Sepsiste Yeni Trend Tedaviler ve Güncel Literatür

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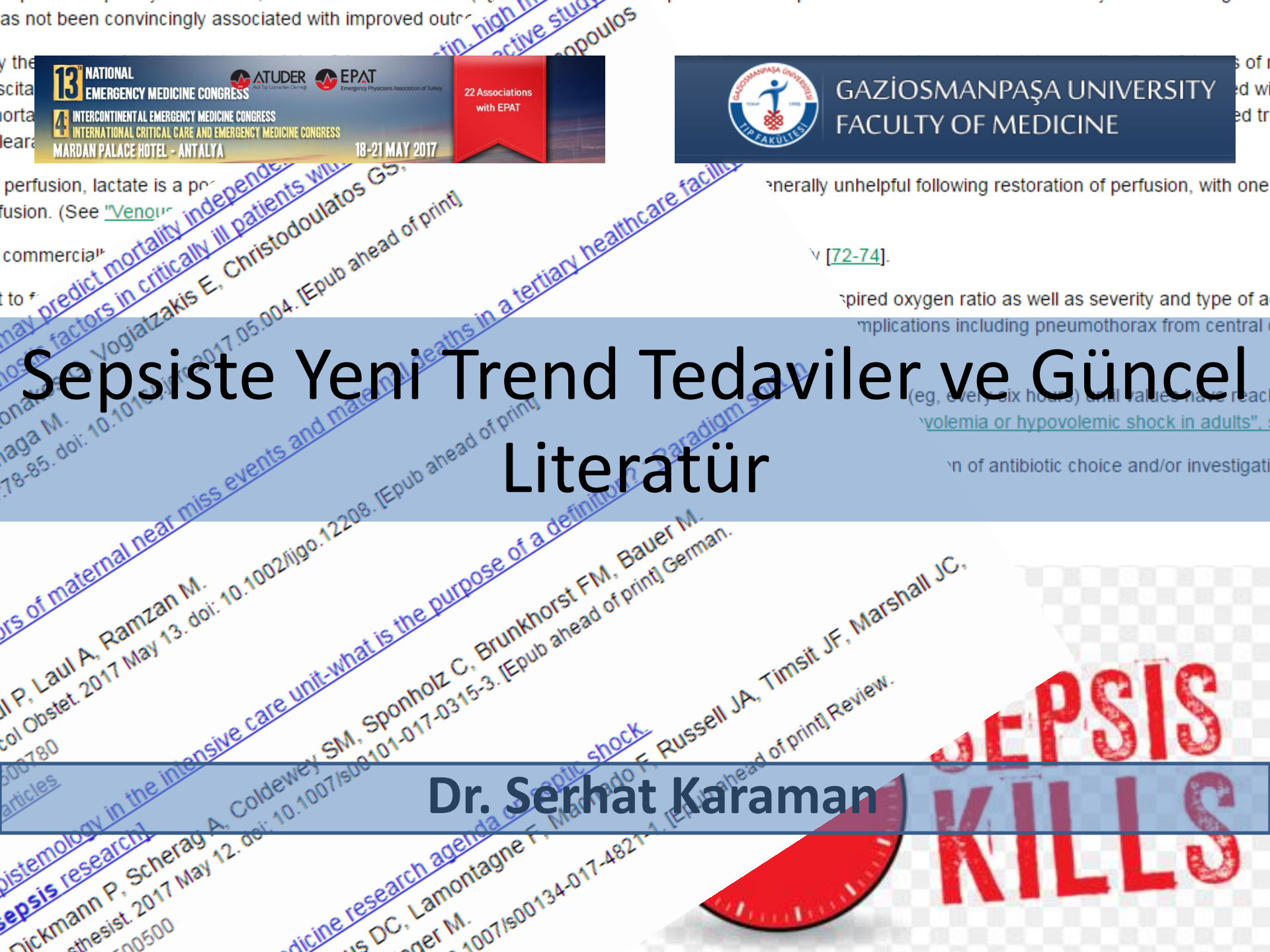


Sepsis

- Enfeksiyona karşı disregüle konak yanıtına bağlı organ disfonksiyonu
- 1.665.000 /yıl sepsis USA
- Sepsisten - septik şoka
- Optimum tedaviyle bile günümüzde
- Sepsiste ≥ % 10, ⬆
- Septik şoklu hatalarda ≥ % 40 ⬆

Perfüzyonun Değerlendirilmesi

- Hipotansiyon (en sık görülen bulgu)
- Kritik hipoperfüzyon (özellikle sepsis başlangıcı - hipotansiyon yokluğunda)
- Perfüzyon bozukluğunun klinik bulguları:

  Sistolik kan basıncı [SBP] <90 mmHg

  Ortalama arter basıncı <70 mmHg

  SBP> 40 mmHg ⇩

Kötü Uç Organ Perfüzyon Belirtileri

- Ciltte ısı artışı ve kızarıklık (erken faz)
- Cilt soluk – soguk (şoka ilerledikçe)
- Taşikardi > 90
- Obtundasyon veya huzursuzluk
- Oligüri veya anüri
- Hastalık veya ilaçlar değiştirilebilir
- Uygun bir taşikardi göstermeyebilir (yaşlı hastalar, diyabetik hastalar ve beta bloker)
- Ciddi ve uzun süreli taşikardi (genç hastalar)
- Kronik hipertansiyonu olan hastalar,

(**rölatif hipotansiyon & kritik hipoperfüzyon**).

Terapötik Öncelikler

- Sıvıların ve antibiyotiklerin erken uygulanması (damar yolu)
- Hipoksemi ve hipotansiyon (destekleyici tedavinin erkenden başlatılması)
- Sistemik inflamatuvar yanıt sendromundan (SIRS) sepsisin ayırt edilmesi
- Enfeksiyon varsa, mümkün olan en kısa sürede tanımlanmalı ve tedavi
- Cerrahi bir prosedür (drenaj)
- İlk öncelik solunum yollarının stabilize edilmesi
- Periferik dokulara perfüzyonun yeniden sağlanması ve antibiyotikler

Solunum Stabilizasyonu

- Ek oksijen verilmeli
- Oksijenasyon puls oksimetre (sürekli)
- Entübasyon ve mekanik ventilasyon (Ensefalopati ve deprese bilinç seviyesi)

Venöz Erişim Kurun

- Mümkün olan en kısa sürede venöz giriş yapılmalı
- İlk resüsitasyon için periferik venöz giriş yeterli
- Santral venöz kateter (CVC) (iv sıvılar – vazopresörler - kan ürünlerini - kan örneği)
- Venöz basıncı (CVP) ve merkezi venöz oksihemoglobin doyumunu (ScvO2)
- SVC'nın temel amacı ScVO2 ve CVP'nin ölçümüdür;

