinik değerlendirmenin birlikte kullanılması **önerilir.**
  - Zayıf öneri, düşük kanıt kalitesi

Surviving Sepsis Campaign 2021

Meta-Analysis > Crit Care. 2018 Aug 15;22(1):191. doi: 10.1186/s13054-018-2125-7.

Effect of procalcitonin-guided antibiotic treatment on clinical outcomes in intensive care unit patients with infection and sepsis patients: a patient-level meta-analysis of randomized trials

Yannick Wirz [1], Marc A Meier [1], Lila Bouadma [2], Charles E Luyt [3], Michel Wolff [2],

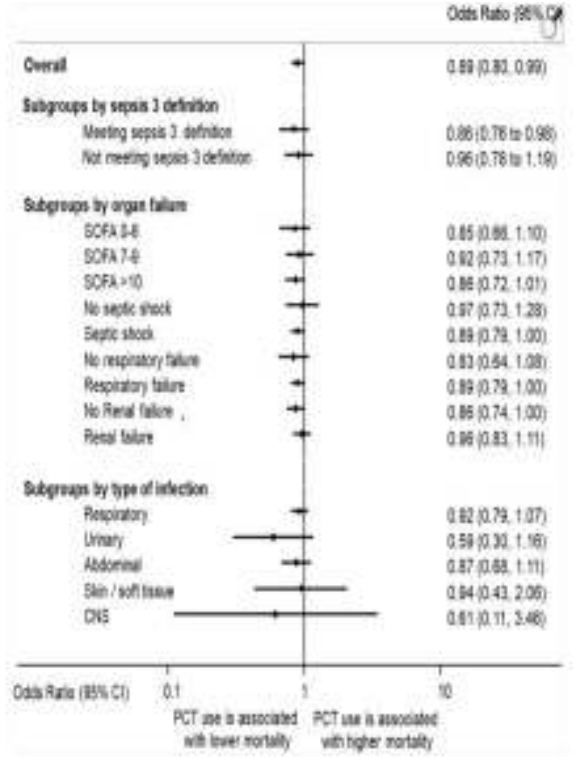
Abstract

Background: The clinical utility of serum procalcitonin levels in guiding antibiotic treatment decisions in patients with sepsis remains unclear. This patient-level meta-analysis based on 11 randomized trials investigates the impact of procalcitonin-guided antibiotic therapy on mortality in intensive care unit (ICU) patients with infection, both overall and stratified according to sepsis definition, severity, and type of infection.

Methods: For this meta-analysis focusing on procalcitonin-guided antibiotic management in critically ill patients with sepsis of any type, in February 2018 we updated the database of a previous individual patient data meta-analysis which was limited to patients with respiratory infections only. We used individual patient data from 11 trials that randomly assigned patients to receive antibiotics based on procalcitonin levels (the "procalcitonin-guided" group) or the current standard of care (the "controls"). The primary endpoint was mortality within 30 days. Secondary endpoints were duration of antibiotic treatment and length of stay.

Results: Mortality in the 2252 procalcitonin-guided patients was significantly lower compared with the 2230 control group patients (21.1% vs 23.7%; adjusted odds ratio 0.89, 95% confidence interval (CI) 0.8 to 0.99; $p = 0.03$). These effects on mortality persisted in a subgroup of patients meeting the sepsis 3 definition and based on the severity of sepsis (assessed on the basis of the Sequential Organ Failure Assessment (SOFA) score, occurrence of septic shock or renal failure, and need for vasopressor or ventilatory support) and on the type of infection (respiratory, urinary tract, abdominal, skin, or central nervous system), with interaction for each analysis being > 0.05. Procalcitonin guidance also facilitated earlier discontinuation of antibiotics, with a reduction in treatment duration (9.3 vs 10.4 days; adjusted coefficient −1.19 days, 95% CI −1.73 to −0.66; $p < 0.001$).

