KUISCID
KOÇ UNIVERSITY - İŞBANK
CENTER FOR INFECTIOUS DISEASES

Sepsis Tanısında Prokalsitonin ile Antiyotik Kullanımı

Dr. Önder Ergönül

14 Mart 2023

Sunum Planı

Sepsisin erken tanısının önemi

Biyobelirteçlerin önemi ve farkları

Klinik uygulamalar

Gram Negatif Enfeksiyonlarda Direnç ve 30 günlük Fatalite

	Acinetobacter	Klebsiella	E.coli	P.aureginosa
	OR (95% CI), p	OR (95% CI), p	OR (95% CI), p	OR (95% CI), p
Pneumonia	1.38 (1.08-1.77) p=0.01	3.25 (2.32-4.55), p<0.001	2.61 (1.54-4.41), p<0.001	1.65 (1.16-2.34), p=0.005
Age>65	1.47(1.15-1.88), p=0.002	1.42 (1.09-1.85), p=0.009	2.62 (1.7-4.04), p<0.001	-
2018 vs 2015	1.15 (1.05-1.24), p=0.001	1.1 (1.02-1.22), p=0.014	-	-
BSI	-	1.53 (1.1-2.13), p=0.01	-	-
R-carbepenem	-	1.46 (1.12-1.92), p=0.005	2.75 (1.5-5.02), p=0.001	1.51 (1.06-2.14), p=0.022
R-colistin	-			4.1 (2.34-7.19), p=0.005

Aydin M, et al EJCMID 2020

Developments in Emerging and Existing Infectious Diseases
Series Editors: Önder Ergönül and Füsun Can

2

ANTIMICROBIAL STEWARDSHIP

Edited by

Céline Pulcini, Önder Ergönül, Füsun Can, Bojana Beović

ESCMID
MANAGING INFECTIONS PROMOTING SCIENCE

ESGAP
ESCMID STUDY GROUP FOR ANTIBIOTIC POLICIES
European Society of Clinical Microbiology and Infectious Diseases

AP

Yerleştirme (kurumsallaştırma) Bilimi

Flottorp et al. Implementation Science 2013:

