# Antibiyotik Yönetişiminde Prokalsitonin Testinin Rolü?

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Enfeksiyon Hastalıkları ve Klinik Mikrobiyoloji ABD

Ankara Şehir Hastanesi

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# Sunum Planı

1. Antibiyotik yönetişiminde Biyomarkerlar
2. PCT test kinetiği
3. Literatürde PCT temelli algoritmalar
4. Özel popülasyonlarda PCT temelli algoritmalar
5. Hastalık ciddiyeti ve mortalite değerlendirmesinde PCT testi
6. Olgu örnekleriyle PCT
7. Atellica® IM B·R·A·H·M·S PCT Testi

# Antibiotic resistance – an increasing threat to human health

Antibiotic resistance is the ability of bacteria to combat the action of one or more antibiotics. Humans and animals do not become resistant to antibiotics, but bacteria carried by humans and animals can.

The burden of infections with bacteria resistant to antibiotics on the European population is comparable to that of influenza, tuberculosis and

**33000 deaths**

Each year, 33000 people die from an infection due to bacteria resistant to antibiotics. This is comparable to the total number of passengers of more than 100 medium-sized airplanes.

**75 %** healthcare-associated infections

## Solutions

There is still time to turn the tide
ensure that antibiotics remain ef

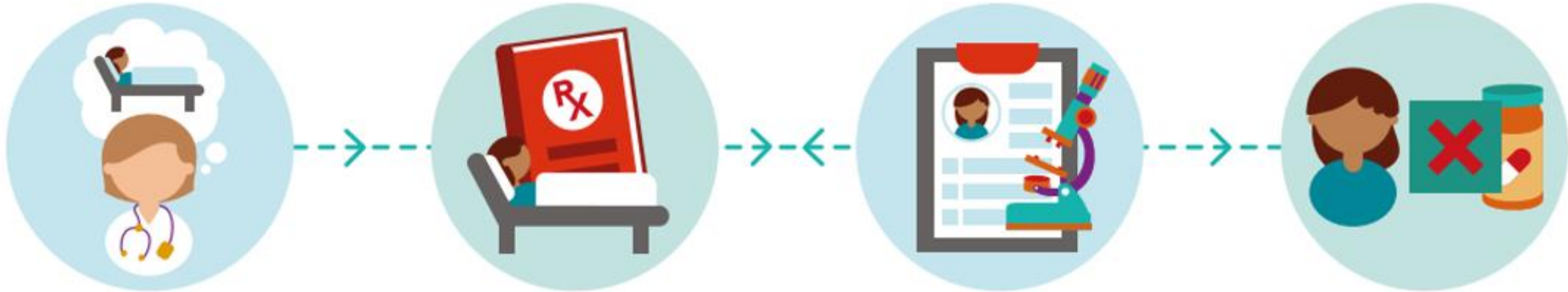
Using a
prudent
they are

- ✓ **Antimikrobiyal yönetişim programlarının uygulanması**
- ✓ **Antibiyotiklerin rasyonel kullanımı**
- ✓ **Kısa süreli tedaviler**

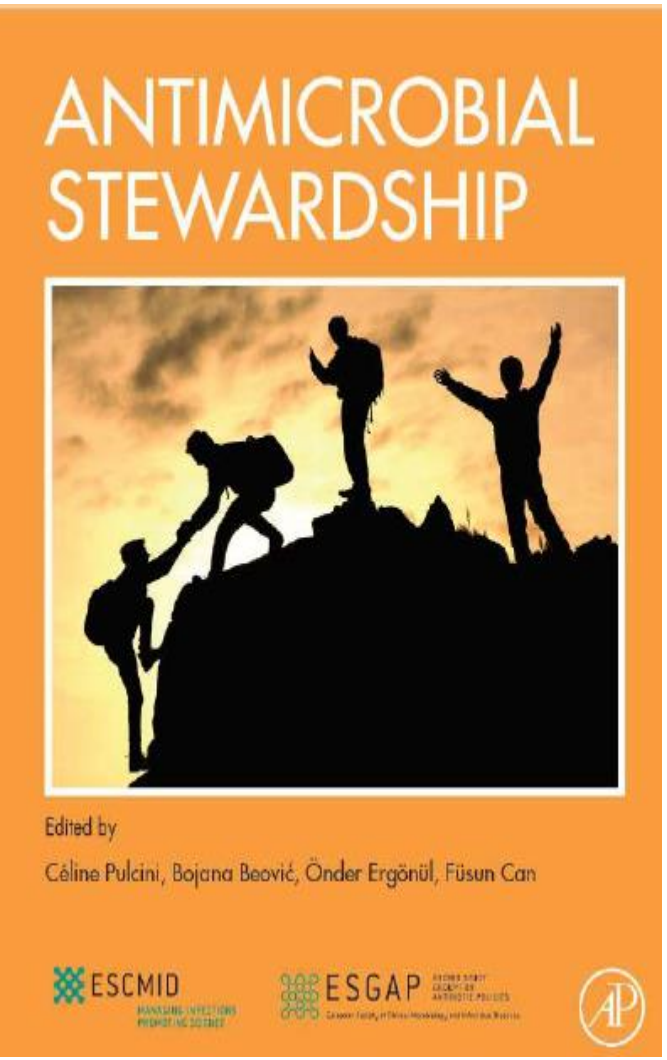
# ANTIMICROBIAL STEWARDSHIP PROGRAMMES IN HEALTH-CARE FACILITIES IN LOW- AND MIDDLE-INCOME COUNTRIES

World Health Organization

## Uygun antibiyotik tedavisi




| Endikasyon? | Tedavi | Tedavi Optimizasyonu | Tedavi Süresi |
|---|---|---|---|
| Bakteriyel/ viral enfeksiyon? | Ciddi hastalık? | Endikasyon doğru mu? | Kısa süreli tedavi? |
| İnflamasyon? | Olası patojenler? | Antibiyotik uygunluğu? | PCT temelli algoritmalar |
| Mikrobiyolojik testler? | Ampirik tedavi? | Kültür sonuçları? | |
| Biyomarkerlar? PCT? | | De-eskalasyon? | |

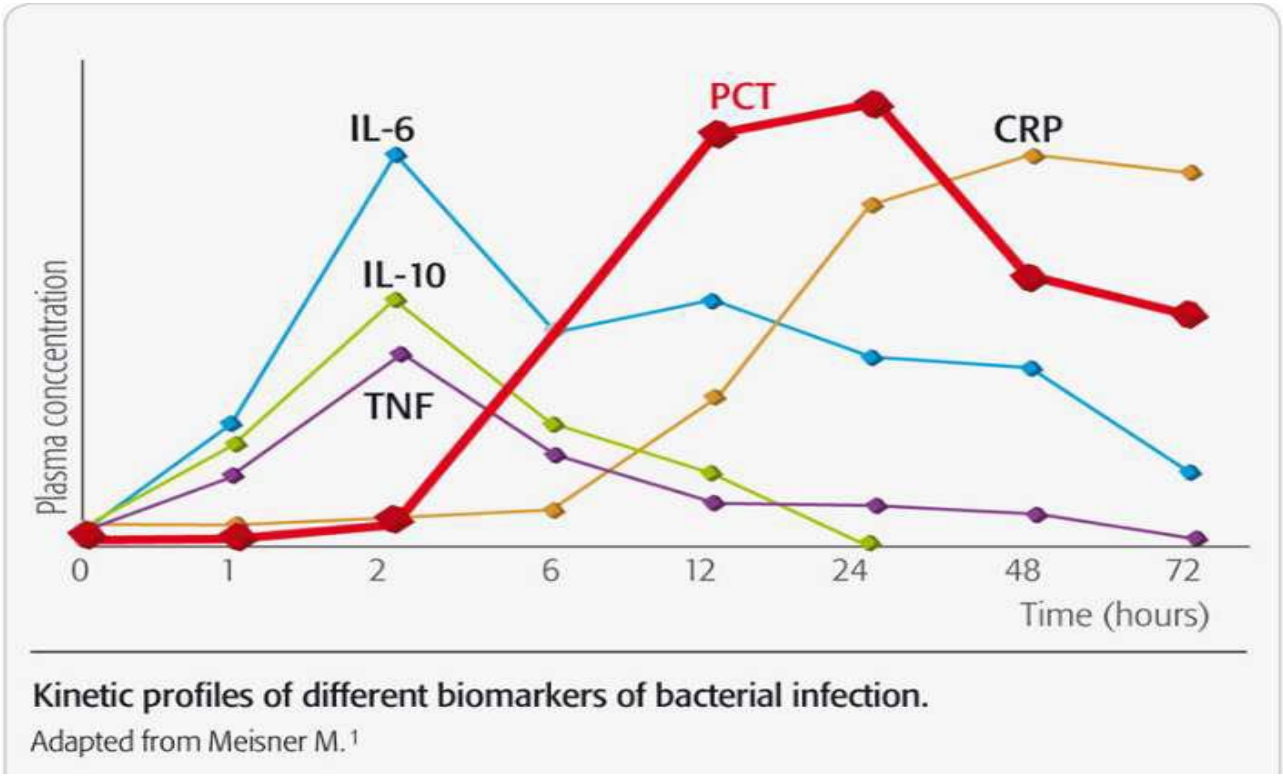



Chapter 6

# Rapid Diagnostics and Biomarkers for Antimicrobial Stewardship

- ✓**Enfeksiyon hastalarında non-spesifik semptom ve bulgular!!!**
- ✓**İnflamasyon ve nonenfeksiyöz durumlarda benzer bulgular**
- ✓**Biyomarkerlar; gereksiz antibiyotik kullanımını ⬇**
- ✓**Güvenilir, ulaşılabilir olmalı**
- ✓**Hızlı sonuç vermeli, kolay yorumlanabilir olmalı!!!!**
- ✓**İyi tanısal ve prognostik performans**
- ✓**Sensitivite ve spesifitesi yüksek olmalı**

# Bakteriyel Enfeksiyonlarda Farklı Biyomarkerların Kinetiği




Kinetic profiles of different biomarkers of bacterial infection.
Adapted from Meisner M.[1]

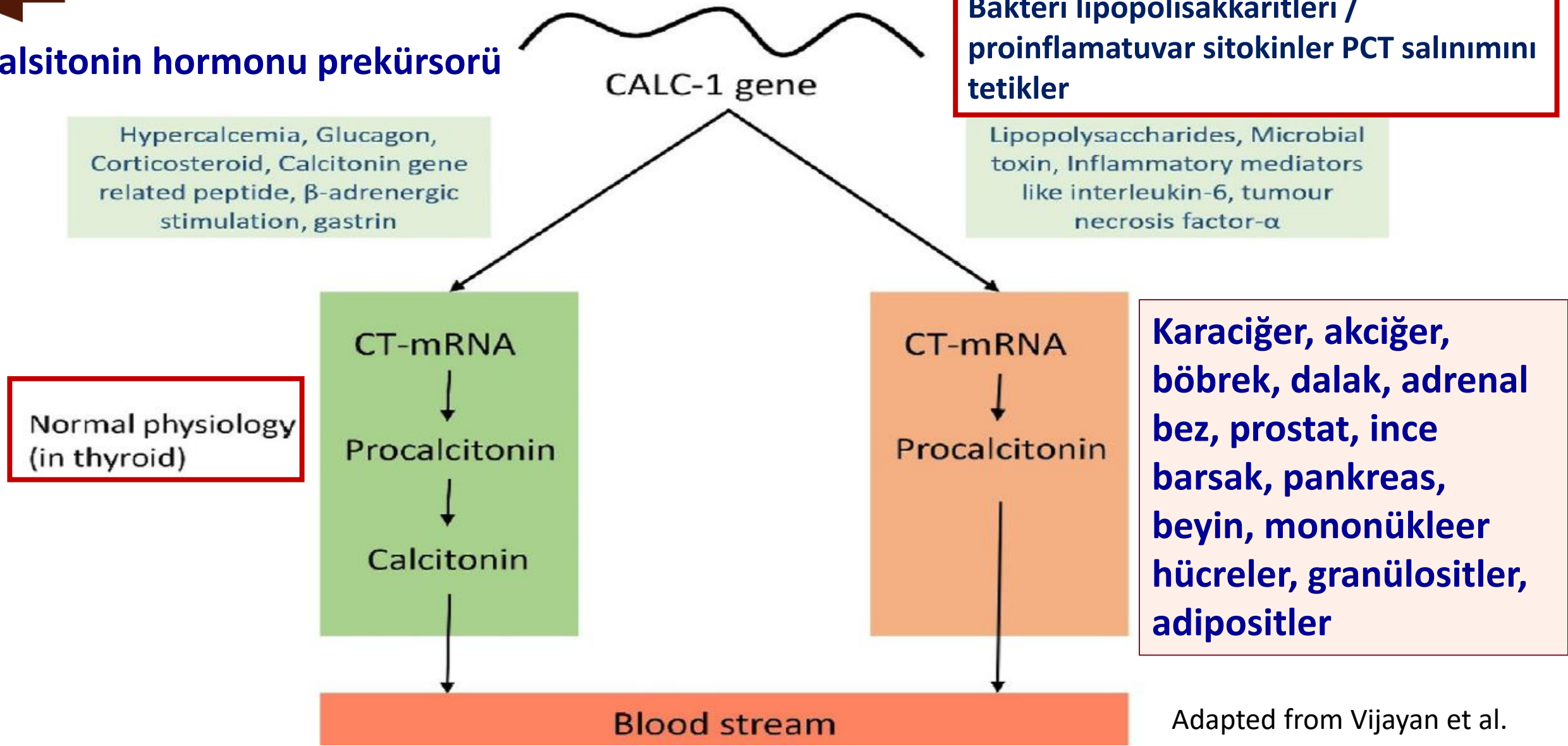
**PCT 3 - 4 saatte yükselir, 12-24 saatte pik yapar**
**IL-6 ve TNF hızla pik yapar, hızla normale döner**

**PCT; IL-6, CRP ve laktat'a göre daha sensitif ve spesifiktir**

# Prokalsitonin

**Kalsitonin hormonu prekürsorü**

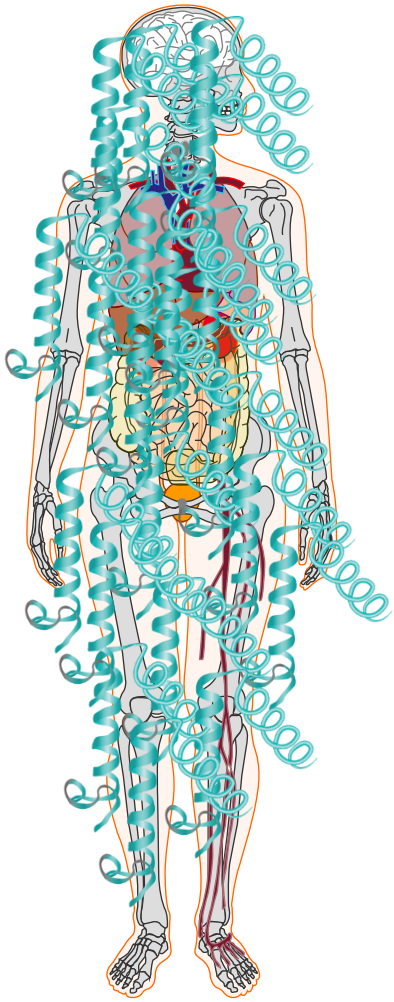
**Bakteri lipopolisakkaritleri / proinflamatuvar sitokinler PCT salınımını tetikler**

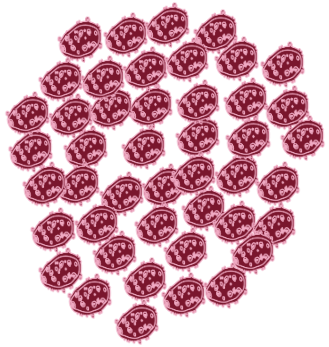



**Karaciğer, akciğer, böbrek, dalak, adrenal bez, prostat, ince barsak, pankreas, beyin, mononükleer hücreler, granülositler, adipositler**

Adapted from Vijayan et al.

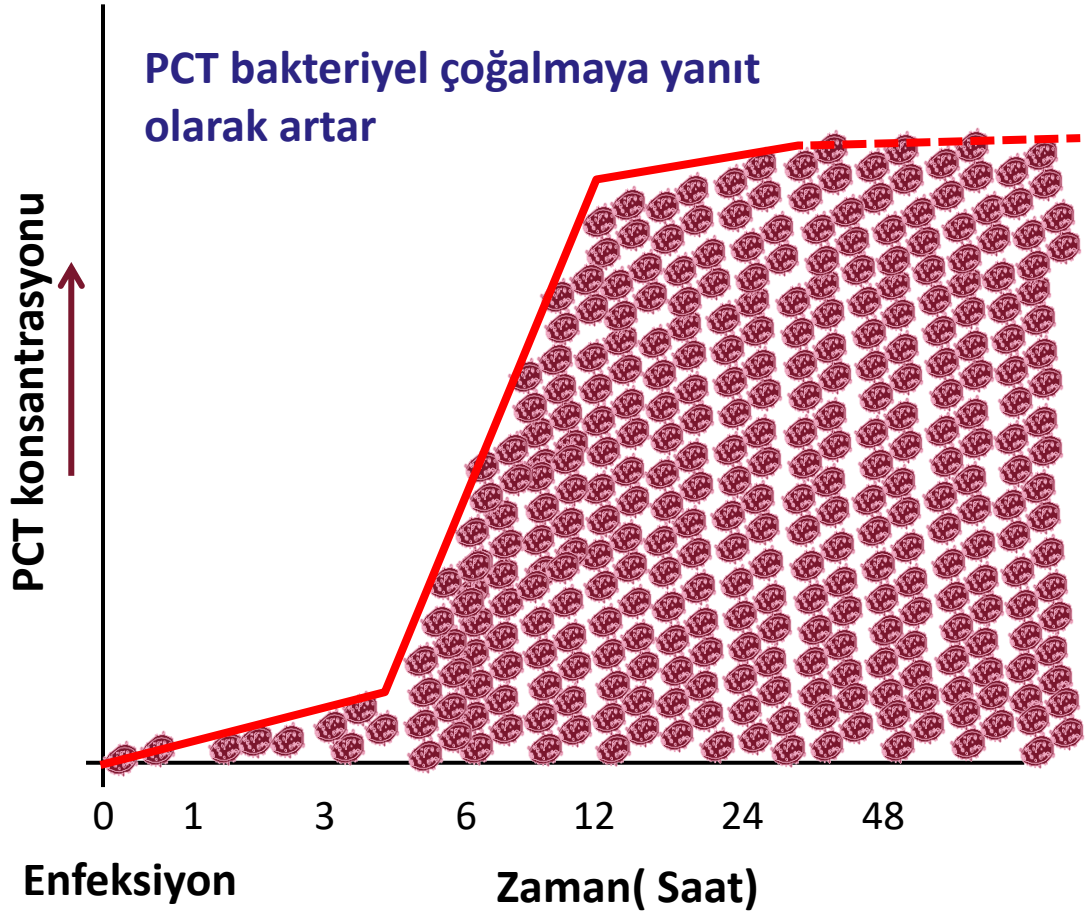
# Bakteriyel enfeksiyon varlığında PCT çok sayıda organ / dokudan salınarak dolaşıma geçer!!