(Continued on next page)

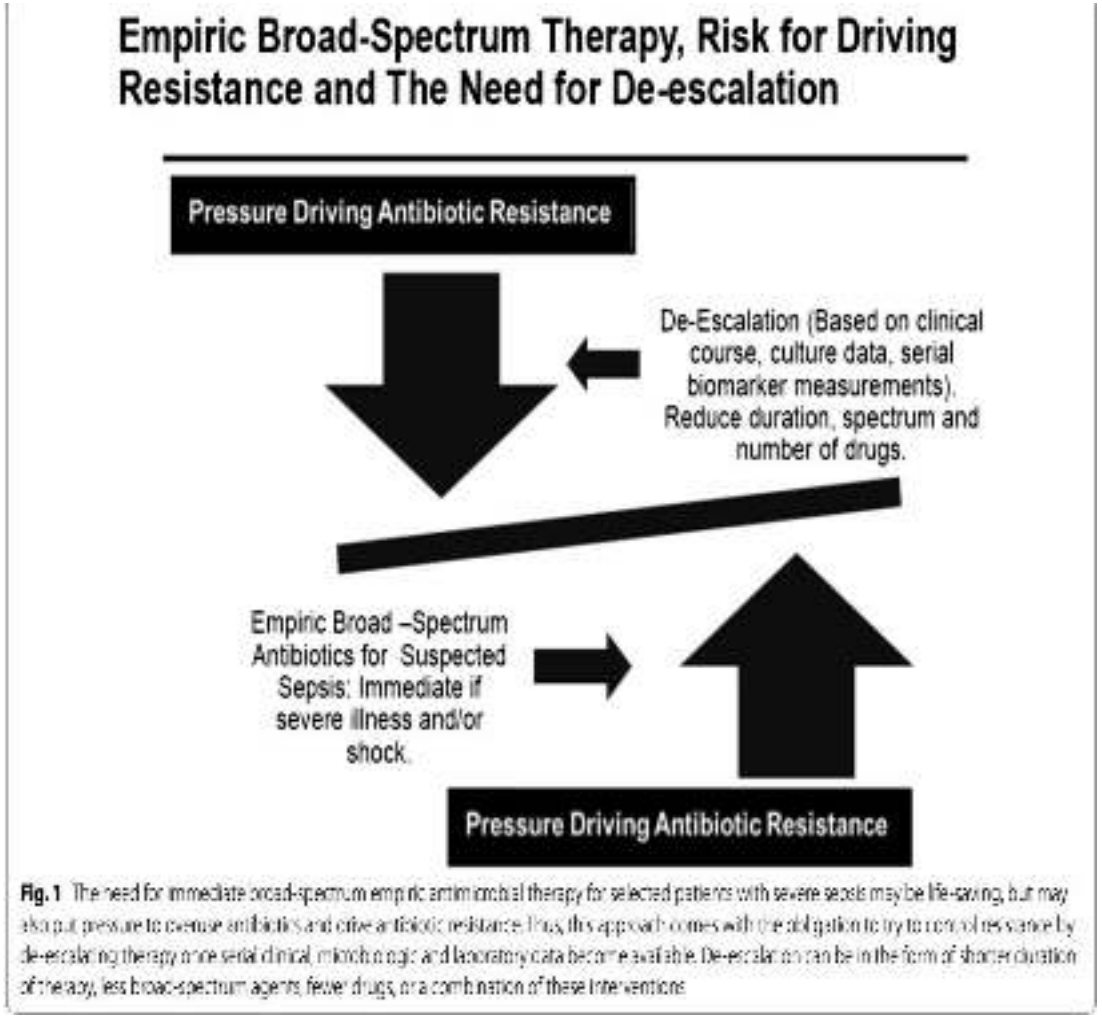


Forest plot showing 30-day mortality. Association of procalcitonin (PCT)-guided antibiotic stewardship and mortality in predefined subgroups. CI confidence interval, CNS central nervous system, SOFA Sequential Organ Failure Assessment

Tedavi izlemi

- Hasta günlük olarak yeniden değerlendirilmeli, PCR, Gram boyama ve kültür sonuçları mevcutsa spektrum daraltılmalı.
- Septik şoklu hastalarda kan kültür pozitiflik oranı %25.
- Kültür üremesi yoksa, klinik ve laboratuvar verileri mevcut olduğunda antibiyotik tedavisi azaltılmalı.
- Enfeksiyon dışlanırsa antimikrobiyal tedavi kesilmeli.