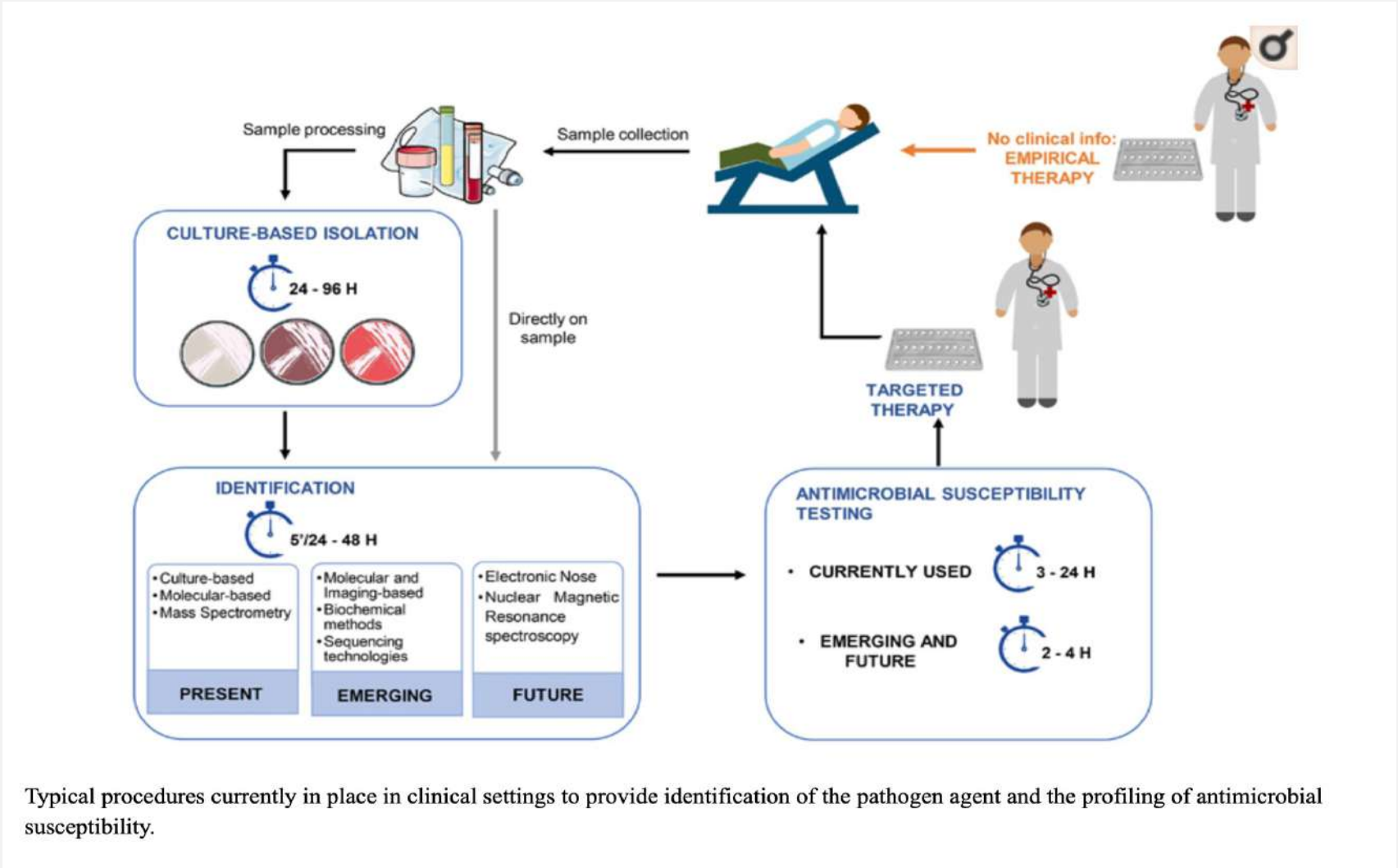
7 ana başlıkta 57 engel

1. *Rehberlere ait faktörler*
2. *Bireysel mesleksel faktörler*
3. *Hasta faktörü*
4. *Profesyonel etkileşim*
5. *Teşvik ve kaynaklar*
6. *Kurumsal değişim kapasitesi*
7. *Sosyal, politik ve hukuksal faktörler*

10 Altın Kural

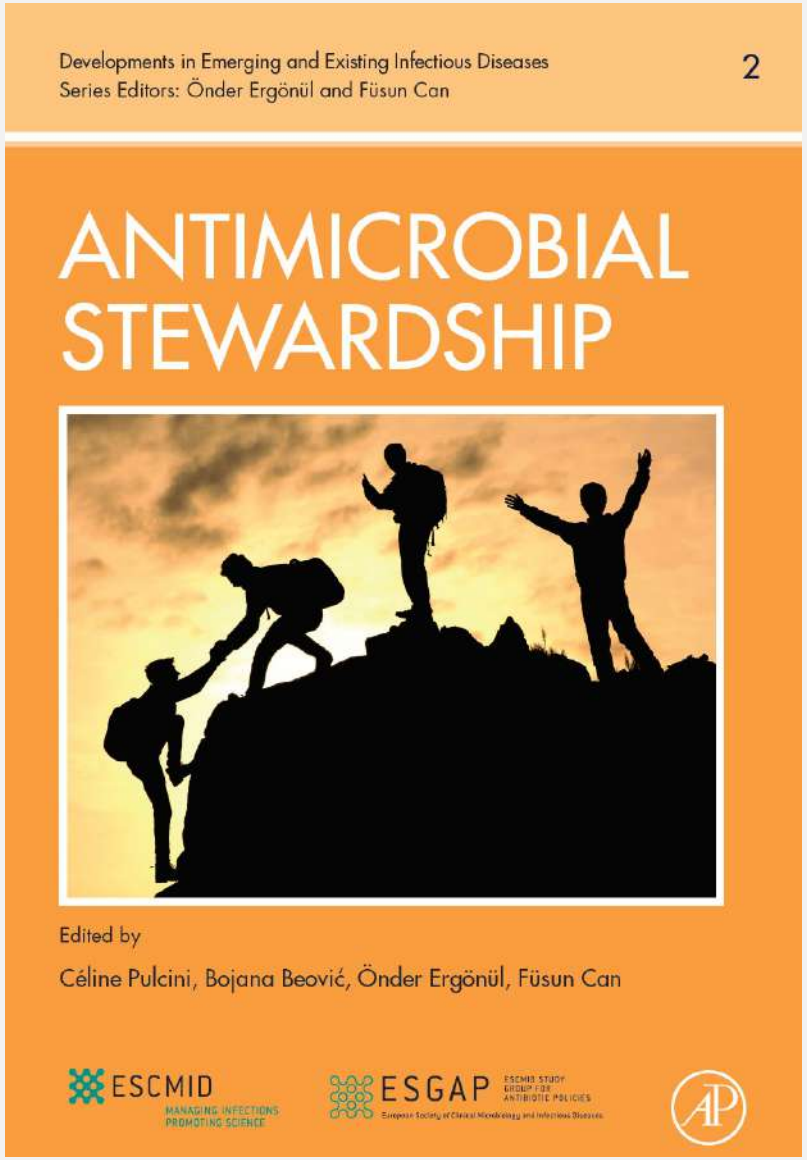
1. Strateji Oluşturmak
2. İnfeksiyon Kontrolü uygulamaları
3. Öncelikli sorunları bilmek: yerel direnç oranları
4. Yerel klinik yollar
5. Laboratuvar: hızlı tanı
6. Farmakodinami/farmakokinetik
7. Günlük takip: daraltma (de-eskelasyon) ve iv-oral değişme
8. Ölçme: uygunluk ve miktar (kantite)
9. Bilgi işlemleri desteği
10. Profilaksi (Cerrahi profilaksi)

Sepsiste Hızlı Tanı



Typical procedures currently in place in clinical settings to provide identification of the pathogen agent and the profiling of antimicrobial susceptibility.

