

LABORATUVAR SONUÇLARINI TEDAVİ ETMİYORUZ

AKUT FAZ REAKTANLARI

15 MART 2019 , ANTALYA
XX.KLİMİK



esin
şenol

SİNYAL→HUMORAL SİSTEM VE
FAGOSİTLER→ÖZGÜN OLMAYAN, KOORDİNE BİR
REAKSİYON → HUMORAL/SALGISAL
KOMPONENTLER↑ VEYA↓

**AFP:İNFLAMASYON SIRASINDA PLAZMA
DÜZEYLERİ:%25↑VEYA↓PROTEİNLER**

HEPATOSİTLERDEN→MAKROFAJ, MONOSİT,

HEM AKUT HEM KRONİK İNFLAMASYONDA ARTAR

İNFEKSİYON

TRAVMA

İNFAKT

İNFLAMATUVAR ARTRİT

OTOİMMUN

SİSTEMİK İNFLAMATUVAR HASTALIKLAR

BAZI MALİNİTELER



AKUT FAZ REAKTANLARI

- **Tanı: İnflamatuvar Yanıt**
 - Etyoloji : Viral vs Bakteriyel, İnfeksiyon vs İnfeksiyon Dışı
 - Erken
- **Tedavi:**
 - Erken
 - Doğru
 - Yeterli süre
- **Prognostik**
 - İnfeksiyonun şiddeti
 - Tedavi yanıtı

A

- Artış gösterenler
 - ESR
 - **CRP**
 - Fibrinojen
 - Haptoglob
 - C3
 - Ferritin
 - **Serum Am**
 - Prokalsitonin

TABLE 1. HUMAN ACUTE-PHASE PROTEINS.

Proteins whose plasma concentrations increase

Complement system

- C3
- C4
- C9
- Factor B
- C1 inhibitor
- C4b-binding protein
- Mannose-binding lectin

Coagulation and fibrinolytic system

- Fibrinogen
- Plasminogen
- Tissue plasminogen activator
- Urokinase
- Protein S
- Vitronectin
- Plasminogen-activator inhibitor 1

Antiproteases

- α_1 -Protease inhibitor
- α_1 -Antichymotrypsin
- Pancreatic secretory trypsin inhibitor
- Inter- α -trypsin inhibitors

Transport proteins

- Ceruloplasmin
- Haptoglobin
- Hemopexin

Participants in inflammatory responses

- Secreted phospholipase A₂
- Lipopolysaccharide-binding protein
- Interleukin-1-receptor antagonist
- Granulocyte colony-stimulating factor

Others

- C-reactive protein
- Serum amyloid A
- α_2 -Acid glycoprotein
- Fibronectin
- Ferritin
- Angiotensinogen

Proteins whose plasma concentrations decrease

- Albumin
- Transferrin
- Transthyretin
- α_2 -HS glycoprotein
- Alpha-fetoprotein
- Thyroxine-binding globulin
- Insulin-like growth factor I
- Factor XII

ri

tin
in





CRP

- CRP, inflamatuvar reaksiyonlarda ,karaciğerden sentezlenen bir protein (PENTRAXİN: Patern Recognition Moleküller), patojenlerin tanınması, eliminasyonu, nekrotik ve apopitotik hücrelerin temizlenmesi
- 4-6 sa.sentezlenir- **8 sa. 2 misli olur**, 36-50 saatte maksimuma ulaşır-Plazma y.ö:19 sa; inflamasyon iyileşirse: 4-7 sa., %50 ↓ /gün, ama genellikle **normale dönmesi 1 haftayı bulur**
 - 20-200 ng/ml değerlerine ulaşmaktadır.
- İnvazif bakteriyel infeksiyonlarda → **15-40 KAT**
- Viral infeksiyonlarda → **3-5 KAT**
 - Grip, CMV gibi viral infeksiyonlarda da 10 kattan fazla artış olabilmektedir.

CRP

- Bakteriyel İnfeksiyonlar:10-50 mg/dL (100-500 mg /L)
- **>100 mg/L ve >500 mg/L: %80-85 ve >%90**
BAKTERİYEL
- YAŞ için : REFERANS DEĞER ÜST SINIR (mg/dl)=YAŞ
- 0.3-1 mg/dL (3-10 mg/L) : Düşük Düzeyli İnflamasyon
(Metabolik disfonksiyon,Obezite,İnsülin Direnci):
Metabolik Tetiklenmiş
İnflamasyon:Meta/Parainflamasyon
- >1mg/dL : 10 mg /L: Klinik Olarak Önemli İnflamasyon

ERİTROSİT SEDİMENTASYON HIZI

DOLAYLI BİR AFR-pozitif yüklü, asimetrik plazma proteinleri; Fibrinojen ve immunglobülinler

24-48 sa. başlar-haftalar

Fibrinojen y.ö:100 sa., IgG:21 gün

**SİSTEMİK VE LOKALİZE
İNFLAMATUVAR VE
İNFEKSİYONLAR
NEOPLAZMALAR
DOKU HASARI / İSKEMİ
TRAVMA**

YAŞ/CİNSİYET:YAŞ/2:ERKEK,

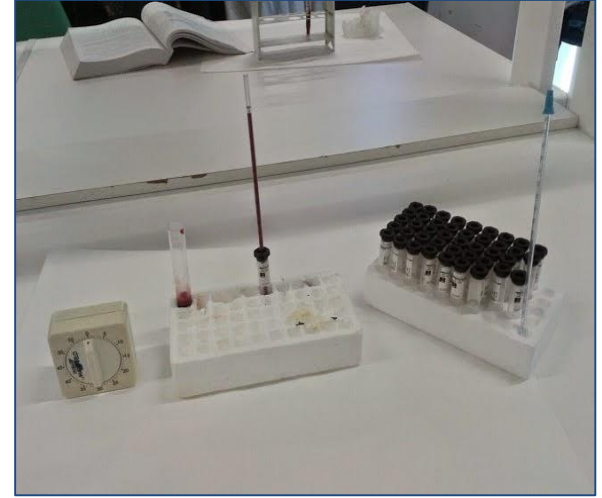
YAŞ+10/2:KADIN

ANEMİ

RENAL HASTLALIKLAR-60 -100

mm/hr

OBEZİTE : CRP (IL-6)