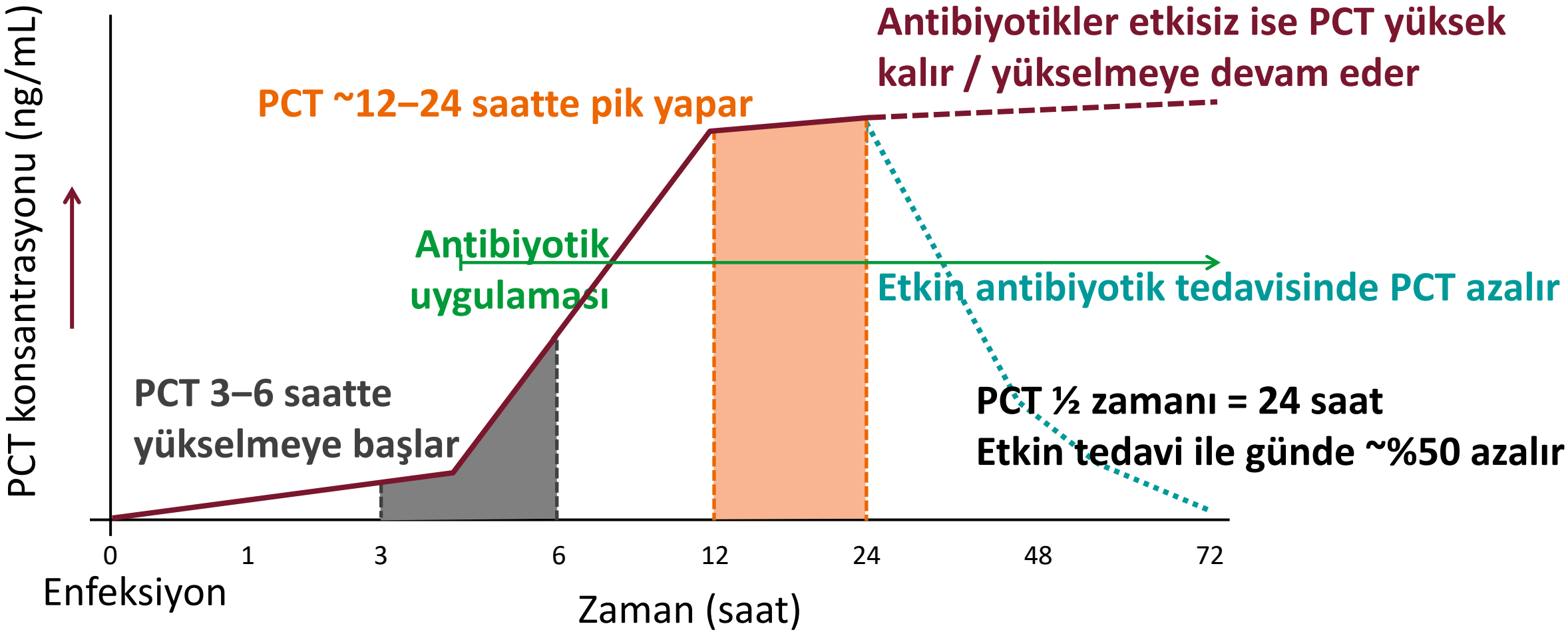
Vücutta bakteriyel çoğalma

Enfekte organ /dokularda PCT salınımının tetiklenmesi



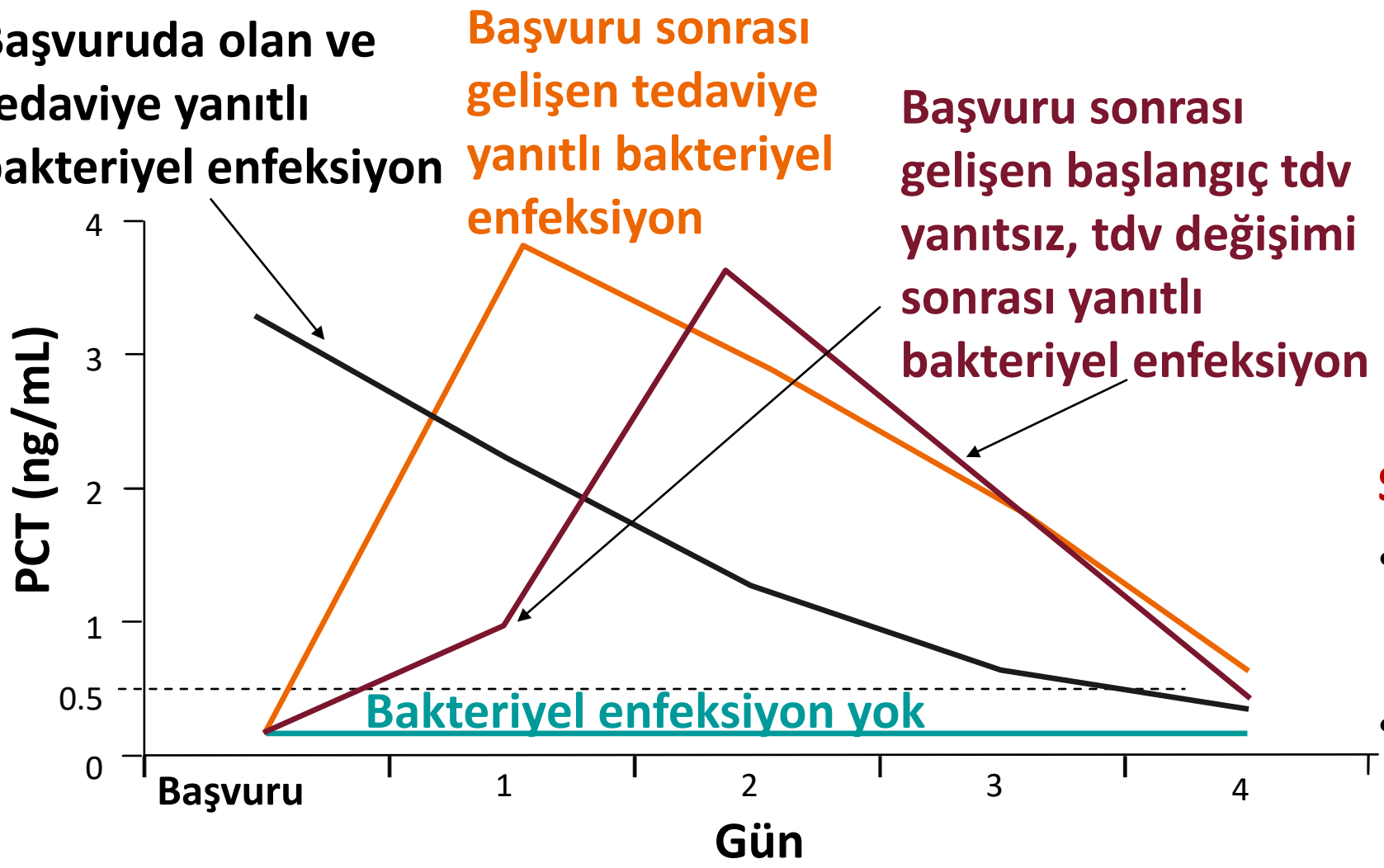

Botos I, et al. Structure 2011;19:447-59.
Brunkhorst FM, et al. Intensive Care Med 1998;24:888-9.

# Seri PCT ölçümü antibiyotik yönetişimine katkı sağlar!!!




Schuetz P, et al. Arch Intern Med. 2011;171(15):1322-31.

# PCT seri takibi -hastane yatış sürecinde tanısal değere sahiptir!!




**Seri prokalsitonin ölçümü:**

- **Bakteriyel enfeksiyon riskinin değerlendirilmesi**
- **Antibiyotik etkinliğinin değerlendirilmesi**


Schuetz P, et al. Arch Intern Med. 2011;171(15):1322-31.

Siemens Healthineers Atellica® IM B·R·A·H·M·S Procalcitonin Assay package insert, 11200767_EN Rev. 01, 2018-07.

Case report PCT examples courtesy of M. Broyles, Pharm D. Five Rivers Medical Center, Pocahontas, AR.

FDA NEWS RELEASE

# FDA clears test to help manage antibiotic treatment for lower respiratory tract infections and sepsis

**23 Şubat 2017**

- ✓ **Alt solunum yolu infeksiyonlarında antibiyotik başlama /kesme kararında**
- ✓ **Sepsis hastalarında antibiyotik tedavisinin kesilmesi kararında klinisyenlere yardımcı**

**FDA Brahms PCT testi kullanımını onayladı**

infection, as a biomarker to help make antibiotic management decisions in patients with

https://www.fda.gov/NewsEvents/Newsroom/ PressAnnouncements/ucm543160.htm·

# Rehber Önerileri & FDA Onayı???

- ✓ Sepsis 2021 rehberinde PCT testinin tedavi başlangıcında kullanımına karşı öneri mevcut
  - ✓ Sensitivite ve spesifite🡻 (%77 & %79)
  - ✓ Mortalite ve yatış süresi üzerine anlamlı etkisi bildirilmemiş

- ✓ IDSA 2019 Pnömoni Rehberi; Toplum kaynaklı pnömonide başlangıç PCT ‘ye bakılmaksızın antibiyotik başlanmasını öneriyor

- ✓ IDSA HAP/VAP rehberi PCT duyarlılık ve özgüllüğü HAP ve VAP için >% 90 olmak şartıyla antibiyotik başlama kararında klinik kriterlere ek olarak kullanılabilir

  %67 ve %83 dolayısıyla tdv başlangıcında PCT önermiyor

1 Antibiyotik yönetişimi ve Biyomarkerlar

2 PCT test kinetiği

3 Literatürde PCT temelli algoritmalar

4 Özel popülasyonlarda PCT temelli algoritmalar

5 Hastalık ciddiyeti ve mortalite değerlendirmesinde PCT testi

6 Olgu örnekleriyle PCT

7 Atellica® IM B·R·A·H·M·S PCT Testi

Open Forum Infectious Diseases

MAJOR ARTICLE

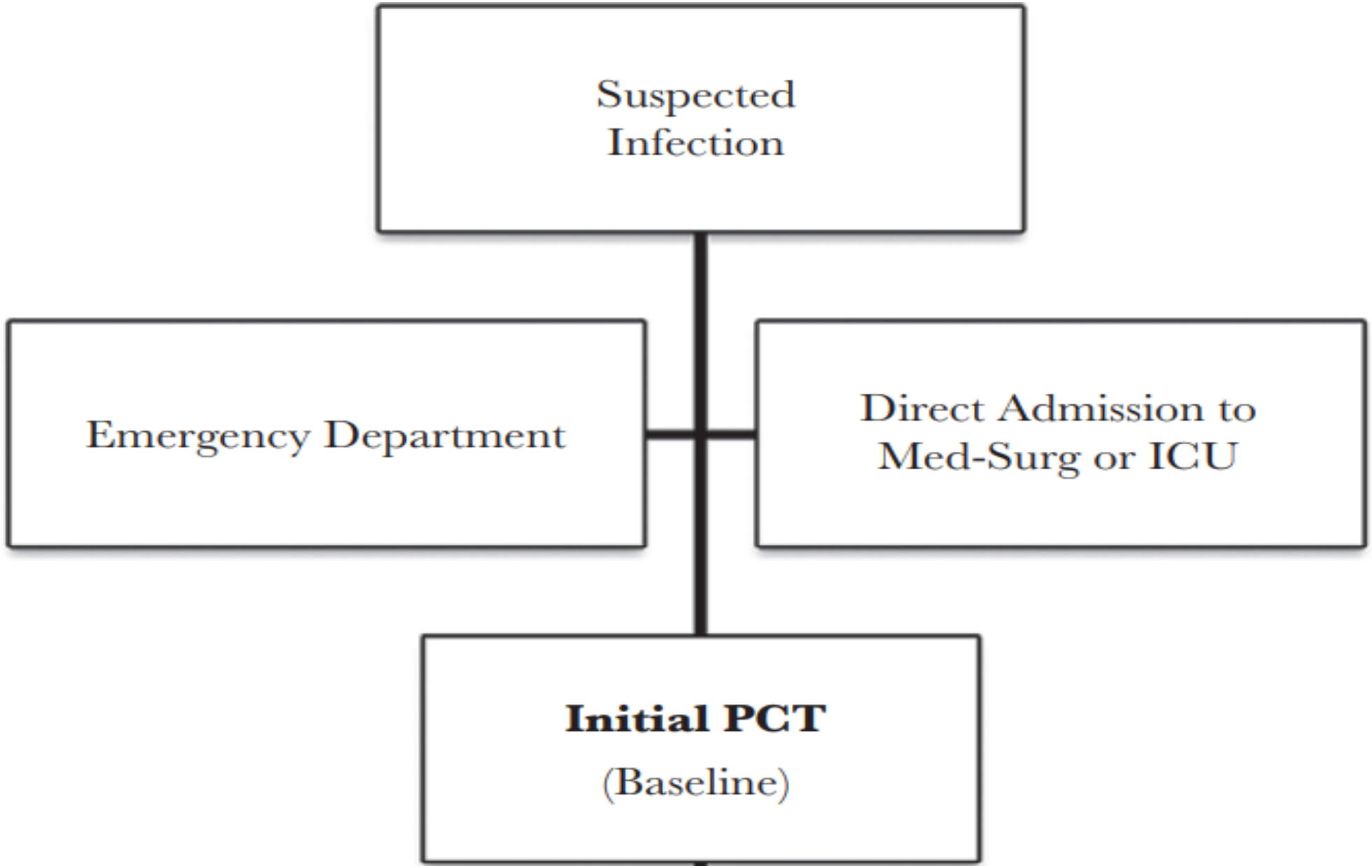
# Impact of Procalcitonin-Guided Antibiotic Management on Antibiotic Exposure and Outcomes: Real-world Evidence

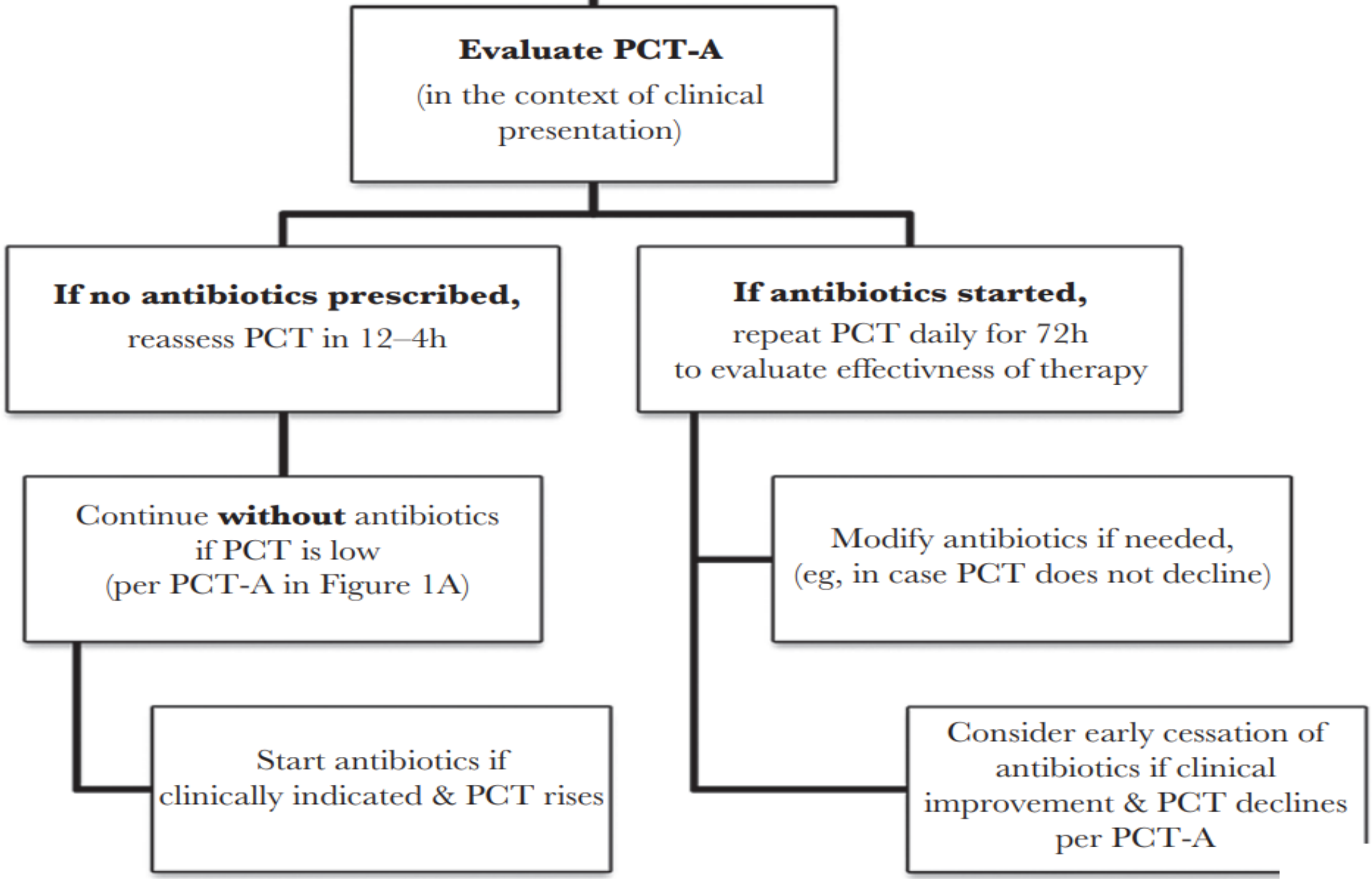
***Methods.*** A single-center, retrospective cohort study was conducted to evaluate the impact of adding PCT-A to stewardship