Maugeri G, et al. Identification and Antibiotic-Susceptibility Profiling of Infectious Bacterial Agents: A Review of Current and Future Trends. *Biotechnol J*. 2019;14(1):e1700750.



Chapter 6

Rapid Diagnostics and Biomarkers for Antimicrobial Stewardship

José R. Paño Pardo
Hospital Clínico Universitario "Lozano Blesa", Instituto de Investigación Sanitaria Aragón, Zaragoza, Spain

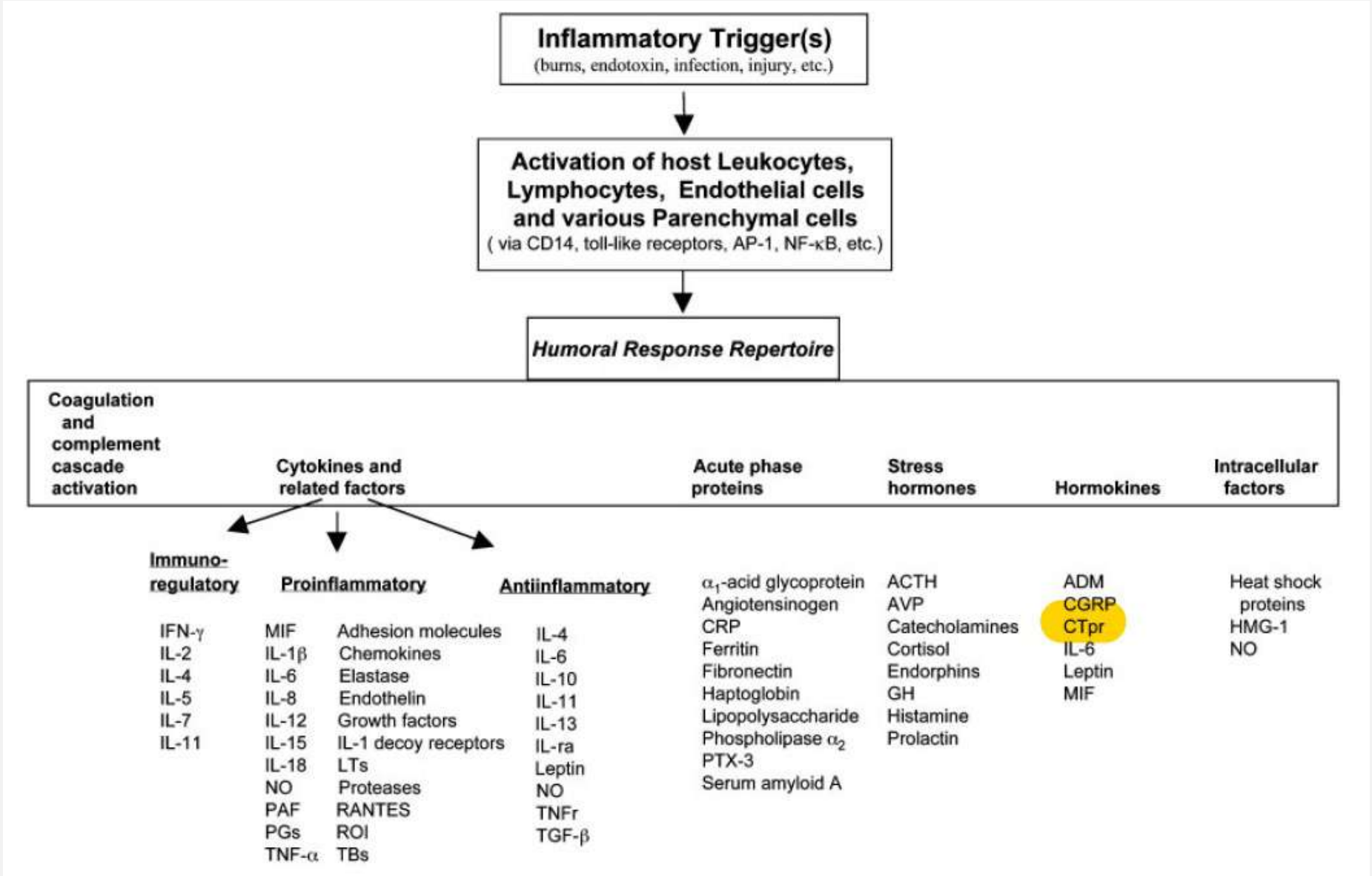
Antimikrobiyal Yönetim

- Enfeksiyon ve kolonizasyon ayrımı
- Empirik kullanım
  - De-eskalasyon
  - modifikasyon
- Süre
- Uygun sonlandırma