ESR AZALMASI

ERİTROSİT ANOMALİLERİ

LÖKOSİTOZ

KALP YETMEZLİĞİ

HİPOFİBRİNOJENEMİ

KAŞEKSİ

SAFRA TUZLARI DÜZEYİNİN

ÇOK YÜKSEK OLMASI

TEKNİK NEDENLER

ESR>100 mm/hr

- ENFEKSİYON
 - SBE
 - APSE
 - OSTEOMİYELİT
- KOLLAJEN DOKU HASTALIKLARI
 - POLİMİYALJİ ROMATİKA
 - DEV HÜCRELİ ARTERİT
 - RA
 - SLE
- MALİGNİTE
 - MM
 - LENFOMA
 - LÖSEMİ
 - KANSER

SPESİFİTE

İNFEKSİYON:0.97

MALİNİTE:0.96

PPV:%90 –HASTALIK

SİCKNESS İNDEX.0.99

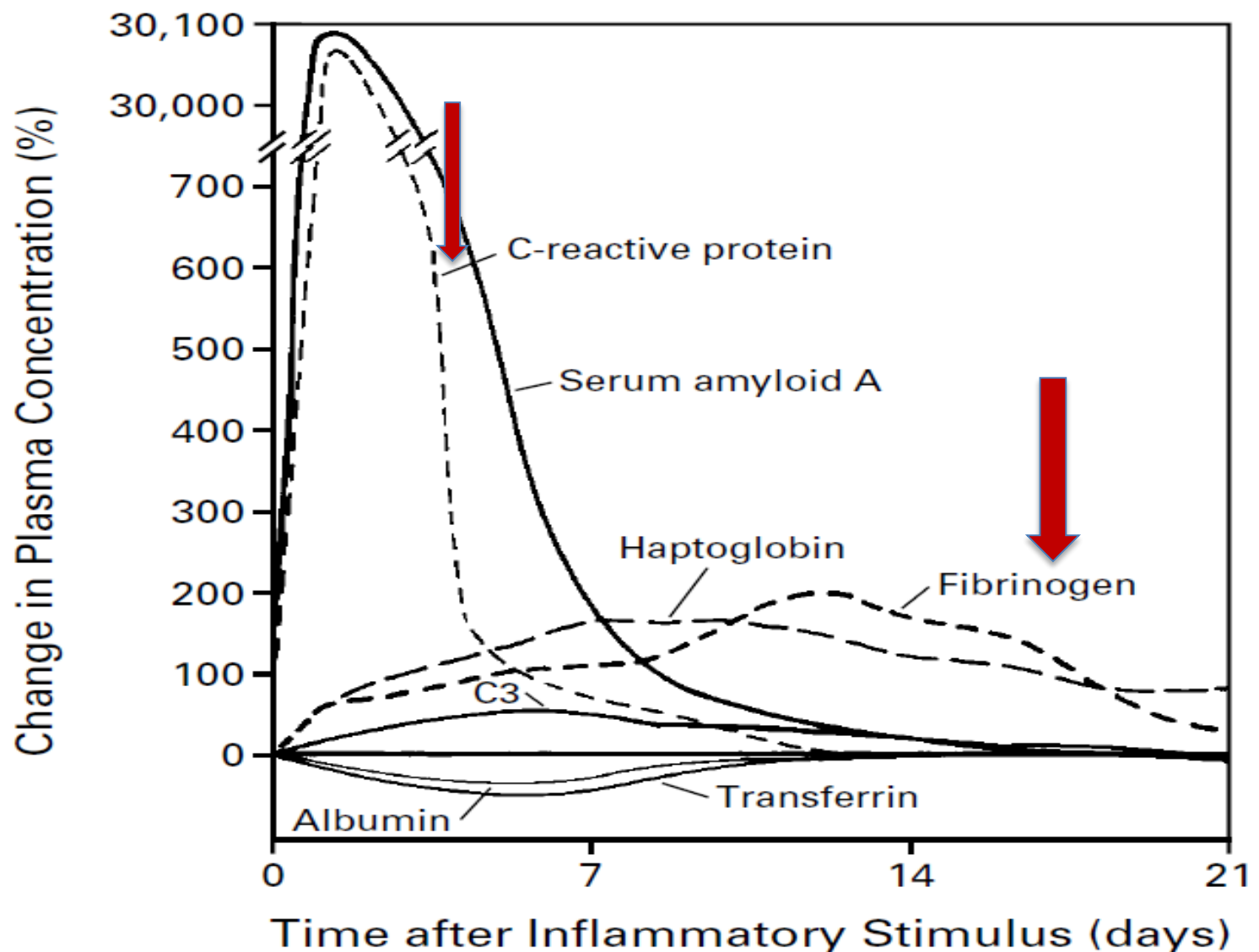


Figure 1. Characteristic Patterns of Change in Plasma Concentrations of Some Acute-Phase Proteins after a Moderate Inflammatory Stimulus.