- ✓ **Retropektif kohort; tek merkez**
- ✓ **PCT algoritması + antimikrobiyal yönetişim uygulanan 4 yıllık dönem (1167 hasta)& Sadece AMY uygulanan dönem (985 hasta) iv antibiyotik kullanımı açısından karşılaştırılmış**
- ✓ **Antimikrobiyal tedavi günü median 9 vs 17, p<0.0001**
- ✓ **AMY programlarına PCT eklenmesi ile antibiyotik ilişkili yan etkilerde**

**Table 1. Cohort Characteristics of Patients in the Pre-PCT Implementation and Post-PCT Implementation Groups**

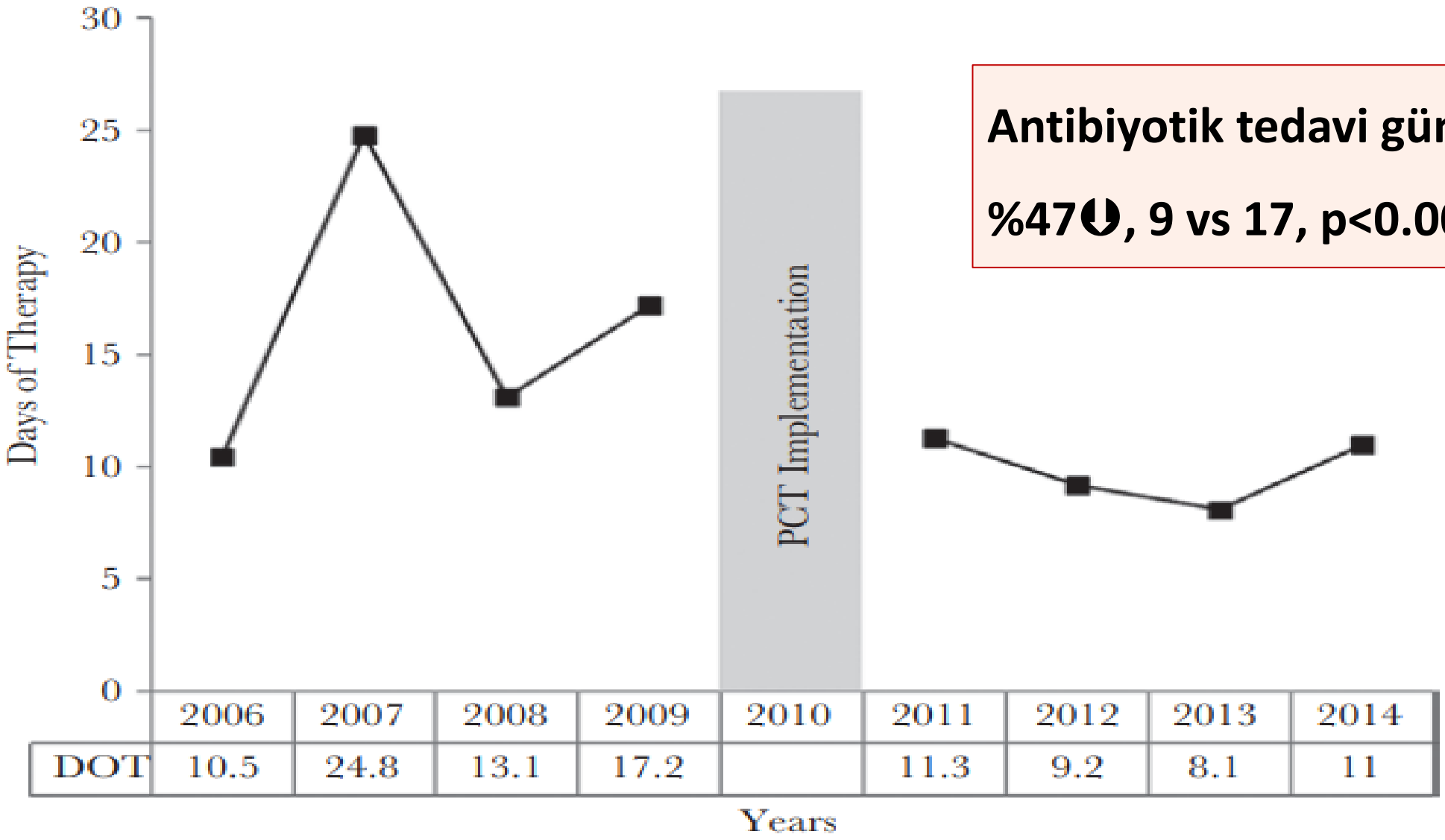
| Characteristic | Pre-PCT (2006–2009) (n = 985) | Post-PCT (2011–2014) (n = 1167) | *P* Value |
|---|---|---|---|
| Age, median (IQR), y | 72 (61–83) | 73 (62–83) | .25 |
| Male gender, % | 42.4 | 43.6 | .61 |
| Case mix index, mean | 1.026 | 1.032 | .06 |
| Discharge diagnosis, n (%) | | | |
| Pneumonia | 589 (59.8) | 641 (54.9) | .02 |
| COPD | 166 (16.9) | 291 (18.8) | <.001 |
| Kidney and genitourinary infection | 122 (12.4) | 121 (10.4) | .14 |
| Sepsis | 13 (1.3) | 90 (7.7) | <.001 |
| Skin and skin structure infection | 62 (6.3) | 71 (6.1) | .83 |
| Biliary tract infection | 23 (2.3) | 15 (1.3) | .07 |
| Osteomyelitis | 10 (1.0) | 10 (0.9) | .70 |
| ICU admission, n (%) | 77 (7.82) | 93 (7.97) | .90 |


Suspected Infection
Emergency Department
Direct Admission to Med-Surg or ICU
Initial PCT
(Baseline)


Evaluate PCT-A
(in the context of clinical presentation)
If no antibiotics prescribed,
reassess PCT in 12–4h
If antibiotics started,
repeat PCT daily for 72h
to evaluate effectivness of therapy
Continue without antibiotics if PCT is low (per PCT-A in Figure 1A)
Modify antibiotics if needed, (eg, in case PCT does not decline)
Start antibiotics if clinically indicated & PCT rises
Consider early cessation of antibiotics if clinical improvement & PCT declines per PCT-A

| Antibiotic Initiation | | |
|---|---|---|
| PCT Value | Antibiotic Use Recommendation | Discussion |
| <0.1 ng/mL | Strongly discouraged | ○ Repeat in 12 to 24 hours if needed<br>○ <0.1 ng/mL consider nonbacterial diagnosis |
| 0.1 – 0.24 ng/mL | Discouraged | |
| >0.24 – 0.5 ng/mL | Encouraged | ○ Consider repeating every 24 hours to evaluate the opportunity for early cessation |
| >0.5 ng/mL | Strongly encouraged | |

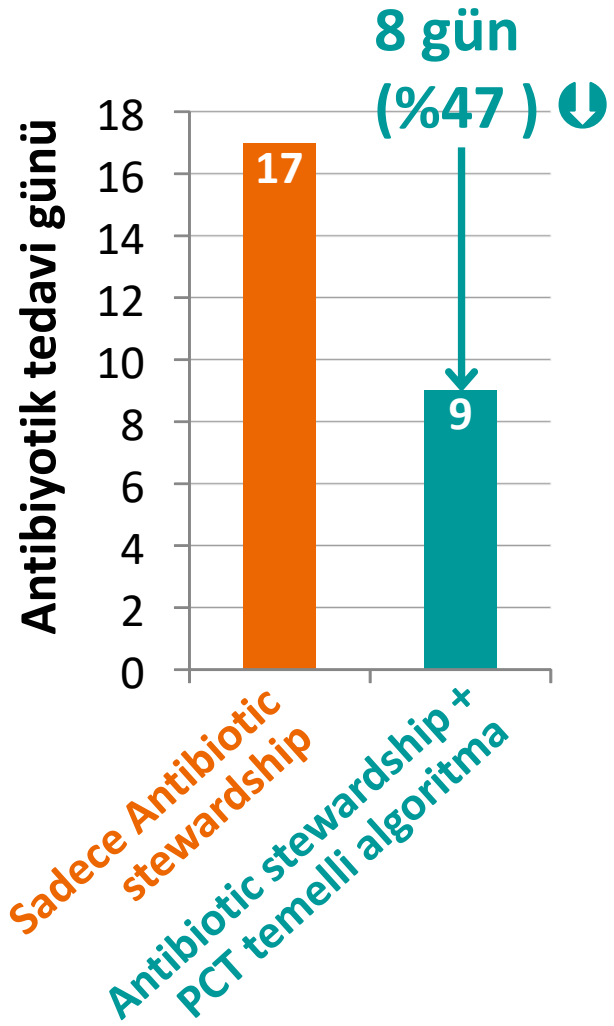
| Antibiotic Discontinuation* | | |
|---|---|---|
| PCT Value | Antibiotic Use Recommendation | Discussion |
| <0.25 ng/mL or drop by 90% | Cessation strongly encouraged | * Not recommended for the immunocompromised, endocarditis, osteomyelitis, and skin & skin structure infectionis |
| 0.25 to 0.5 ng/mL or drop by 80% | Cessation encouraged | |
| >0.5 ng/mL and drop <80% | Continuation encouraged | |

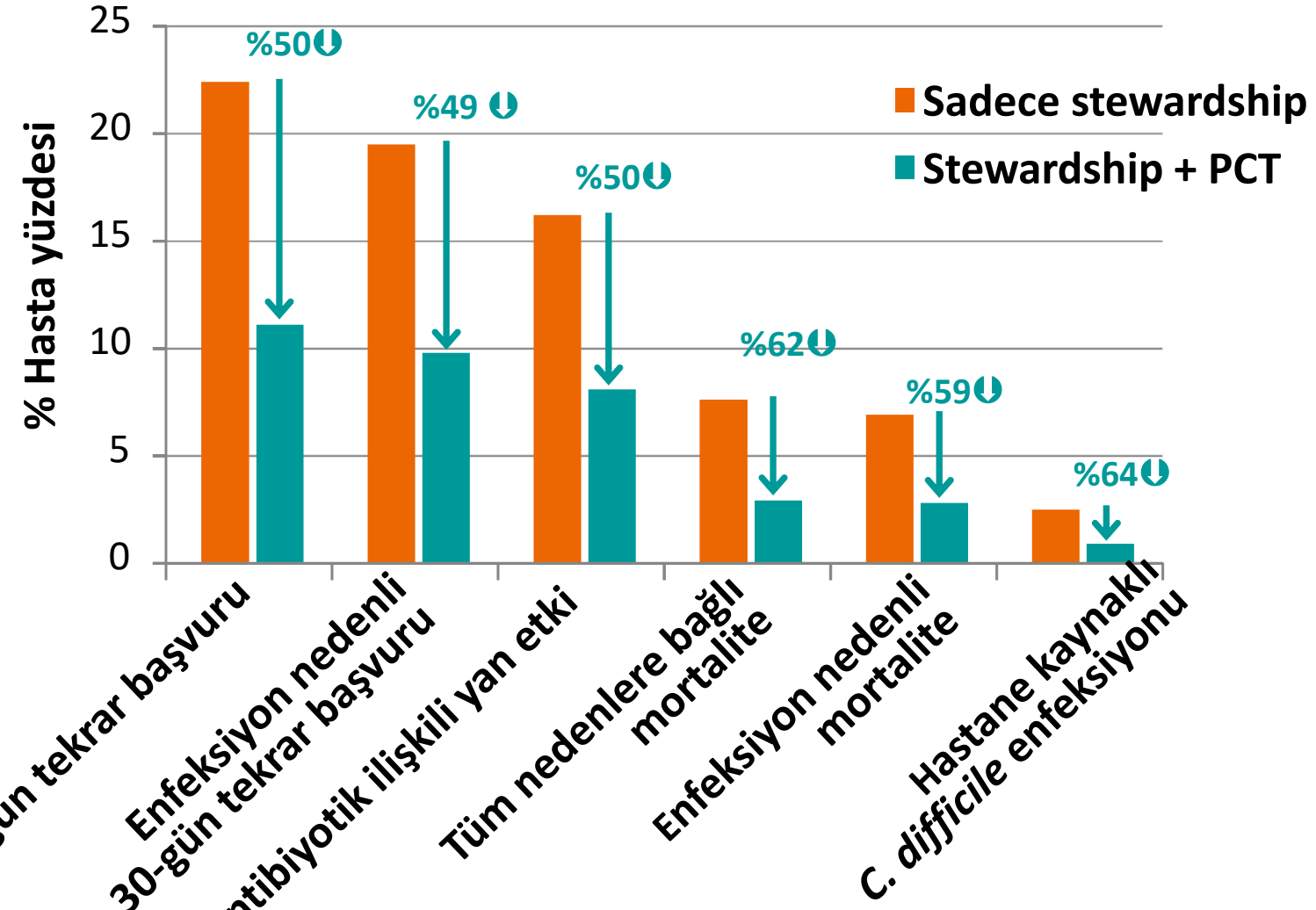



**Antibiyotik tedavi gününde**

**%47↓, 9 vs 17, p<0.0001**

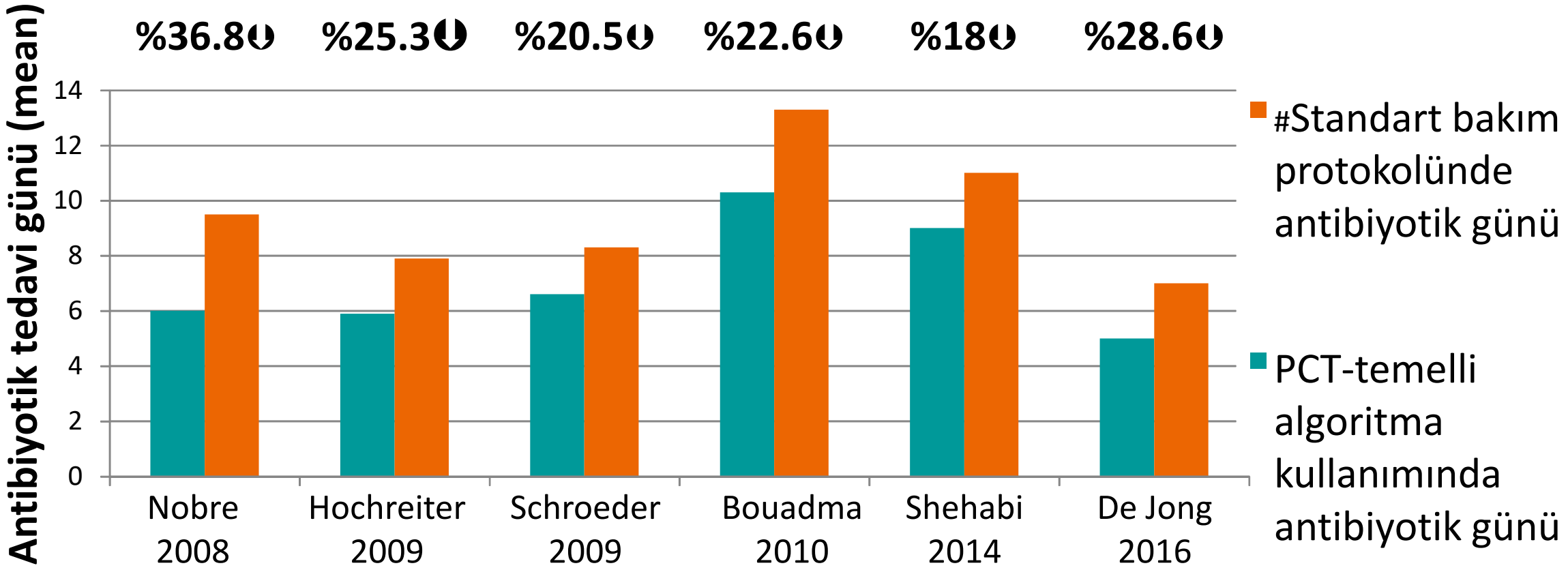
# PCT algoritmalarının antimikrobial yönetişim programlarına eklenmesi antibiyotik tedavi süresini kısaltmada etkili!!!




Broyles MR. Open Forum Infect Dis 2017;4. DOI: 10.1093/ofid/ofx213.