(terapötik etkiyi takip etmeyi hedeflediği değere ilişkin randomize çalışmaların kanıtı çelişkili)

45 dk içinde

(Sıvıların ve antibiyotiklerin uygulanmasını geciktirmemeli)

- Tam kan sayımı, biyokimya (KCFT), D-dimer seviyesi dahil koagülasyon çalışmaları
- Serum laktat (> 2 mmol / L veya normal) sepsisin ciddiyetini - terapötik yanıtı izlemek
- Arteriyel kan gazı (AKG) analizi - asidoz, hipoksemi veya hiperkapni
- Periferik kan kültürleri (en az iki farklı bölgeden aerobik ve anaerobik kültürler)
- İdrar ve mikrobiyolojik kültürler (balgam, idrar, yara veya cerrahi alan, vücut sıvıları)
- Kateterden hem de periferik bölgeden kan alınmalı

45 dk içinde

- Şüpheli enfeksiyon yerini hedef alan görüntüleme gereklidir (göğüs radyografisi, göğüs - karında bilgisayarlı tomografi)

- Prokalsitonin ölçülmesi !

Ancak giderek daha popüler

Antibiyotik tedavisinin değerlendirilmesinde tanısal değeri tartışmalı !

Başlangıç Resüsitasyon Tedavisi

- Perfüzyonun hızlı restorasyonu ve antibiyotiklerin erken uygulanması
- Doku perfüzyonu çoğunlukla, ilk üç saat içinde 30 mL / kg kristaloidler intravenöz sıvıların agresif uygulaması
- Ampirik antibiyotik tedavisi enfeksiyondan şüphelendiği organizmaları / bölgeleri hedef alır ve tercihen ilk saat içinde uygula

(Early Goal-Directed Therapy [EGDT])

- Sepsis tedavisine yönelik protokol tabanlı bir yaklaşım (early goal-directed therapy [EGDT]) kullanılan birkaç büyük randomize çalışmaya dayanmakta

Early goal-directed therapy in the treatment of severe sepsis and septic shock.

- Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, Peterson E, Tomlanovich M, Early Goal-Directed Therapy Collaborative Group N Engl J Med. **2001;**345(19):1368.

- BACKGROUNDGoal-directed therapy has been used for severe sepsis and septic shock in the intensive care unit. This approach involves adjustments of cardiac preload, afterload, and contractility to balance oxygen delivery with oxygen demand. The purpose of this study was to evaluate the efficacy of early goal-directed therapy before admission to the intensive care unit.

- METHODSWe randomly assigned patients who arrived at an urban **emergency department** with severe sepsis or septic shock to receive either six hours of early goal-directed therapy or standard therapy (as a control) before admission to the intensive care unit. Clinicians who subsequently assumed the care of the patients were blinded to the treatment assignment. In-hospital mortality (the primary efficacy outcome), end points with respect to resuscitation, and Acute Physiology and Chronic Health Evaluation (APACHE II) scores were obtained serially for 72 hours and compared between the study groups.

- RESULTSOf the **263** enrolled patients, **130** were randomlyassigned to early goal-directed therapy and **133** to standard therapy; there were no significant differences between the groups with respect to base-line characteristics. **In-hospital mortality** was **30.5 percent** in the group assigned to early goal-directed therapy, as compared with **46.5 percent** in the group assigned to standard therapy (P = 0.009). During the interval from 7 to 72 hours, the patients assigned to early goal-directed therapy had a significantly higher mean (+/-SD) central venous oxygen saturation (70.4+/-10.7 percent vs. 65.3+/-11.4 percent), a lower lactate concentration (3.0+/-4.4 vs. 3.9+/-4.4 mmol per liter), a lower base deficit (2.0+/-6.6 vs. 5.1+/-6.7 mmol per liter), and a higher pH (7.40+/-0.12 vs. 7.36+/-0.12) than the patients assigned to standard therapy (P<or = 0.02 for all comparisons). During the same period, mean APACHE II scores were significantly lower, indicating less severe organ dysfunction, in the patients assigned to early goal-directed therapy than in those assigned to standard therapy (13.0+/-6.3 vs. 15.9+/-6.4, P<0.001).

- CONCLUSIONS Early goal-directed therapy provides **significant benefits** with respect to outcome in patients with severe sepsis and septic shock.

A randomized trial of protocol-based care for early septic shock

- Investigators, Yealy DM, Kellum JA, Huang DT, Barnato AE, Weissfeld LA, Pike F, Terndrup T, Wang HE, Hou PC, LoVecchio F, Filbin MR, Shapiro NI, Angus DC N Engl J Med. **2014;**370(18):1683.

- BACKGROUNDIn a single-center study published more than a decade ago involving patients presenting to the emergency department with severe sepsis and septic shock, mortality was markedly lower among those who were treated according to a 6-hour protocol of early goal-directed therapy (EGDT), in which intravenous fluids, vasopressors, inotropes, and blood transfusions were adjusted to reach central hemodynamic targets, than among those receiving usual care. We conducted a trial to determine whether these findings were generalizable and whether all aspects of the protocol were necessary.

- METHODSIn 31 emergency departments in the United States, we randomly assigned patients with septic shock to one of three groups for 6 hours of resuscitation: protocol-based EGDT; protocol-based standard therapy that did not require the placement of a central venous catheter, administration of inotropes, or blood transfusions; or usual care. The primary end point was 60-day in-hospital mortality. We tested sequentially whether protocol-based care (EGDT and standard-therapy groups combined) was superior to usual care and whether protocol-based EGDT was superior to protocol-based standard therapy. Secondary outcomes included longer-term mortality and the need for organ support.
- RESULTSWe enrolled **1341 patients**, of whom 439 were randomly assigned to protocol-based EGDT, 446 to protocol-based standard therapy, and 456 to usual care. Resuscitation strategies differed significantly with respect to the monitoring of central venous pressure and oxygen and the use of intravenous fluids, vasopressors, inotropes, and blood transfusions. By 60 days, there were 92 deaths in the protocol-based EGDT group (21.0%), 81 in the protocol-based standard-therapy group (18.2%), and 86 in the usual-care group (18.9%) (relative risk with protocol-based therapy vs. usual care, 1.04; 95% confidence interval [CI], 0.82 to 1.31; P=0.83; relative risk with protocol-based EGDT vs. protocol-based standard therapy, 1.15; 95% CI, 0.88 to 1.51; P=0.31). There were no significant differences in 90-day mortality, 1-year mortality, or the need for organ support.

- CONCLUSIONS In a multicenter trial conducted in the tertiary care setting, protocol-based resuscitation of patients in whom septic shock was diagnosed in the emergency department did not improve outcomes. (Funded by the National Institute of General Medical Sciences; ProCESS ClinicalTrials.gov number, NCT00510835.).