Modified from Gitlin and Colten⁵ with the permission of the

Erythrocyte Sedimentation Rate and C-reactive Protein Measurements and Their Relevance in Clinical Medicine

Christopher Bray, MD, PhD; Lauren N. Bell, PhD; Hong Liang, PhD; Rasha Haykal, MD; Farah Kaiksow, MD; Joseph J. Mazza, MD; Steven H. Yale, MD

WMJ • DECEMBER 2016

Table 1. Conditions Associated With a Change in CRP and ESR

Conditions Associated With a Mild Rise in CRP	Conditions Associated With a Major Rise in CRP	Conditions Associated With a Mild Rise in ESR	Conditions Associated With a Major Rise in ESR
<ul style="list-style-type: none"> • Viral Infections • Late pregnancy <p>Mucosal Infections</p> <ul style="list-style-type: none"> • Periodontitis • Stomatitis • Sinusitis • Bagnitis • Intestinal hyperpermeability • Bacterial translocation <p>Noninfectious Causes of Mild Inflammation</p> <ul style="list-style-type: none"> • Obesity • Insulin resistance • Pancreatitis • Smoking • Uremia • Cardiac Ischemia • Oral hormone replacement therapy • Sleep disturbance • Chronic fatigue • Mild alcohol consumption • Depression • Increasing age 	<ul style="list-style-type: none"> • Active inflammation • Severe bacterial infection • Burns 	<ul style="list-style-type: none"> • Increasing age • Female gender • Pregnancy • Anemia • Red blood cell abnormalities (including macrocytosis) <p>Technical factors:</p> <ul style="list-style-type: none"> • Dilutional problem • Increased temperature of specimen • Tilted ESR tube <p>Elevated fibrinogen level:</p> <ul style="list-style-type: none"> • Inflammation • Infection • Malignancy • Diabetes • Renal disease • Heart disease • Collagen vascular diseases 	<ul style="list-style-type: none"> • Malignancy • Temporal arteritis • Renal disease • Collagen vascular diseases

Abbreviations: ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.

CRP VE ESR UYUŞMAZLIKLARI

Table 2. Discordant Values in Hospitalized Patients

High ESR/Low CRP

- Infections (Bone and joint)
- Connective tissue disease (SLE)
- Ischemic stroke
- Malignancy
- Renal insufficiency
- Low serum albumin

High CRP/Low ESR

- Infections (urinary tract, gastrointestinal tract, lung and bloodstream)
- Myocardial infarction
- Venothromboembolic disease
- Rheumatoid arthritis
- Low serum albumin

Abbreviations: ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; SLE, systemic lupus erythematosus.

