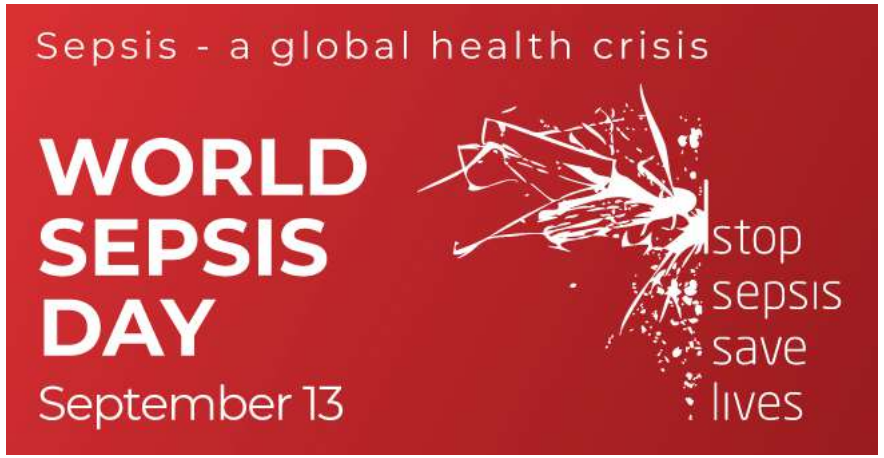


Sepsis ve Septik Şokta Antibiyotik Kullanım İlkeleri

Doç. Dr. Güle Çınar

Ankara Üniversitesi Tıp Fakültesi

İnfeksiyon Hastalıkları ve Klinik Mikrobiyoloji Anabilim Dalı

- 2017'de dünya çapında 48,9 milyon vaka ve 11 milyon sepsise bağlı ölüm
- Tüm küresel ölümlerin %20'sinden sorumlu

World Health Organization

Health Topics | Countries | Newsroom | Emergencies

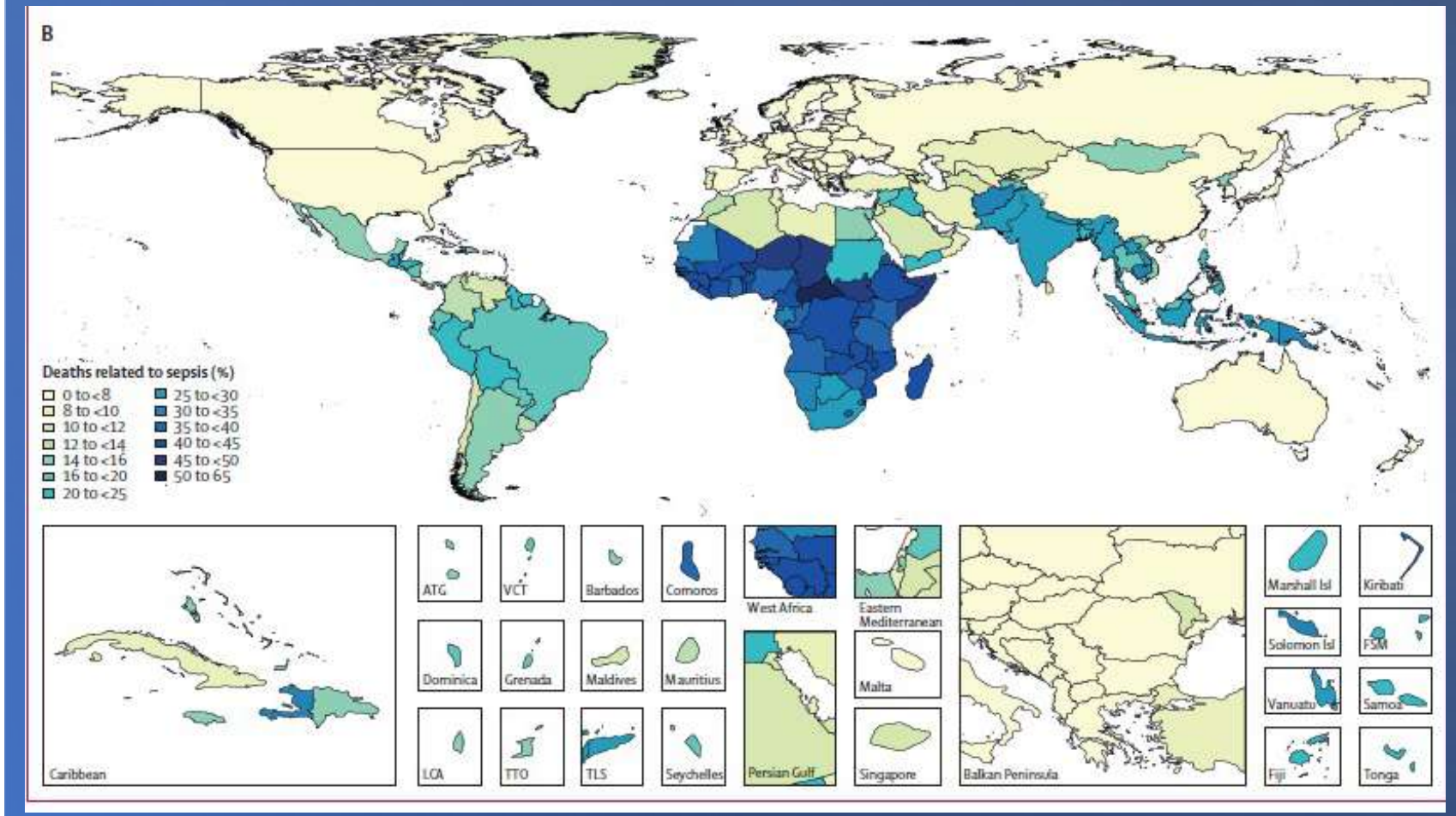
Home / News / WHO calls for global action on sepsis - cause of 1 in 5 deaths worldwide

WHO calls for global action on sepsis - cause of 1 in 5 deaths worldwide

Global, regional, and national sepsis incidence and mortality, 1990–2017: analysis for the Global Burden of Disease Study

Kristina E Rudd, Sarah Charlotte Johnson, Kareha M Agesa, Katya Anne Shackelford, Derrick Tsoi, Daniel Rhodes Kievlan, Danny V Colombara, Kevin S Ikuta, Niranjan Kissoon, Simon Finfer, Carolin Fleischmann-Struzek, Flavia R Machado, Konrad K Reinhart, Kathryn Rowan, Christopher W Seymour, R Scott Watson, T E oin West, Fatima Marinho, Simon I Hay, Rafael Lozano, Alan D Lopez, Derek C Angus, Christopher J L Murray, Mohsen Naghavi

www.thelancet.com Vol 395 January 18, 2020



Sepsis: network pathophysiology and implications for early diagnosis

Jaskirat Arora,[1] Asher A. Mendelson,[2] and Alison Fox-Robichaud[1]

[1]Department of Medical Sciences, McMaster University, Hamilton, Ontario, Canada and [2]Section of Critical Care Medicine, Department of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, Manitoba, Canada

AMERICAN JOURNAL OF PHYSIOLOGY
REGULATORY, INTEGRATIVE AND COMPARATIVE PHYSIOLOGY

Am J Physiol Regul Integr Comp Physiol 324: R613–R624, 2023.
First published March 6, 2023; doi:10.1152/ajpregu.00003.2023

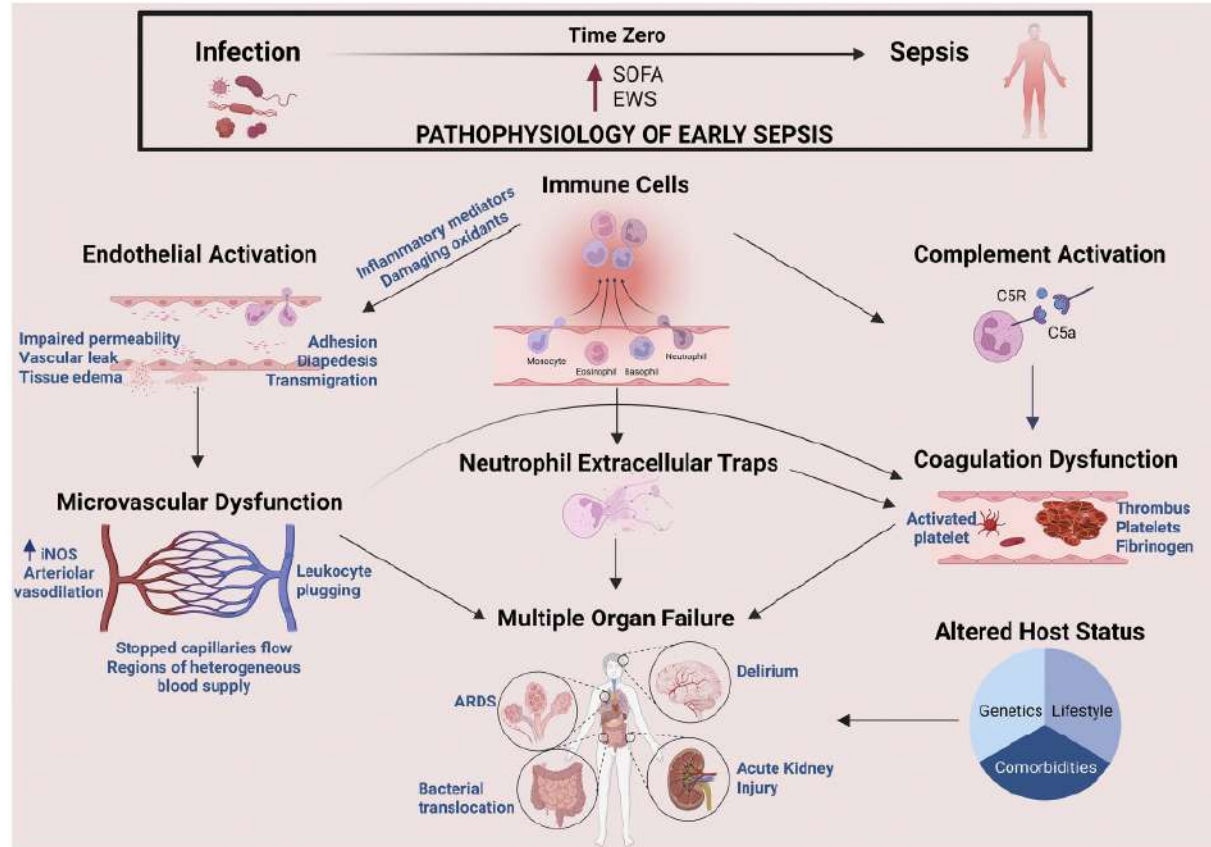


Figure 1. Pathophysiology of sepsis. A schematic outline of the critical switch from infection to sepsis is termed "Time Zero." The host-defense mediators elicit exaggerated immune cell response stimulating the complement system and collaterally damaging the endothelium and microvasculature. This figure was created with BioRender.com. ARDS, acute respiratory distress syndrome; EWS, early warning score; iNOS, inducible nitric oxide synthase; SOFA, sequential organ failure assessment.

Sepsis: network pathophysiology and implications for early diagnosis

Jaskirat Arora,[1] Asher A. Mendelson,[2] and Alison Fox-Robichaud[1]
[1]Department of Medical Sciences, McMaster University, Hamilton, Ontario, Canada and [2]Section of Critical Care Medicine, Department of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, Manitoba, Canada

AMERICAN JOURNAL OF PHYSIOLOGY
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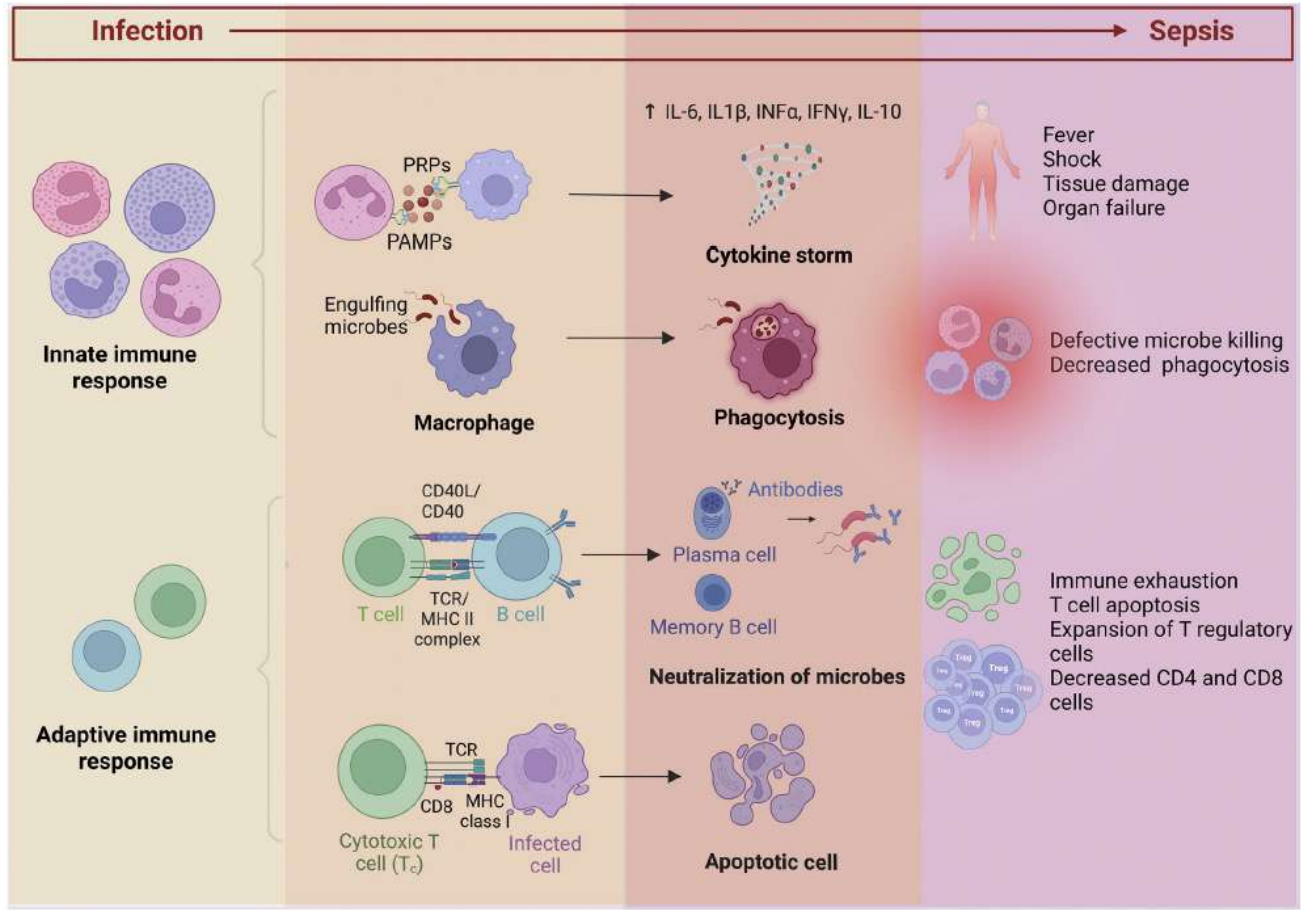