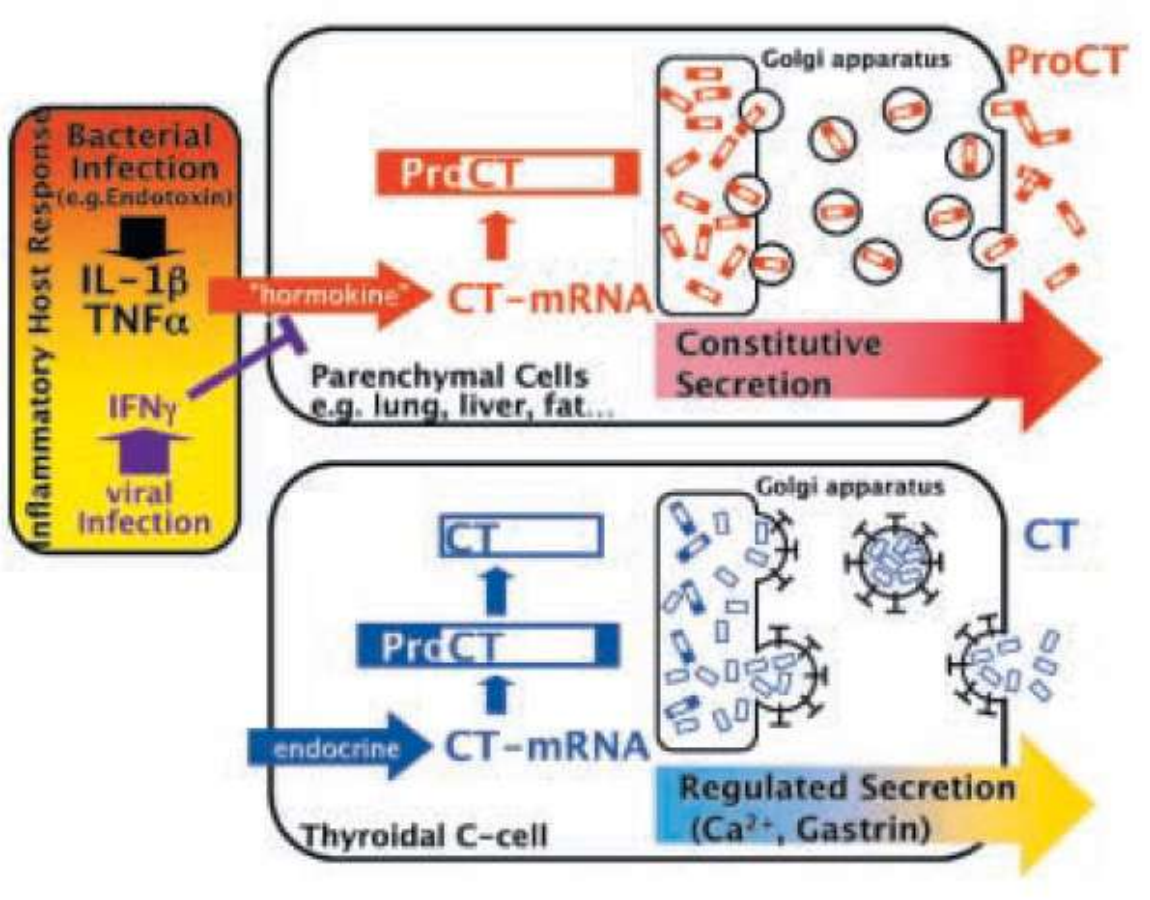
TABLE 3 Potentially Useful Biomarkers for Infectious Diseases

Biomarker
• White blood cell count
• Eosinophil count (inverse)
• Fibrinogen
• Erythrocyte sedimentation rate (ESR)
• C-reactive protein (CRP)
• Procalcitonin (PCT)
• Interleukin-6
• sTREM-1
• Soluble urokinase-type plasminogen activator receptor (suPAR)
• Proadrenomedullin (pro-ADM)
• Presepsin

Pulcini, Ergonul, Can, Beovic. Antimicrobial stewardship 2017, Elsevier


Inflammatory Trigger(s)
(burns, endotoxin, infection, injury, etc.)
Activation of host Leukocytes, Lymphocytes, Endothelial cells and various Parenchymal cells
(via CD14, toll-like receptors, AP-1, NF-κB, etc.)
Humoral Response Repertoire
Coagulation and complement cascade activation
Cytokines and related factors
Acute phase proteins
Stress hormones
Hormokines
Intracellular factors
Immuno-regulatory
IFN-γ
IL-2
IL-4
IL-5
IL-7
IL-11
Proinflammatory
MIF
IL-1β
IL-6
IL-8
IL-12
IL-15
IL-18
NO
PAF
PGs
TNF-α
Adhesion molecules
Chemokines
Elastase
Endothelin
Growth factors
IL-1 decoy receptors
LTs
Proteases
RANTES
ROI
TBs
Antiinflammatory
IL-4
IL-6
IL-10
IL-11
IL-13
IL-ra
Leptin
NO
TNFr
TGF-β
α1-acid glycoprotein
Angiotensinogen
CRP
Ferritin
Fibronectin
Haptoglobin
Lipopolysaccharide
Phospholipase α2
PTX-3
Serum amyloid A
ACTH
AVP
Catecholamines
Cortisol
Endorphins
GH
Histamine
Prolactin
ADM
CGRP
CTpr
IL-6
Leptin
MIF
Heat shock proteins
HMG-1
NO