Early, Goal-Directed Therapy for Septic Shock - A Patient-Level Meta-Analysis.

- PRISM Investigators **N Engl J Med. 2017**

- Background After a single-center trial and observational studies suggesting that early, goal-directed therapy (EGDT) reduced mortality from septic shock, three multicenter trials (ProCESS, ARISE, and ProMISe) showed no benefit. This meta-analysis of individual patient data from the three recent trials was designed prospectively to improve statistical power and explore heterogeneity of treatment effect of EGDT.

- Methods We harmonized entry criteria, intervention protocols, outcomes, resource-use measures, and data collection across the trials and specified all analyses before unblinding. After completion of the trials, we pooled data, excluding the protocol-based standard-therapy group from the ProCESS trial, and resolved residual differences. The primary outcome was 90-day mortality. Secondary outcomes included 1-year survival, organ support, and hospitalization costs. We tested for treatment-by-subgroup interactions for 16 patient characteristics and 6 care-delivery characteristics.

- Results We studied 3723 patients at 138 hospitals in seven countries. **Mortality at 90 days was similar for EGDT** (462 of 1852 patients [24.9%]) and usual care (475 of 1871 patients [25.4%]); the adjusted odds ratio was 0.97 (95% confidence interval, 0.82 to 1.14; P=0.68). EGDT was associated with greater mean (±SD) use of intensive care (5.3±7.1 vs. 4.9±7.0 days, P=0.04) and cardiovascular support (1.9±3.7 vs. 1.6±2.9 days, P=0.01) than was usual care; other outcomes did not differ significantly, although average costs were higher with EGDT. Subgroup analyses showed no benefit from EGDT for patients with worse shock (higher serum lactate level, combined hypotension and hyperlactatemia, or higher predicted risk of death) or for hospitals with a lower propensity to use vasopressors or fluids during usual resuscitation.

- Conclusions In this meta-analysis of individual patient data, EGDT did not result in better outcomes than usual care and was associated with higher hospitalization costs across a broad range of patient and hospital characteristics. (Funded by the National Institute of General Medical Sciences and others; PRISM ClinicalTrials.gov number, NCT02030158 .).

EGDT

- Sıvıların ve antibiyotiklerin erken uygulanmasını (1 – 6 saat) tedavi ve yanıt
- Santral venöz oksihemoglobin doyumu (ScvO2) ≥70
- Santral venöz basınç (CVP) 8 ila 12 mmHg
- Ortalama arter basıncı (MAP) ≥65 mmHg
- İdrar çıkışı ≥0.5 mL / kg / saat idi.

Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, Peterson E, Tomlanovich M, Early Goal-Directed Therapy Collaborative Group N Engl J Med. 2001;345(19):1368

- Sepsis şüphesi bulunan 263 hastanın tek merkezli randomize bir çalışması, direkt tedavide ScvO2, CVP, MAP ve idrar çıkışı kullanıldığında sadece CVP, MAP ve idrar çıkışı hedef alanlara kıyasla hastalarda mortaliteyi azalttığını bildirmiştir (% 31 – % 47)

EGDT

- Septik şok, ProCESS, ARISE, ProMISE çok merkezli randomize çalışmalar mortalite yararı olmadığını bildirdi (mortalite% 20 ila 30)

- Hedeflerin bazılarını olağan bakımı kullanan protokollerde de kullanıldığına dikkat çekilmiştir.

Sıvı Tedavisi

- İyi tanımlanmış (500 mL) hızla infüze edilen boluslarda uygulanmalı
- Klinik ve hemodinamik yanıt ve pulmoner ödemin varlığı veya yokluğu (her bolus öncesi – sonrası)
- Kan basıncı ve doku perfüzyonu kabul edilene kadar, pulmoner ödem ortaya çıkana kadar veya sıvının perfüzyonu artıramaması halinde tekrar edilebilir

Sıvı Seçimi

- Randomize çalışmalardan ve meta-analizlerden elde edilen kanıtlar;
- Sepsis veya septik şok tedavisinde albumin solüsyonları ve kristaloid solüsyonlar (Normal serum fizyolojik, Ringer laktat) ile kullanılanlar arasında ikna edici bir fark bulunmamıştır.

- Pentastarch veya hidroksietil nişasta kullanımdan dolayı potansiyel bir zarar tespit etmiştir.

- Hipertonik salin kullanmanın tedavide bir yeri yoktur.

A comparison of albumin and saline for fluid resuscitation in the intensive care unit.

- Finfer S, Bellomo R, Boyce N, French J, Myburgh J, Norton R, SAFE Study Investigators N Engl J Med**. 2004;**350(22):2247

- BACKGROUND
- It remains uncertain whether the choice of resuscitation fluid for patients in intensive care units (ICUs) affects survival. We conducted a multicenter, randomized, double-blind trial to compare the effect of fluid resuscitation with albumin or saline on mortality in a heterogeneous population of patients in the ICU.

- METHODS We randomly assigned patients who had been admitted to the ICU to receive either 4 percent albumin or normal saline for intravascular-fluid resuscitation during the next 28 days. The primary outcome measure was death from any cause during the 28-day period after randomization.

- RESULTSOf the **6997 patients** who underwent randomization, **3497 were assigned to receive albumin** and **3500 to receive saline**; the two groups had similar baseline characteristics. There were 726 deaths in the albumin group, as compared with 729 deaths in the saline group (relative risk of death, 0.99; 95 percent confidence interval, 0.91 to 1.09; P=0.87). The proportion of patients with new single-organ and multiple-organ failure was similar in the two groups (P=0.85). There were no significant differences between the groups in the mean (+/-SD) numbers of days spent in the ICU (6.5+/-6.6 in the albumin group and 6.2+/-6.2 in the saline group, P=0.44), days spent in the hospital (15.3+/-9.6 and 15.6+/-9.6, respectively; P=0.30), days of mechanical ventilation (4.5+/-6.1 and 4.3+/-5.7, respectively; P=0.74), or days of renal-replacement therapy (0.5+/-2.3 and 0.4+/-2.0, respectively; P=0.41).

- CONCLUSIONS In patients in the ICU, **use of either 4 percent albumin or normal saline for fluid resuscitation results in similar outcomes at 28 days.**

Albumin replacement in patients with severe sepsis or septic shock.

- Caironi P, Tognoni G, Masson S, Fumagalli R, Pesenti A, Romero M, Fanizza C, Caspani L, Faenza S, Grasselli G, Iapichino G, Antonelli M, Parrini V, Fiore G, Latini R, Gattinoni L, ALBIOS Study Investigators **N Engl J Med. 2014**;370(15):1412.