Figure 2. Immune system activation in sepsis. During sepsis, the systemic activation of the immune system results in an inflammatory response characterized by cytokine storm with associated fever, shock, and multiple organ dysfunction. The adaptive immune response produces pathogen-specific antibodies with immunological memory for subsequent exposures to the same antigen. Sepsis-induced immunosuppression causes apoptotic depletion of immune cells, immune exhaustion, and decreased CD4 and CD8 cells. This figure was created with BioRender.com. PAMPS, pathogen-associated molecular patterns; PRP, pattern recognition protein; TCR, T-cell receptor.

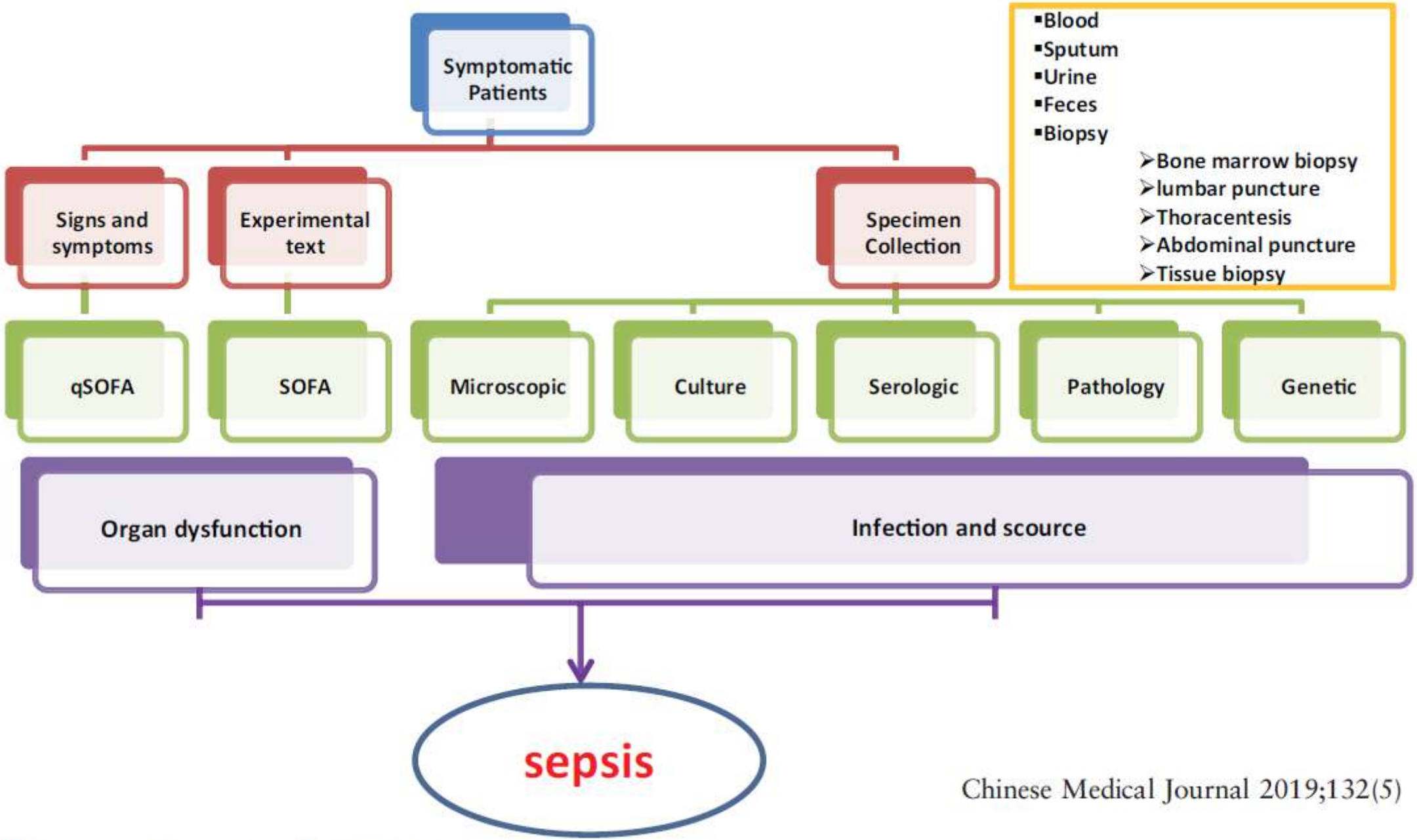
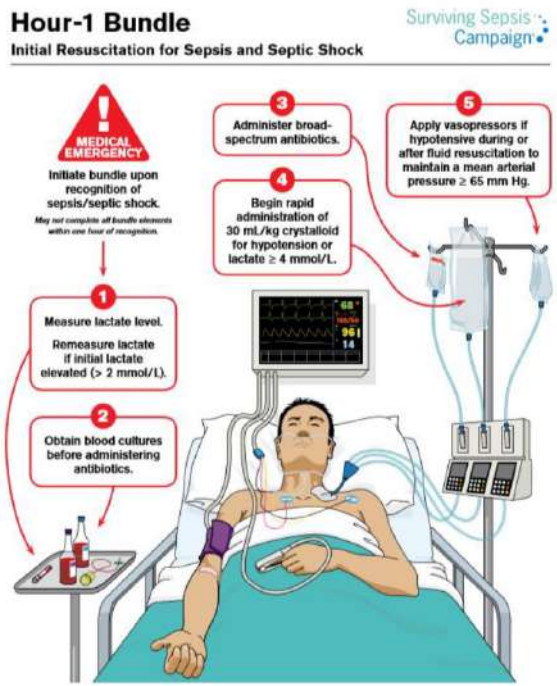


Figure 1: Screening and diagnostic procedures for sepsis and septic shock.



Sepsis Sağkalım Kampanyası İlk 1 saat Paketi	
İlk 1 saatte yapılması gerekenler	**Öneri Gücü ve Kanıt Düzeyi.**
Laktat düzeyini ölç. İlk laktat >2mmol/L ise tekrar ölç.	Zayıf öneri, düşük kanıt kalitesi.
Antibiyotik vermeden önce kan kültürlerini al.	En iyi uygulama (BPS).
Geniş spektrumlu antibiyotik ver.	Güçlü öneri, orta kanıt kalitesi.
Hipotansiyon veya laktat düzeyi >4mmol/L için hızla 30ml/kg kristalloid başla.	Güçlü öneri, düşük kanıt kalitesi.
Hasta sıvı resüsitasyonu süresince veya resüsitasyon sonrasında hipotansif ise >65mmHg ortalama kan basıncı (MAP) değerine ulaşmak amacıyla vazopressör ver.	Güçlü öneri, orta kanıt kalitesi.

İnfeksiyon Hastalıkları Açısından Sepsis Yönetimi

- Nedenin saptanması (İnfeksiyon bulguları)
- Odağın belirlenmesi
- Mikrobiyolojik bulguların değerlendirilmesi
- Antibiyotik tedavisi
- Odağın kontrol edilmesi

Antibiyotik tedavisi zamanlaması

Sepsis – septik şok tanısından sonraki ilk 1 saat içinde IV antibiyotik tedavisi başlanmalıdır.
(güçlü öneri- düşük / çok düşük kalitede kanıt)

Intensive Care Med (2021) 47:1181–1247
https://doi.org/10.1007/s00134-021-06506-y

GUIDELINES

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], Craig M. Coopersmith[5], Craig French[6], Flávia R. Machado[7], Lauralyn Mcintyre[8], Marlies Ostermann[9], Hallie C. Prescott[10], Christa Schorr[11], Steven Simpson[12], W. Joost Wiersinga[13], Fayez Alshamsi[14], Derek C. Angus[15], Yaseen Arabi[16], Luciano Azevedo[17], Richard Beale[9], Gregory Beilman[18], Emilie Belley-Cote[19], Lisa Burry[20], Maurizio Cecconi[21,22], John Centofanti[23], Angel Coz Yataco[24], Jan De Waele[25], R. Phillip Dellinger[11], Kent Doi[26], Bin Du[27], Elisa Estenssoro[28], Ricard Ferrer[29], Charles Gomersall[30], Carol Hodgson[31], Morten Hylander Møller[32], Theodore Iwashyna[33], Shevin Jacob[34], Ruth Kleinpell[35], Michael Klompas[36,37], Younsuck Koh[38], Anand Kumar[39], Arthur Kwizera[40], Suzana Lobo[41], Henry Masur[42], Steven McGloughlin[43], Sangeeta Mehta[44], Yatin Mehta[45], Mervyn Mer[46], Mark Nunnally[47], Simon Oczkowski[3], Tiffany Osborn[48], Elizabeth Papathanassoglou[49], Anders Perner[50], Michael Puskarich[51], Jason Roberts[52,53,54,55], William Schweickert[56], Maureen Seckel[57], Jonathan Sevransky[5], Charles L. Sprung[58,59], Tobias Welte[60], Janice Zimmerman[61] and Mitchell Levy[62]