Ohnuma T, et al. Crit Care Med.



Antibiyotik Tedavi Süresi

- Tedavi süresi başlıca; enfeksiyon odağı, etken mikroorganizma ve hastanın klinik yanıtına göre belirlenir
- Ortalama tedavi süresi **7-10 gün**.
- **Ancak**
  - Yavaş klinik yanıt
  - Drene edilemeyen enfeksiyon odağı
  - *S. aureus* bakteremisi
  - Fungal enfeksiyon
  - Nötropeni dahil immun yetmezlik durumu olan hastalarda daha uzun tedavi gerekebilir.

Review > Clin Microbiol Infect. 2025 Apr;31(4):551-559. doi: 10.1016/j.cmi.2024.11.035. Epub 2024 Dec 4.

Oral switch vs. continued intravenous antibiotic therapy in patients with bacteraemia and sepsis: a systematic review and meta-analysis

Qinyuan Li [1], Qi Zhou [2], Jiangbo Fan [3], Siyuan Huang [3], Yaolong Chen [4], Fujian Song [5],

- 6 RCT + 10 ayarlanmış kohort
- Toplam 7102 hasta
- **Primer sonuç:** Tedavi başarısızlığı
- **Eşik değer (non-inferiority margin):** %10
- **Tedavi Başarısızlığı:**
  - **6 RCT'ye göre:** Oral antibiyotik geçişi, IV tedaviye **non-inferior** (n = 529; OR: 0.89; %95 GA: 0.54–1.48)
- **Hastanede Kalış Süresi:**
  - **Oral geçiş**, kalış süresini anlamlı olarak azalttı; ortalama fark: **–5.19 gün**
- **Bakteremi ve sepsiste erken oral antibiyotik geçişi**, tedavi başarısı açısından IV tedaviye **eşdeğerdir** ve **hastanede kalış süresini azaltır.**

Study eligibility criteria: Study eligibility criteria include randomized controlled trials (RCTs) and cohort studies.

Participants: Participants include patients with bacteraemia and sepsis.

Interventions: Interventions include early transition to oral antibiotics vs. continued IV antibiotics. Early oral switch was defined as 5-9 days for uncomplicated Staphylococcus aureus bacteraemia, <4 weeks for complicated S. aureus bacteraemia, 3-7 days for uncomplicated Streptococcus bacteraemia, and 3-5 days for uncomplicated Enterobacterales bacteraemia.

Assessment of risk of bias: Assessment of risk of bias includes Cochrane risk of bias tool and Newcastle-Ottawa Scale.

Methods of data synthesis: Random-effect models were used to pool the data. The primary outcome was treatment failure. The non-inferiority margin for treatment failure was 10%. The Grading of Recommendations Assessment, Development, and Evaluation approach was used to rate the certainty of the evidence.

Results: In total, 38 studies (6 RCTs, 10 adjusted cohorts, and 22 unadjusted cohorts) involving 11 566 patients were included. A primary analysis of 6 RCTs and 10 adjusted cohorts comprised 7102 patients. High-certainty evidence from six RCTs showed that early transition to oral antibiotics was non-inferior to continued IV therapy for treatment failure (n = 529; OR 0.89; 95% CI: 0.54-1.48). Low-certainty evidence from five adjusted cohorts also found no significant difference in treatment failure between the two groups (n = 929; OR 0.60; 95% CI: 0.29-1.72). Moderate-certainty evidence showed that oral switch therapy significantly reduced hospital stay (n = 2041; mean difference: -5.19 days; 95% CI: -8.16 to -2.22).

Conclusions: Early transition to oral antibiotics was non-inferior to continued IV antibiotic treatment for bacteraemia and sepsis.

Sonuç

Optimal sağkalım için

- Erken tanı
- Hızlı ve uygun antibiyotik tedavisi (geniş spektrumlu)
- Standart bir tedavi yerine hasta bazında bireyselleştirilmiş tedavi gerekli

TEŞEKKÜRLER