- BACKGROUND Although previous studies have suggested the potential advantages of albumin administration in patients with severe sepsis, its efficacy has not been fully established.

- METHODS In this **multicenter**, open-label trial, we randomly assigned **1818 patients** with severe sepsis, in 100 intensive care units (ICUs), to receive either 20% albumin and crystalloid solution or crystalloid solution alone. In the albumin group, the target serum albumin concentration was 30 g per liter or more until discharge from the ICU or 28 days after randomization. The primary outcome was death from any cause at 28 days. Secondary outcomes were death from any cause at 90 days, the number of patients with organ dysfunction and the degree of dysfunction, and length of stay in the ICU and the hospital.

- RESULTS **During the first 7 days, patients in the albumin group, as compared with those in the crystalloid group**, had a higher mean arterial pressure (P=0.03) and lower net fluid balance (P<0.001). The total daily amount of administered fluid did not differ significantly between the two groups (P=0.10). At 28 days, 285 of 895 patients (31.8%) in the albumin group and 288 of 900 (32.0%) in the crystalloid group had died (relative risk in the albumin group, 1.00; 95% confidence interval [CI], 0.87 to 1.14; P=0.94). At 90 days, 365 of 888 patients (41.1%) in the albumin group and 389 of 893 (43.6%) in the crystalloid group had died (relative risk, 0.94; 95% CI, 0.85 to 1.05; P=0.29). No significant differences in other secondary outcomes were observed between the two groups.

- CONCLUSIONS **In patients with severe sepsis, albumin replacement in addition to crystalloids, as compared with crystalloids alone, did not improve the rate of survival at 28 and 90 days.** (Funded by the Italian Medicines Agency; ALBIOS ClinicalTrials.gov number, NCT00707122.).

Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis.

- Perner A, Haase N, Guttormsen AB, Tenhunen J, Klemenzson G,Åneman A, Madsen KR, Møller MH, Elkjær JM, Poulsen LM, Bendtsen A, Winding R, Steensen M, Berezowicz P, Søe-Jensen P, Bestle M, Strand K, Wiis J, White JO, Thornberg KJ, Quist L, Nielsen J, Andersen LH, Holst LB, Thormar K, Kjældgaard AL, Fabritius ML, Mondrup F, Pott FC, Møller TP, Winkel P, Wetterslev J, 6S Trial Group, Scandinavian Critical Care Trials Group N Engl J Med. 2012;367(2):124. Epub **2012** Jun 27.

- BACKGROUND Hydroxyethyl starch (HES) [corrected]is widely used for fluid resuscitation in intensive care units (ICUs), but its safety and efficacy have not been established in patients with severe sepsis.

  METHODS In this **multicenter**, parallel-group, blinded trial, we randomly assigned patients with severe sepsis to fluid resuscitation in the ICU with either 6% HES 130/0.42 (Tetraspan) or Ringer's acetate at a dose of up to 33 ml per kilogram of ideal body weight per day. The primary outcome measure was either death or end-stage kidney failure (dependence on dialysis) at 90 days after randomization.RESULTSOf the **804 patients** who underwent randomization, 798 were included in the modified intention-to-treat population. The two intervention groups had similar baseline characteristics. At 90 days after randomization, 201 of 398 patients (51%) assigned to HES 130/0.42 had died, as compared with 172 of 400 patients (43%) assigned to Ringer's acetate (relative risk, 1.17; 95% confidence interval [CI], 1.01 to 1.36; P=0.03); 1 patient in each group had end-stage kidney failure. In the 90-day period, 87 patients (22%) assigned to HES 130/0.42 were treated with renal-replacement therapy versus 65 patients (16%) assigned to Ringer's acetate (relative risk, 1.35; 95% CI, 1.01 to 1.80; P=0.04), and 38 patients (10%) and 25 patients (6%), respectively, had severe bleeding (relative risk, 1.52; 95% CI, 0.94 to 2.48; P=0.09). The results were supported by multivariate analyses, with adjustment for known risk factors for death or acute kidney injury at baseline.

  CONCLUSIONS Patients with severe sepsis assigned to fluid resuscitation with HES 130/0.42 had an increased risk of death at day 90 and were more likely to require renal-replacement therapy, as compared with those receiving Ringer's acetate. Funded by the Danish Research Council and others; 6S ClinicalTrials.gov number, NCT00962156.).

Sıvı Seçimi

- Açık bir fayda olmaması ve yüksek albümin maliyetinin olmaması nedeniyle, genellikle albumin solüsyonu yerine kristaloid solüsyon
- Bununla birlikte, büyük miktarda kristaloid verildiğinde (hiperkloremi önlemek veya tedavi etmek için)
- Algılanan bir ihtiyaç varsa (zayıf veriler !)
- Kristalloidler arasında bir formun diğerinden daha faydalı olduğunu önermek için herhangi bir kılavuz yok

Ampirik antibiyotik tedavisi (ilk saat)

- Enfeksiyonun yeri / bölgeleri hızlı bir şekilde tanımlanması ve tedavisi (birincil terapötik)
- İlk antibiyotik uygulamasında gecikme, hastane mortalitesinde artış
- Antibiyotik uygulamasında her saat gecikme nedeniyle mortalite riskinde doğrusal bir artış

Empiric antibiotic treatment reduces mortality in severe sepsis and septic shock from the first hour: results from a guideline-based performance improvement program

- Ferrer R, Martin-Loeches I, Phillips G, Osborn TM, Townsend S, Dellinger RP, Artigas A, Schorr C, Levy MM Crit Care Med. **2014;**42(8):1749
- OBJECTIVES Compelling evidence has shown that aggressive resuscitation bundles, adequate source control, appropriate antibiotic therapy, and organ support are cornerstone for the success in the treatment of patients with sepsis. Delay in the initiation of appropriate antibiotic therapy has been recognized as a risk factor for mortality. To perform a retrospective analysis on the Surviving Sepsis Campaign database to evaluate the relationship between timing of antibiotic administration and mortality.
- DESIGN Retrospective analysis of a large dataset collected prospectively for the Surviving Sepsis Campaign.
- SETTING One hundred sixty-five ICUs in Europe, the United States, and South America. PATIENTS A total of **28,150 patients with severe sepsis and septic shock**, from January **2005 through February 2010**, were evaluated.
- INTERVENTIONS Antibiotic administration and hospital mortality.
- MEASUREMENTS AND MAIN RESULTS A total **of 17,990 patients** received antibiotics after sepsis identification and were included in the analysis. In-hospital mortality was 29.7% for the cohort as a whole. There was a statically significant increase in the probability of death associated with the number of hours of delay for first antibiotic administration. Hospital mortality adjusted for severity (sepsis severity score), ICU admission source (emergency department, ward, vs ICU), and geographic region increased steadily after 1 hour of time to antibiotic administration. Results were similar in patients with severe sepsis and septic shock, regardless of the number of organ failure.
- CONCLUSIONS The results of the analysis of this large population of patients with severe sepsis and septic shock demonstrate that delay in first antibiotic administration was associated with increased in-hospital mortality. In addition, there was a linear increase in the risk of mortality for each hour delay in antibiotic administration. These results underscore the importance of early identification and treatment of septic patients in the hospital setting.