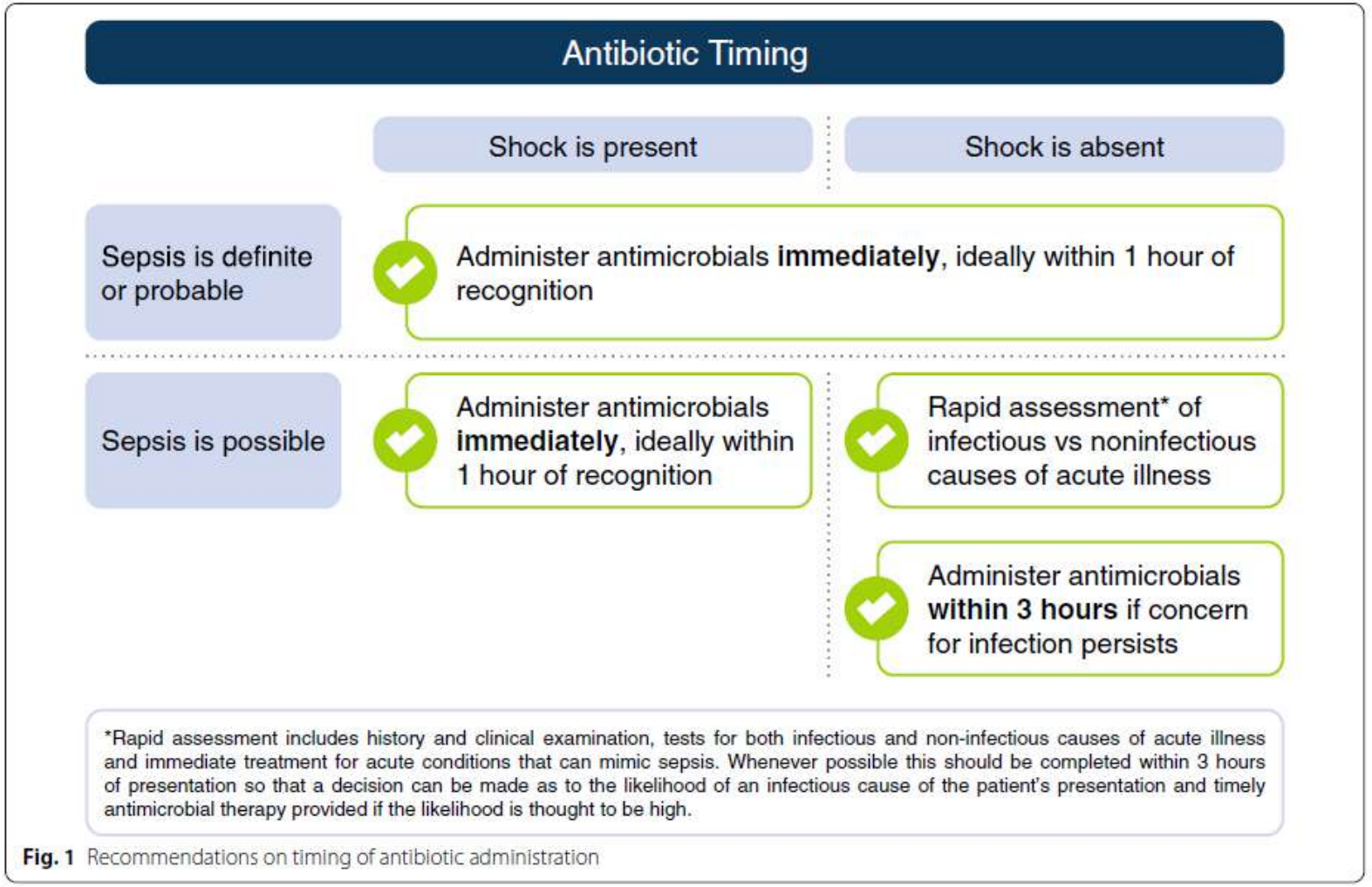


Fig. 1 Recommendations on timing of antibiotic administration

Antibiyotik Zamanlamasının Etkileri

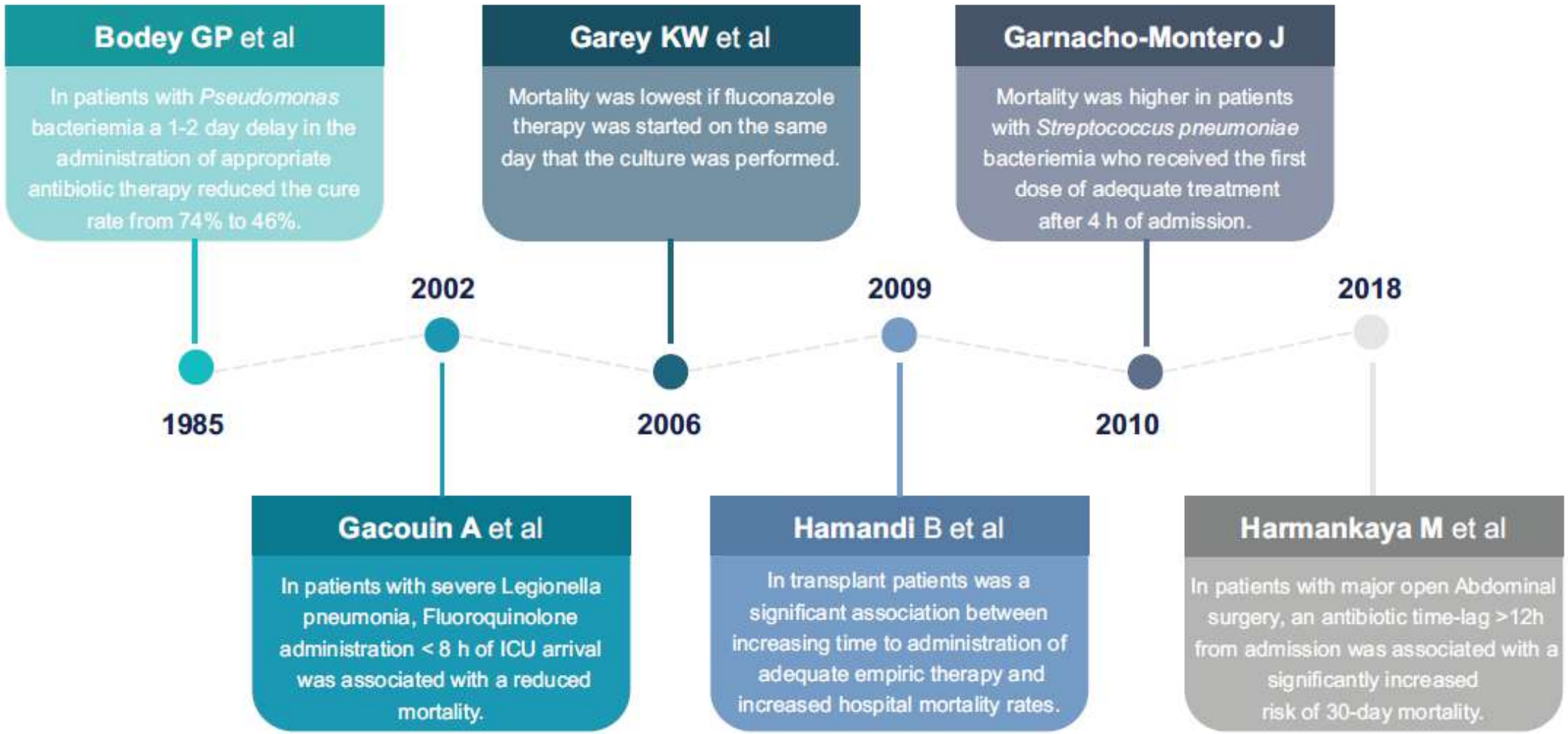


Figure 2. Effects of delayed administration of antibiotics

Published in final edited form as:
N Engl J Med. 2017 June 08; 376(23): 2235–2244. doi:10.1056/NEJMoa1703058.

Time to Treatment and Mortality during Mandated Emergency Care for Sepsis

Christopher W. Seymour, M.D., Foster Gesten, M.D., Hallie C. Prescott, M.D., Marcus E. Friedrich, M.D., Theodore J. Iwashyna, M.D., Ph.D., Gary S. Phillips, M.A.S., Stanley Lemeshow, Ph.D., Tiffany Osborn, M.D., M.P.H., Kathleen M. Terry, Ph.D., and Mitchell M. Levy, M.D.

- 1 Nisan 2014- 30 Haziran 2016 tarihleri arasında New York Eyaleti
- 149 hastanede 49.331 hastanın 40.696'sında (%82,5) 3 saatlik demet 3 saatte tamamlanmış.
- 3 saatlik demetin tamamlanmasına kadar geçen medyan süre 1,30 saat (0,65-2,35)
- Antibiyotiklerin verilmesine kadar geçen medyan süre 0,95 saat (0,35-1,95)
- IV sıvı tedavisinin tamamlanmasına kadar geçen medyan süre 2,56 saat (1,33-4,20)
- 3 saatlik demetin tamamlanmasına kadar geçen süre ile hastane içi mortalite ilişkili (OR, 1.04 per hour; 95% CI, 1.02 to 1.05; P<0.001)
- Antibiyotik uygulamasına kadar geçen süre ile hastane içi mortalite ilişkili

  (OR, 1.04 per hour; 95% CI, 1.02 to 1.05; P<0.001)
- IV sıvı bolusunun tamamlanmasına kadar geçen süre ile mortalite ilişkili değil

  (OR, 1.01 per hour; 95% CI, 0.99 to 1.02; P=0.21)

ORIGINAL ARTICLE

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], and Gabriel J. Escobar[1]

American Journal of Respiratory and Critical Care Medicine Volume 196 Number 7 | October 1 2017

- 35.000 hasta
- Acil servise gelişten antibiyotiklerin uygulanmasına kadar geçen her ek saat, hastane içi ölüm oranında 1,09 artışla ilişkili ("şiddetli" sepsis [laktat ≥ 2, en az bir hipotansiyon epizodu, invaziv olmayan veya invaziv mekanik ventilasyon gerekliliği veya organ disfonksiyonu varlığı] ve septik şoklu hastalar için 1,14);

  “şiddetli” sepsis için %0,4'lük mutlak bir mortalite artışına ve septik şok için %1,8'lik bir mutlak artış

Table 3. Odds Ratios for Hospital Mortality Based on the Time of Antibiotic Administration in Unadjusted and Adjusted Logistic Regression Models

Model	Odds Ratio for Hospital Mortality, per Elapsed Hour until Antibiotic Administration	95% CI	*P* Value
Unadjusted	0.89	0.86–0.91	<0.001
+ Sepsis severity strata	0.96	0.93–0.99	0.013
+ Severity of illness	1.08	1.04–1.12	<0.001
+ Demographics	1.09	1.05–1.13	<0.001
Fully adjusted model, in each subgroup			
Sepsis only	1.09	1.00–1.19	0.046
Severe sepsis only	1.07	1.01–1.24	0.014
Septic shock only	1.14	1.06–1.23	0.001

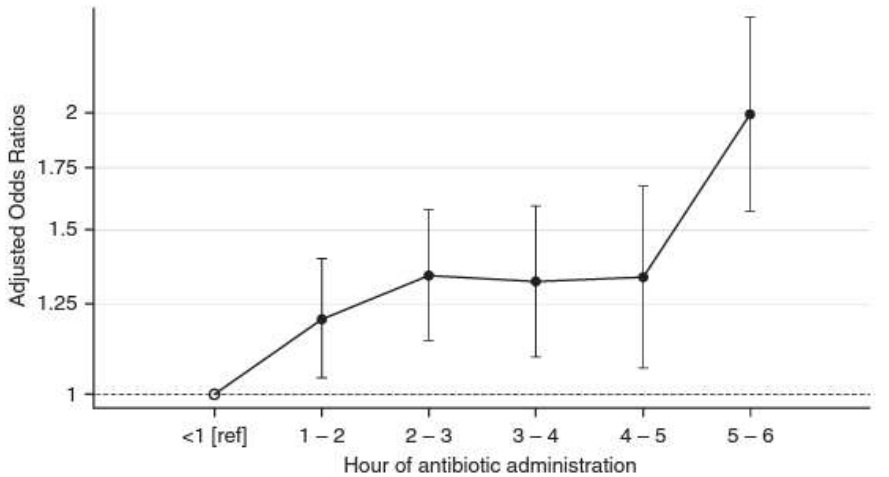


Figure 2. Adjusted odds ratios for hospital mortality comparing patients within each hourly antibiotic administration group with the reference group of patients given antibiotics in <1 hour. The *y-axis* is on logarithmic scale and the *error bars* represent 95% confidence intervals.

CLINICAL INVESTIGATIONS

Supply Chain Delays in Antimicrobial Administration After the Initial Clinician Order and Mortality in Patients With Sepsis*

Kashiouris, Markos G. MD, MPH[1,2]; Zemore, Zachary MD[3]; Kimball, Zachary MD[2]; Stefanou, Christos MD[4]; Fowler, Alpha A. III MD[1]; Fisher, Bernard BS[1]; de Wit, Marjolein MD[1]; Pedram, Sammy MD[1,2]; Sessler, Curtis N. MD, FCCP, FCCM[1,2]

Author Information

Critical Care Medicine 47(10):p 1388-1395, October 2019. | **DOI:** 10.1097/CCM.0000000000003921

- 4429 septik hastadan oluşan bir kohort
- 28 günlük mortalite için OR, antimikrobiyal tedavi 1 saatten fazla sürede uygulandığında↑
- Gecikme 12 saatten fazlaysa medyan 1.85 (1.29-2.65) değerine ulaşmış.

[Original Research **Critical Care**]

CHEST

ED Door-to-Antibiotic Time and Long-term Mortality in Sepsis

Ithan D. Peltan, MD; Samuel M. Brown, MD; Joseph R. Bledsoe, MD; Jeffrey Sorensen, MStat; Matthew H. Samore, MD; Todd L. Allen, MD; and Catherine L. Hough, MD

[155#5 **CHEST** MAY 2019]

- 10.811 hasta
- Acil servise gelişten antibiyotiklerin uygulanmasına kadar geçen sürede her 1 saatlik gecikme; Hastane içi ölüm olasılığını 1,16 ↑

1 yıllık ölüm olasılığını 1,10 ↑

(hipotansiyonu olanlarda 1,13 ve hipotansiyonu olmayanlarda 1,09)

TABLE 2] Adjusted Association of Door-to-Antibiotic Time and Mortality in ED Patients With Sepsis

Variable	1-Year Mortality			In-Hospital Mortality			30-Day Mortality			90-Day Mortality		
	Adjusted OR[a] (95% CI)		*P* Value	Adjusted OR[a] (95% CI)		*P* Value	Adjusted OR[a] (95% CI)		*P* Value	Adjusted OR[a] (95% CI)		*P* Value
Door-to-antibiotic time, h	1.10	(1.05-1.14)	< .001	1.16	(1.07-1.26)	< .001	1.12	(1.06-1.18)	< .001	1.09	(1.04-1.15)	< .001
Door-to-antibiotic time > 1 h	1.26	(0.98-1.62)	.070	1.32	(0.91-1.92)	.14	1.12	(0.83-1.52)	.46	1.24	(0.94-1.65)	.13
Door-to-antibiotic time > 3 h	1.27	(1.13-1.43)	< .001	1.42	(1.13-1.80)	.003	1.28	(1.08-1.52)	.005	1.32	(1.14-1.52)	< .001
Door-to-antibiotic time interval												
≤ 1 h	Reference			Reference			Reference			Reference		
> 1 to ≤ 2 h	1.19	(0.91-1.56)	.20	1.29	(0.87-1.93)	.21	0.97	(0.70-1.35)	.85	1.17	(0.86-1.58)	.31
> 2 to ≤ 3 h	1.20	(0.92-1.56)	.18	1.20	(0.79-1.82)	.39	1.19	(0.86-1.65)	.30	1.17	(0.87-1.59)	.30
> 3 to ≤ 4 h	1.40	(1.06-1.85)	.018	1.61	(1.03-2.53)	.036	1.29	(0.90-1.83)	.16	1.47	(1.07-2.01)	.019
> 4 to ≤ 5 h	1.41	(1.04-1.91)	.025	1.39	(0.82-2.37)	.22	1.28	(0.86-1.91)	.23	1.43	(1.00-2.03)	.049
> 5 to ≤ 6 h	1.84	(1.31-2.57)	< .001	2.28	(1.26-4.16)	.007	1.87	(1.20-2.92)	.006	1.90	(1.28-2.81)	.001
> 6 h	2.02	(1.40-2.90)	< .001	3.45	(1.78-6.67)	< .001	2.06	(1.25-3.40)	.004	1.74	(1.11-2.73)	.015

[a]Adjusted for pooled triage acuity score; receipt of prehospital medical care; MEDS score; SOFA score; initial vital signs (systolic blood pressure, abnormal Glasgow Coma Scale, heart rate, temperature, respiratory rate, and oxygen saturation); ED disposition (ICU vs ward); comorbidity score; marital status; insurance type; age; sex; Hispanic ethnicity or non-white race; hospital; non-English preferred language; initial WBC count; and initial lactate level tested and > 2 mmol/L. See Table 1 legend for expansion of abbreviations.