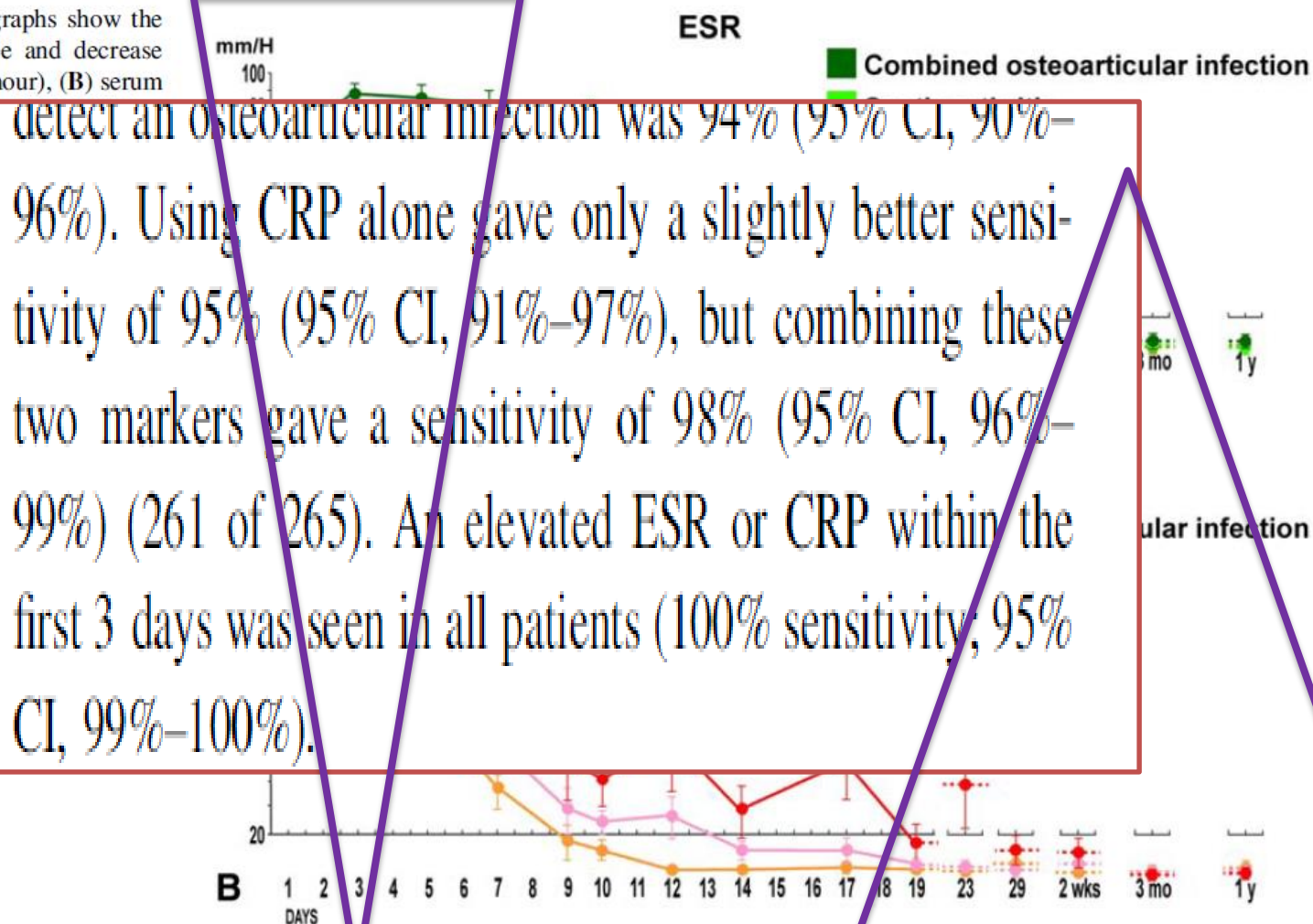
SENSİTİVİTE: %75 VE %77

Sensitivity of Erythrocyte Sedimentation Rate and C-reactive Protein in Childhood Bone and Joint Infections

Markus Pääkkönen MD, Markku J. T. Kallio MD, Pentti E. Kallio MD, Heikki Peltola MD

Clin Orthop Relat Res (2010) 468:861–866

Fig. 1A–C The graphs show the pattern of increase and decrease of (A) ESR (mm/hour), (B) serum CRP (mg/L), and (C) serum CRP (mg/L) in patients with SA, and OM. CRP was taken 1 to 29 days after diagnosis and 2 weeks and 1 year after diagnosis.



Prokalsitonin (PCT)

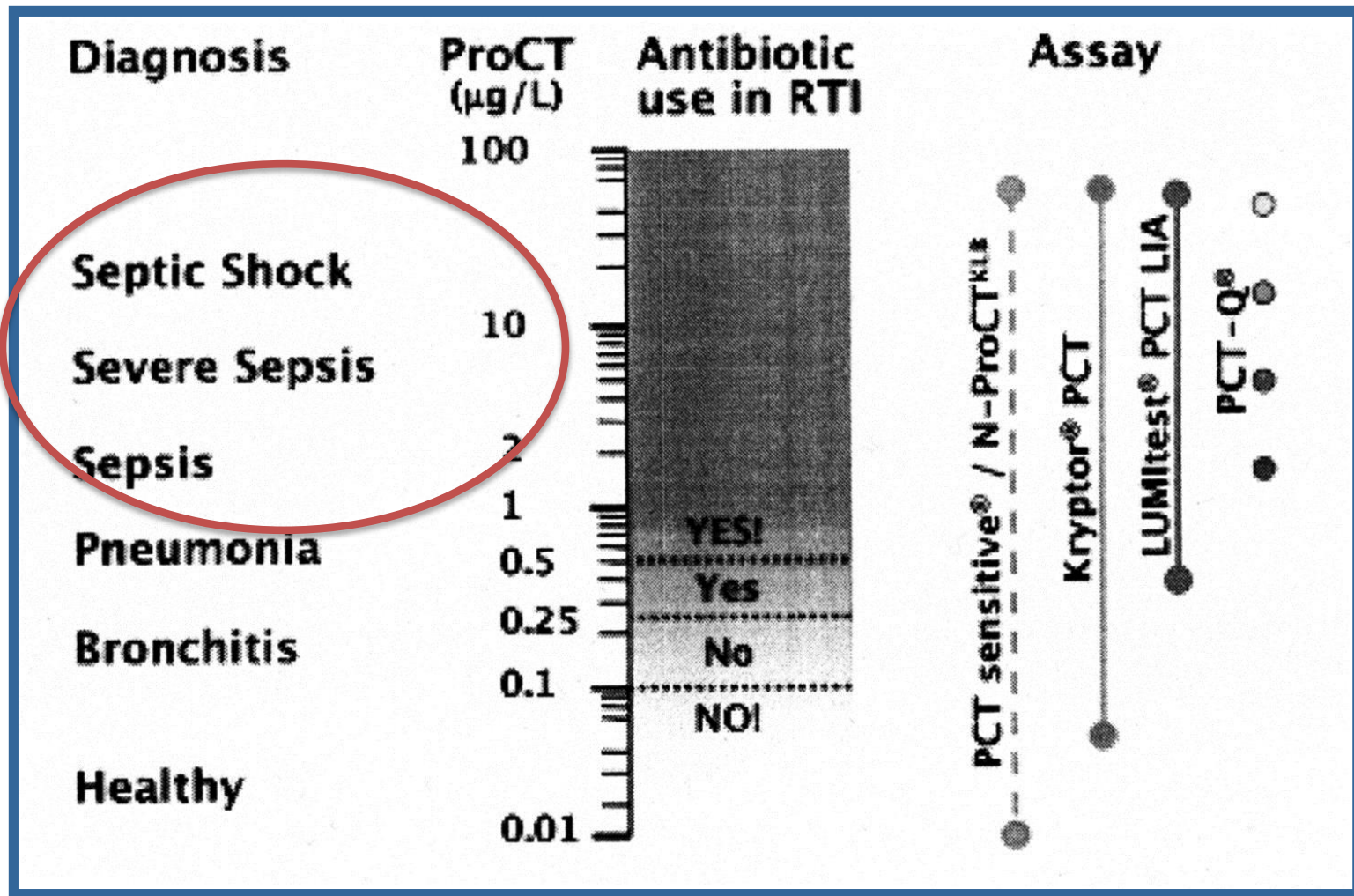
- Kalsitonin propeptidi
- “HORMOKİN” MEDIATÖRLERİN PROTOTİPİDİR
- Normal olarak tiroid bezinin C hücrelerinde üretilir ve sağlıklı kişilerde düzeyi çok düşüktür.
- **İndüklenme:** Bakteriyel endotoksin, ekzotoksin, sitokinler; **endotoksin** ve **TNF- α**
- 3-4 sa. te yükselir, 6-8 sa. Pik, 24 sa. Bu seviyede kalır
- Özellikle YBÜ: sepsis tanısında ve prognoz tayininde yardımcı
 - **50 mg/L** prokalsitonin **olası** veya **kesin** sepsis tanısında %98.5 duyarlılık ve %75 özgüllük