Uygun Antibiyotik

- 2124 hastanın prospektif kohort çalışması, uygun olmayan antibiyotik seçiminin şaşırtıcı derecede yaygın olduğunu ortaya koymuştur (%32)
- Bu hastalarda mortalite, uygun antibiyotik kullananlara kıyasla belirgin artış (%34 - %18)
- Kurumsal protokoller, kalite iyileştirme tedbiri olarak zamanlamaya hitap etmelidir !

Antibiyotik Seçimi

- Alınan son antibiyotikler
- Önceki organizmalar
- Komorbiditeleri (diyabet, organ yetmezliği)
- İmmün kusurları (HİV)
- İnvaziv cihazların varlığı
- Gram boyama verileri ve lokal prevalans ve direnç paternleri
- Topluluk ya da hastane edinimi
- Antimikrobiyal seçim her bir bireye göre yapılmalı

Antibiyotik Seçimi

- Sepsis hastalarının çoğunda olası tüm patojenlere yer vermek için bir veya daha fazla antimikrobiyal antibiyotik ile ampirik geniş spektrumlu terapi önerilmekte
- Hem gram (+) hem de gram (-) bakterilere
- Belirtilirse mantarlara (Candida)
- Nadiren virüslere (Influenza)

Antibiyotik Seçimi

- Septik şok hastaları muhtemel patojenler ve yerel antibiyotik duyarlılıklarına sahip organizmalara bağlı olarak iki farklı sınıftan (kombinasyon terapisi) en az iki antimikrobiyal kombinasyon terapisi almalı
- Kombinasyon terapisi, bilinen veya şüpheli bir patojeni birden fazla ajan ile kapsamak amacıyla verilen çoklu antibiyotikler olarak tanımlanır.

Sepsisli hastalardan izole edilen organizmalar

- Escherichia coli (en yaygın)
- Staphylococcus aureus
- Klebsiella pneumoniae
- Streptococcus pneumoniae

Pathogens and antimicrobial susceptibility profiles in critically ill patients with bloodstream infections: a descriptive study.

Savage RD, Fowler RA, Rishu AH, Bagshaw SM, Cook D, Dodek P, Hall R, Kumar A, Lamontagne F, Lauzier F, Marshall J, Martin CM, McIntyre L, Muscedere J, Reynolds S, Stelfox HT, Daneman N

CMAJ Open. 2016;4(4):E569. Epub 2016 Oct 13.

RESULTS: A total of 1416 pathogens were isolated from 1202 patients. The most common organisms were Escherichia coli (217 isolates [15.3%]), Staphylococcus aureus (175 [12.4%]), coagulase-negative staphylococci (117 [8.3%]), Klebsiella pneumoniae (86 [6.1%]) and Streptococcus pneumoniae (85 [6.0%]). The contribution of individual pathogens varied by site. For 13 ICUs, gram-negative susceptibility rates were high for carbapenems (95.4%), tobramycin (91.2%) and piperacillin-tazobactam (90.0%); however, the proportion of specimens susceptible to these agents ranged from 75.0%-100%, 66.7%-100% and 75.0%-100%, respectively, across sites. Fewer gram-negative bacteria were susceptible to fluoroquinolones (84.5% [range 64.1%-97.2%]). A total of 145 patients (12.1%) had infections caused by highly resistant microorganisms, with significant intersite variation (range 2.6%-24.0%, $\chi 2 = 57.50$, $p<0.001$).

- Klinisyen risk faktörleri bulunduğu zaman diğer potansiyel patojenleri göz önünde bulundurmalı
- Metisiline dirençli S. aureus – hastane dışı artış
- Tam bir "high-end" yükleme dozu kullanarak sepsis ve septik şok olan hastalarda dozun maksimize edilmesine dikkat edilmeli
- Yüksek pik konsantrasyonlarında antimikrobiyal konsantrasyonda daha yüksek klinik başarı oranları bildirilmiştir
- Aralıklı doz rejimleri ile karşılaştırıldığında antibiyotiklerin sürekli infüzyonu halen araştırılmaktadır

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

- Roberts JA, Abdul-Aziz MH, Davis JS, Dulhunty JM, Cotta MO, Myburgh J, Bellomo R, Lipman J Am J Respir Crit Care Med. **2016**;194(6):68

- RATIONALE Optimization **ofβ-lactam antibiotic dosing** for critically ill patients is an intervention that may improve outcomes in severe sepsis.
- OBJECTIVES In this individual patient data **meta-analysis of critically** ill patients with severe sepsis, we aimed to compare clinical outcomes of those treated with continuous versus intermittent infusion ofβ-lactam antibiotics.
- METHODSWe identified relevant randomized controlled trials comparing continuous versus intermittent infusion ofβ-lactam antibiotics in critically ill patients with severe sepsis. We assessed the quality of the studies according to four criteria. We combined individual patient data from studies and assessed data integrity for common baseline demographics and study endpoints, including hospital mortality censored at 30 days and clinical cure. We then determined the pooled estimates of effect and investigated factors associated with hospital mortality in multivariable analysis.
- MEASUREMENTS AND MAIN RESULTS We identified three randomized controlled trials in which researchers recruited a total of **632 patients** with severe sepsis. The two groups were well balanced in terms of age, sex, and illness severity. **The rates of hospital mortality** and clinical cure for the continuous versus intermittent infusion groups were 19.6% versus 26.3% (relative risk, 0.74; 95% confidence interval, 0.56-1.00; P = 0.045) and 55.4% versus 46.3% (relative risk, 1.20; 95% confidence interval, 1.03-1.40; P = 0.021), respectively. In a multivariable model, intermittentβ-lactam administration, higher Acute Physiology and Chronic Health Evaluation II score, use of renal replacement therapy, and infection by nonfermenting gram-negative bacilli were significantly associated with hospital mortality. Continuousβ-lactam administration was not independently associated with clinical cure.