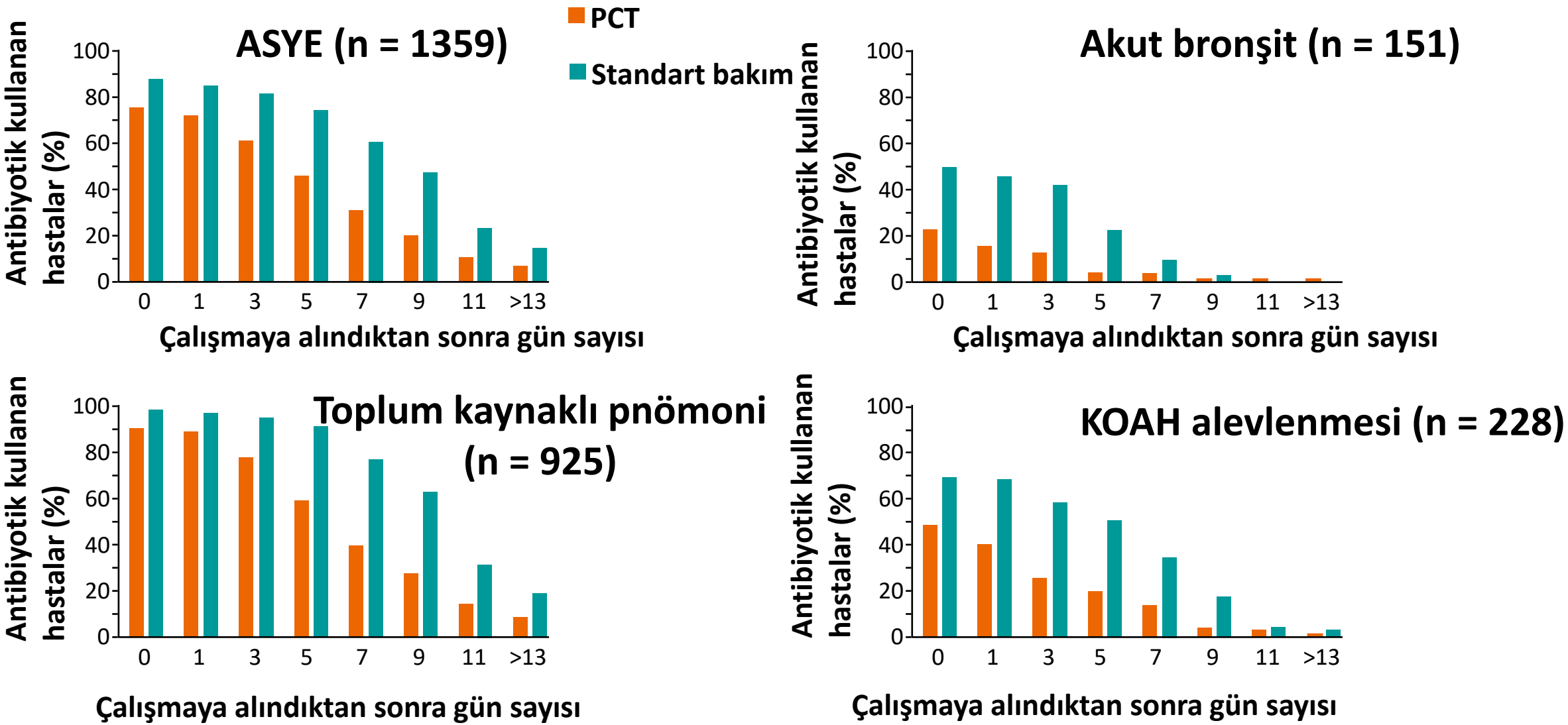
# YBÜ'de takipli kritik hastalarda antibiyotik kesme kararında PCT kullanımını öneren çok sayıda çalışma mevcut





Bouadma L, et al. The Lancet 2010;375:463-74.
de Jong E, et al. The Lancet Infectious Diseases 2016;16:819-27.
Hochreiter M, et al. Crit Care 2009;13:R83.
Nobre V, et al. Am J Respir Crit Care Med 2008;177:498-505.
Schroeder S, et al. Langenbecks Arch Surg 2009;394:221-6.
Shehabi Y, et al. Am J Respir Crit Care Med 2014;190:1102-10.

# ProHOSP çalışması: PCT temelli algoritmalar ASYE'de antibiyotik maruziyetini ⬇




Schuetz P, et al. JAMA 2009; 302(10):1059-66.

# Olası / konfirme ASYE / Sepsis hastalarında antibiyotik kararında PCT kullanımı

## Antibiyotik kesme önerisi

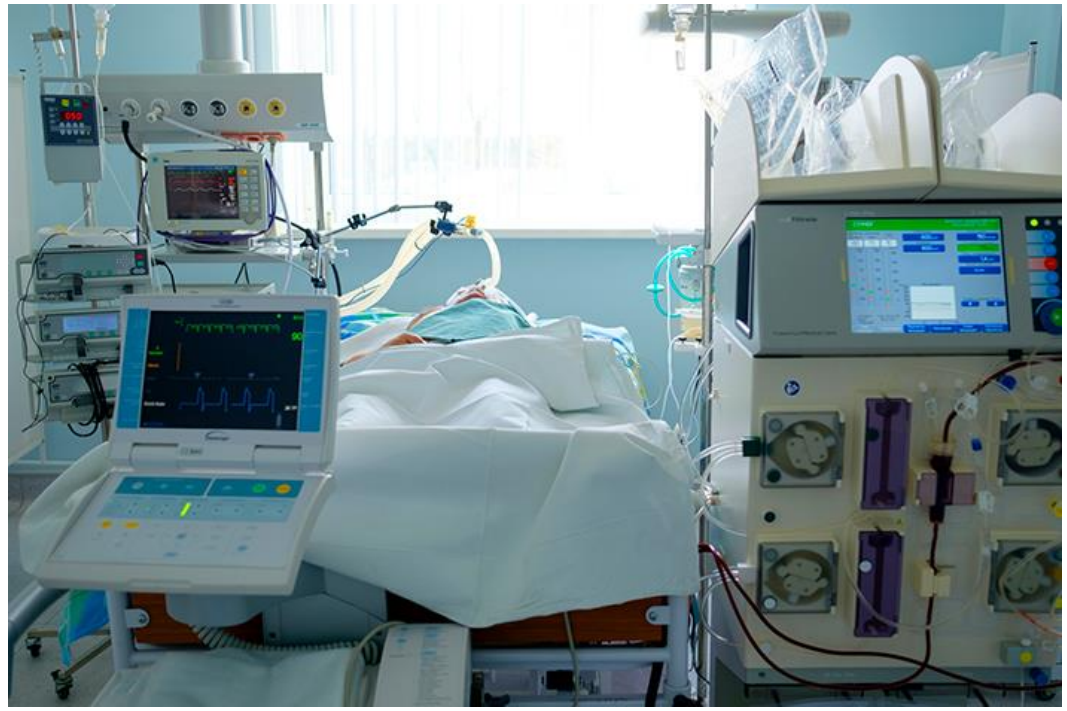
| Durum | Öneri |
|---|---|
| ASYE (komplike olmayan pnömoni, KOAH alevlenmesi) | PCT ≤0.25 ng/mL<br>veya<br>İlk ölçüme göre PCT >80% ↓ |
| Konfirme / olası sepsis | PCT ≤0.50 ng/mL<br>veya<br>İlk ölçüme göre PCT >80% ↓ |

Schuetz P, et al. Arch Intern Med. 2011;171(15):1322-31.

Siemens Healthineers Atellica® IM B·R·A·H·M·S Procalcitonin Assay package insert, 11200767_EN Rev. 01, 2018-07.

# Sepsis sıklıkla Acil servis veya YBÜ'de saptanmaktadır

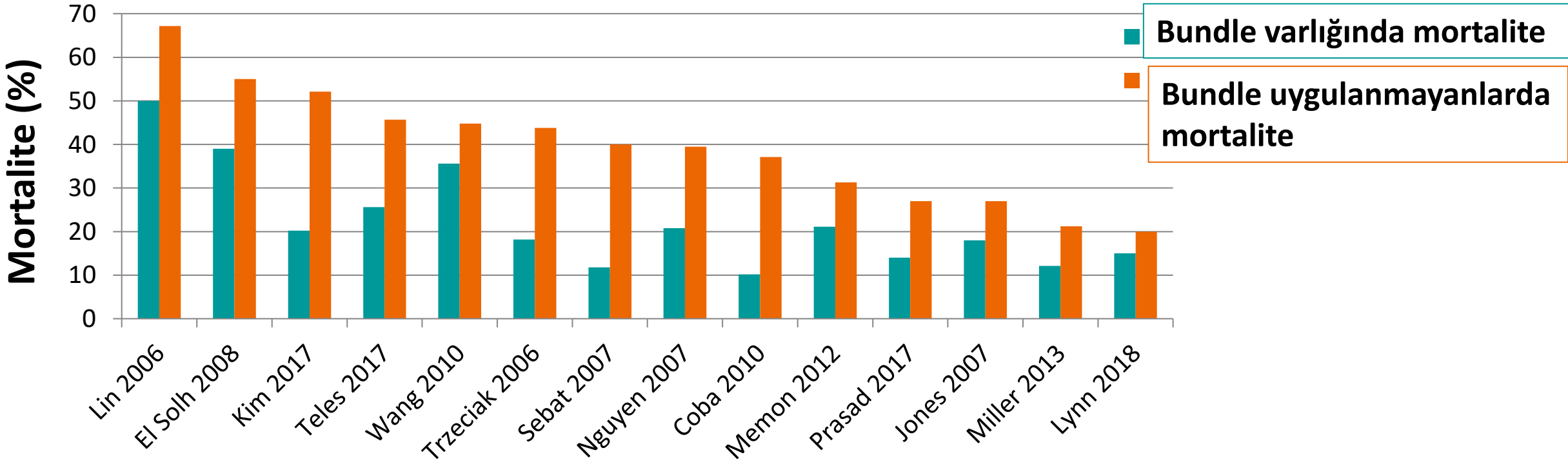

**~85% Toplum kaynaklı**



**~15% Nozokomiyal**

Jones SL, et al. Med Care 2016;54:303-10.

# Sepsis erken tanısı ve tedavi bundle uyumu mortalite

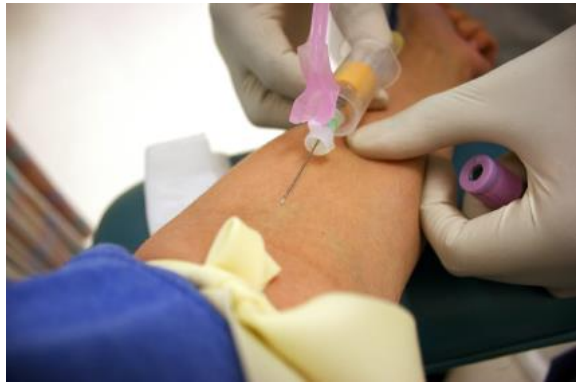




Lin SM, et al. Shock 2006;26:551-7.
El Solh AA, et al. J Am Geriatr Soc 2008;56:272-8.
Kim M, et al. West J Emerg Med 2017;18:1098-107.
Teles F, et al. J Intensive Care 2017;5:45
Wang Z. Critical Care 2010;14.
Trzeciak S, et al. Chest 2006;129:225-32.
Sebat F, et al. Crit Care Med 2007;35:2568-75.
Nguyen HB, et al. Crit Care Med 2007;35:1105-12.
Coba V. Critical Care 2010;14.
Memon JI, et al. Crit Care Res Pract 2012;2012:273268.
Prasad PA, et al. Anesth Analg 2017;125:507-13.
Jones AE, et al. Chest 2007;132:425-32.
Miller RR 3rd, et al. Am J Respir Crit Care Med 2013;188:77-82.
Lynn NB, et al. Am J Infect Control 2018.

# Surviving Sepsis Rehberi: 1 saat içinde uygulanması önerilen sepsis bundle

**Time 0: Acil servise başvuru**



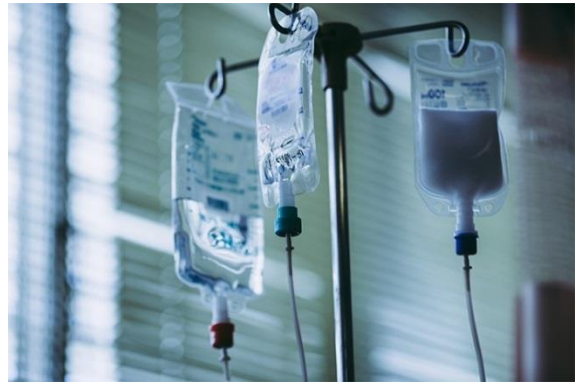
**Step 1. Biyomarker testleri**

- **WBC**
- **Rutin biyokimya**
- **CRP**
- **Laktat**

**PCT**

**Erken tanı için yardımcı bir test**

**Step 2. Olası odaklardan kültür alınması**



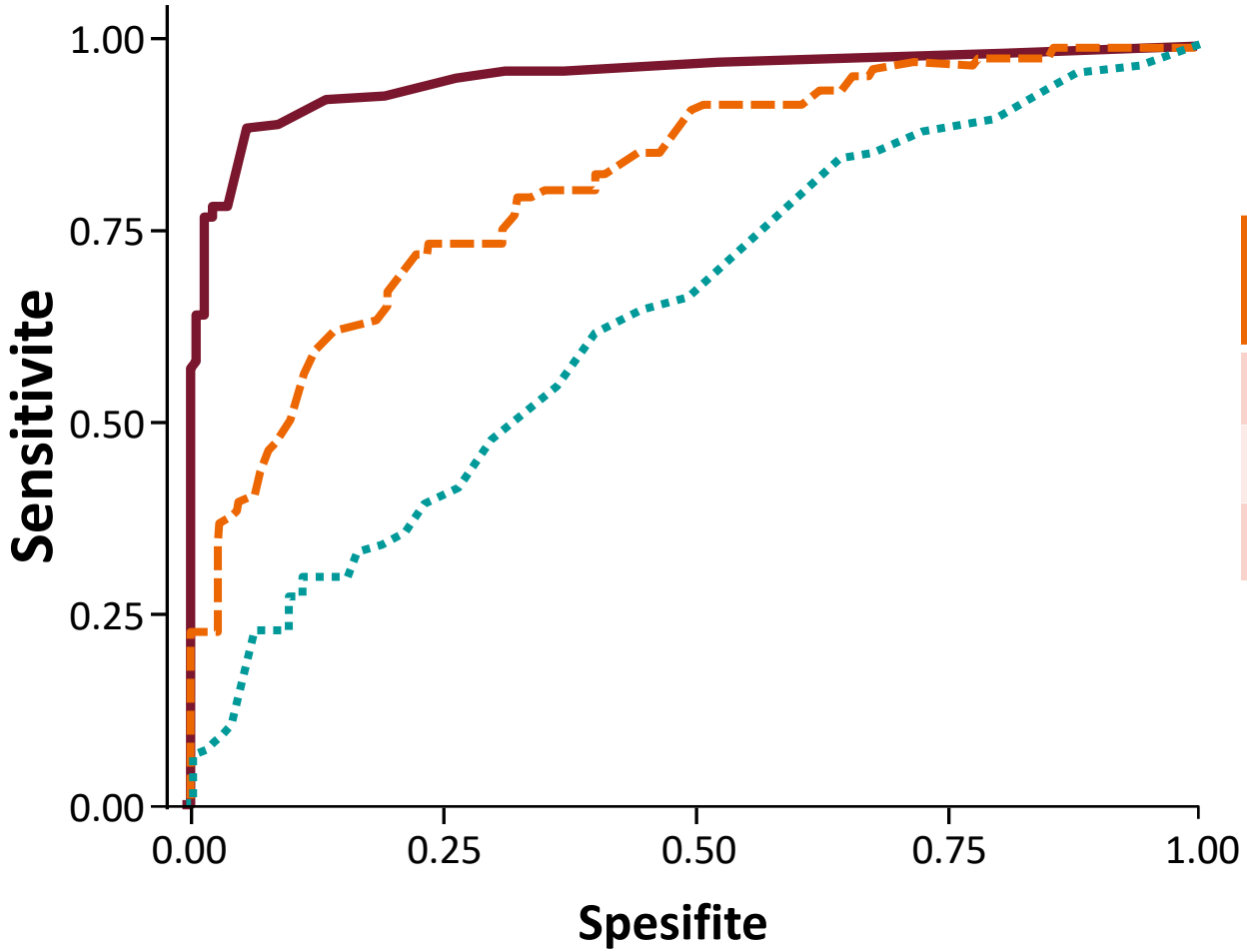
**Step 3. Olası patojenleri kapsayacak antibiyotik tedavisi başlanması**

**Step 4. Hipotansiyon varlığında kristaloid sıvı replasmanı**

**Step 5. Vazopressör ihtiyacının değerlendirilmesi**

Levy MM, et al. Crit Care Med 2018;46 1000.

# Sepsis'te PCT diğer biyomarkerlara göre daha iyi tanısal performansa sahiptir!!




| Biyomarker | Cut-off | Sens (%) | Spes (%) | NPV (%) | PPV (%) |
|---|---|---|---|---|---|
| PCT | 1 ng/mL | 89 | 94 | 90 | 94 |
| CRP | 100 mg/L | 71 | 78 | 74 | 75 |
| Laktat | 2 mmol/L | 40 | 77 | 58 | 61 |

Müller B, et al. Crit Care Med 2000;28:977-83.