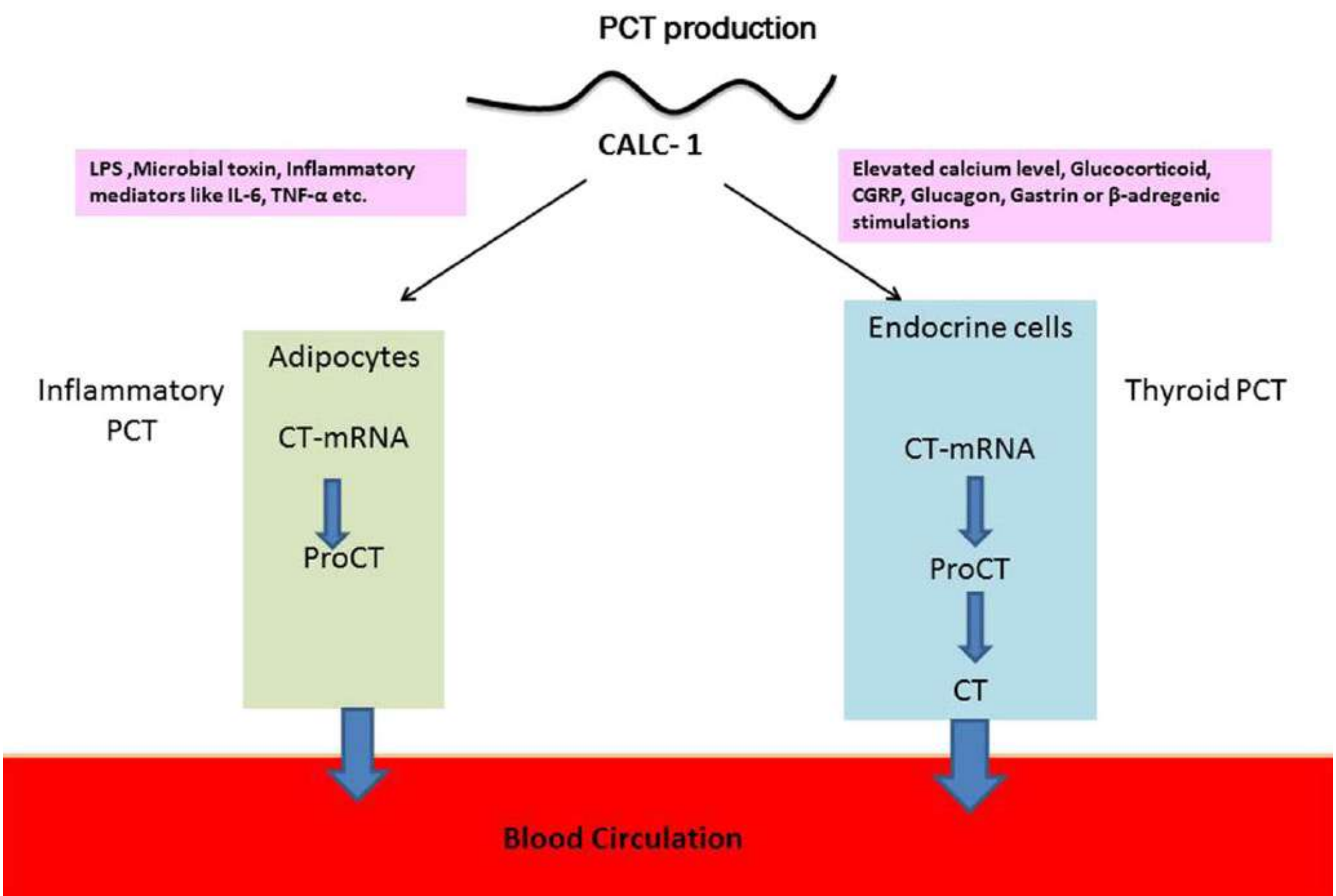
Prokalsitonin Nasıl, Nereden ve Ne Zaman Salınır?