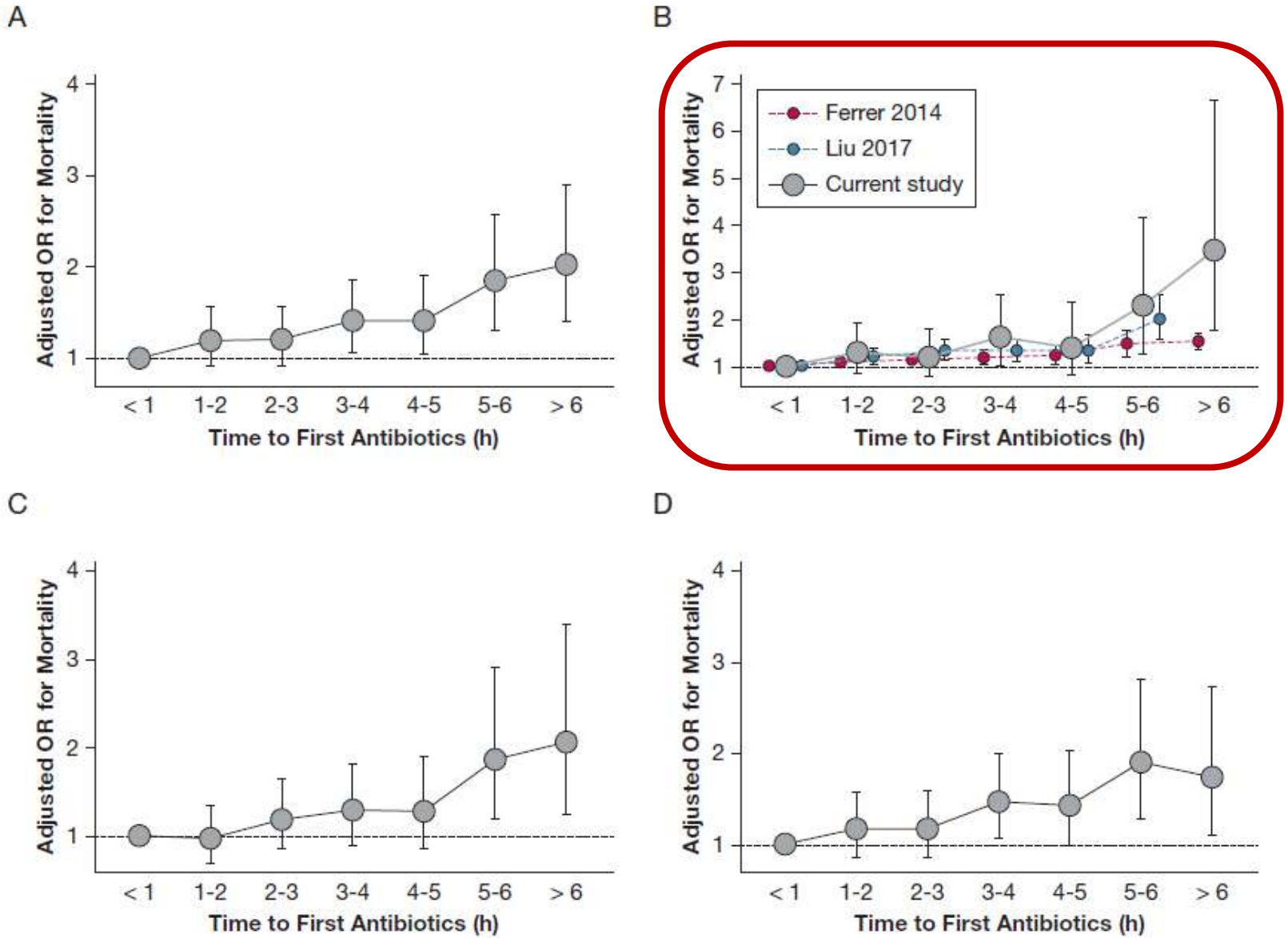


Figure 2 – *Adjusted association of mortality with door-to-antibiotic time, comparing each hourly interval following the first hour to door-to-antibiotic time ≤ 1 h for (A) 1-year mortality, (B) hospital mortality, (C) 30-day mortality, and (D) 90-day mortality. For hospital mortality, results from the current analysis are compared with risk-adjusted associations with hospital mortality reported by Ferrer et al[9] and Liu et al.[10] Figure adapted with permission of the American Thoracic Society from Liu et al[10] and with permission from Elsevier from Peltan and Liu.[34] The American Journal of Respiratory and Critical Care Medicine is an official journal of the American Thoracic Society.*

The Association Between Antibiotic Delay Intervals and Hospital Mortality Among Patients Treated in the Emergency Department for Suspected Sepsis*

Taylor, Stephanie Parks MD[1]; Anderson, William E. MS[2]; Beam, Kent MD[1]; Taylor, Brice MD[1]; Ellerman, Justin MD[3]; Kowalkowski, Marc A. PhD[2]

Author Information

Critical Care Medicine 49(5):p 741-747, May 2021. | **DOI:** 10.1097/CCM.0000000000004863

- 12 acil serviste şüpheli infeksiyon ve eşzamanlı organ disfonksiyonuna dair klinik kanıt bulunan 24.093 yetişkin
- Retrospektif
- Tanı→ Antibiyotik orderı; medyan süre 2,7 saat (6 saat=mortalite)
- Antibiyotik orderı→ İnfüzyon; medyan süre 0,6 saat (>1.5 saat=mortalite)

J Crit Care 74 (2023) 154221

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.journals.elsevier.com/journal-of-critical-care

Identifying high-risk phenotypes and associated harms of delayed time-to-antibiotics in patients with ICU onset sepsis: A retrospective cohort study

Wenhan Hu, Hui Chen, Haofei Wang, Qingyun Peng, Jinlong Wang, Wei Huang, Airan Liu, Jingyuan Xu, Qing Li, Chun Pan, Jianfeng Xie, Yingzi Huang

Jiangsu Provincial Key Laboratory of Critical Care Medicine, Department of Critical Care Medicine, Zhongda Hospital, School of Medicine, Southeast University, No. 87, Dingjiaqiao Road, Gulou District, Nanjing 210009, PR China

- 6246 hasta
- Genel 28 günlük ölüm oranı %12.7
- Antibiyotiklere geçiş süresinde gecikme, yoğun bakımda 28 günlük mortalite artışı ile ilişkili (HR 1.12, %95 CI 1.08–1.18)

- 4 farklı sepsis sınıfı; Sınıf 1 = Solunum fonksiyon bozukluğu
  Sınıf 2 = Kardiyovasküler fonksiyon bozukluğu
  Sınıf 3 = Çoklu organ fonksiyon bozukluğu
  Sınıf 4 = Nörolojik fonksiyon bozukluğu

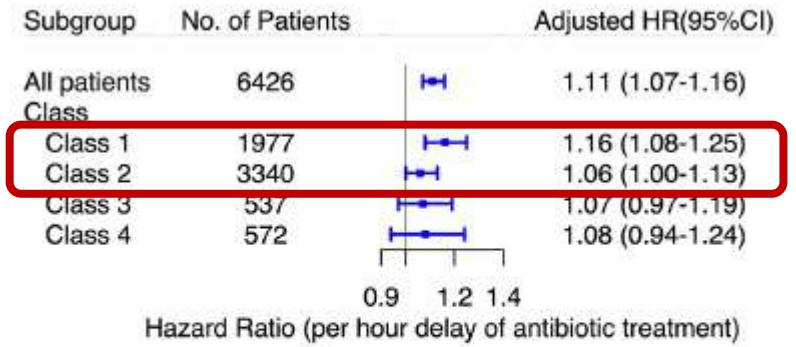


Fig. 4. Association of time-to-antibiotics and 28-day mortality in different phenotypes. HR = Hazard ratio; CI = Confidence interval; Class 1 = Respiropathic; Class 2 = Cardiopathic; Class 3 = Hepatopathic; Class 4 = Neuropathic.

International Journal of Antimicrobial Agents 61 (2023) 106732

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

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

Hot Topic

Sepsis and antibiotics: When should we deploy a parachute?

Sharon Einav[a,b], Marc Leone[c,d,*], Ignacio Martin-Loeches[e,f]

[a] Hebrew University School of Medicine, Jerusalem, Israel
[b] Intensive Care Unit of the Shaare Zedek Medical Center, Jerusalem, Israel
[c] Department of Anesthesiology and Intensive Care Unit, North Hospital, Assistance Publique Hôpitaux Universitaires de Marseille, Marseille, France
[d] Aix Marseille University, Marseille, France
[e] Department of Intensive Care Medicine, Multidisciplinary Intensive Care Research Organization (MICRO), Leinster, Dublin, Ireland
[f] Pulmonary Intensive Care Unit, Respiratory Institute, Hospital Clinic of Barcelona, IDIBAPS (Institut d'Investigacions Biomèdiques August Pi i Sunyer), University of Barcelona, CIBERes, Barcelona, Spain

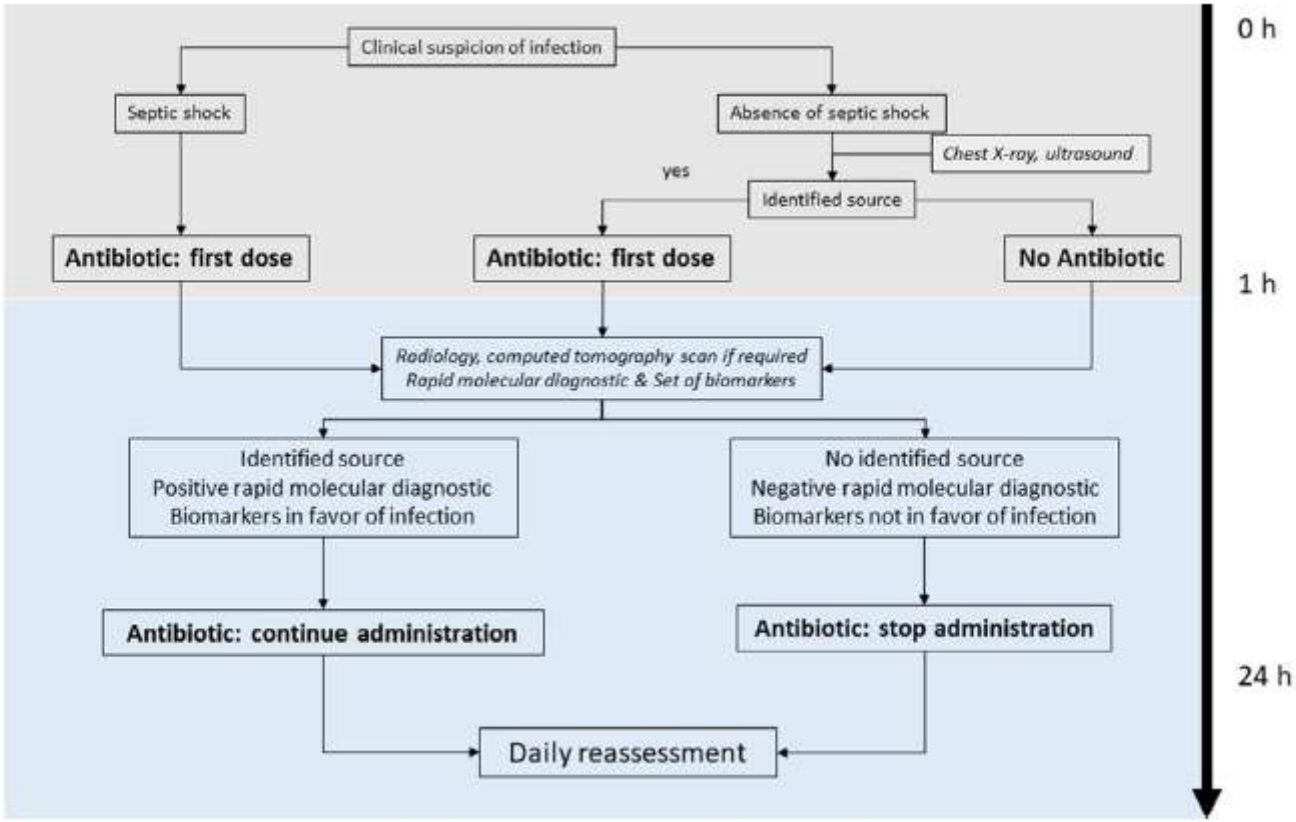


Fig. 1. Decision tree to start (or not) antibiotics in the first hour.