Clin Chem Lab Med 2019; 57(9)

Opinion Paper

Philipp Schuetz*, All
Howard Gluck, Juan
Lay Hoon Kwa, Stefa
A. Shlyapnikov, Giuli

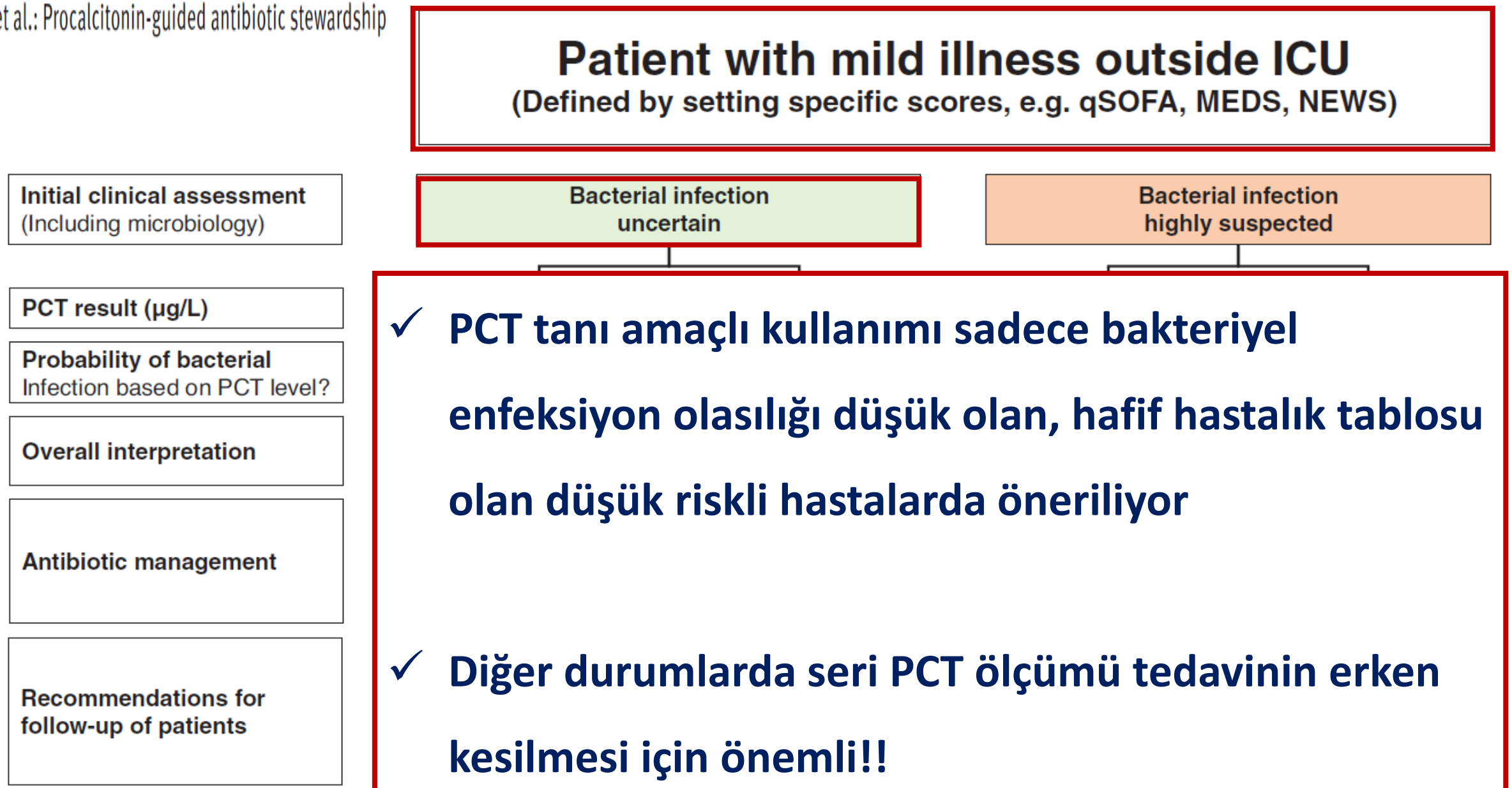
# Procalcitonin (PCT)-guided antibiotic stewardship: an international experts consensus on optimized clinical use

- ✓12 ülkeden 19 uzman Konsensus Raporu
- ✓PCT testinin farklı tanı ve departmanlarda optimal kullanımı, klinik algoritmaların geliştirilmesi ve PCT cutt-offlarının belirlenmesi

- ✓Klinik hastalık ciddiyeti
- ✓Bakteriyel enfeksiyon olasılığı (klinik/laboratuvar/radyolojik)
- ✓PCT temelli algoritmalar
- ✓Devamlı eğitim ve düzenli geri bildirim yapılmalı

> birlikte kullanılmalı

Schuetz et al.: Procalcitonin-guided antibiotic stewardship




- ✓ **PCT tanı amaçlı kullanımı sadece bakteriyel enfeksiyon olasılığı düşük olan, hafif hastalık tablosu olan düşük riskli hastalarda öneriliyor**
- ✓ **Diğer durumlarda seri PCT ölçümü tedavinin erken kesilmesi için önemli!!**

* Caution in patients with immuno-suppression (including HIV), CF, pancreatitis, trauma, pregnancy, high volume transfusion, malaria; PCT-guided stewardship should not be applied to patients with chronic infections (e.g. abscess, osteomyelitis, endocarditis)

# Patient with moderate illness outside ICU

**(Defined by setting specific scores, e.g. qSOFA, MEDS, NEWS)**

| **Initial clinical assessment** (Including microbiology) | **Bacterial infection uncertain** | | **Bacterial infection highly suspected** | |
|---|---|---|---|---|
| **PCT result (µg/L)** | **<0.25** | **≥0.25** | **<0.25** | **≥0.25** |
| **Probability of bacterial** Infection based on PCT level? | **Low probability** | **High probability** | **Low probability** | **High probability** |
| **Overall interpretation** | **Bacterial infection unlikely** | **Bacterial infection likely** | **Bacterial infection possible** | **Bacterial infection highly likely** |
| **Antibiotic management** | Use empiric Abx based on clinical judgement, consider other diagnostic tests | Use Abx based on clinical judgement | Use empiric Abx based on clinical judgement, consider other diagnostic tests | Use Abx based on clinical judgement |
| **Recommendations for follow-up of patients** | Use repeated PCT test within 6–24 h to early stop Abx to if PCT still <0.25 µg/L | Use PCT every 24–48 h for monitoring and discontinuation of Abx if PCT <0.25 µg/L or drop by 80% | Consider 2nd PCT test within 24 h to stop Abx if PCT still <0.25 µg/L | Use PCT every 24–48 h for monitoring and discontinuation of Abx if PCT <0.25 µg/L or drop by 80% |

# Patient with severe illness in ICU

**(Defined by setting specific scores, e.g. qSOFA, SOFA, APACHE)**

| **Initial clinical assessment** (Including microbiology) | **Bacterial infection uncertain** | | **Bacterial infection highly suspected** | |
|---|---|---|---|---|
| **PCT result (µg/L)** | **<0.5** | **≥0.5** | **<0.5** | **≥0.5** |
| **Probability of bacterial** Infection based on PCT level? | **Low probability** | **High probability** | **Low probability** | **High probability** |
| **Overall interpretation** | **Bacterial infection unlikely** | **Bacterial infection likely** | **Bacterial infection possible** | **Bacterial infection highly likely** |
| **Antibiotic management** | Use empiric Abx based on clinical judgement, consider other diagnostic tests | Use Abx based on clinical judgement | Use empiric Abx based on clinical judgement, consider other diagnostic tests | Use Abx based on clinical judgement |
| **Recommendations for follow-up of patients** | Use PCT within 24–48 h for monitoring and discontinuation of Abx if PCT still <0.5 µg/L | Use PCT every 24–48 h for monitoring and discontinuation of Abx if PCT <0.5 µg/L or drop by 80% | Consider 2nd PCT test within 24 h to stop Abx if PCT still <0.5 µg/L | Use PCT every 24–48 h for monitoring and discontinuation of Abx if PCT <0.5 µg/L or drop by 80% |

Clin Chem Lab Med 2019; 57(9): 1308–1318 DE GRUYTER

Opinion Paper

Philipp Schuetz*, Albertus Beishuizen, Michael Broyles, Ricard Ferrer, Gaetan Gavazzi, Eric Howard Gluck, Juan González del Castillo, Jens-Ulrik Jensen, Peter Laszlo Kanizsai, Andrea Lay Hoon Kwa, Stefan Krueger, Charles-Edouard Luyt, Michael Oppert, Mario Plebani, Sergey A. Shlyapnikov, Giulio Toccafondi, Jennifer Townsend, Tobias Welte and Kordo Saeed

# Procalcitonin (PCT)-guided antibiotic stewardship: an international experts consensus on optimized clinical use

**Sonuç olarak;**

**✓PCT testinin antibiyotik yönetişim algoritmalarına eklenmesi solunum yolu enfeksiyonu ve sepsisli hastaların tanı ve tedavi yönetimine katkı sağlar**

**✓PCT algoritmaları akut enfeksiyonlar için kullanılabilir**

**✓Abse, osteomiyelit, endokardit gibi kronik enfeksiyonlarda kullanılmamalıdır**

**✓İmmünsüpresiflerde, pankreatit, travma, gebelik varlığında, test öncesi antibiyotik alanlarda dikkatle yorumlanmalıdır, yanıltıcı olabilir**

Clin Chem Lab Med 2019; 57(9): 1308–1318 DE GRUYTER

Opinion Paper

Philipp Schuetz*, Albertus Beishuizen, Michael Broyles, Ricard Ferrer, Gaetan Gavazzi, Eric Howard Gluck, Juan González del Castillo, Jens-Ulrik Jensen, Peter Laszlo Kanizsai, Andrea Lay Hoon Kwa, Stefan Krueger, Charles-Edouard Luyt, Michael Oppert, Mario Plebani, Sergey A. Shlyapnikov, Giulio Toccafondi, Jennifer Townsend, Tobias Welte and Kordo Saeed

# Procalcitonin (PCT)-guided antibiotic stewardship: an international experts consensus on optimized clinical use

✓Bulgular yüksek sensitiviteye sahip cut off ≤ 0.06µg/L olan valide testler için geçerli

✓Mevcut çalışmaların çoğu yüksek sensitiviteye sahip KRYPTOR immunassay (BRAHMS PCT) ile yapılmıştır

✓Standart tedavi süreleri yerine bireyselleştirilmiş kısa süreli tedavi uygulamalarına olanak sağlayarak global bakteriyel direnç krizinin aşılmasına yardımcı olabilir

Sager et al. BMC Medicine (2017) 15:15
DOI 10.1186/s12916-017-0795-7

BMC Medicine

MINIREVIEW Open Access

# Procalcitonin-guided diagnosis and antibiotic stewardship revisited

- ✓ **PCT antimikrobiyal yönetişimdeki yeri ile ilgili çalışmaların çoğu sepsis ve ASYE hastalarında**
- ✓ **İYE, post-op enfeksiyonlar, menenjit, kalp yetmezliği olan hastalar (sekonder pnömoni?) da da PCT klinik kullanımı mevcut (sensitivite ve spesifitesi, dikkatli yorumlanmalı!)**
- ✓ **PCT kinetiği hastalık ciddiyeti ve hastalığın rezolüsyonu hakkında da bilgi vermekte**

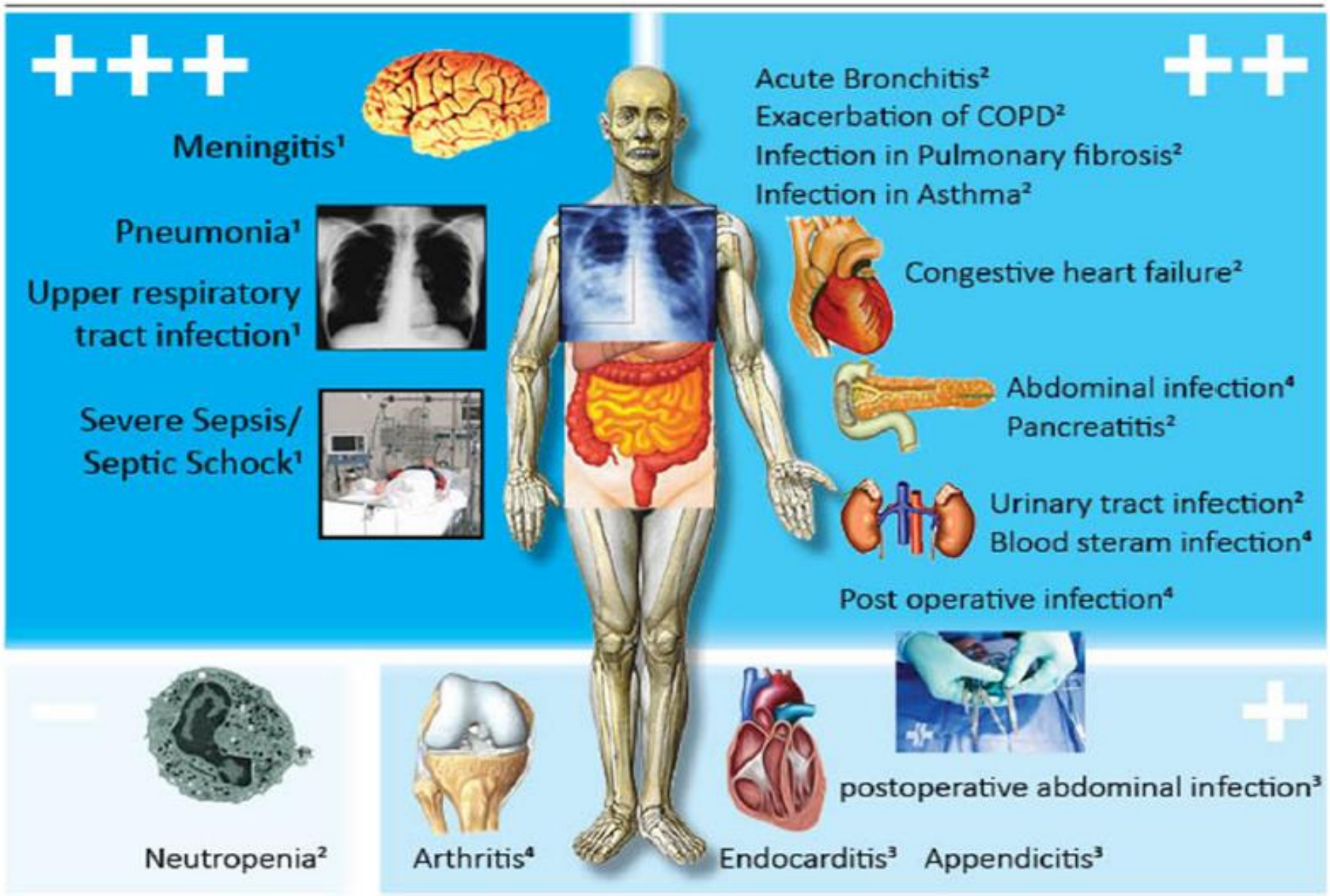
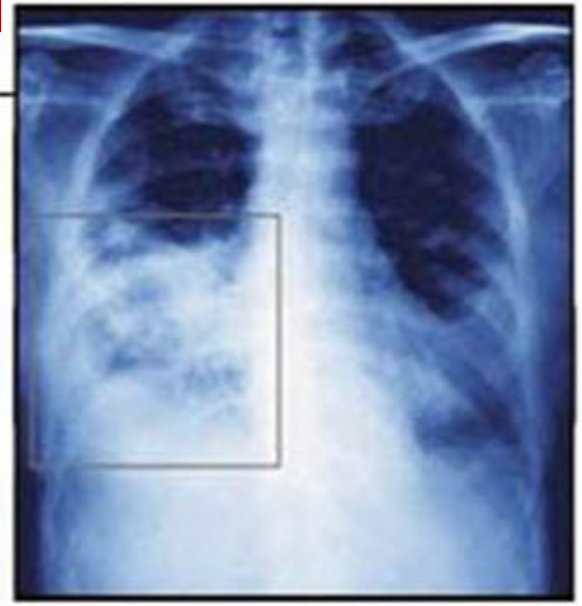
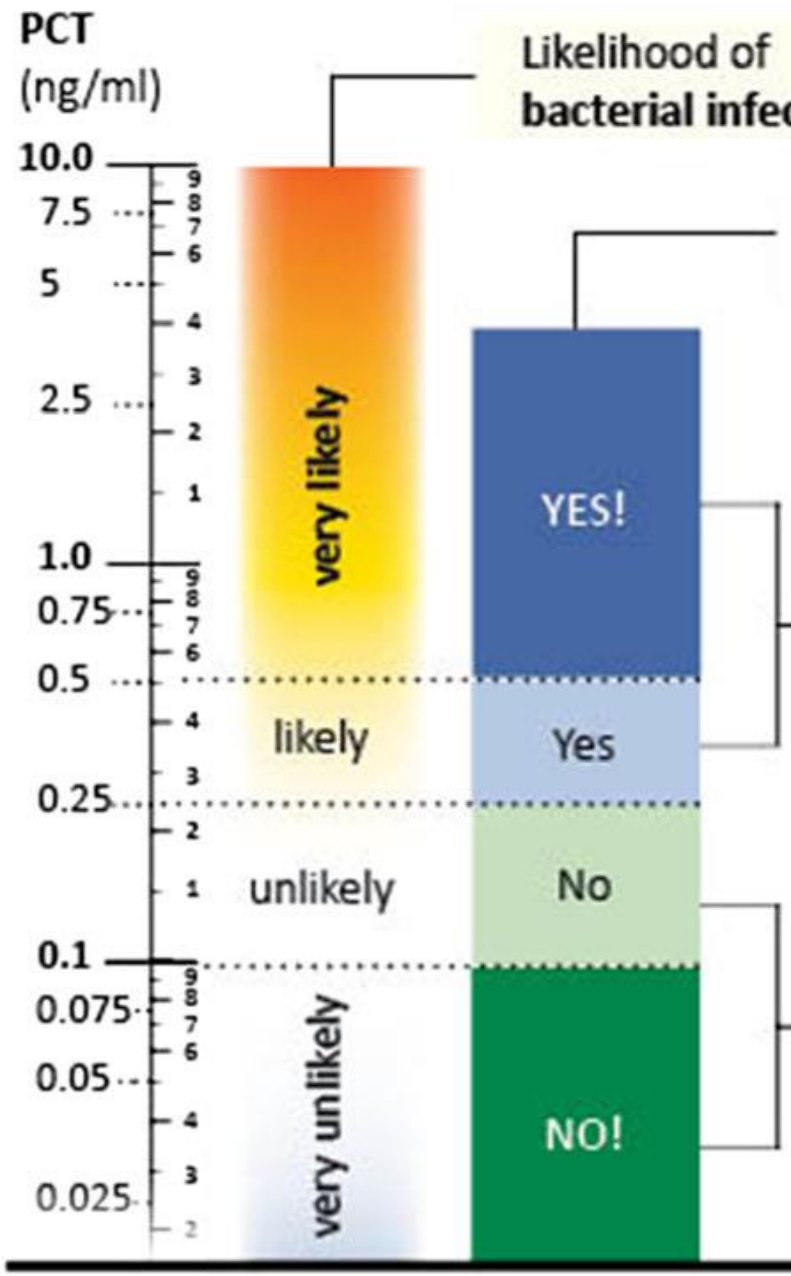



**Fig. 1** Summary of evidence regarding procalcitonin (PCT) for diagnosis and antibiotic stewardship in organ-related infections. While for some infections, intervention studies have investigated benefit and harm of using PCT for diagnosis and antibiotic stewardship (*left side*), for other infections only results from diagnostic (observation) studies are available (*right side*). +: moderate evidence in favor of PCT; ++: good evidence in favor of PCT; +++: strong evidence in favor of PCT; – no evidence in favor of PCT