- CONCLUSIONS **Compared with intermittent dosing, administration ofβ-lactam antibiotics by continuous infusion in critically ill patients with severe sepsis is associated with decreased hospital mortality.**

Tedavi Yanıtı

- Sıvılar ve ampirik antibiyotikler uygulandıktan sonra terapötik yanıt sıklıkla değerlendirilmeli
- Klinik, hemodinamik ve laboratuvar parametreleri
- Sıvı tedavisine ilk 6- 24 saat içinde yanıt
- Yanıt daha çok sıvı yönetimini etkiler
- Antimikrobik tedavi ve kaynak kontrolü

Klinik Takip

- Ortalama arter basıncının (MAP) iyileştirilmesi , ≥ 65 mmHg
- İdrar çıkışı, saatlik ≥0.5 mL / kg
- Kalp hızı
- Solunum sayısı
- Deri rengi
- Sıcaklık
- Nabız oksimetresi
- Zihinsel durum

*High versus low blood-pressure target in patients with septic shock.
**Higher versus lower blood pressure targets for vasopressor therapy in shock: a multicentre pilot randomized controlled trial.

- MAP için ideal hedef bilinmemektedir.
- 65-70 mmHg (düşük hedef) veya 80-85 mmHg (yüksek hedef MAP) hedef MAP'a randomize edilen bir çalışma, daha yüksek bir MAP hedeflemede **mortalite yararı olmadığını** bildirmiştir.
- Daha yüksek MAP'lı hastalarda **atriyal fibrilasyon insidansı** daha yüksekti (yüzde 7'ye karşı yüzde 3), bu da> 80 mmHg'lik bir MAP'ı hedeflemenin potansiyel olarak zararlı olduğunu düşündürmektedir.

High versus low blood-pressure target in patients with septic shock.

Asfar P, Meziani F, Hamel JF, Grelon F, Megarbane B, Anguel N, Mira JP, Dequin PF, Gergaud S, Weiss N, Legay F, Le Tulzo Y, Conrad M, Robert R, Gonzalez F, Guitton C, Tamion F, Tonnelier JM, Guezennec P, Van Der Linden T, Vieillard-Baron A, Mariotte E, Pradel G, Lesieur O, Ricard JD, HervéF, du Cheyron D, Guerin C, Mercat A, Teboul JL, Radermacher P, SEPSISPAM Investigators

N Engl J Med. 2014;370(17):1583.

Higher versus lower blood pressure targets for vasopressor therapy in shock: a multicentre pilot randomized controlled trial.

Lamontagne F, Meade MO, Hébert PC, Asfar P, Lauzier F, Seely AJE, Day AG, Mehta S, Muscedere J, Bagshaw SM, Ferguson ND, Cook DJ, Kanji S, Turgeon AF, Herridge MS, Subramanian S, Lacroix J, Adhikari NKJ, Scales DC, Fox-Robichaud A, Skrobik Y, Whitlock RP, Green RS, Koo KKY, Tanguay T, Magder S, Heyland DK, Canadian Critical Care Trials Group.

Intensive Care Med. 2016;42(4):542. Epub 2016 Feb 18.

Hemodinami

- Sıvı tedavisi yanıtı (statik veya dinamik belirleyici)
- İleri sıvı yönetimini belirlemek için kullanılmalı
- Tedavi yanıt vermeyi tahmin etmede statik belirleyicilerden (CVP gibi) ziyade daha doğru oldukları için dinamik belirleyiciler tercih
- Kullanımlarının mortalite gibi klinik olarak etkili sonuçlar geliştirip geliştirmediği kanıtlanmamış !

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

- Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, Kumar A, Sevransky JE, Sprung CL, Nunnally ME, Rochwerg B, Rubenfeld GD, Angus DC, Annane D, Beale RJ, Bellinghan GJ, Bernard GR, Chiche JD, Coopersmith C, De Backer DP, French CJ, Fujishima S, Gerlach H, Hidalgo JL, Hollenberg SM, Jones AE, Karnad DR, Kleinpell RM, Koh Y, Lisboa TC, Machado FR, Marini JJ, Marshall JC, Mazuski JE, McIntyre LA, McLean AS, Mehta S, Moreno RP, Myburgh J, Navalesi P, Nishida O, Osborn TM, Perner A, Plunkett CM, Ranieri M, Schorr CA, Seckel MA, Seymour CW, Shieh L, Shukri KA, Simpson SQ, Singer M, Thompson BT, Townsend SR, Van der Poll T, Vincent JL, Wiersinga WJ, Zimmerman JL, Dellinger RP **Intensive Care Med. 2017**;43(3):304.
- OBJECTIVETo provide an update to "Surviving Sepsis Campaign Guidelines for Management of Sepsis and Septic Shock: 2012".DESIGNA consensus committee of 55 international experts representing 25 international organizations was convened. Nominal groups were assembled at key international meetings (for those committee members attending the conference). A formal conflict-of-interest (COI) policy was developed at the onset of the process and enforced throughout. A stand-alone meeting was held for all panel members in December 2015. Teleconferences and electronic-based discussion among subgroups and among the entire committee served as an integral part of thedevelopment.METHODSThe panel consisted of five sections: hemodynamics, infection, adjunctive therapies, metabolic, and ventilation. Population, intervention, comparison, and outcomes (PICO) questions were reviewed and updated as needed, and evidence profiles were generated. Each subgroup generated a list of questions, searched for best available evidence, and then followed the principles of the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system to assess the quality of evidence from high to very low, and to formulate recommendations as strong or weak, or best practice statement when applicable.RESULTSThe Surviving Sepsis Guideline panel provided 93 statements on early management and resuscitation of patients with sepsis or septic shock. Overall, 32 were strong recommendations, 39 were weak recommendations, and 18 were best-practice statements. No recommendation was provided for four questions.CONCLUSIONSSubstantial agreement exists among a large cohort of international experts regarding many strong recommendations for the best care of patients with sepsis. Although a significant number of aspects of care have relatively weak support, evidence-based recommendations regarding the acute management of sepsis and septic shock are the foundation of improved outcomes for these critically ill patients with high mortality.