Biyobelirteçler

Gerçek sepsisi diğer inflamatuar durumlardan zamanında ve uygun maliyetli bir şekilde ayırt etmeli, tedaviye yanıtı izleyebilmeli, hem tedavinin ne zaman başlatılacağına hem de ne zaman güvenli bir şekilde durdurulacağına rehberlik etmelidir.

Biomarkers to start antibiotics

Recommendation
16. For adults with suspected sepsis or septic shock, we **suggest against** using procalcitonin plus clinical evaluation to decide when to start antimicrobials, as compared to clinical evaluation alone *Weak recommendation, very low quality of evidence*

- 3 RKT çalışma (n = 1769 YBÜ hastası) meta-analizi;

  Kısa dönem mortalite (RR 0,99; %95 CI 0,86–1,15)

  YBÜ kalış süresi (MD 0,19 gün; %95 CI - 0,98-1,36)

  Hastanede kalış süresi (MD 7.00 gün; %95 CI - 26.24-12.24) fark yok

- Sepsis veya septik şok şüphesi olan yetişkinler için, tek başına klinik değerlendirmeye kıyasla, antimikrobiyallere ne zaman başlanacağına karar vermek için prokalsitoninle birlikte klinik değerlendirme kullanılması önerilmemekte

Intensive Care Med (2023) 49:142–153
https://doi.org/10.1007/s00134-022-06956-y

NARRATIVE REVIEW

How to use biomarkers of infection or sepsis at the bedside: guide to clinicians

Pedro Póvoa[1,2,3*], Luís Coelho[1,3], Felipe Dal-Pizzol[4,5], Ricard Ferrer[6,7], Angela Huttner[8,9], Andrew Conway Morris[10,11,12], Vandack Nobre[13], Paula Ramirez[14,15], Anahita Rouze[16], Jorge Salluh[17,18], Mervyn Singer[19], Daniel A. Sweeney[20], Antoni Torres[21,22,23,24], Grant Waterer[25] and Andre C. Kalil[26]

Wirz et al. Critical Care (2018) 22:191
https://doi.org/10.1186/s13054-018-2125-7

Critical Care

REVIEW Open Access

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[3], Charles E. Luyt[4], Michel Wolff[3], Jean Chastre[4], Florence Tubach[5], Stefan Schroeder[6], Vandack Nobre[7], Djillali Annane[8], Konrad Reinhart[9], Pierre Damas[10], Maarten Nijsten[11], Arezoo Shajiei[11], Dylan W. deLange[12], Rodrigo O. Deliberato[13], Carolina F. Oliveira[14], Yahya Shehabi[15,16], Jos A. H. van Oers[17], Albertus Beishuizen[18], Armand R. J. Girbes[19], Evelien de Jong[19], Beat Mueller[1,2] and Philipp Schuetz[1,2*]

- 11 araştırma, meta-analiz;

  Prokalsitonin kılavuzluğunda antibiyotiklerin erken kesilmesi tedavi süresinde kısalmayı kolaylaştırmış

  (2252 prokalsitonin kılavuzluğunda hastada 9,3 gün ve 2230 kontrol hastasında 10,4 gün) ; $p < 0.001$)

  Prokalsitonin rehberliğinde önemli ölçüde daha düşük mortalite ile ($p<0.001$)

- Sepsis yönetimi için biyobelirteçler, antibiyotik tedavisine ne zaman başlanacağını belirlemekten çok tedavi süresine rehberlik etmede daha değerlidir.

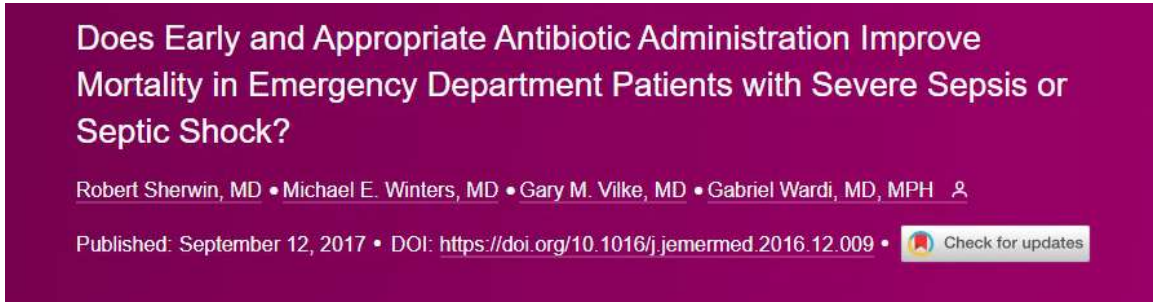
Uygun Antibiyotik Seçimi

- Ampirik-Nedensel ajan(lar) ve duyarlılıklar bilinmeden önce, optimal antibiyotik tedavisi seçimi, dirençli organizmaların lokal prevalansına, dirençli organizmalar için hasta risk faktörlerine ve hastalığın ciddiyetine bağlı

- Hedefe yönelik-Nedensel ajan(lar) ve duyarlılıklar bilindikten sonra başlanan ya da düzenlenen tedavi

Uygun Antibiyotik Seçimi---Prognoz açısından

- 2005 – 2015
- 1552 makale özeti
- Tanıdan sonra1 saat içinde uygun antimikrobiyal tedavi alan septik şoklu hastalar, mortalitede en büyük fayda


Does Early and Appropriate Antibiotic Administration Improve Mortality in Emergency Department Patients with Severe Sepsis or Septic Shock?

Robert Sherwin, MD • Michael E. Winters, MD • Gary M. Vilke, MD • Gabriel Wardi, MD, MPH

Published: September 12, 2017 • DOI: https://doi.org/10.1016/j.jemermed.2016.12.009 • Check for updates

International Journal of Antimicrobial Agents
Volume 56, Issue 6, December 2020, 106184

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

Matteo Bassetti [a 1], Jordi Rello [b c 1], Francesco Blasi [d e], Herman Goossens [f], Giovanni Sotgiu [g], Lara Tavoschi [h], Evan J. Zasowski [i], Mick R. Arber [j], Rachael McCool [j], Jacoby V. Patterson [j], Christopher M. Longshaw [k], Sara Lopes [k], Davide Manissero [l], Sean T. Nguyen [k], Keiko Tone [k], Stefano Aliberti [d e]

- 2007-2015
- 143 çalışma
- Uygun tedavi alanlarda mortalite daha düşük [OR = 0.44, 95% CI 0.38–0.50]
- Hastanede kalış süresi daha az [MD−2.54 days (95% CI −5.30-0.23)]
- Tedavi başarısızlığı insidansı, uygun tedavi alan hastalarda, uygun olmayan tedavi alan hastalara kıyasla önemli ölçüde daha düşük
  [OR = 0.33, 95% CI 0.16–0.66].

Uygun Ampirik Antibiyotik Seçiminde Yol Göstericiler

Uygun Ampirik Antibiyotik Seçimi

Doğru hedef:

İnfeksiyon odağı

Patojenik mikroorganizmalar

Doğru ajan:

Hastane florası antibiyotik duyarlılık profili

Antibiyotik maruziyeti öyküsü

Renal fonksiyon

Karaciğer fonksiyonları

Gebelik

Alerji

İlaç etkileşimleri

Doğru doz:

FK / FD

Renal fonksiyon

Karaciğer fonksiyonları


Clinical Microbiology and Infection 26 (2020) 151–157

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Narrative review

Burden of bacterial bloodstream infection—a brief update on epidemiology and significance of multidrug-resistant pathogens

W.V. Kern [1,2,*], S. Rieg [1]

Doğru Hedef

- Hastanede yatan hastalarda en sık odaklar alt solunum yolu, intraabdominal, kan dolaşımı, idrar yolu infeksiyonları

- Başlıca kan dolaşımı izolatları: *S.aureus, E. coli*, Klebsiella türleri, *Pseudomonas aeruginosa*, Enterokoklar, Streptokoklar ve koagülaz negatif stafilokoklar

- 88 ülkeden 15.000 YBÜ hastasının dahil edildiği Yoğun Bakımda Genişletilmiş İnfeksiyon Prevalansı (EPIC III) çalışmasında, hastaların %65'inde en yaygın gram negatif patojenler olmak üzere en az 1 pozitif mikrobiyolojik kültür (%67,n = 3540)

- Gram pozitif mikroorganizmalar (%37, n = 1946)—*S. aureus, S. pneumoniae, Enterococcus spp.* en yaygın

JAMA. 2020 Apr 21; 323(15): 1478–1497. PMCID: PMC7093816
Published online 2020 Mar 24. doi: 10.1001/jama.2020.2717 PMID: 32207816

Prevalence and Outcomes of Infection Among Patients in Intensive Care Units in 2017

Jean-Louis Vincent, MD, PhD,[81] Yasser Sakr, MD, PhD,[2] Mervyn Singer, MB, BS,[3] Ignacio Martin-Loeches, MD,[4,5] Flavia R. Machado, MD, PhD,[6] John C. Marshall, MD,[7] Simon Finfer, MB, BS,[8] Paolo Pelosi, MD,[9,10] Luca Brazzi, MD, PhD,[11] Dita Aditianingsih, MD, PhD,[12] Joan-François Timsit, MD, PhD,[13] Bin Du, MD,[14] Xavier Wittebole, MD,[15] Jan Máca, MD,[16] Santhana Kannan, MD,[17] Luis A. Gorordo-Delsol, MD,[18] Jan J. De Waele, MD,[19] Yatin Mehta, MD,[20] Marc J. M. Bonten, MD,[21] Ashish K. Khanna, MD,[22,23] Marin Kollef, MD,[24] Mariesa Human, RN,[25] and Derek C. Angus, MD, MPH[26], for the EPIC III Investigators

Emergency Medicine Clinics of North America
Volume 32, Issue 4, November 2014, Pages 835-849

Emergency Department Antimicrobial Considerations in Severe Sepsis

Robert S. Green MD, FRCPC, FRCP(Edin) [a,b], Sean K. Gorman BSc(Pharm), PharmD [c]

Doğru Ajan

Ampirik tedavi

- Bakterisidal etkili
- IV yol

- Doğru ampirik antimikrobiyal tedavi, belirli bir hastada belirli bir infeksiyona neden olan en olası patojenleri kapsamayı amaçlar.

  (Tüm olası patojenleri kapsayan geniş spektrumlu antibiyotikler)

- Ampirik antimikrobiyal tedaviye karar verirken, sadece patojenle ilgili faktörleri değil, aynı zamanda yaş, kilo, alerjiler, komorbiditeler ve organ disfonksiyonu varlığı gibi tedaviyi etkileyebilecek hasta ile ilgili faktörleri de dikkate almak önemlidir.
- ÇİD risk değerlendirmesi, önceki antibiyotik maruziyeti, son 90 gün içinde uzun süreli hastanede kalış süresi ile son hastaneye yatış, dirençli suşlar ile kolonizasyon, invaziv cihazların varlığı, lokal direnç verileri

Doğru Doz

- Antibiyotik dozajının sepsis ve septik şok hastalarında spesifik antibiyotik farmakokinetik (FK) / farmakodinamik (FD) özelliklerine göre optimize edilmesi anlamına gelir.

- Etkili bir tedavi elde etmek için infeksiyon bölgelerinde yeterli miktarda antibiyotik bulunmalıdır.

- Şiddetli infeksiyon ve septik şok koşulları altında, antibiyotik konsantrasyonu büyük ölçüde etkilenir.
    - Doku hipoperfüzyonu
    - Üçüncü boşluk fenomeni
    - Hipoproteinemi
    - Organ işlev bozukluğu

Published in final edited form as:
Lancet Infect Dis. 2014 June ; 14(6): 498–509. doi:10.1016/S1473-3099(14)70036-2.