# Acil servise başvuran ASYE düşünülen hastada PCT algoritması



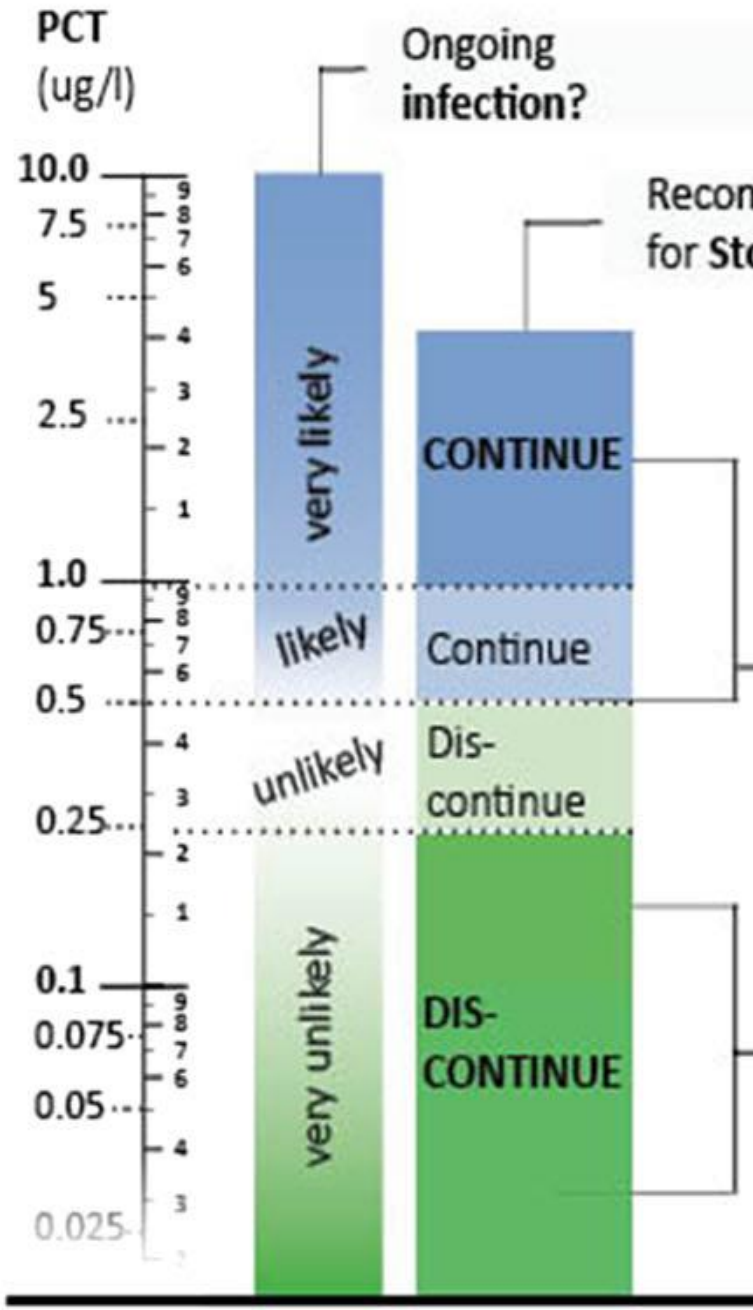



**Important considerations** and **overruling criteria**

- Consider the course of PCT (dynamic monitoring)
- If antibiotics are initiated:
  - Repeat PCT on days 3, 5, 7; stop antibiotics using the same cut offs
  - if peak PCT levels are very high, then stop when 80-90% decrease of peak
  - If PCT remains high, consider treatment failure

- If Antibiotics are withheld, control PCT after 6-24 hours
- Initial antibiotics can be considered in case of:
  - Respiratory or hemodynamic instability, severest comorbidities, ICU admission
  - PCT < 0.1 ug/L: CAP with PSI V or CURB >3, COPD with GOLD IV
  - PCT < 0.25 ug/L: CAP with PSI IV & V or CURB >2, COPD with GOLD III & IV

# YBÜ'de yatan sepsisli hastada PCT algoritması




Important **considerations** and **overruling criteria**

- Consider the course of PCT
- If antibiotics are continued:
  - Daily measurement of PCT; discontinue antibiotics when PCT decreases >80% of the peak level or an absolute PCT value <0.5ng/ml is reached.
  - If PCT remains high, consider treatment failure.

- Always consider clinical course of patients in addition to PCT levels.
- If Antibiotics are discontinued, close clinical evaluation is recommended.

**Table 1** Overview of studies investigating the use of procalcitonin in different types and sites of infections

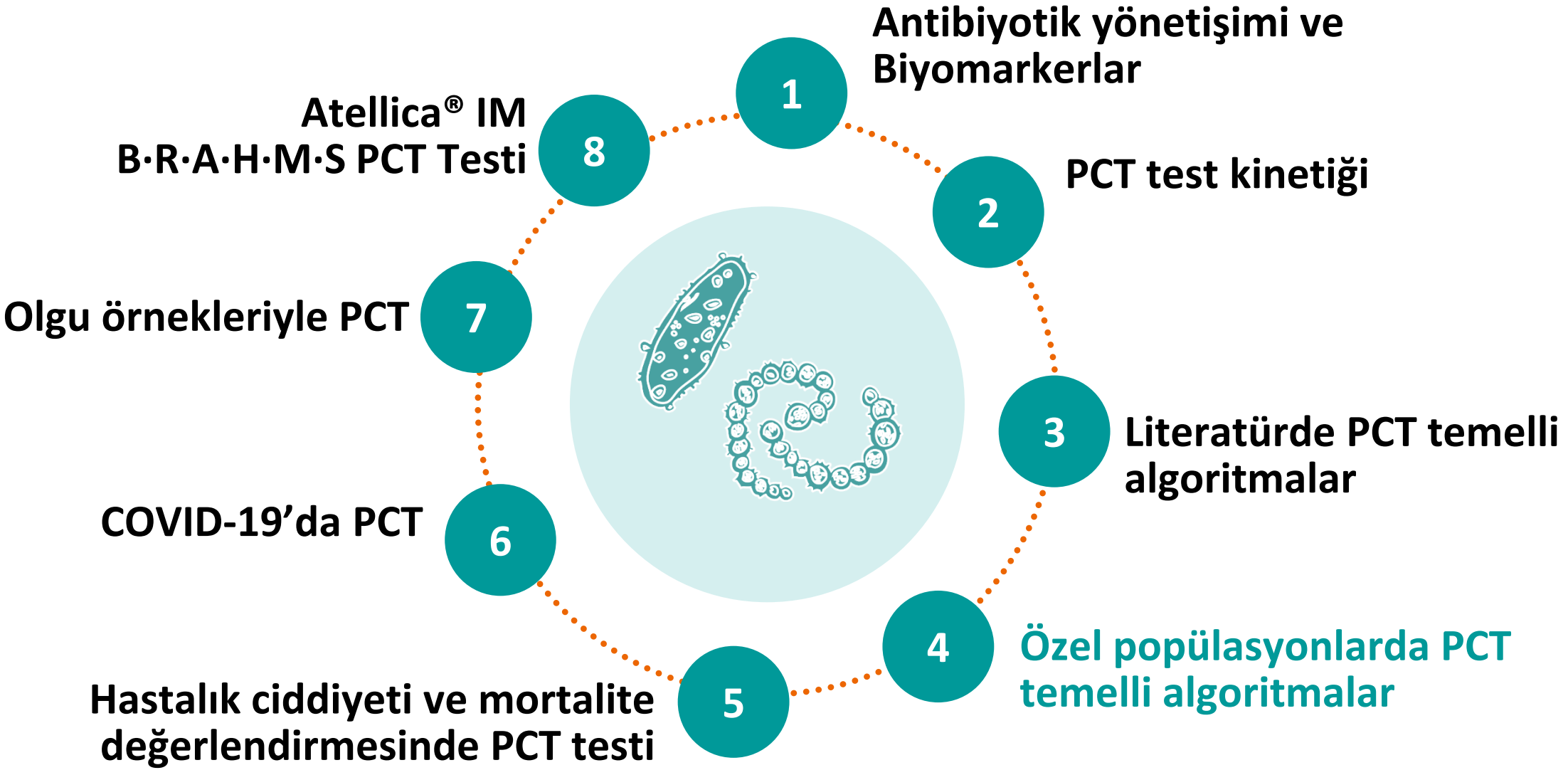
| | Type of infection | New studies since 2010? | Study design | PCT cut-off (μg/L) | Benefit of PCT use? | Main conclusions | Selected references since 2012 |
|---|---|---|---|---|---|---|---|
| Pulmonary | AECOPD | yes | RCT (N = 120), meta-analysis | <0.25 | ++ | PCT reduces initiation of antibiotic treatment in the ED without adverse outcomes | [7, 12] |
| | Asthma | yes | RCT (N = 216) | <0.1–0.25 | ++ | PCT reduces initiation of antibiotic treatment in the ED without adverse outcomes | [89] |
| | Bronchitis | yes (Registry) | RCT, real-life (Registry) | <0.1–0.25 | ++ | PCT reduces initiation of antibiotic treatment in the ED without adverse outcomes | [42] |
| | Community-acquired pneumonia | yes | RCT, meta-analysis (N = 4467) real-life (Registry) | <0.1–0.25; 80–90% decrease | +++ | PCT shortens length of antibiotic therapy in the ED and hospital ward without adverse outcomes | [7] |
| | Pulmonary fibrosis | yes | RCT (N = 78) | <0.25 | ++ | PCT reduces initiation of antibiotic treatment in the ED without adverse outcomes | [15] |
| | Upper respiratory tract infections | no | RCT (N = 458, 702) | <0.1–0.25 | +++ | PCT reduces initiation of antibiotic treatment in primary care without | [90, 91] |

**Table 1** Overview of studies investigating the use of procalcitonin in different types and sites of infections

| | Type of infection | New studies since 2010? | Study design | PCT cut-off (μg/L) | Benefit of PCT use? | Main conclusions | Selected references since 2012 |
|---|---|---|---|---|---|---|---|
| Heart | Congestive heart failure | yes | Observational, RCT (secondary analysis, N = 110) | <0.21–0.25 | ++ | PCT helps in identification of bacterial superinfection in acute heart failure, may be helpful in guiding antibiotic treatment | [38, 43] |
| | Endocarditis | no | Observational, meta-analysis | <0.5 | + | PCT is a predictor of poor outcome, diagnostic value similar to CRP | [67, 68] |
| Abdominal | Abdominal infections with peritonitis | yes | Observational | <0.5; 80% decrease | ++ | PCT-guided therapy was associated with lower antibiotic exposure with no difference in mortality | [66] |
| | Appendicitis | yes | Observational, meta-analysis | NR | + | PCT is a marker of complicated appendicitis, low value for diagnosing appendicitis | [92] |
| | Pancreatitis | yes | RCT (N = 71) | <0.5 | ++ | PCT reduces antibiotic exposure compared to prophylactic antibiotic treatment without adverse outcomes | [65] |
| | Urinary tract infections | yes | RCT (N = 125) | <0.25 | ++ | PCT reduces antibiotic exposure without adverse effects | [47] |

**Table 1** Overview of studies investigating the use of procalcitonin in different types and sites of infections

| | Type of infection | New studies since 2010? | Study design | PCT cut-off (μg/L) | Benefit of PCT use? | Main conclusions | Selected references since 2012 |
|---|---|---|---|---|---|---|---|
| Blood | Blood stream infection | yes | Observational | <0.25–1.47 | ++ | PCT levels correlate with risk for positive blood cultures | [19, 27] |
| | Neutropenia | yes | RCT (N = 62) | NR | – | PCT is not useful to manage antibiotic therapy, but PCT was a marker of bacteremia | [93] |
| | Severe sepsis/ shock | yes | RCT (N = 1575) | <0.5; 80% decrease | +++ | PCT reduces antibiotic exposure and 3 month mortality in the ICU | [30] |
| Postoperative | Postoperative abdominal infection | yes | Observational, meta-analysis | NR | + | Low PCT post-surgical ensure safe discharge, PCT is similar to CRP | [58, 59] |
| | Postoperative infections | yes | RCTs, Observational | <0.5–2.0 | ++ | Low PCT suggests absence of perioperative infection and enables early discharge | |
| Other | Arthritis | yes | Observational | <0.5 | + | PCT identifies infection in patients with rheumatoid arthritis | [94] |
| | Erysipelas | yes | Observational | <0.1 | + | PCT differentiates erysipelas from DVT | [81] |
| | Meningitis | no | RCT, meta-analysis (N = 2058) | <0.5 | +++ | PCT reduces AB treatment during viral outbreak; serum PCT with CSF lactate reliably identifies bacterial meningitis | [72, 74] |


1
Antibiyotik yönetişimi ve Biyomarkerlar
2
PCT test kinetiği
3
Literatürde PCT temelli algoritmalar
4
Özel popülasyonlarda PCT temelli algoritmalar
5
Hastalık ciddiyeti ve mortalite değerlendirmesinde PCT testi
6
COVID-19'da PCT
7
Olgu örnekleriyle PCT
8
Atellica® IM B·R·A·H·M·S PCT Testi

# Procalcitonin in special patient populations: Guidance for antimicrobial therapy

Am J Health-Syst Pharm. 2020;77:1-13

**Summary.** In the presence of bacterial infection, nonneuroendocrine PCT is produced in response to bacterial toxins and inflammatory cytokines, resulting in markedly elevated levels of serum PCT. Cytokine induction in nonbacterial inflammatory processes activated by acute care surgery may alter the interpretation of PCT levels. The reliability of PCT assessment has also been questioned in patients with renal dysfunction, cardiac compromise, or immunosuppression. In many special populations, serum PCT may be elevated at baseline and increase further in the presence of infection; thus, higher thresholds for diagnosing infection or de-escalating therapy should be considered, although the optimal threshold to use in a specific population is unclear. Procalcitonin-guided antimicrobial therapy may be recommended in certain clinical situations.

# Procalcitonin in special patient populations: Guidance for antimicrobial therapy

Am J Health-Syst Pharm. 2020;77:1-13

**Conclusion.** Procalcitonin may be a reliable marker of infection even in special populations with baseline elevations in serum PCT. However, due to unclear threshold values and the limited inclusion of special populations in relevant clinical trials, PCT levels should be considered along with clinical criteria, and antibiotics should never be initiated or withheld based on PCT values alone. Procalcitonin measurement may have a role in guiding de-escalation of antibiotic therapy in special populations; however, the clinician should be aware of disease states and concomitant therapies that may affect interpretation of results.

**Table 1.** Recommendations for Procalcitonin Use in Special Populations

| Clinical Condition | Effect on PCT | Recommendation(s)[a] | PCT Threshold | Level of Evidence |
|---|---|---|---|---|
| Chronic kidney disease | • Inconsistent increase in PCT reported<br>• Proposed hypothesis: proinflammatory metabolites stimulate nonneuroendocrine pathway of PCT production | • Consider a higher PCT threshold for ruling in bacterial infection | • >0.85-1.5 ng/mL[24,25] | • Single-center, prospective, observational studies[24,25] |
| Acute kidney injury | • Inconsistent increase in PCT reported<br>• PCT levels also associated with disease severity in patients with AKI | • Consider a higher PCT threshold for ruling in bacterial infection | • >0.42-2 ng/mL[28,29]<br>• 7.13 ng/mL with failure per RIFLE criteria[29] | • Retrospective, observational studies[28,29] |

| Clinical Condition | Effect on PCT | Recommendation(s)[a] | PCT Threshold | Level of Evidence |
|---|---|---|---|---|
| Chronic RRT (HD or PD) | • Baseline PCT levels higher in ESRD but increase reliably with infection<br>• PCT levels high prior to each HD or PD session and PCT cleared to varying degrees | • Consider a higher PCT threshold for ruling in bacterial infection<br>• Measure PCT level prior to HD | • >1.5 ng/mL in detecting severe infection or sepsis[20] | • Single-center, prospective, observational study[20]; meta-analysis[26] |
| Continuous RRT | • PCT removed by convection (primarily) and adsorption<br>• Effect on plasma PCT levels is limited with conventional modes of CRRT<br>• Significant PCT clearance with high-cutoff CRRT membranes | • Must be aware of specific CRRT parameters to assess potential impact on PCT utility<br>• With conventional CRRT, PCT may remain a useful diagnostic marker | • No specific threshold recommended[23,35-37] | • Single-center, prospective, observational studies[23,35-37] |

| | | | | |
|---|---|---|---|---|
| Cardiogenic shock | • Elevated PCT is associated with infection, sepsis, and mortality | • Consider measuring PCT to predict infection, sepsis, and mortality | • ≥2 ng/mL for infection[50]<br>• >10 ng/mL for sepsis[52]<br>• >10 ng/mL for mortality in patients receiving ECMO[53] | • Prospective observational[50]<br>• Retrospective[52, 53] |
| Cardiac surgery | • Elevated PCT is associated with infection and postoperative complications | • Consider measuring PCT to predict infection and postoperative complications | • 1-9.4 ng/mL for infection[54,55,57,60,66,67]<br>• 2.95-5 ng/mL for complications[56,58] | • Retrospective[54]<br>• Prospective observational[55-58,66,67]<br>• Systematic review[60] |
| Heart failure | • Elevated PCT is associated with death, rehospitalization, and infection | • Consider measuring PCT to predict death, rehospitalization, and infection | • ≥0.2 ng/mL for death and rehospitalization[71]<br>• 0.086-0.657 ng/mL for infection[75] | • Multicenter randomized, double-blind placebo controlled[71]<br>• Retrospective[75] |

| Clinical Condition | Effect on PCT | Recommendation(s)[a] | PCT Threshold | Level of Evidence |
|---|---|---|---|---|
| Surgery | • Elevated PCT is associated with infection and mortality<br>• PCT-guided antibiotic therapy led to shorter duration of antibiotic therapy and reduced antibiotic costs without increase in negative outcomes | • Consider measuring PCT to predict infection and mortality<br>• Consider using PCT-guided antibiotic therapy | • >1.5 ng/mL for postoperative infection[55]<br>• 1.44 ng/mL for mortality; 0.75 ng/mL for morbidity and mortality[77]<br>• PCT-guided antibiotic treatment resulted in shorter length of treatment and reduced costs without increase in negative outcomes[78] | • Prospective observational[55]<br>• Retrospective[77]<br>• Prospective randomized[78] |
| Burns | • Elevated PCT is associated with infection and sepsis | • Consider measuring PCT to predict infection and sepsis | • Variable (0.5-3 ng/mL) for sepsis and infection[79,81,82,84,85-89,91]<br>• 5.12 ng/mL for bloodstream infection[90] | • Retrospective observational[79,81,90]<br>• Small, prospective observational[82-86,91]<br>• Meta-analyses[88,89] |

| | | | | |
|---|---|---|---|---|
| Hematologic malignancy | • PCT level not expected to be significantly affected by malignancy<br>• Elevations with engraftment syndrome and GVHD after HSCT, T cell–directed therapies | • Avoid using PCT for management of antimicrobials if a confounding condition/medication is present<br>• Consider using along with clinical criteria to facilitate antimicrobial discontinuation during febrile neutropenia | • >0.5 ng/mL for bacterial infection in febrile neutropenia[115]<br>• >2 ng/mL for risk of severe sepsis or septic shock[117] | • Prospective observational studies and meta-analysis[115]<br>• Single-center randomized controlled trial[120] |
| Solid tumors | • Elevations with medullary thyroid cancer, small cell lung cancer | • Avoid using PCT for management of antimicrobials if a confounding oncologic condition is present<br>• Consider using along with clinical criteria to facilitate antimicrobial discontinuation during febrile neutropenia | • >0.5 ng/mL for bacterial infection in febrile neutropenia[115] | • Prospective observational studies and meta-analysis[115] |