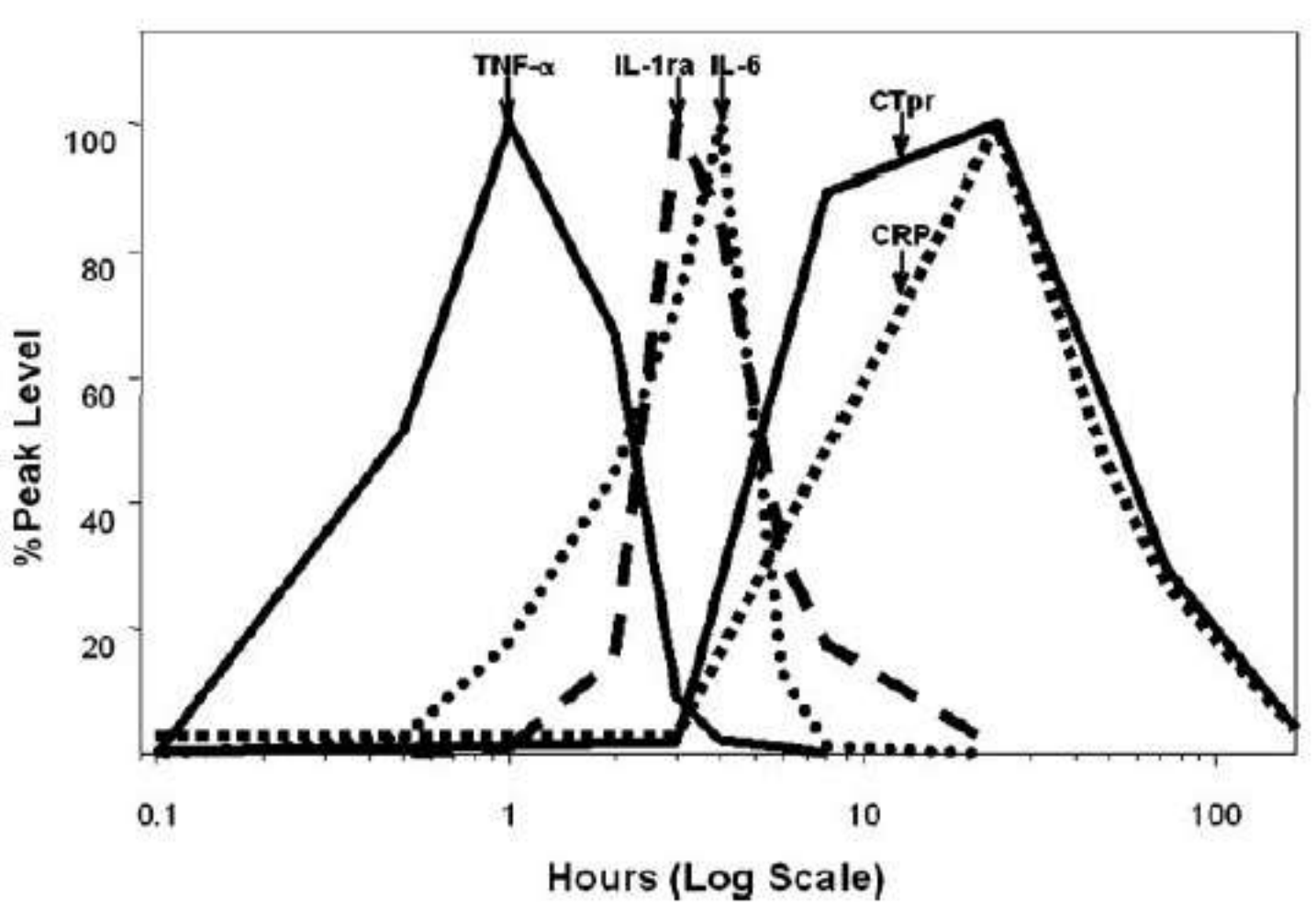
Inflammation

No inflammation

Christ-Crain M & Muller B. Procalcitonin in bacterial infectioons, hype, hope, more or less. Swiss Med Weekly 2005.