Farklı Klinik Tablolarda PCT deęerleri

Klinik durum	PCT d�zeyi (ng/ml)
Normal kiřiler	<0.5
Kronik inflamatuvar s�re�ler ve otoimm�n hastalıklar	<0.5
Viral infeksiyonlar	<0.5
Hafif veya orta řiddette bakteriyel lokal infeksiyonlar	<0.5
SIRS, multiple travma, yanıklar	0.5-2.0
Ciddi, bakteriyel infeksiyonlar, sepsis,MODS	>2 (10-100)

- Prokalsitonin CRP den daha pahalı
- İnfeksiyon dışı durumlarda da artabilir
 - Yanıklar, ciddi travma,
 - Büyük cerrahi işlemler,
 - Uzamış dolaşım yetmezliği ...

**ANCAK SEPSİSDEKİ KADAR YÜKSEK DEĞERLERE
ULAŞMAZ**



PCT: İNFEKSİYONDA TANISAL VE PROGNOSTİK DEĞERİ

- Meta-analiz: Sistemik bakteriyel enfeksiyonlarda -kaynaktan bağımsız
- **Bakteriyel vs Viral**
- **Bakteriyel vs Enfeksiyon dışı**
- CRP; **Duyarlılık %75, Spesifite %67 : %86 ,%70**
- PCT; **Duyarlılık %88, Spesifite %81 :%92, %73**

PCT: İNFEKSİYONDA TANISAL VE PROGNOSTİK DEĞERİ

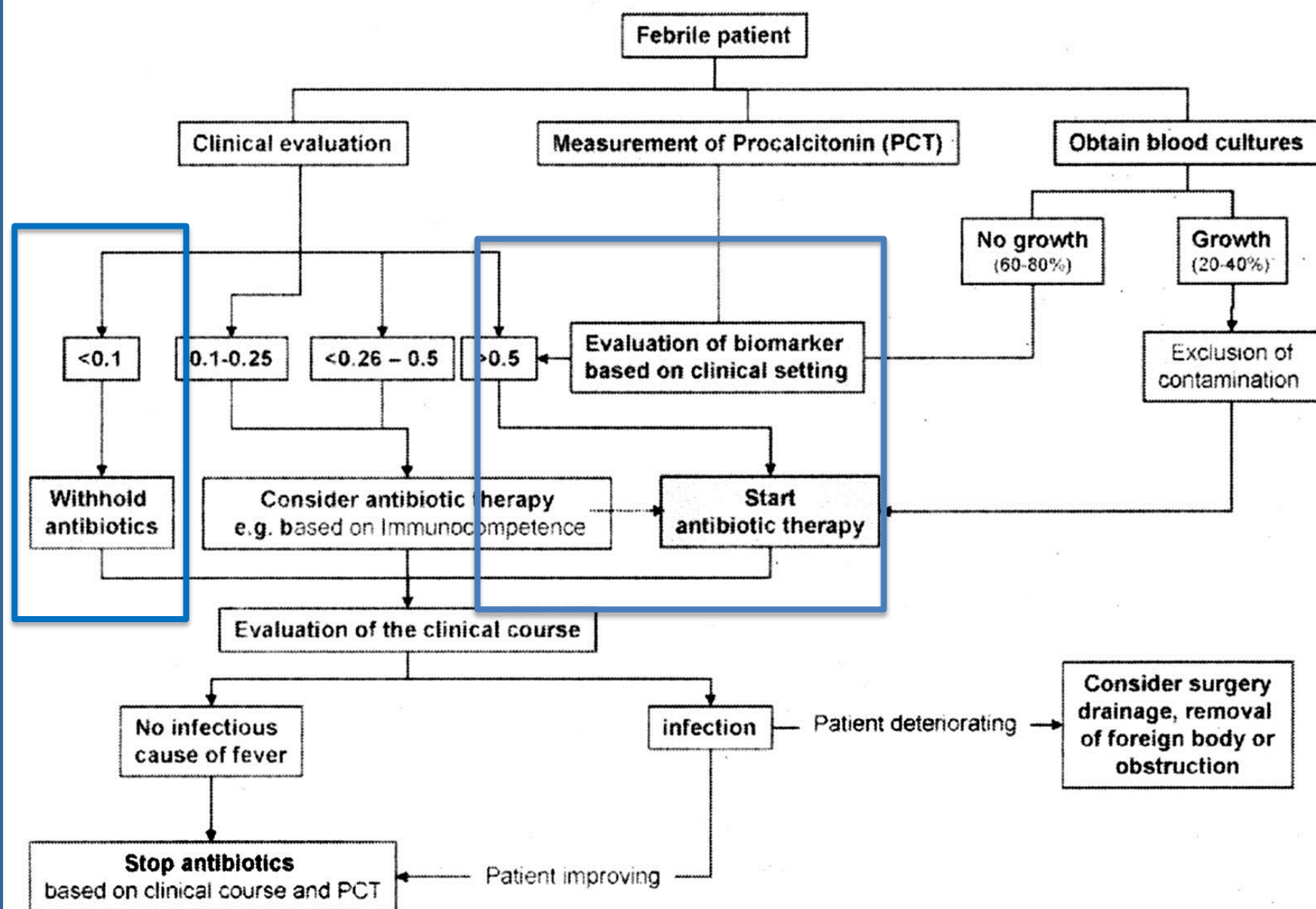
- İnflamatuvar Yanıtın Erken Göstergesi; Erken Yükselir, NPD Daha İyi

• Bakteriyel enfeksiyonu olan hastalarda antibakteriyel tedavinin başlanmasından sonra geçen 24 saat içinde prokalsitonin düzeyinde %30'dan fazla düşme olması uygun antibiyotiğin başlanmış olduğunu ve enfeksiyonun kontrol altına alınmış olduğunu gösterir.