1 Antibiyotik yönetişimi ve Biyomarkerlar

2 PCT test kinetiği

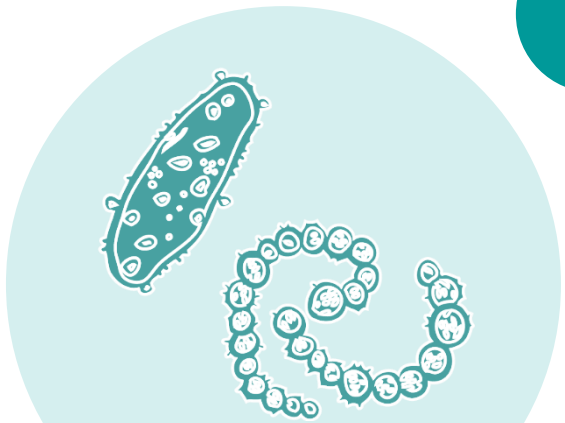
3 Literatürde PCT temelli algoritmalar

4 Özel popülasyonlarda PCT temelli algoritmalar

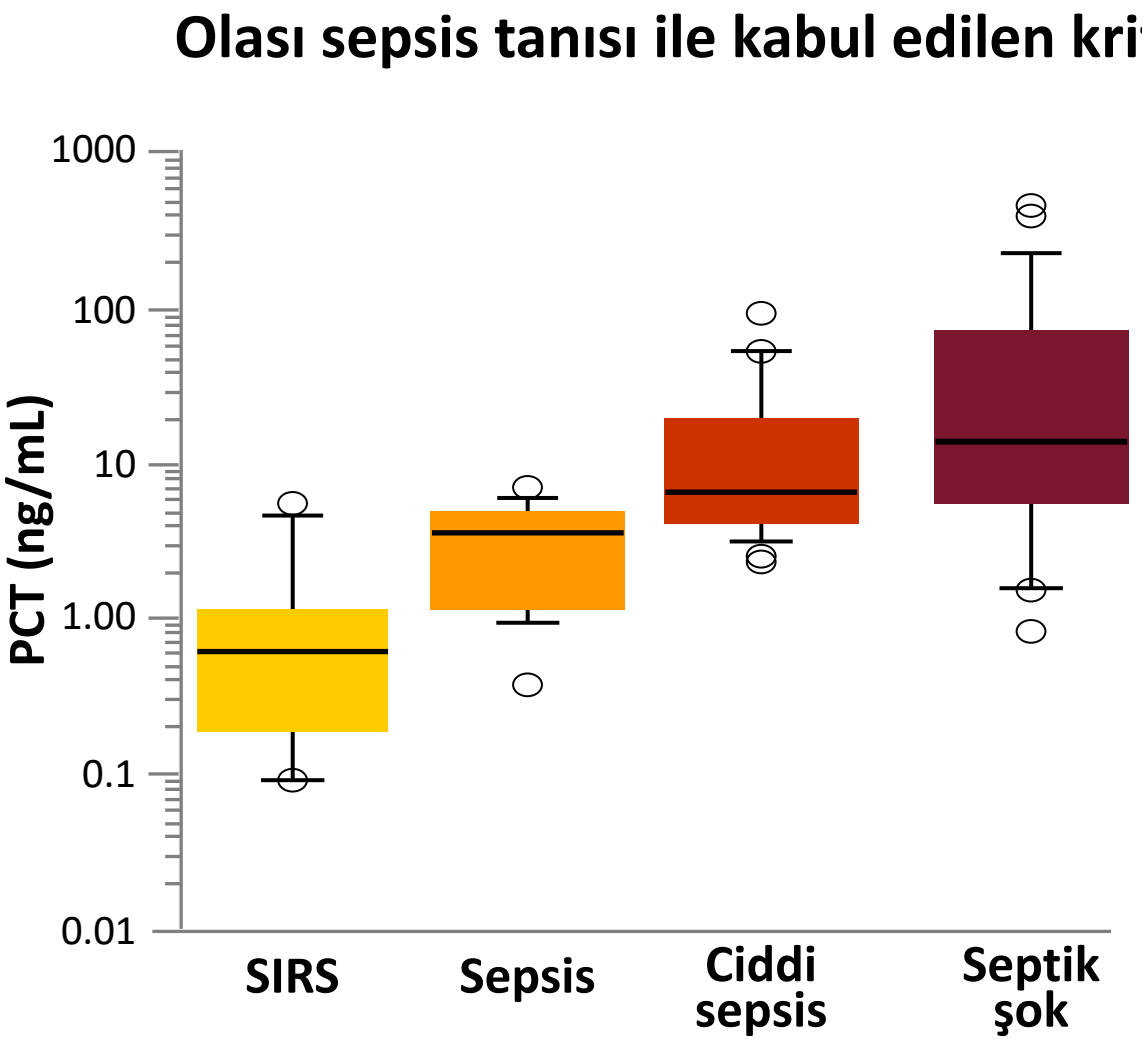
5 Hastalık ciddiyeti ve mortalite değerlendirmesinde PCT testi

6 Olgu örnekleriyle PCT

7 Atellica® IM B·R·A·H·M·S PCT Testi



# PCT düzeyi hastalık ciddiyeti ile ilişkilidir!!




Harbarth S, et al. Am J Respir Crit Care Med

# Serial Procalcitonin Predicts Mortality in Severe Sepsis Patients: Results From the Multicenter Procalcitonin MOnitoring SEpsis (MOSES) Study

Philipp Schuetz, MD, MPH[1]; Robert Birkhahn, MD[2]; Robert Sherwin, MD[3]; Alan E. Jones, MD[4];

**Objectives:** To prospectively validate that the inability to decrease procalcitonin levels by more than 80% between baseline and day 4 is associated with increased 28-day all-cause mortality

- ✓**Prospektif 13 merkezli kohort çalışma (646 hasta);**
- ✓**YBÜ'ye yatırılan sepsis hastalarında 0-4. günde PCT düzeyinde >%80 28 günlük mortalite üzerine etkisi araştırılıyor**

days.

Critical Care Medicine May 2017, Vol 45, No 5

# PCT septik şok'a progresyon ve 28 günlük mortalite riskinin belirlenmesinde kullanılabilir!!!

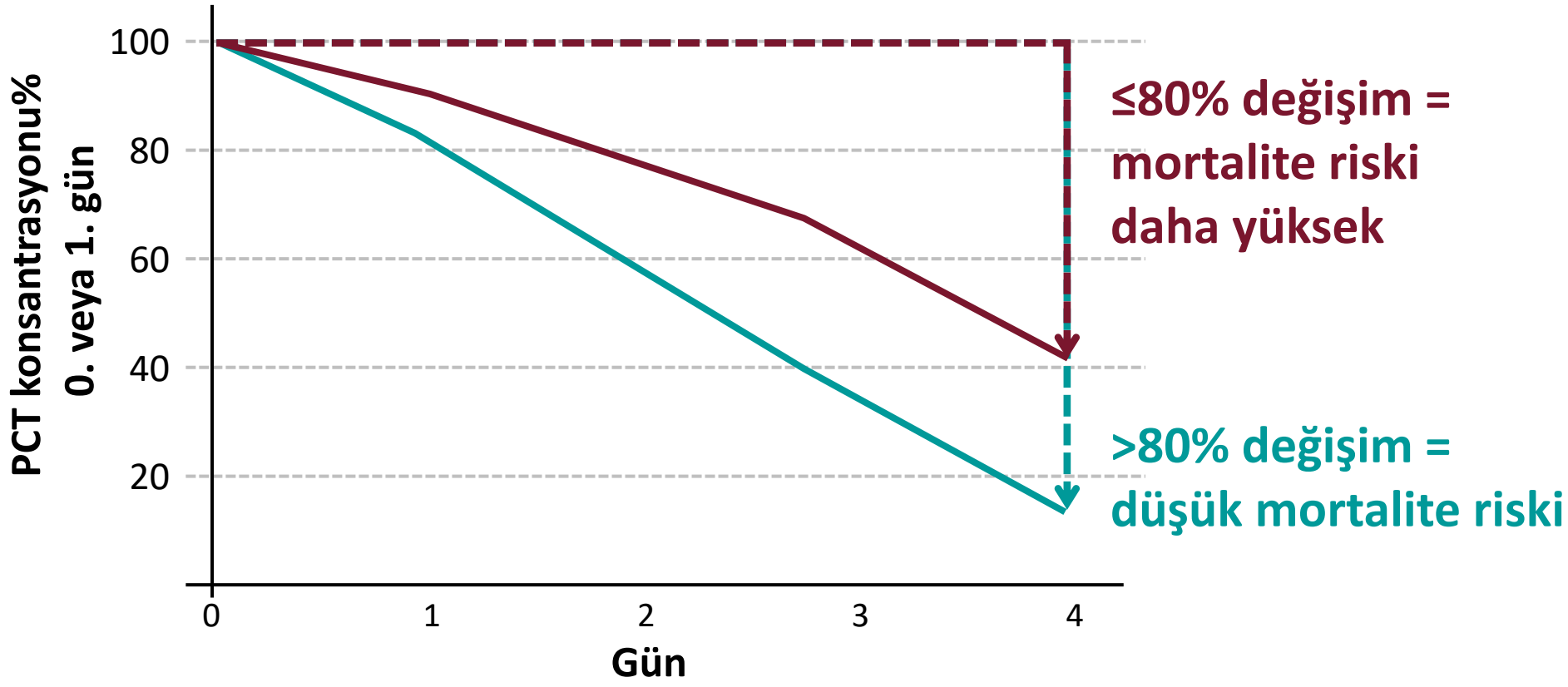
**YBÜ yatışı 1. günü**

**> 2.0 ng/mL**
**Yüksek risk**

**0.5–2.0 ng/mL**
**Klinik ile değerlendirilmeli**
**6–24 saat içinde test tekrarı**

**< 0.5 ng/mL**
**Düşük risk**

**Bazal (0. veya 1. gün) ve 4. gün PCT değişimi 28. gün mortaliteyi öngördürür**




Schuetz P, et al. Crit Care Med 2017;45(5):781-9.

# Serial Procalcitonin Predicts Mortality in Severe Sepsis Patients: Results From the Multicenter Procalcitonin MOnitoring SEpsis (MOSES) Study

Philipp Schuetz, MD, MPH[1]; Robert Birkhahn, MD[2]; Robert Sherwin, MD[3]; Alan E. Jones, MD[4];

**Conclusions:** Results of this large, prospective multicenter U.S. study indicate that inability to decrease procalcitonin by more than 80% is a significant independent predictor of mortality and may aid in sepsis care. (*Crit Care Med* 2017; 45:781–789)

✓**Sepsis hastalarında PCT düzeyinde >%80🡻 olmaması bağımsız mortalite prediktörüdür!**

✓**28 günlük mortaliteyi dışlamada negatif prediktif değer = %89.0**

1 Antibiyotik yönetişimi ve Biyomarkerlar

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6 Olgu örnekleriyle PCT

7 Atellica® IM B·R·A·H·M·S PCT Testi

# Benzer semptomlarla başvuran iki hastada rasyonel antibiyotik kullanımı için PCT testinin rolü?

**Hasta 1**

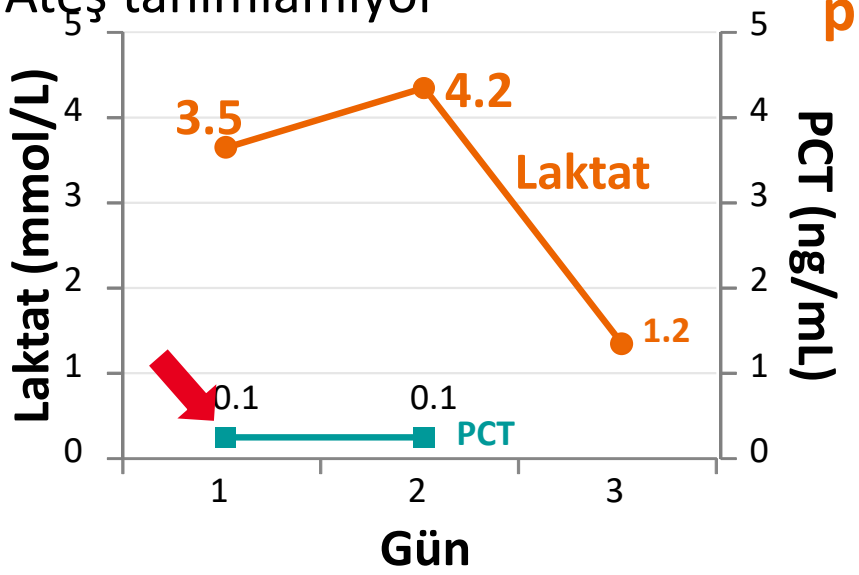
- Nefes darlığı
- Hafif hipoksi
- PAAG'de bilateral yamalı infiltrat
- WBC yüksekliği ılımlı sola kayma
- Sarı-yeşil balgam
- Ateş tanımlamıyor

**PAAG benzer görünümde**

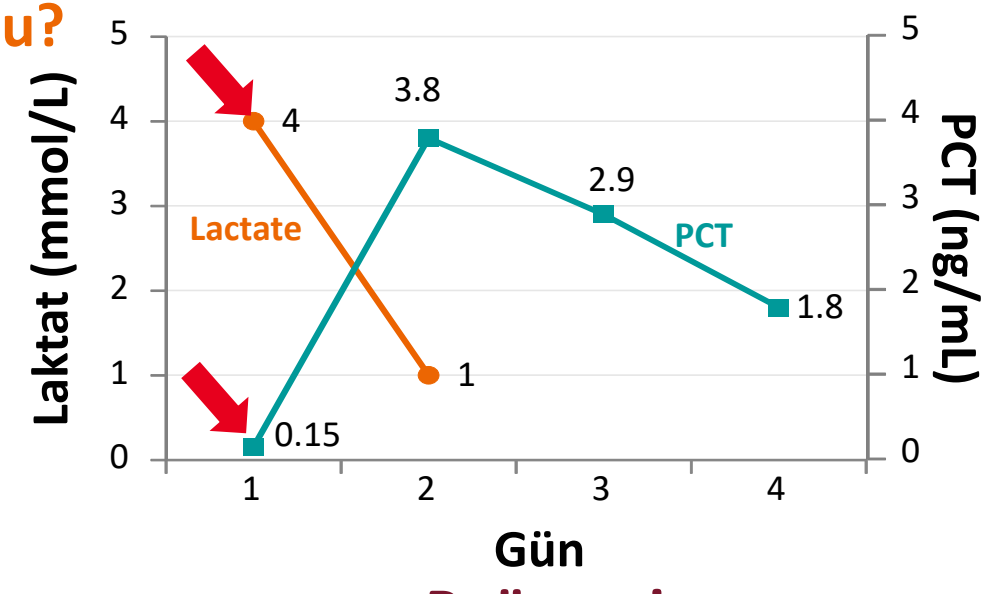
**Bu hastaların herhangi birinde pnömoni mevcut mu?**

**Hasta 2**

- Nefes darlığı
- Hafif hipoksi
- PAAG'de bilateral yamalı infiltrat
- Balgam boyamasında gram-pozitif zincir koklar