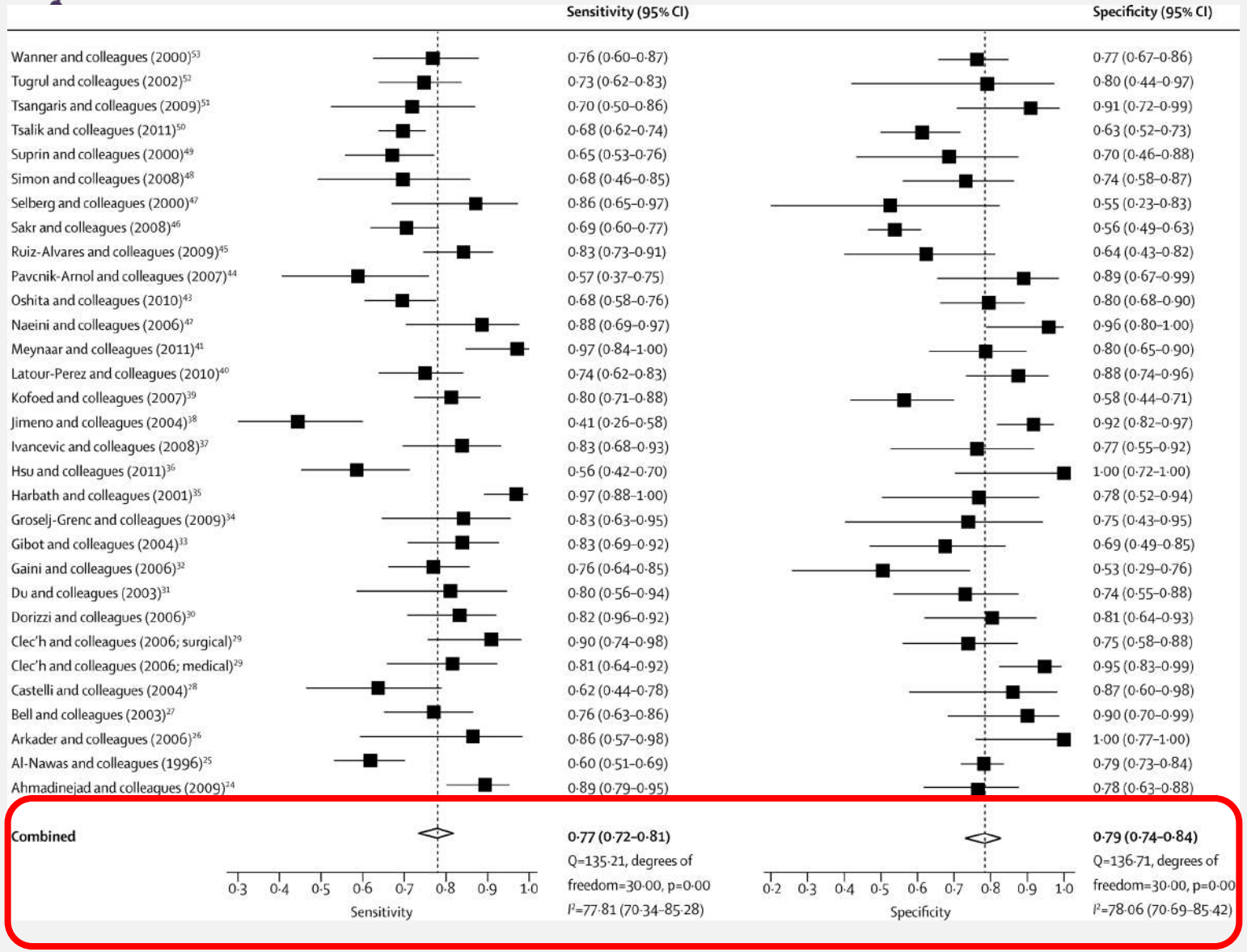

PCT production
CALC- 1
LPS ,Microbial toxin, Inflammatory mediators like IL-6, TNF-α etc.
Elevated calcium level, Glucocorticoid, CGRP, Glucagon, Gastrin or β-adregenic stimulations
Inflammatory PCT
Adipocytes
CT-mRNA
ProCT
Endocrine cells
CT-mRNA
ProCT
CT
Thyroid PCT
Blood Circulation