Statik Belirleyiciler

- MAP
- CVC ölçümleri kullanılmıştır:

8 ila 12 mmHg hedefinde CVP

ScvO2 ≥70 (PAC'den ≥65 yüzde)

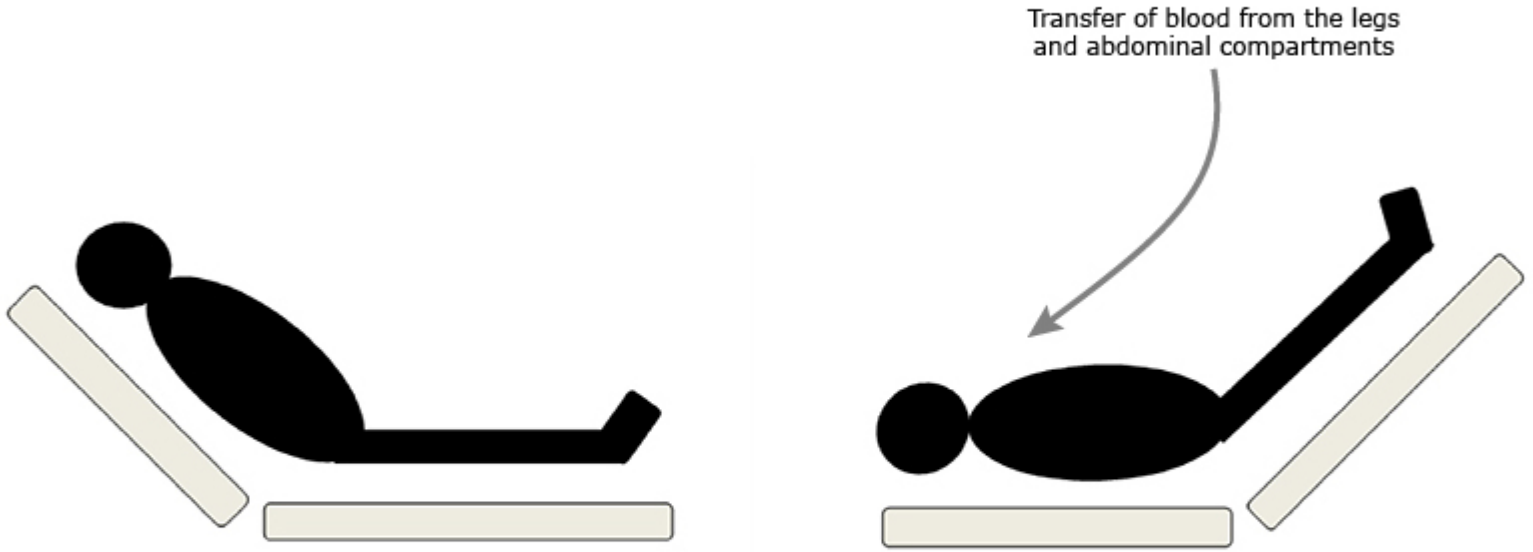
- Septik şoklu hastaların erken dönemdeki protokol tabanlı bir tedavide bu parametrelere bir mortalite fayda rapor etmiş olsa da, o zamandan beri yayınlanan denemeler (ProCESS, ARISE, ProMISe) kullanımları ile ilişkili mortalite yararı bildirmemiştir

Dinamik Belirleyiciler

- Vena kava çap
- Radial arter nabız basıncı
- Aortik kan akışı tepe hızı
- Sol ventrikül çıkış yolu hız-zaman integrali
- Brakiyal arter kan akımı hızındaki değişiklikleri
- Sıvı yanıtının dinamik belirleyicileri
- Hastalar sinüs ritminde olduğu ve pasif yeterli bir tidal hacim ile havalandırılmaları durumunda, statik önlemlerden daha üstün
- Aktif olarak nefes alan veya düzensiz kalp ritmi olan hastalarda, pasif bacak kaldırma manevrasına (ekokardiyografi, arteriyel puls dalga formu analizi veya pulmoner arter kateterizasyonu ile ölçülür) yanıt olarak kardiyak output bir artış da sıvı yanıtını öngörür.
- Bunların arasından seçim yapmak durumu teknik uzmanlığa bağlı olmakla birlikte, pasif bir bacak kaldırma manevrası daha doğru ve yapılabilir

(Mortalite, ventilatörden ayrı günleri raporlayan ileriye dönük çalışmalara ihtiyaç duyulmakta)

Passive leg raising maneuver for fluid responsiveness



Passive leg raising maneuver. After starting with the head elevated to 45 degrees, rapidly repositioning the patient with legs elevated to 30 to 45 degrees allows autotransfusion of blood from the legs into the thorax. An increase in cardiac output suggests that the patient might be fluid responsive.

Adapted From: Marik PE, Monnet X, Teboul JL. Hemodynamic parameters to guide fluid therapy. Ann Intensive Care 2011; 1:1. Reproduced under the terms of the Creative Commons Attribution License.

Graphic 109407 Version 1.0

Laboratuvar

Lactate clearance –

Optimum frekans ?

Düşene kadar sepsisli hastalarda serum laktatını takip ederiz (her altı saatte bir)

Kılavuzlar, laktatın normalleştirilmesini desteklemektedir

Laktat tek başına resüsitasyon takibi için olumlu bulunmamakta

Lactate clearance

- [(başlangıç laktat - laktat>2 saat) /başlangıç laktat]x 100
- Resüsitasyonun ilk 12 saati boyunca laktat kütlesi ve laktat aralığı değişimi etkili bir potansiyel belirteç olarak değerlendirilmiştir
- Bir meta-analizi, laktat kılavuzlu resüsitasyonun laktatsız resüsitasyona kıyasla **mortalitede bir azalmaya** neden olduğunu bildirmiştir
- Diğer meta-analizler, normal bakımı veya ScvO2 normalizasyonu ile karşılaştırıldığında laktat temizleme stratejileri kullanıldığında az miktarda mortalite fayda bildirmiştir

Early lactate clearance-guided therapy in patients with sepsis: a meta-analysis with trial sequential analysis of randomized controlled trials.
Gu WJ, Zhang Z, Bakker J
Intensive Care Med. 2015;41(10):1862.

Department of Anesthesiology, Affiliated Drum Tower Hospital of Medical College of Nanjing University, Nanjing, China.
26154408

PubMed
Early goal-directed therapy for severe sepsis and septic shock: A living systematic review.
Simpson SQ, Gaines M, Hussein Y, Badgett RG
J Crit Care. 2016;36:43.

Lactate

- Venöz / arteriyel kanda?
- Her kurum kendi korelasyonuna bakmalı
- 2014 meta analiz Bloom 0,25 (Normal değerlerde)
- 2016 Paguet prospektif çalışmada 0,6mmol/L
- 2016 prospektif çalışmada 0,4 mmol/L, iyi bir korelasyon
- VKG sepsiste lactate düzeyi için tarama yöntemi ?
- Özellikle ≤ 2mmol/L ise AKG da da ≤ 2mmol/L

Vazopresörler

- Yeterli sıvı resüsitasyonuna rağmen hipotansif
- Kardiyojenik pulmoner ödem geliştiren hasta

- Küçük randomize çalışmaların ve gözlemsel çalışmaların meta-analizlerine dayanarak, pratikte bir paradigma değişikliği meydana geldi, çünkü çoğu uzman bu popülasyonda dopamini değil ilk seçenek ajan olarak **norepinefrin**'i tercih etmeyi tercih etti