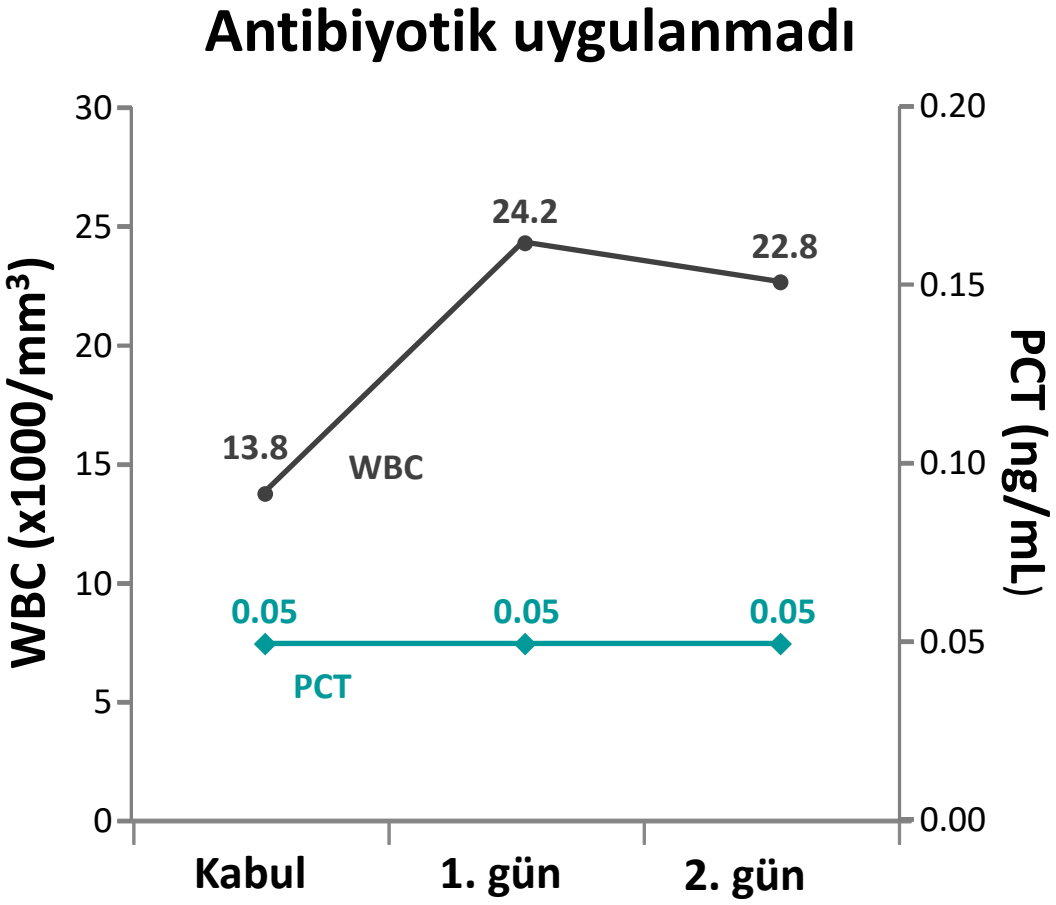

**Konjestif kalp yetmezliği**

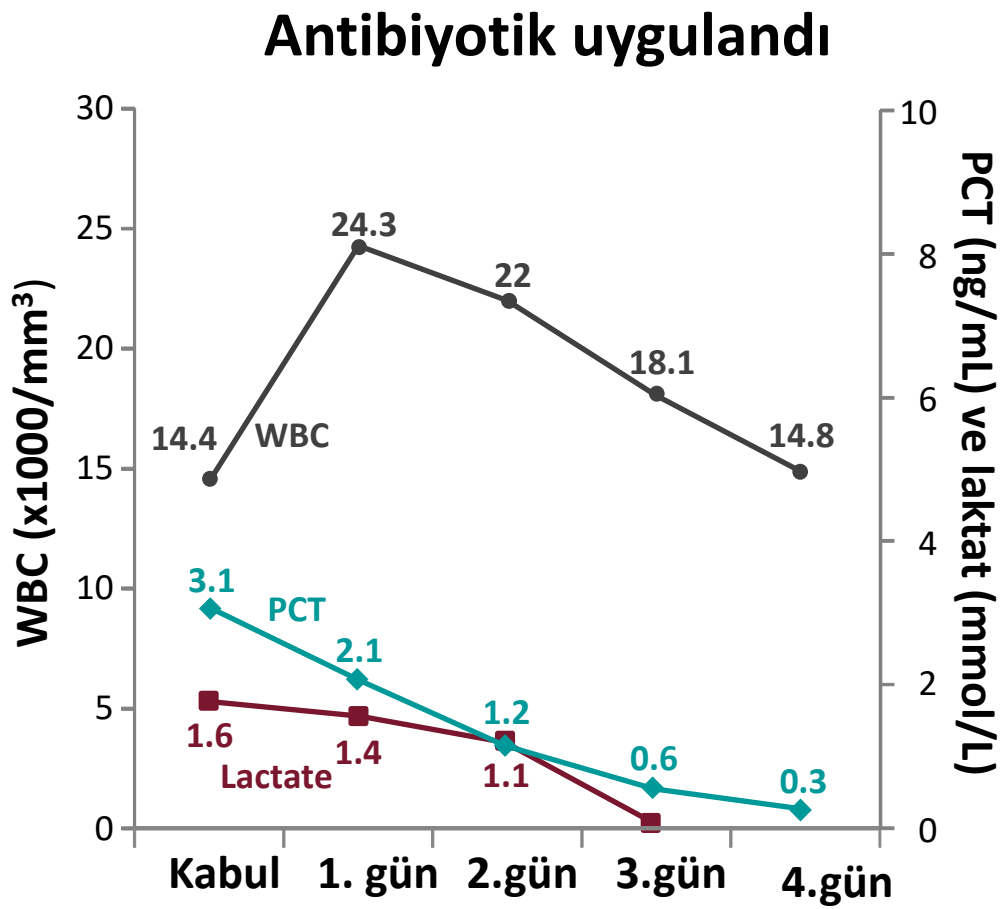



**Pnömoni**

Courtesy of E. Gluck MD, Swedish Covenant Hospital, Chicago, IL.

# KOAH alevlenmesi ile iki farklı zamanda acil servise başvuran hastanın PCT temelli algoritma kullanılarak yönetimi

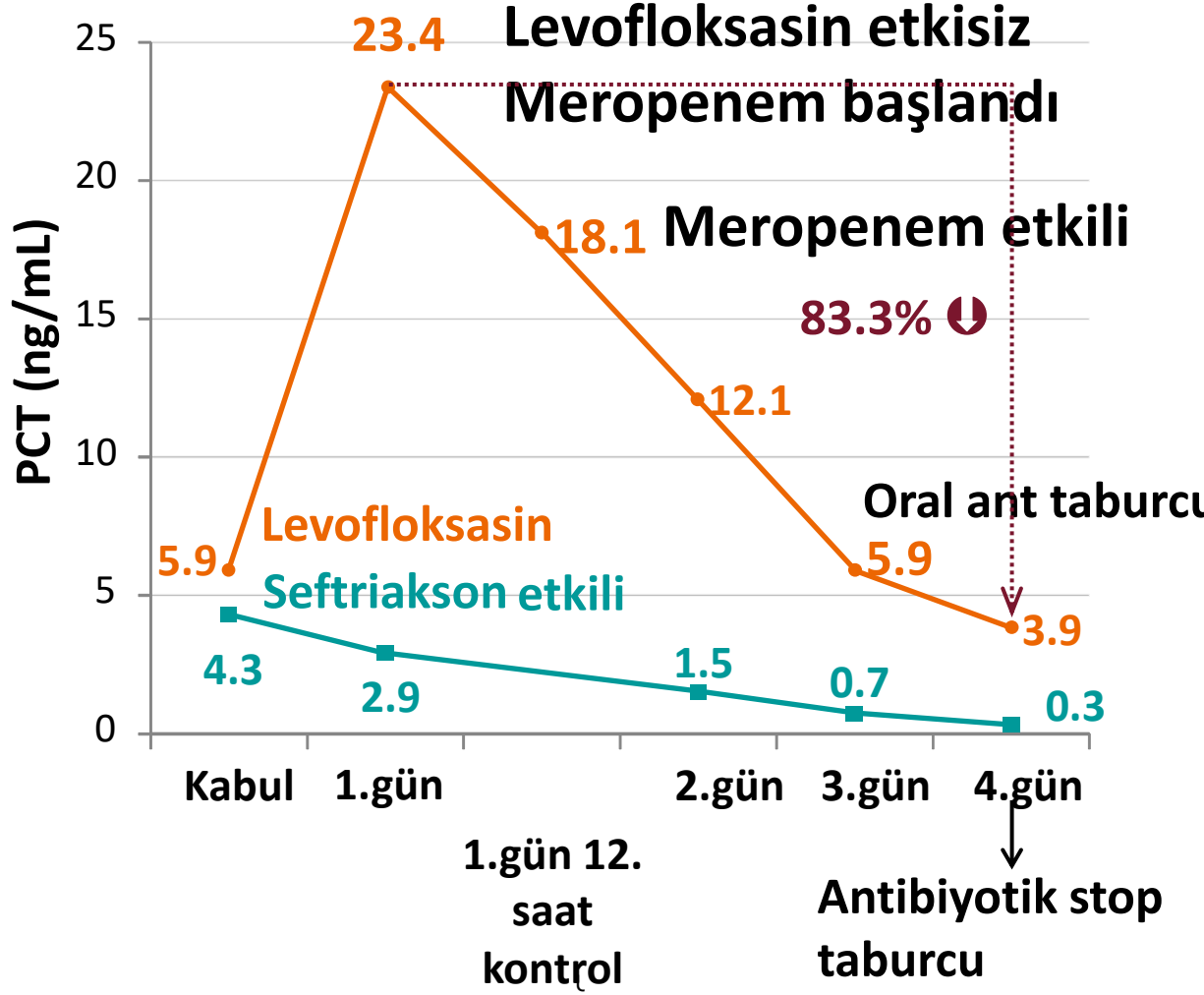



Courtesy of M. Broyles, Pharm D. Five Rivers Medical Center, Pocahontas, AR.

# 9 ay ara ile İYE uyumlu klinik ile başvuran hastanın PCT temelli algoritma kullanılarak yönetimi

| 56y,kadın | İlk başvuru | 2. başvuru |
|---|---|---|
| Semptomlar | Ateş, dizüri, bulantı, kusma | Ateş, dizüri, bulantı, kusma |
| Ateş | 39.6°C | 39.3°C |
| SS | 19 | 18 |
| TA | 142/84 | 156/86 |
| Nabız | 95 | 91 |
| WBC | 28.400 | 26.400 |
| Laktat | 1.9 mmol/L | 1.8 mmol/L |
| Kreatinin | 1.6 mg/dl | 1.8 mg/dl |
| Tam idrar tetkiki | • Nitrit pozitif<br>• Lökosit esteraz+<br>• 4+ bakteriüri | • Nitrit pozitif<br>• Lökosit esteraz+<br>• 4+ bakteriüri |




Courtesy of M. Broyles, Pharm D. Five Rivers Medical Center, Pocahontas, AR.

# Prevalence of Discordant Procalcitonin Use at an Academic Medical Center



Gregory B Seymann, MD ✉, Nicholas Bevins, MD, PhD, Christina Wu, MD, Robert Fitzgerald, PhD

*American Journal of Clinical Pathology*, aqab201,
https://doi.org/10.1093/ajcp/aqab201
**Published:** 11 December 2021 **Article history** ▾

## Objectives

Despite multiple trials demonstrating that procalcitonin (PCT) is an effective tool for antibiotic stewardship, inconsistent application in real-world settings continues to fuel controversy regarding its clinical utility. We sought to determine rates of concordance between PCT results and antibiotic prescribing in hospitalized patients.

## Methods

*We performed a retrospective review of all inpatient encounters at an academic tertiary care health system with a PCT result between February 2017 and October 2019.* Concordant prescribing *was defined as starting or continuing antibiotics following an elevated PCT (>0.5 ng/mL) finding and withholding or stopping antibiotics following a low PCT (< 0.1 ng/mL) finding.*

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## Results

Antibiotic prescribing decisions were discordant from the PCT level in 32.5% of our sample. Among patients not receiving antibiotics at the time of testing, 25.9% (430 of 1,662) were prescribed antibiotics despite a low PCT result. Among patients already receiving antibiotics, treatment was continued despite a low PCT level in 80.4% (728 of 906) of cases. Enhanced decision support tools introduced during the study period had no impact on PCT use for antibiotic decisions.

## Conclusions

Overall concordance between PCT results and antibiotic use is relatively low in a real-world setting. The potential value of PCT for antibiotic stewardship may not be fully realized.

1. Antibiyotik yönetişimi ve Biyomarkerlar
2. PCT test kinetiği
3. Literatürde PCT temelli algoritmalar
4. Özel popülasyonlarda PCT temelli algoritmalar
5. Hastalık ciddiyeti ve mortalite değerlendirmesinde PCT testi
6. Olgu örnekleriyle PCT
7. Atellica® IM B·R·A·H·M·S PCT Testi

| Different Performance /Limited clinical evidence = Different Clinical Utility | | | | | | |
|---|---|---|---|---|---|---|
| **FDA cleared Claims** | **FAS/ LoQ (ng/mL)** | **ICU** | **ED** | **Wards** | **28-Day Mortality Risk** | **Antibiotic Stewardship** |
| **B·R·A·H·M·S PCT** [1-8] | <0.1 | ✓ | ✓ | ✓ | ✓ | ✓ |
| Diazyme PCT [9] | 0.2 | ✓ | ✗ | ✗ | ✗ | ✗** |
| Access PCT [10] | <0.1 | ✓ | ✗ | ✗ | ✗ | ✗*** |

**510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION DECISION SUMMARY**

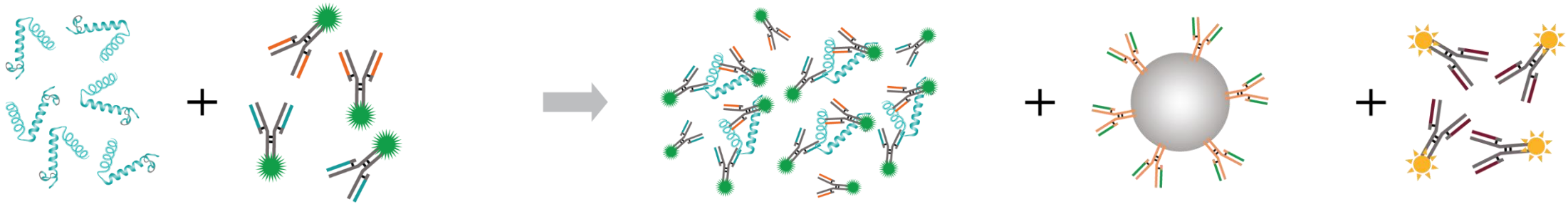
**Warnings and Precautions:**

** **"…The Diazyme PCT assay is not indicated to be used as an aid in decision making on antibiotic therapy for patients …"** [9]

*** **"…The Access PCT assay is not indicated to be used as an aid in decision making on antibiotic therapy for patients…"** [10]

[1] https://www.accessdata.fda.gov/cdrh_docs/reviews/K070310.pdf; [2] https://www.accessdata.fda.gov/cdrh_docs/reviews/k170652.pdf; [3] https://www.accessdata.fda.gov/cdrh_docs/reviews/K181002.pdf; [4] https://www.accessdata.fda.gov/cdrh_docs/reviews/K173927.pdf; [5] https://www.accessdata.fda.gov/cdrh_docs/reviews/K173683.pdf; [6] https://www.accessdata.fda.gov/cdrh_docs/reviews/K172713.pdf; [7] https://www.accessdata.fda.gov/cdrh_docs/reviews/K071146.pdf; [8] https://fda.report/PMN/K200236; [9] https://www.accessdata.fda.gov/cdrh_docs/reviews/K162297.pdf ; [10] https://www.accessdata.fda.gov/cdrh_docs/reviews/K192271.pdf

# Atellica IM B·R·A·H·M·S PCT Assay format



PCT in serum or plasma sample (100 µL)

Ancillary reagent: two different fluorescein-labeled anti-PCT mouse mAb (45 µL)

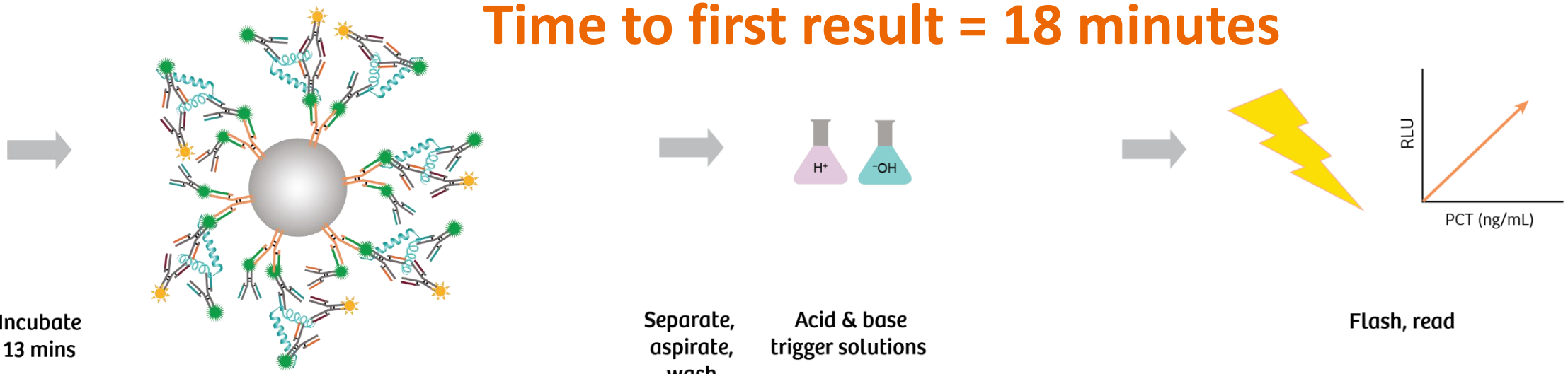
Incubate 3 mins

Antibody-PCT conjugate + unbound antibody

anti-fluorescein mouse MAb coupled to paramagnetic microparticles (100 µL)

Lite reagent: Acridinium ester-labeled anti-PCT antibody conjugate (50 µL)

## Time to first result = 18 minutes




Incubate 13 mins

Separate, aspirate, wash

Acid & base trigger solutions

Flash, read

Siemens Healthineers Atellica® IM B·R·A·H·M·S Procalcitonin Assay package insert, 11202687_EN Rev. 01, 2018-08

# Atellica IM B·R·A·H·M·S PCT Test Karakteristikleri

## Hızlı sonuç verir; 18 dk

## Sensitivitesi yüksek

- LoQ = 0.04 ng/mL

## Test stabilitesi nedeniyle performansı iyi:

- 60 gün reagent stabilitesi mevcut
- Kalibrasyon stabilitesi ~ 82 gün

## B·R·A·H·M·S KRYPTOR testi ile uyumluluk oranı

- % 99.3 positive agreement
  (95%CI = 98.1–99.7%)
- % 95.0 negative agreement
  (95%CI = 87.8–98.0%)
- Overall agreement = %98.7
  (95% CI = 97.5–99.4%)

## Farklı örneklerde çalışılabilir

- Serum
- EDTA plazma
- Lityum heparin plazma
- Sodyum heparin plazma

## Ölçüm aralığı geniş

- 0.03 ng/mL – 50.00 ng/mL
- ≥50 ng/mL örnekler için otomatize dilüsyon mümkün (1:20)

## Beklenen normal değer

< 0.05 ng/mL

Siemens Healthineers Atellica® IM B·R·A·H·M·S Procalcitonin Assay package insert, 11202687_EN Rev. 01, 2018-08

# Atellica IM B·R·A·H·M·S PCT testi

## Klinik değerlendirme ve diğer laboratuvar testleri ile birlikte;

- Kritik hastaların YBÜ kabulünde PCT testi;  sepsis/ septik şok'a ilerleme riskinin değerlendirilmesinde
- Ciddi sepsis/ septik şok hastalarında seri PCT ölçümü ve değişim yüzdesi değerlendirilerek 28 günlük mortalite riskinin değerlendirilmesinde
- Acil servis / serviste yatan düşük riskli, olası / konfirme ASYE hastalarında (toplum kaynaklı pnömoni, akut bronşit, KOAH alevlenmesi vb) antibiyotik tedavi kararında yardımcı bir test
- Olası veya konfirme sepsiste antibiyotik kesme kararında kullanılabilir