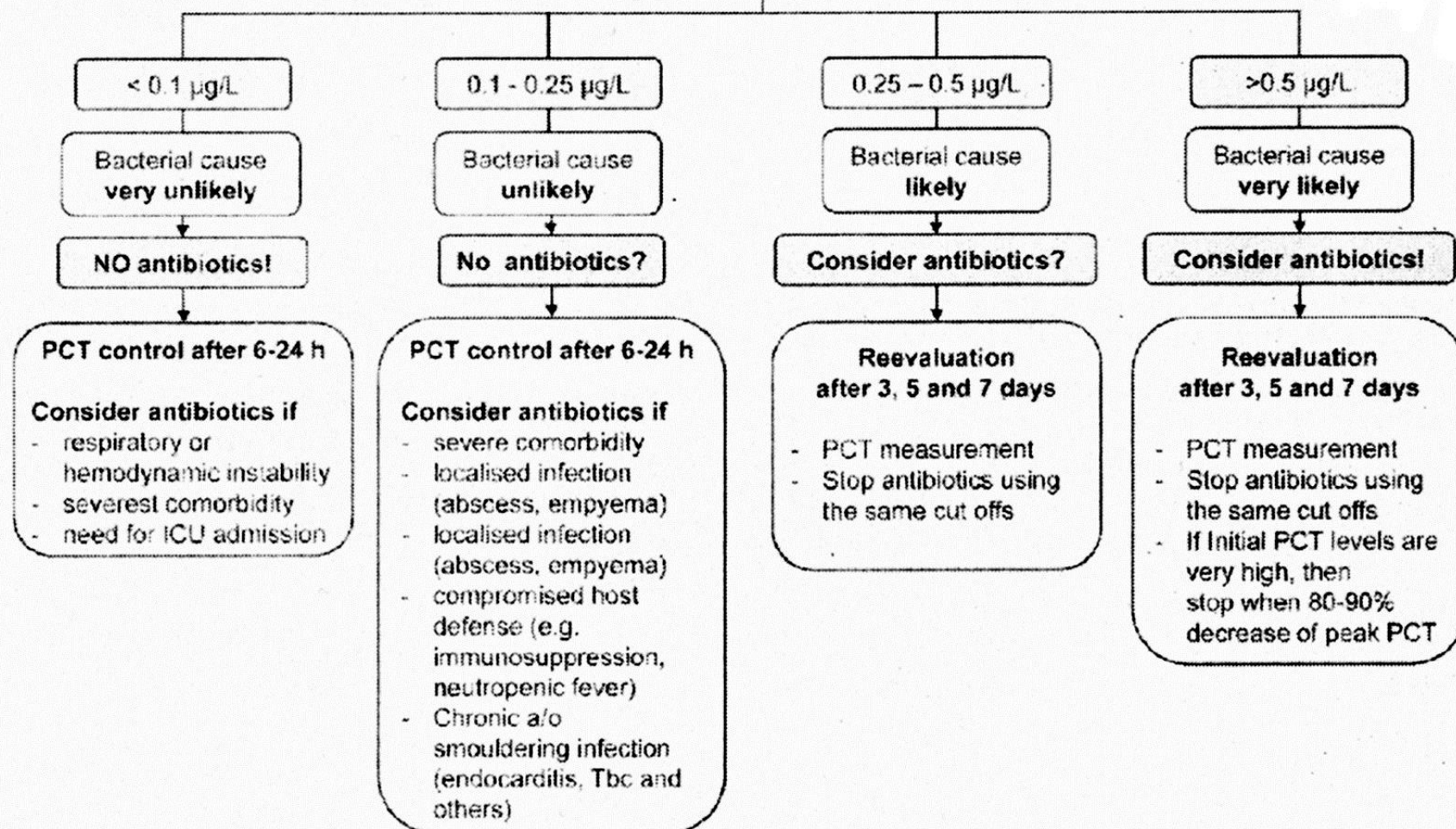
- VAP; Tamamlayıcı Tanı Kriteri, Prognostik Parametre
- İnfektif Endokarditte Bağımsız Prediktör

PCT - KULLANIM ALANLARI

- Sepsis
- FUO
- SYİ
- Menenjit
- Endokardit
- Pankreatit
- Otoimmün hastalıklar
- Postoperatif
- İmmüsuprese hasta
- Transplantasyon



Procalcitonin (PCT)-guided Antibiotic Treatment



Common causes of false-negative and false-positive results:

false-positive (ie, falsely high levels in the absence of a bacterial infection):

newborns (physiologically) during first days of life [78]

acute respiratory distress syndrome [79, 80]

acute attacks of plasmodium falciparum malaria [61]

systemic fungal infections (eg candidiasis, aspergillosis) [81]

severe mechanical trauma [82]

following surgical trauma [83]

administration of monoclonal or polyclonal anti-thymocyte globulin in the treatment of acute rejection after transplantation [84]

chemical pneumonitis [85]

severe burns and heat strokes [86, 87]

patients with medullary thyroid cancer, small cell cancer of the lung, carcinoid, tumours with paraneoplastic hormone production [88]

inflammation associated with “cytokine storms”, eg IL β , in familial Mediterranean fever, therapeutic infusions of TNF α for melanoma [13, 16]

false-negative (ie, falsely low levels in the presence of a bacterial infection):

early course of infections [17]

localised infections [58]

subacute endocarditis [55, 56]