Challenges and Potential Solutions – Individualised Antibiotic Dosing at the Bedside for Critically Ill Patients: a structured review

Prof Jason A. Roberts, PhD[1,2], Mr Mohd Hafiz Abdul Aziz, BPharm[1], Prof Jeffrey Lipman, MD[1,2], Prof Johan W. Mouton, PhD[3], Prof Alexander A. Vinks, PhD[4], Dr Timothy W. Felton, MBBS[5], Prof William W. Hope, PhD[6], Dr Andras Farkas, PharmD[7], A/Prof Michael N. Neely, MD[8], Jerome J. Schentag, PharmD[9], Prof George Drusano, MD[10], Dr Otto R. Frey, PhD[11], Dr Ursula Theuretzbacher, PhD[12], and Dr Joseph L. Kuti, PharmD[13] On behalf of The International Society of Anti-Infective Pharmacology (ISAP) and the PK/PD Study Group of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID)

Normal	Normal organ fonksiyonu	Normal Dağılım Hacmi	Normal Plazma Konsantrasyonu
SEPSİS	Kapiller geçirgenlikte ↑	Dağılım hacmi ↑	Azalmış Plazma Konsantrasyonu
	Kardiyak output↑ Metabolizma ↑	CrCl ↑	Azalmış Plazma Konsantrasyonu
	Hipoproteinemi	Serbest ilaç ↑	Artmış Plazma Konsantrasyonu
	Organ Disfonksiyonu	CrCl ↓	Artmış Plazma Konsantrasyonu

TABLE 1 Overview of the significant pharmacokinetic alterations of antibiotics in patients with sepsis, along with practical recommendations

Hydrophilic antibiotics	Lipophilic antibiotics
Aminoglycosides (Amikacin, Gentamicin) Beta-lactams (Penicillins, Cephalosporins, Carbapenems) Glycopeptides (Vancomycin, Teicoplanin) Lipopeptides (Daptomycin) Polymixin (Colistin)	Clindamycin Fluoroquinolones (Ciprofloxacin, Levofloxacin) Macrolides (Azithromycin) Metronidazole Oxazolidinones (Linezolid) Rifampin Tetracyclines (Tigecycline)

Condition	PK changes	Recommendation	PK changes	Recommendation
Sepsis	↓Absorption of most routes ↑V_d	• IV administration is the preferred route. • A loading dose is required.	↓Absorption of most routes →V_d	• IV administration is the preferred route. • A loading dose is NOT required.
ARC	↑CL	• Administer more frequent doses or higher daily doses. • Consider prolonged or continuous infusion. • When possible, TDM should be utilized.	→CL	• Dose adjustment is NOT required.
AKI	↑V_d ↓CL	• A larger loading dose is required (especially for beta-lactams). • No adjustments need to be made for maintenance dosing. • When possible, TDM should be utilized. • Clinical judgment is paramount.	→V_d →CL	• Dose adjustment is NOT required for initial therapy. • Clinical judgment is paramount.
Liver failure	→CL	• Dose adjustment is NOT required.	↓CL	• Reduce dose.

Abbreviations: AKI, acute kidney injury; ARC, augmented renal clearance; CL, drug clearance; IV, intravenous; PK, pharmacokinetics; TDM, therapeutic drug monitoring; V_d, volume of distribution.

Table 3 Guidance for PK/PD-based dosing for specific drug classes

Drug or drug class	PK/PD index associated with bacterial killing or efficacy	Drug concentration target	Considerations for optimised dosing[a]	References
Antibacterials				
Aminoglycosides	AUC_{0-24}/MIC; C_{max}/MIC	AUC 70–100 C_{max}/MIC 8–10	Use extended interval dosing with patient weight and kidney function	[237]
Beta-lactams	$fT_{>MIC}$	C_{min} > MIC	Use prolonged infusions, consider patient weight and kidney function	[253]
Colistin	AUC_{0-24}/MIC	Unspecified	Use patient weight and kidney function	[259]
Daptomycin	AUC_{0-24}/MIC; C_{max}/MIC	AUC_{0-24}/MIC > 200	Use patient weight and kidney function	[237]
Fluoroquinolones	AUC_{0-24}/MIC; C_{max}/MIC	AUC_{0-24}/MIC 80–125	Use kidney function	[237]
Vancomycin	AUC_{0-24}/MIC	AUC_{0-24}/MIC 400	Use patient weight and kidney function	[260]
Antifungals				
Fluconazole	AUC_{0-24}/MIC	AUC_{0-24}/MIC 100	Use patient weight and kidney function	[261]
Posaconazole	AUC_{0-24}/MIC	C_{min} 1–4 mg/L	Use formulation-specific dose	[261]
Voriconazole	AUC_{0-24}/MIC	C_{min} 2–6 mg/L	Use patient weight	[261]

AUC_{0-24} ratio of area under the concentration–time curve from 0 to 24 h, *MIC* minimum inhibitory concentration, *$fT_{>MIC}$* time overdosing interval that free (unbound) drug is maintained above the MIC, *C_{max}* maximum concentration in a dosing interval, *C_{min}* minimum concentration in a dosing interval

[a] Other considerations than those listed may have been listed in studies in critically ill patient sub-populations

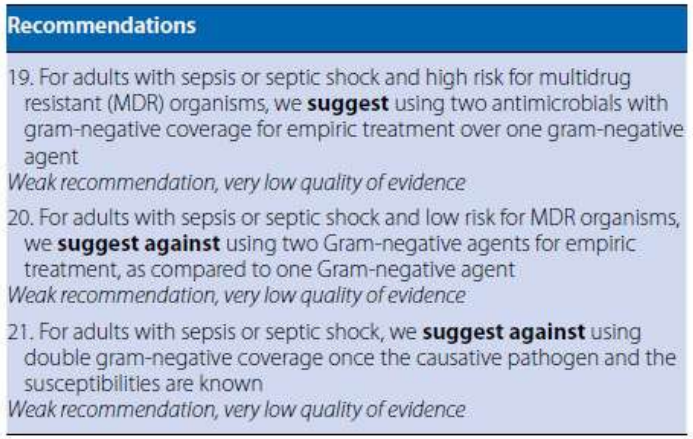
Terapötik ilaç izlemi, çoğu antibiyotiğin dozlanmasına yardımcı olarak kullanılabilir.

Vankomisin
Gentamisin
Amikasin

Doğru ajan hangisi?

- Hasta özellikleri
- İnfeksiyon kaynağı
- Nedensel ajanlar
- Antibiyotik direnç modelleri

- Önceki yıl içinde antibiyotiğe dirençli organizmalarla kanıtlanmış infeksiyon veya kolonizasyon
- Sağlık hizmetleriyle ilişkili
- Önceki 90 gün içinde geniş spektrumlu antibiyotik kullanımı
- Seçici sindirim dekontaminasyonu



Recommendations

19. For adults with sepsis or septic shock and high risk for multidrug resistant (MDR) organisms, we **suggest** using two antimicrobials with gram-negative coverage for empiric treatment over one gram-negative agent

Weak recommendation, very low quality of evidence

20. For adults with sepsis or septic shock and low risk for MDR organisms, we **suggest against** using two Gram-negative agents for empiric treatment, as compared to one Gram-negative agent

Weak recommendation, very low quality of evidence

21. For adults with sepsis or septic shock, we **suggest against** using double gram-negative coverage once the causative pathogen and the susceptibilities are known

Weak recommendation, very low quality of evidence

Doğru ajan hangisi?

- MRSA açısından yüksek risk taşıyan sepsis veya septik şoklu yetişkinler için, MRSA kapsamına sahip ampirik antimikrobiyaller

- MRSA infeksiyonu veya kolonizasyonu öyküsü
- Yakın zamanda IV antibiyotik kullanımı
- Tekrarlayan deri infeksiyonları veya kronik yaralar
- İnvaziv cihazların varlığı
- Hemodiyaliz
- Yakın zamanda hastaneye yatış
- Hastalığın ciddiyeti

Recommendations

17. For adults with sepsis or septic shock at high risk of methicillin resistant staph aureus (MRSA), we **recommend** using empiric antimicrobials with MRSA coverage over using antimicrobials without MRSA coverage

Best Practice statement

18. For adults with sepsis or septic shock at low risk of methicillin resistant staph aureus (MRSA), we **suggest against** using empiric antimicrobials with MRSA coverage, as compared with using antimicrobials without MRSA coverage

Weak recommendation, low quality of evidence

ScienceDirect

Clinical Microbiology and Infection

Available online 11 January 2023

In Press, Corrected Proof What's this?

Original article

Effects of empiric antibiotic treatment based on hospital cumulative antibiograms in patients with bacteraemic sepsis: a retrospective cohort study

Chia-Ming Chang[1 2 3], Ming-Shun Hsieh[2 4], Chi-Ju Yang[5], Chorng-Kuang How[1 2], Pau-Chung Chen[3 6 7 8 9], Yu-Hsiang Meng[1 2]

- Acil servise başvuran bakteriyemik sepsisli hastalarda hastane kümülatif antibiyogramlarına dayalı olarak farklı uygunluk derecelerine sahip ampirik antibiyotiklerin etkilerini değerlendirmek

- Retrospektif kohort çalışması Şubat 2016 - Aralık 2018'e kadar acil serviste kan kültürü raporu pozitif olan sepsisli yetişkin hastalar – 1055 hasta

GAD ile uyum ≥%70 olan ampirik antibiyotikler;

- Hastane içi ölümlerde azalma (düzeltilmiş olasılık oranı, 0,46; %95 CI, 0,28-0,77)
- 30 günlük mortalitede azalma (düzeltilmiş olasılık oranı, 0,53; %95 CI, 0,33-0,86)
- Yoğun bakım ünitesinde kalış süresinde 1,60 gün kısalma (%95 CI, -3,00 -0,20)

Antimicrobial Agents and Chemotherapy®

CLINICAL THERAPEUTICS

Monoterapi mi kombinasyon mu?

Impact of Empirical Antibiotic Regimens on Mortality in Neutropenic Patients with Bloodstream Infection Presenting with Septic Shock

Mariana Chumbita,[a] Pedro Puerta-Alcalde,[a] Carlota Gudiol,[b,c,d] Nicole Garcia-Pouton,[a] Júlia Laporte-Amargós,[b,d] Andrea Ladino,[c] Adaia Albasanz-Puig,[b,d] Cristina Helguera,[f] Alba Bergas,[b] Ignacio Grafia,[a] Enric Sastre,[b] María Suárez-Lledó,[g] Xavier Durà,[b,d] Carlota Jordán,[a] Francesc Marco,[h,i] Maria Condom,[j] Pedro Castro,[k] Jose A. Martínez,[a] Josep Mensa,[a] Alex Soriano,[a] Jordi Carratalà,[b,d] Carolina Garcia-Vidal[a]

February 2022 Volume 66 Issue 2 e01744-21

- 2010- 2019 iki prospektif kohort
- Septik şok olan ve olmayan KDİ atakları
- KDİ'li 1563 hastanın 257'inde (%16) septik şok

- Gram negatif septik şok %81
- Gram-pozitif kok %22
- Candida türleri %5

- Ampirik β-laktam + amikasin diğer aktif antibiyotiklerle kombine edildiğinde en düşük mortalite
- Amikasin tek aktif antibiyotik olduğunda, mortalite %90

- Ampirik spesifik Gram-pozitif kapsayıcı antibiyotik eklenmesinin mortalite üzerinde hiçbir etkisi yok (P = 0.022)

TABLE 4 Risk factors for overall mortality, by univariate and multivariate analysis[a]

Risk factor	Univariate OR (95% CI)	*P* value	Multivariate OR (95% CI)	*P* value
Male sex	0.78 (0.48–1.30)	0.346		
Age ≥70 yr	2.23 (1.20–4.15)	**0.010**	2.36 (1.19–4.68)	**0.014**
Acute leukemia	0.65 (0.38–1.13)	0.125		
Non-Hodgkin lymphoma	0.94 (0.52–1.72)	0.847		
Multiple myeloma	0.90 (0.37–2.19)	0.811		
Chronic leukemia	8.78 (1.10–69.63)	**0.014**	5.02 (0.60–42.22)	0.138
Solid neoplasia	0.96 (0.57–1.64)	0.906		
Hematopoietic stem cell transplantation	1.29 (0.67–2.48)	0.446		
Any comorbidity	1.04 (0.62–1.75)	0.870		
Corticosteroid therapy	1.16 (0.71–1.89)	0.560		
Nosocomial acquisition	1.41 (0.86–2.31)	0.177		
Pulmonary source	2.06 (1.06–4.01)	**0.032**	1.35 (0.58–3.18)	0.486
Endogenous/unknown source	0.60 (0.37–0.98)	**0.043**	0.69 (0.39–1.23)	0.211
Catheter-related BSI	0.81 (0.35–1.87)	0.615		
Acute kidney injury	2.48 (1.41–4.37)	**0.001**	2.60 (1.39–4.90)	**0.003**
Empirical β-lactam	0.26 (0.73–0.94)	**0.037**	0.41 (0.08–2.16)	0.294
Empirical carbapenem	0.94 (0.58–1.55)	0.819		
Empirical β-lactam plus aminoglycoside	0.30 (0.18–0.50)	**<0.001**	0.32 (0.18–0.57)	**<0.001**
Empirical β-lactam plus specific Gram-positive coverage	0.69 (0.41–1.17)	0.169		
Amikacin as the only active antibiotic	7.84 (0.98–62.83)	**0.025**	15.24 (1.73–134.45)	**0.014**
β-Lactam as the only active antibiotic	1.81 (1.01–3.26)	**0.046**	1.66 (0.72–3.82)	0.236
Coagulase-negative staphylococci	0.34 (0.09–1.34)	0.193		
Staphylococcus aureus	2.10 (0.40–11.01)	0.462		
Enterococcus spp.	1.19 (0.44–3.23)	0.734		
Streptococcus spp.	1.08 (0.45–2.55)	0.867		
E. coli	0.97 (0.58–1.62)	0.901		
Klebsiella spp.	0.80 (0.39–1.64)	0.541		
Pseudomonas aeruginosa	1.32 (0.76–2.29)	0.329		
MDR *P. aeruginosa*	3.19 (0.87–11.71)	0.096		
MDR-GNB	1.57 (0.77–3.18)	0.208		
Candidemia	4.82 (1.05–22.22)	**0.042**	2.18 (0.34–13.94)	0.411
Polymicrobial	1.86 (0.86–3.99)	0.108		
Inappropriate empirical antibiotic therapy for GNB or *Candida* spp.	5.74 (2.14–15.38)	**<0.001**	3.81 (1.31–11.11)	**0.014**

[a]Abbreviations: ESBL, extended-spectrum β-lactamase; MDR, multidrug resistant; GNB, Gram-negative bacilli. Boldface indicates statistically significant values (*P* value < 0.05).