Vazopresörler

- **Norepinefrini birinci ajan olarak tekli ajan olarak destekleyen veriler**
- Vasopressörle bir başka vazopressör karşılaştıran sayısız denemeden elde edilmiştir
- Nöroleptin ile fenilefrin
- norepinefrin ile vasopressin
- norepinefrin ile terlipressin
- norepinefrin ile epinefrin
- vazopressin ile terlipressin
- Karşılaştırmalarda mortalite, yoğun bakımda veya hastanede kalış sürelerinde ya da böbrek yetmezliği insidansında ikna edici farklılık bulamamasına rağmen [2012]
- iki 2012 meta-analizinde, septik şok sırasında **dopamin alan hastalar arasında mortalitenin arttığı** bildirildi Norepinefrin alanlar (yüzde 53 ila 54, buna karşılık yüzde 48 ila 49)
- Dopamin, norepinefrin'e göre iki kat **daha sık aritmik olay** tespit edildi.
- Sepsisli hastalarda vazopressörün ilk seçimi sıklıkla bireyselleştirilmekte
- Dopamin düşük doz böbrekleri korunma" amacıyla kullanılmamalı

Association Between US Norepinephrine Shortage and Mortality Among Patients With Septic Shock.

- Vail E, Gershengorn HB, Hua M, Walkey AJ, Rubenfeld G, Wunsch H **JAMA. 2017**;317(14):1433.
- Importance **Drug shortages** in the United States are common, but their effect on patient care and outcomes has rarely been reported.
- ObjectiveTo assess changes to patient care and outcomes associated with a 2011 national shortage of norepinephrine, the first-line vasopressor for septic shock. Design, Setting, and ParticipantsRetrospective cohort study of **26 US hospitals** in the Premier Healthcare Database with a baseline rate of norepinephrine use of at least 60% for patients with septic shock. The cohort included adults with septic shock admitted to study hospitals between July 1, 2008, and June 30, 2013 (n = **27 835**).ExposuresHospital-level norepinephrine shortage was defined as any quarterly (3-month) interval in 2011 during which the hospital rate of norepinephrine use decreased by more than 20% from baseline.Main Outcomes and MeasuresUse of alternative vasopressors was assessed and a multilevel mixed-effects logistic regression model was used to evaluate the association between admission to a hospital during a norepinephrine shortage quarter and in-hospital mortality.ResultsAmong 27 835 patients (median age, 69 years [interquartile range, 57-79 years]; 47.0% women) with septic shock in 26 hospitals that demonstrated at least 1 quarter of norepinephrine shortage in 2011, norepinephrine use among cohort patients declined from 77.0% (95% CI, 76.2%-77.8%) of patients before the shortage to a low of 55.7% (95% CI, 52.0%-58.4%) in the second quarter of 2011; phenylephrine was the most frequently used alternative vasopressor during this time (baseline, 36.2% [95% CI, 35.3%-37.1%]; maximum, 54.4% [95% CI, 51.8%-57.2%]). Compared with hospital admission with septic shock during quarters of normal use, hospital admission during quarters of shortage was associated with an increased rate of in-hospital mortality (9283 of 25 874 patients [35.9%]vs 777 of 1961 patients [39.6%], respectively; absolute risk increase = 3.7% [95% CI, 1.5%-6.0%]; adjusted odds ratio = 1.15 [95% CI, 1.01-1.30]; P = .03).

- Conclusions and Relevance Among patients with septic shock in US hospitals affected by the 2011 norepinephrine shortage, the most commonly administered alternative vasopressor was phenylephrine. Patients admitted to these hospitals during times of shortage had higher in-hospital mortality.

Epinefrine & Fenilefrin

- 26 hastaneden yaklaşık 28.000 hasta
- Norepinefrin temin edilemediği dönemlerinde
- Fenilefrin en yakın alternatif ajandır (kullanım% 36'dan yüzde 54 ")
- Aynı dönemde, septik şoktan mortalite oranı yüzde 36'dan yüzde 40'a yükseldi.
- Bunun fenilefrin ile doğrudan ilişkili olup olmadığı bilinmemektedir.

İlave Tedaviler

- glukokortikoidler
- inotropik ajanlar
- kırmızı kan hücresi (RBC) transfüzyonu
- rutin olarak uygulanmaz
- refrakter vakalar veya özel durumlar için kullanılabileceğini kabul etmektedir.

Lower versus higher hemoglobin threshold for transfusion in septic shock.

- Holst LB, Haase N, Wetterslev J, Wernerman J, Guttormsen AB, Karlsson S, Johansson PI, Aneman A, Vang ML, Winding R, Nebrich L, Nibro HL, Rasmussen BS, Lauridsen JR, Nielsen JS, Oldner A, PettiläV, Cronhjort MB, Andersen LH, Pedersen UG, Reiter N, Wiis J, White JO, Russell L, Thornberg KJ, Hjortrup PB, Müller RG, Møller MH, Steensen M, Tjäder I, Kilsand K, Odeberg-Wernerman S, SjøbøB, Bundgaard H, ThyøMA, Lodahl D, Mærkedahl R, Albeck C, Illum D, Kruse M, Winkel P, Perner A, TRISS Trial Group, Scandinavian Critical Care Trials Group N Engl J Med. 2014;371(15):1381. Epub 2014 Oct 1.

- BACKGROUND Blood transfusions are frequently given to patients with septic shock. However, the benefits and harms of different **hemoglobin thresholds for transfusion** have not been established.
- METHODS In this **multicenter**, parallel-group trial, we randomly assigned patients in the intensive care unit (ICU) who had septic shock and a hemoglobin concentration of **9 g** per deciliter or less to receive 1 unit of leukoreduced red cells when the hemoglobin level was **7 g** per deciliter or less (lower threshold) or when the level was 9 g per deciliter or less (higher threshold) during the ICU stay. The primary outcome measure was death by 90 days after randomization.
- RESULTS We analyzed data from **998 of 1005 patients** (99.3%) who underwent randomization. The two intervention groups had similar baseline characteristics. In the ICU, the lower-threshold group received a median of 1 unit of blood (interquartile range, 0 to 3) and the higher-threshold group received a median of 4 units (interquartile range, 2 to 7). At 90 days after randomization, 216 of 502 patients (43.0%) assigned to the lower-threshold group, as compared with 223 of 496 (45.0%) assigned to the higher-threshold group, had died (relative risk, 0.94; 95% confidence interval, 0.78 to 1.09; P=0.44). The results were similar in analyses adjusted for risk factors at baseline and in analyses of the per-protocol populations. The numbers of patients who had ischemic events, who had severe adverse reactions, and who required life support were similar in the two intervention groups.

- CONCLUSIONS **Among patients with septic shock, mortality at 90 days and rates of ischemic events and use of life support were similar among those assigned to blood transfusion at a higher hemoglobin threshold and those assigned to blood transfusion at a lower threshold; the latter group received fewer transfusions.**