Acute Phase Reactants in Infections: Evidence-Based Review and a Guide for Clinicians

Anurag Markanday^{1,2,3}

OFID 2015

Table 1. Acute Phase Reactants


ESR	Extremely elevated ESR (>100 mm/hour)-high specificity for infection, malignancy, or arteritis. Rises within 24–48 hours of the onset of inflammation and falls back slowly with resolution.
CRP	Begins to rise after 12–24 hours and peaks within 2–3 days. Low levels of CRP elevation with values between 2 and 10 mg/L measured by a “high sensitivity CRP” assay seen in noninfectious “metabolic inflammatory” states such as cardiac ischemia, uremia, or smoking.
PCT	Detectable within 3–4 hours and peaks within 6–24 hours. Elevated levels not seen in other noninfectious inflammatory conditions such as polymyalgia, inflammatory bowel disease, polyarteritis nodosa, systemic lupus erythematosus, gout, and temporal arteritis. More sensitive and specific than CRP for distinguishing bacterial from noninfectious causes of inflammation
Others	Apolipoproteins: SAA proteins Coagulation Pathway: Fibrinogen, Protein S, Plasminogen Complement System: C3, C4, C9, Factor B, C1 inhibitor Antiproteases: Alpha-1 antitrypsin, Alpha-1 acid glycoprotein Proteins: Haptoglobin, Hemopexin, Hepcidin, Ferritin, Ceruloplasmin Cytokines: IL-1, IL-6, tumor necrosis factor-alpha

Table 3. Acute Phase Reactants in Specific Infections

Clinical Infection	Acute-phase reactant (ESR-mm/hour, CRP-mg/L, PCT-ng/mL)
Cellulitis and Erysipelas Necrotizing Skin and Soft Tissue Infections (NSSTIs)	CRP >70 and ESR >50 have a higher predictive value for the duration of hospital stay, which is an indirect index of severity [14, 15]. CRP >150 may suggest a higher likelihood of NSSTI [16]. PCT ratio of more than 1.14 between postoperative day 1 and day 2 after surgical debridement associated with favorable clinical recovery [18].
Osteomyelitis Spondylodiscitis Prosthetic Joint Infection	CRP >32 and ESR >70 helpful in distinguishing osteomyelitis from cellulitis in diabetic foot infections [19, 50]. CRP, PCT decrease rapidly with treatment. Fall in previously elevated ESR is a marker for response to treatment [20, 50]. Both ESR (median value 60) and CRP have high sensitivity for diagnosis of pyogenic spondylodiscitis. Decreasing values (25–50%) in the first 4 weeks of treatment suggest favorable prognosis [22, 23]. CRP may remain elevated for up to 6 weeks and ESR for up to 26 weeks after prosthetic joint surgery. Serum IL-6, CRP, and ESR have the best diagnostic value. Likelihood of infection very low if both ESR and CRP are normal. Procalcitonin has a low sensitivity [26, 27].
Meningitis Neurosurgical infections	Serum and cerebrospinal PCT levels likely have a high diagnostic accuracy in bacterial meningitis [44, 45]. CSF lactate at a cutoff of 35 mg/dL has a high negative likelihood ratio for distinguishing bacterial from viral meningitis [51]. Serum PCT levels of >0.15 have a high diagnostic value for bacterial infections after neurosurgical procedures [46, 47].
Infective Endocarditis	An initial value of PCT >0.5 is predictor for poor outcome. High levels of CRP (>122) after first week of treatment and slow decline are indicators of poor outcome [48, 49].
Pyelonephritis in children	PCT level >0.5 is associated with high likelihood of pyelonephritis and renal scars in pediatric patients with urinary tract infection [52].

Abbreviations: CRP, C-reactive protein; CSF, cerebrospinal fluid; ESR, erythrocyte sedimentation rate; IL, interleukin; PCT, procalcitonin.

C-Reactive Protein on Postoperative Day 1: a Predictor of Early Intra-abdominal Infections After Bariatric Surgery

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Obesity Surgery

<https://doi.org/10.1007/s11695-018-3240-x>

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The normal range for CRP is defined as less than 5 mg/L.

Abstract

Background Early intra-abdominal infections (IAI) compromise short-term outcomes in bariatric surgery. The timely detection of IAI is challenging but essential to prevent major sequelae of such complications. C-reactive protein (CRP) is a reliable marker for detecting IAI after colorectal surgery. In bariatric surgery, data on CRP as a marker for IAI are limited, particularly for postoperative day one (POD1).

Objective The objective of this study was to assess CRP on POD1 as a predictor for early IAI (within 7 days following surgery) in patients after laparoscopic sleeve gastrectomy (LSG) and Roux-en-Y gastric bypass (LRYGB).

Methods Patients with bariatric surgery between 08/2010 and 06/2017 were included. The predictive capacity of CRP for early IAI was determined using a receiver operating characteristics (ROC) analysis.