Mortality in neutropenic patients with BSI and septic shock was extremely high (55%). Most series of patients with septic shock and BSI including nonneutropenic

IV Bolus mu Uzamış infüzyon mu?

- Uzun süreli beta-laktam infüzyonu

Established in 1871
Swiss Medical Weekly
Formerly: Schweizerische Medizinische Wochenschrift
An open access, online journal • www.smw.ch
Review article: Biomedical intelligence | Published 10 October 2016, doi:10.4414/smw.2016.14368
Cite this as: Swiss Med Wkly. 2016;146:w14368

Prolonged administration of β-lactam antibiotics – a comprehensive review and critical appraisal

Michael Osthoff[a,b], Martin Siegemund[c], Gianmarco Balestra[d], Mohd H. Abdul-Aziz[e,f], Jason A. Roberts[f,g,h]

Table 1: Pharmacokinetic/pharmacodynamic properties of selected antibiotics that correlate with efficacy.

	Pharmacodynamic kill characteristics		
	Time dependent	Concentration dependent	Concentration dependent with time dependence
Antibiotic	Penicillins Cephalosporins Carbapenems Linezolid Clarithromycin Clindamycin	Aminoglycosides Metronidazole Daptomycin Fluoroquinolones	Fluoroquinolones Azithromycin Glycopeptides Tetracyclines Tigecycline Linezolid Aminoglycosides
Optimal PK/PD index (and target examples for selected drugs)	$T_{>MIC}$ e.g. 40–100% $T_{>MIC}$ for β-lactams	C_{max}:MIC e.g. C_{max}:MIC 8–10 for aminoglycosides	AUC_{0-24}:MIC e.g. $AUC0_{-24}$:MIC ≥400 for vancomycin
Objective	Maximise duration of exposure	Maximise concentration	Maximise amount of drug exposure
Measures	Frequent administration or prolonged infusion dosing	Infrequent (once daily) administration of high doses	Administration of a high total daily dose

MIC = minimal inhibitory concentration; PK/PD = pharmacokinetics/pharmacodynamics; AUC_{0-24}:MIC = the ratio of the area under the concentration time curve during a 24-hour period to MIC; C_{max}:MIC = the ratio of the maximum plasma concentration to MIC; $T_{>MIC}$ = time that the drug concentration is above the MIC;
Note: For some antibiotics therapeutic efficacy may be correlated with more than one pharmacokinetic/pharmacodynamic parameter (e.g. aminoglycosides or fluoroquinolones).

Recommendation
25. For adults with sepsis or septic shock, we **suggest** using prolonged infusion of beta-lactams for maintenance (after an initial bolus) over conventional bolus infusion *Weak recommendation, moderate quality of evidence*

ORIGINAL ARTICLE

Continuous versus Intermittent β-Lactam Infusion in Severe Sepsis
A Meta-analysis of Individual Patient Data from Randomized Trials

Jason A. Roberts[1,2,3,4], Mohd-Hafiz Abdul-Aziz[2,5], Joshua S. Davis[6,7], Joel M. Dulhunty[1,2,8], Menino O. Cotta[1,2,3,4], John Myburgh[9,10], Rinaldo Bellomo[11,12], and Jeffrey Lipman[1,2]

American Journal of Respiratory and Critical Care Medicine Volume 194 Number 6 | September 15 2016

- İki meta-analiz, uzun süreli beta-laktam infüzyonu ile azalan kısa vadeli mortaliteyi (RR 0.70; %95 CI 0.57-0.87) destekleyen benzer sonuçlar

- Uzun süreli infüzyondan önce bir yükleme dozu antibiyotiğin uygulanması, etkili beta-laktam konsantrasyonlarına ulaşmada gecikmeleri önlemek için gereklidir.

ARTICLES | VOLUME 18, ISSUE 1, P108-120, JANUARY 2018

Prolonged versus short-term intravenous infusion of antipseudomonal β-lactams for patients with sepsis: a systematic review and meta-analysis of randomised trials

Konstantinos Z Vardakas, MD • Georgios L Voulgaris, PharmD • Athanasios Maliaros, BSc • Prof George Samonis, MD • Prof Matthew E Falagas, MD

Reviews

Clinical outcomes of continuous vs intermittent meropenem infusion for the treatment of sepsis: A systematic review and meta-analysis

Peng Chen[1,A–F], Fuchao Chen[2,F], Jiexin Lei[3,F], Benhong Zhou[1,F]

[1] Department of Pharmacy, Renmin Hospital of Wuhan University, China
[2] Department of Pharmacy, Dongfeng Hospital, Hubei University of Medicine, Shiyan, China
[3] Department of Endocrinology, Renmin Hospital of Wuhan University, China

A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of the article

Advances in Clinical and Experimental Medicine, ISSN 1899–5276 (print), ISSN 2451–2680 (online) Adv Clin Exp Med. 2020;29(8):993–1000

Uzamış infüzyon mu devamlı infüzyon mu?

- 1.191 katılımcının yer aldığı yedi çalışma meta-analize dahil
- Mortalite (RR= 0,66, %95 CI 0,46-0,98, p = 0,03)
- Klinik iyileşme oranı (RR = 1,15, %95 CI = 1,02–1,30, p = 0,026)
- Mikrobiyolojik eradikasyon (RR = 1,20, %95 CI = 1,01–1,42, p = 0,04)

Table 2. Other outcomes of continuous compared to intermittent meropenem infusion for the treatment of sepsis

Outcomes	Studies	Patients		RR/WMD (95% CI)	Heterogeneity (I^2, P)	p-value
		continuous group	intermittent group			
Length of ICU stay	3	166	166	−1.40 (−2.19, −0.61)	66%; 0.65	0.005
Hospital length of stay	3	288	296	−1.87 (−2.23, −1.50)	41%; 0.18	<0.01
ICU survival	4	378	386	−0.30 (−0.73, 0.13)	0%; 0.54	0.62
ICU-free days	4	378	386	−0.11 (−0.54, 0.32)	12%; 0.57	0.60
Emergence of resistance	2	332	340	−16.23 (−29.86, −2.59)	88%; 0.004	0.02

ICU – intensive care unit.

Deeskalasyon

- Hastanede daha kısa kalış süresiyle ilişkili (MD -5,56 gün; %95 GA -7,68 ila -3,44)

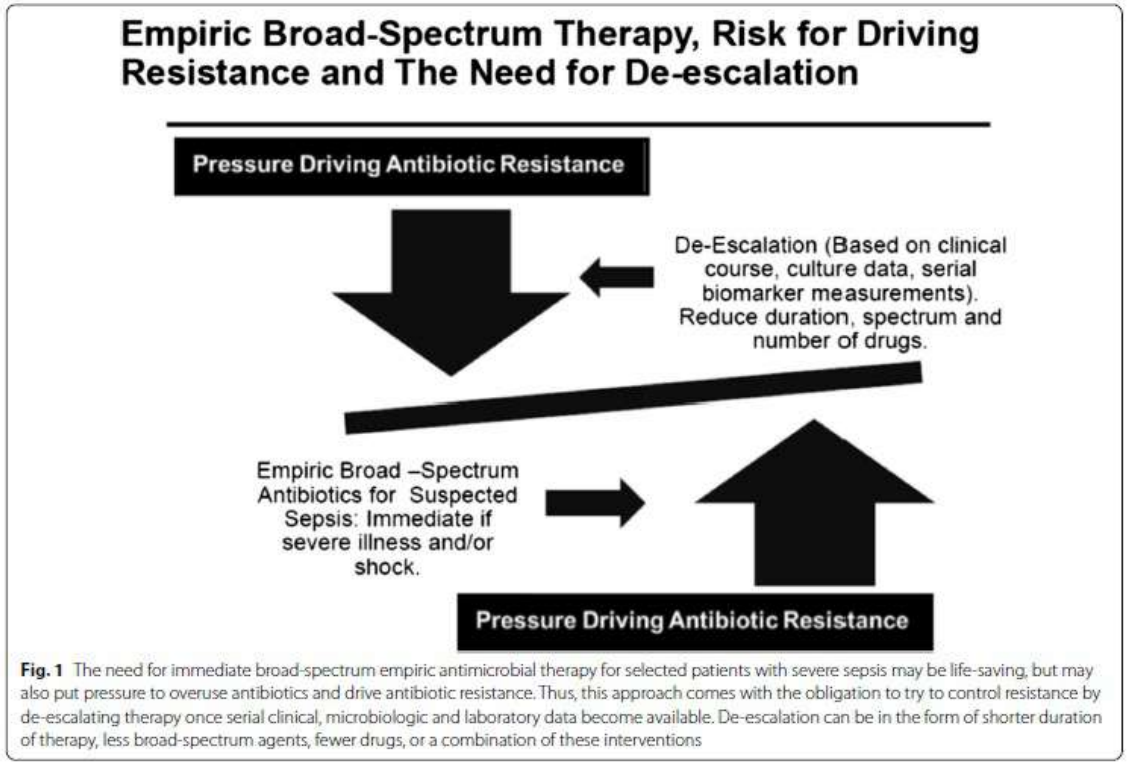


Fig. 1 The need for immediate broad-spectrum empiric antimicrobial therapy for selected patients with severe sepsis may be life-saving, but may also put pressure to overuse antibiotics and drive antibiotic resistance. Thus, this approach comes with the obligation to try to control resistance by de-escalating therapy once serial clinical, microbiologic and laboratory data become available. De-escalation can be in the form of shorter duration of therapy, less broad-spectrum agents, fewer drugs, or a combination of these interventions

Clinical Infectious Diseases

REVIEW ARTICLE

A Systematic Review of the Definitions, Determinants, and Clinical Outcomes of Antimicrobial De-escalation in the Intensive Care Unit

Alexis Tabah,[1,2,a] Menino Osbert Cotta,[1,2,3,a] Jose Garnacho-Montero,[6] Jeroen Schouten,[7] Jason A. Roberts,[1,2,3] Jeffrey Lipman,[1,2,4] Mark Tacey,[5] Jean-François Timsit,[8,9] Marc Leone,[10] Jean Ralph Zahar,[11] and Jan J. De Waele[12]; for the Working Group for Antimicrobial Use in the ICU

Original Research | 6 August 2019

Excess Antibiotic Treatment Duration and Adverse Events in Patients Hospitalized With Pneumonia

A Multihospital Cohort Study

Valerie M. Vaughn, MD, MSc, Scott A. Flanders, MD, Ashley Snyder, MS, Anna Conlon, PhD, ... See More

Author, Article, and Disclosure Information

https://doi.org/10.7326/M18-3640

Tedavi süresi

- Kısa süreli tedavi uzun kadar etkili ve daha az olumsuz sonuçla ilişkili

Recommendation
30. For adults with an initial diagnosis of sepsis or septic shock and adequate source control, we **suggest** using shorter over longer duration of antimicrobial therapy *Weak recommendation, very low quality of evidence*

Recommendation
31. For adults with an initial diagnosis of sepsis or septic shock and adequate source control where optimal duration of therapy is unclear, we **suggest** using procalcitonin AND clinical evaluation to decide when to discontinue antimicrobials over clinical evaluation alone *Weak recommendation, low quality of evidence*

Clinical Microbiology and Infection 28 (2022) 550–557

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Original article

Seven-versus 14-day course of antibiotics for the treatment of bloodstream infections by Enterobacterales: a randomized, controlled trial

José Molina [1, 2], Enrique Montero-Mateos [3], Julia Praena-Segovia [1, 2], Eva León-Jiménez [4], Clara Natera [5], Luis E. López-Cortés [2, 6], Lucía Valiente [7], Clara M. Rosso-Fernández [2, 8], Marta Herrero [1, 2], Ana I. Aller-García [4], Ángela Cano [5], Belén Gutiérrez-Gutiérrez [2, 6], Ignacio Márquez-Gómez [7], Rocío Álvarez-Marín [1, 2], Carmen Infante [1, 2], Cristina Roca [1, 2], Adoración Valiente-Méndez [2, 6], Jerónimo Pachón [2, 9], José María Reguera [7], Juan Enrique Corzo-Delgado [4], Julián Torre-Cisneros [5, 10], Jesús Rodríguez-Baño [2, 6, 9], José Miguel Cisneros [1, 2, 9, *] on behalf of the SHORTEN trial team[†]

Table 3
Distribution of patients per desirability of outcome ranking (DOOR) in the per protocol cohort

	7 days ($n = 93$) n (%)	14 days ($n = 108$) n (%)
Cure without incidences	69 (74.2)	77 (71.3)
Cure with relapsing fever	10 (10.8)	6 (5.6)
Cure with a severe adverse event	12 (12.9)	16 (14.8)
Not cured	1 (1.1)	3 (2.8)
Death	1 (1.1)	6 (5.6)
Probability of a better DOOR/RADAR score in the experimental arm[a]	**77.7% (95%CI 76.8–78.5)**	

[a] Detailed score calculations are provided in Supplementary Material File 8.