Results In 523 patients (68.5% female, LSG = 358, LRYGB = 165), 16 (3%) early IAI were observed. ROC analysis revealed a significant predictive capacity of POD1 CRP for early IAI, with a sensitivity and a specificity of 81.2 and 94.3%, respectively, at a CRP cut-off value of 70 mg/L. In patients with confirmed early IAI, 81.3% had a CRP level ≥ 70 mg/L (LSG 85.7%, LRYGB 77.8%). The negative predictive value for a CRP level < 70 mg/L was 99.4% overall and was 100 and 98% for LSG and LRYGB, respectively.


Conclusion In patients with a CRP level < 70 mg/L on POD1, early IAI can be excluded with high accuracy in bariatric patients. Thus, early postoperative CRP may be used to assess the risk of early IAI in enhanced recovery programs.

ESR VE CRP

- Etiyoloji belirlemede; sensitivite ve spesifite sorunu
- Olasılığın **en yüksek** ve **en düşük** olduğu durumlarda kullanışlı
- ESR ve CRP farklılıkları en çok kronik inflamatuvar durumlarda
- PCT pahalı ama erken ve prognostik
- Çoklu ko-morbidite ve eşlik eden inflamatuvar durumlar; kombine ,akılcı kullanım
- AKILCI KULLANIM; ŞÜPHELENİLEN KLİNİK DURUM İÇİN , TEST KISITLILIKLARI, DİNAMİKLERİ



Combined use of serum (1,3)- β -D-glucan and procalcitonin for the early differential diagnosis between candidaemia and bacteraemia in intensive care units

Daniele Roberto Giacobbe^{1*†} , Malgorzata Mikulska^{1†}, Mario Tumbarello², Elisa Furfaro¹, Marzia Spadaro¹, Angela Raffaella Losito², Alessio Mesini¹, Gennaro De Pascale³, Anna Marchese⁴, Marco Bruzzzone⁵, Paolo Pelosi^{6,7}, Michele Mussap⁸, Alexandre Molin⁶, Massimo Antonelli³, Brunella Posteraro⁹, Maurizio Sanguinetti¹⁰, Claudio Viscoli¹, Valerio Del Bono¹ and on behalf of ISGRI-SITA (Italian Study Group on Resistant Infections of the Società Italiana Terapia Antinfettiva)

Abstract

Background: This study aimed to assess the combined performance of serum (1,3)- β -D-glucan (BDG) and procalcitonin (PCT) for the differential diagnosis between candidaemia and bacteraemia in three intensive care units (ICUs) in two large teaching hospitals in Italy.

Methods: From June 2014 to December 2015, all adult patients admitted to the ICU who had a culture-proven candidaemia or bacteraemia, as well as BDG and PCT measured closely to the time of the index culture, were included in the study. The diagnostic performance of BDG and PCT, used either separately or in combination, was assessed by calculating the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and positive and negative likelihood ratios (LR+ and LR-). Changes from pre-test probabilities to post-test probabilities of candidaemia and bacteraemia were inferred from Fagan's nomograms.

Results: One hundred and sixty-six patients were included, 73 with candidaemia (44%) and 93 with bacteraemia (56%). When both markers indicated candidaemia (BDG ≥ 80 pg/ml and PCT < 2 ng/ml) they showed higher PPV (96%) compared to 79% and 66% for BDG or PCT alone, respectively. When both markers indicated bacteraemia (BDG < 80 pg/ml and PCT ≥ 2 ng/ml), their NPV for candidaemia was similar to that of BDG used alone (95% vs. 93%). Discordant BDG and PCT results (i.e. one indicating candidaemia and the other bacteraemia) only slightly altered the pre-test probabilities of the two diseases.

Conclusions: The combined use of PCT and BDG could be helpful in the diagnostic workflow for critically ill patients with suspected candidaemia.

Keywords: *Candida*, Bloodstream infections, BSI, Sepsis, Fungal antigens, Non-culture-based methods, Biomarker, Critically ill patients

YENİ BİYOMARKERLAR

Table 3 Promising new biomarkers of infection

Biomarker	Biological, structural and/or pathophysiological characteristics	Available data
sTREM-1	Surface receptor of mature polymorphonuclear and monocytes up-regulated when exposed to bacterial and fungal pathogens	Diagnostic value for pneumonia and meningitis and prognostic value in sepsis (3)
suPAR/ CD87	Constitutive cellular receptor in endothelium and leucocyte up-regulated during inflammatory and immune response	Prognostic value in sepsis. Possible useful for antibiotic management in sepsis (3)
ProADM	Adrenomedullin precursor (mediator of cell proliferation and hormone regulation) with increased secretion during immune response to bacterial and viral infection	Prognostic value in pneumonia (3)
Presepsin	Glycoprotein receptor of monocytes/macrophages	Diagnostic and prognostic value in sepsis (3)
PTX3	Protein produced by various cells (monocytes, neutrophils and endothelial cells) in response to proinflammatory cytokines and bacterial products; acts as part of the innate immune system by activating the classical and lectin complement pathways; closely related to CRP as both are members of the pentraxin family	Candidate prognostic marker in sepsis (50,51)

sTREM-1, soluble triggering receptor expressed on myeloid cells-1; suPAR, soluble urokinase-type plasminogen receptor; ProADM, proadrenomedullin; PTX3, pentraxin-3; CRP, C-reactive protein.

**DİNLEDİĞİNİZ İÇİN
TEŞEKKÜRLER...**

SORULARINIZ?

Prof. Dr. Esin Şenol

**“LABORATUVAR SONUÇLARINI
TEDAVİ ETMİYORUZ”**

**20. TÜRK KLİNİK
MİKROBİYOLOJİ VE İNFEKSİYON
HASTALIKLARI KONGRESİ**

**13-16 MART
GLORIA GOLF RESORT HOTEL
BELEK/ANTALYA**