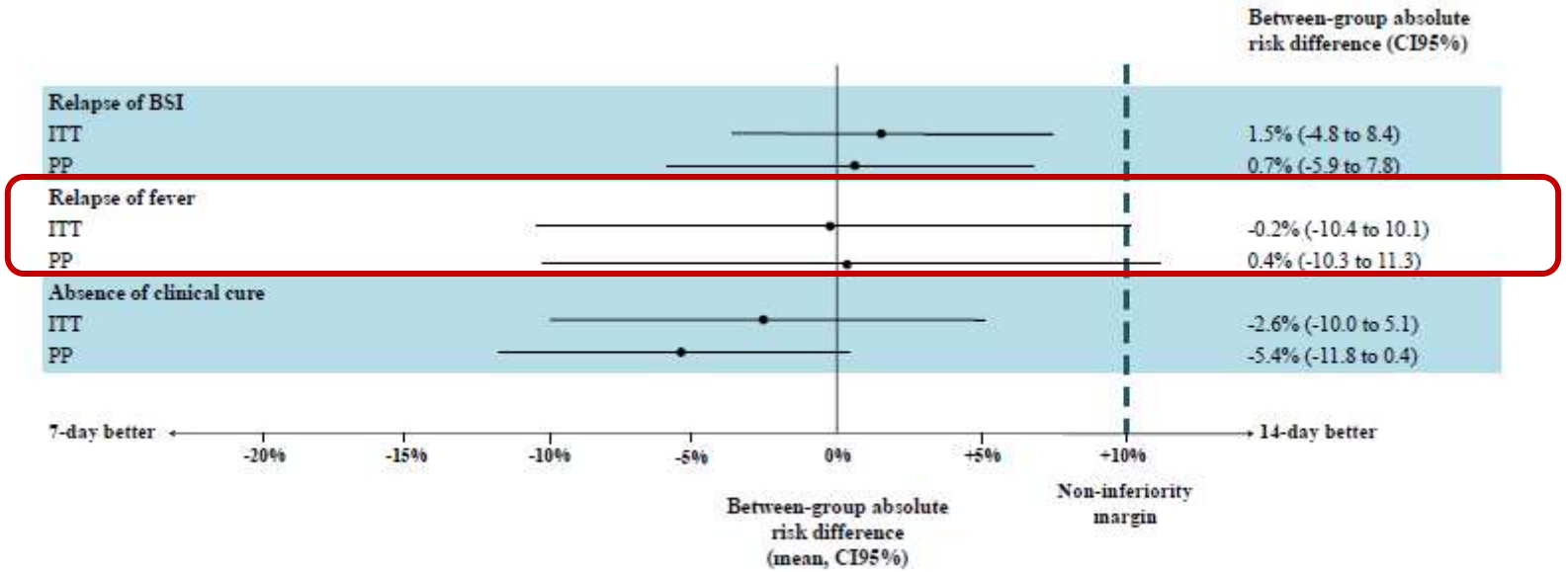


Fig. 3. Non-inferiority analysis for clinical outcome measures.

The Journal of Infectious Diseases

SUPPLEMENT ARTICLE

Considerations for Empiric Antimicrobial Therapy in Sepsis and Septic Shock in an Era of Antimicrobial Resistance

Jeffrey R. Strich,[1,2] Emily L. Heil,[3] and Henry Masur[1]

Table 1. Site-Specific Empiric Antibiotic Guideline Recommendations[a]

Site of Infection	Initial Empiric Therapy	Other Considerations
Pulmonary		
CAP [19]	Multidrug therapy with a beta-lactam (ampicillin + sulbactam, ceftriaxone, or ceftaroline) and a macrolide (azithromycin clarithromycin)	Risk factors for MRSA and/or *Pseudomonas aeruginosa*: add vancomycin or linezolid for MRSA coverage, replace standard CAP therapy with pseudomonal coverage such as piperacillin-tazobactam, cefepime, meropenem, or imipenem
	Monotherapy with a respiratory fluoroquinolone (levofloxacin or moxifloxacin)	Recommendation based on "local validation" of risk factors for community onset MRSA or *P aeruginosa* or prior isolation of these organisms in the previous year, particularly from respiratory specimens
HAP/VAP [20]	Multidrug therapy with vancomycin or linezolid and piperacillin-tazobactam, cefepime, ceftazidime, imipenem, meropenem, or aztreonam	Two antipseudomonal antibiotics from different classes (addition of fluoroquinolones, aminoglycosides, or polymyxins) if prior intravenous antibiotic use within 90 days for HAP/VAP and septic shock at time of VAP, ARDS preceding VAP, 5 or more days of hospitalization before VAP, or acute renal replacement therapy before VAP If prior colonization with carbapenem-resistant *Enterobacteriales* or KPC-producing organism ceftazidime-avibactam and meropenem-vaborbactam should be considered but further efficacy data is needed Empiric regimens should be informed by local distribution of pathogens and their antimicrobial susceptibilities
Central nervous system		
Healthcare-associated ventriculitis and meningitis [21]	Vancomycin and cefepime, ceftazidime or meropenem	Beta-lactam choice based on local in vitro susceptibility patterns. If carbapenem-resistant *Acinetobacter* is suspected addition of meropenem and colistin or polymyxin B
Meningitis [22]	Vancomycin and ceftriaxone	Age >50, alcohol abuse or immunocompromised: add ampicillin Penetrating head trauma, CSF shunt or postneurosurgery vancomycin and cefepime, ceftazidime or meropenem Clinical presentation suggestive of *Rickettsial* or *Ehrlichial* disease add doxycycline
Skin and soft tissue		
Necrotizing fasciitis including Fournier gangrene [23]	Multidrug therapy with vancomycin or linezolid and piperacillin-tazobactam, a carbapenem, or ceftriaxone and metronidazole	Prompt surgical consultation is recommended for patient with aggressive infections associated with signs of systemic toxicity or suspicion of necrotizing fasciitis or gas gangrene
Nonpurulent cellulitis/erysipelas (severe) [23]	Vancomycin and piperacillin-tazobactam	Emergent surgical inspection to rule out necrotizing process
Purulent furuncle/ carbuncle/abscess (severe) [23]	Vancomycin, daptomycin, linezolid, telavancin, or ceftaroline	Incision and drainage as indicated
Intra-abdominal		
Community onset extrabiliary (mild) [24]	Cefoxitin, ertapenem, moxifloxacin, or tigecycline	Healthcare setting with high prevalence of ESBL-producing *Enterobacteriales* or >20% of *Pseudomonas* resistant to ceftazidime consider carbapenem or piperacillin-tazobactam
Community onset extrabiliary (severe) [24]	Imipenem-cilastatin, meropenem, doripenem or piperacillin-tazobactam	Healthcare associated: imipenem-cilastatin, meropenem, or piperacillin-tazobactam, levofloxacin or cefepime each along with metronidazole, vancomycin added to each regimen
Community onset biliary (mild to moderate) [24]	Cefazolin, cefuroxime, or ceftriaxone	Empiric therapy should be driven by local microbiological data and source control performed as indicated
Community onset biliary severe or cholangitis [24]	Imipenem-cilastatin, meropenem, or piperacillin-tazobactam, Levofloxacin or cefepime each in combination with metronidazole	
Genitourinary		
Acute pyelonephritis (IDSA archived) [25]	Ceftriaxone, trimethoprim-sulfamethoxazole, or ciprofloxacin	Requiring hospitalization: intravenous fluoroquinolone, aminoglycoside, extended-spectrum cephalosporin, extended-spectrum penicillin, or carbapenem with choice of agents based on local resistance data Do not use fluoroquinolone if >10% resistance prevalence or trimethoprim-sulfamethoxazole in areas of high resistance

Impact of Source Control in Patients With Severe Sepsis and Septic Shock*

Maria Luisa Martínez, MD[1]; Ricard Ferrer, MD, PhD[2,3]; Eva Torrents, MD[1]; Raquel Guillamat-Prats, PhD[3]; Gemma Gomà, RN[1]; David Suárez, MSc, PhD[4]; Luis Álvarez-Rocha, MD[5]; Juan Carlos Pozo Laderas, MD, PhD[6]; Ignacio Martín-Loeches, MD, PhD[7]; Mitchell M. Levy, MD, FCCP, FCCM[8]; Antonio Artigas, MD, PhD[1,3]; for the Edusepsis Study Group

(*Crit Care Med* 2017; 45:11–19)

Odak kontrolü

Azuhata *et al. Critical Care* 2014, **18**:R87
http://ccforum.com/content/18/3/R87

CRITICAL CARE

RESEARCH Open Access

Time from admission to initiation of surgery for source control is a critical determinant of survival in patients with gastrointestinal perforation with associated septic shock

Takeo Azuhata[1*], Kosaku Kinoshita[1], Daisuke Kawano[1], Tomonori Komatsu[1], Atsushi Sakurai[1], Yasutaka Chiba[2] and Katsuhisa Tanjho[1]

- En geç 6-12 saat içinde odak kontrolü
- Mortalite ile ilişkili
- Aslında, infeksiyöz odakların kontrol edilememesi septik durumu geri dönüşümsüz olarak şiddetlendirecektir.
- Akciğer infeksiyonları gibi eradike edilemeyen bazı infeksiyöz odaklar için bile, pnömoninin kontrolü için yeterli balgam drenajı antibiyotiklerden önemli olabilir.
- Yetersiz balgam drenajı sıklıkla uzun süreli pnömoniye yol açar, bu da ikili hatta üçlü ikincil infeksiyona, ilaca dirençli bakterilerin yaygınlığına ve kalıcı hastalığa yol açar.

6D

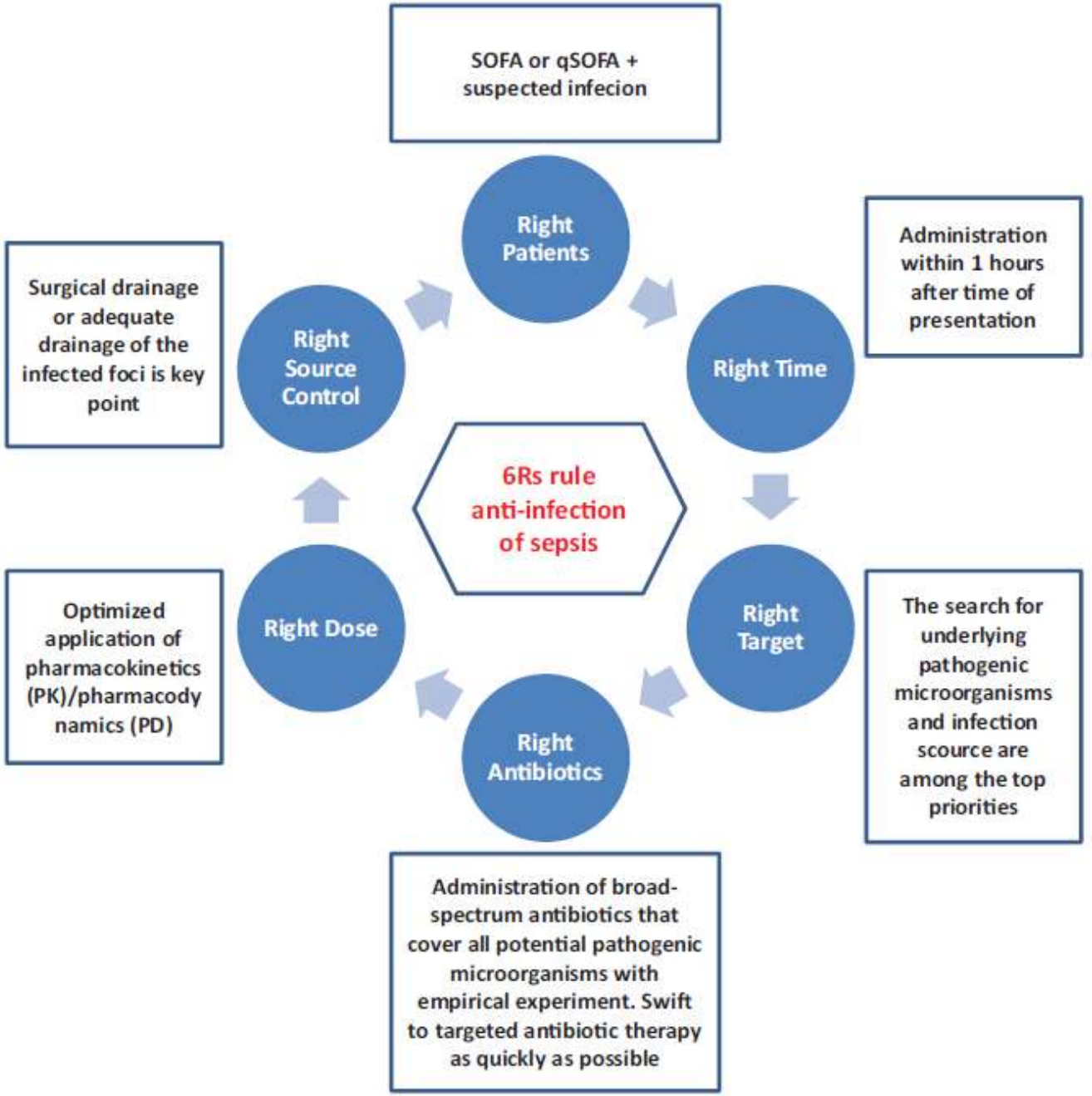


Figure 2: The standard flowchart of the new 6Rs rule for anti-infection therapy for sepsis and septic shock. Right patients is the first to be considered. It is necessary to find evidence of the pathogen and conduct appropriate anti-infective treatment in a short period of time. Adequate drainage of infected foci is a key factor. If an infection cannot be clearly identified or drainage cannot be performed effectively, the flowchart principles should be reconsidered to achieve infection treatment and control.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