Prokalsitonin Kinetiği

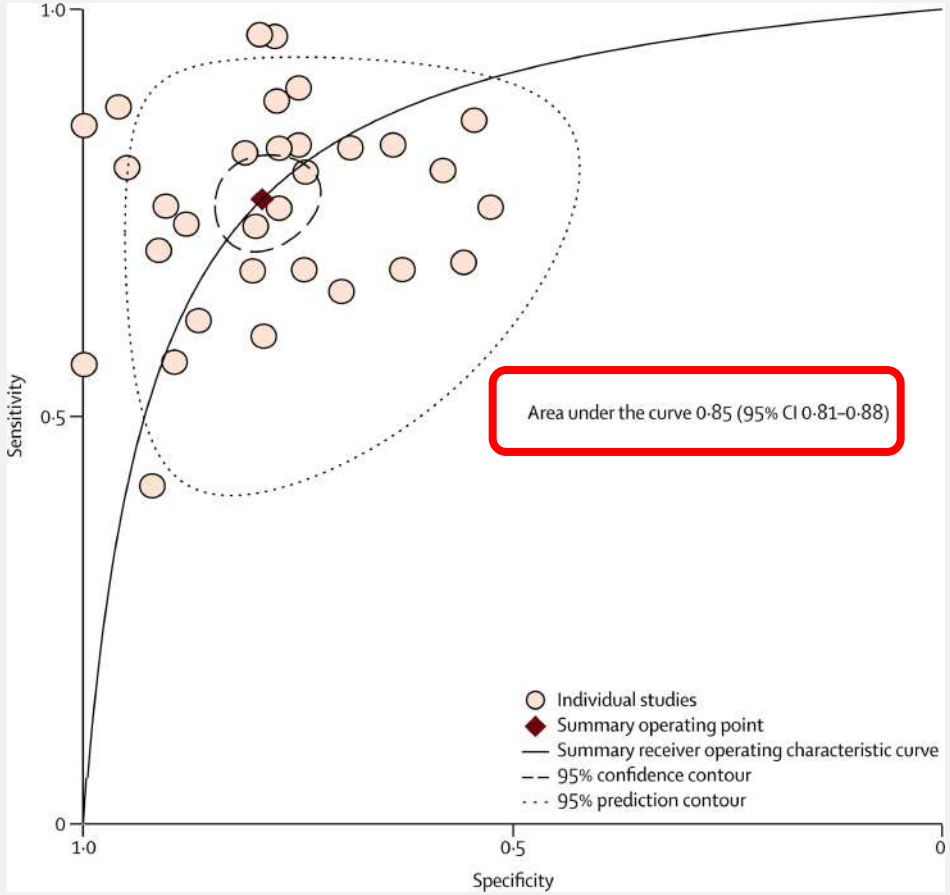


- 2-4 saatte yükselir
- 24-48 saatte tepe noktası
- Enflamasyondan sonra azalır
- 1—1.5 gün sonra %50 azalır.
- Böbrek yetmezliğinde kinetiği değişir.

Sepsiste Prokalsitonin: Duyarlılık ve Özgünlük

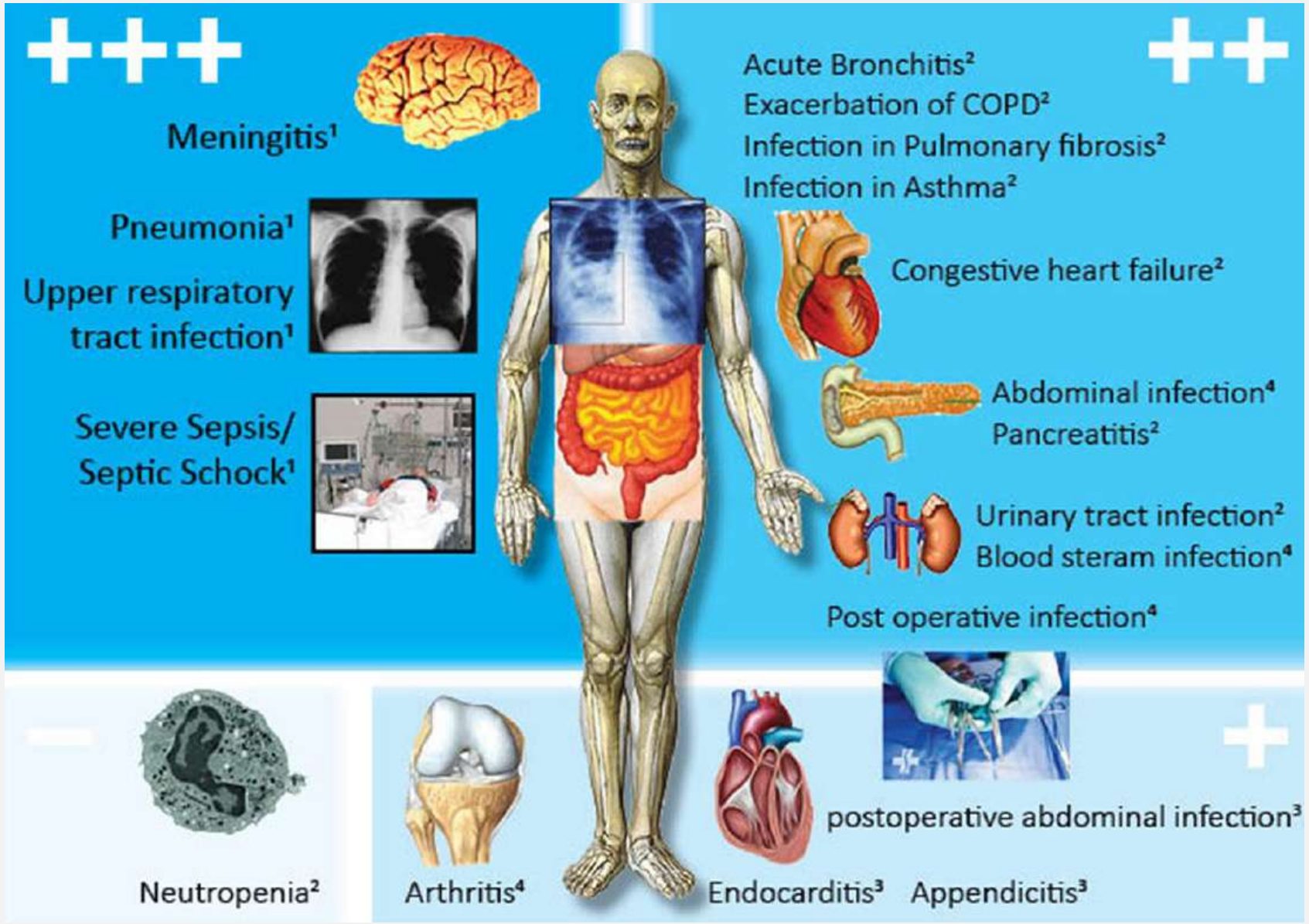


30 reports
3244 patients



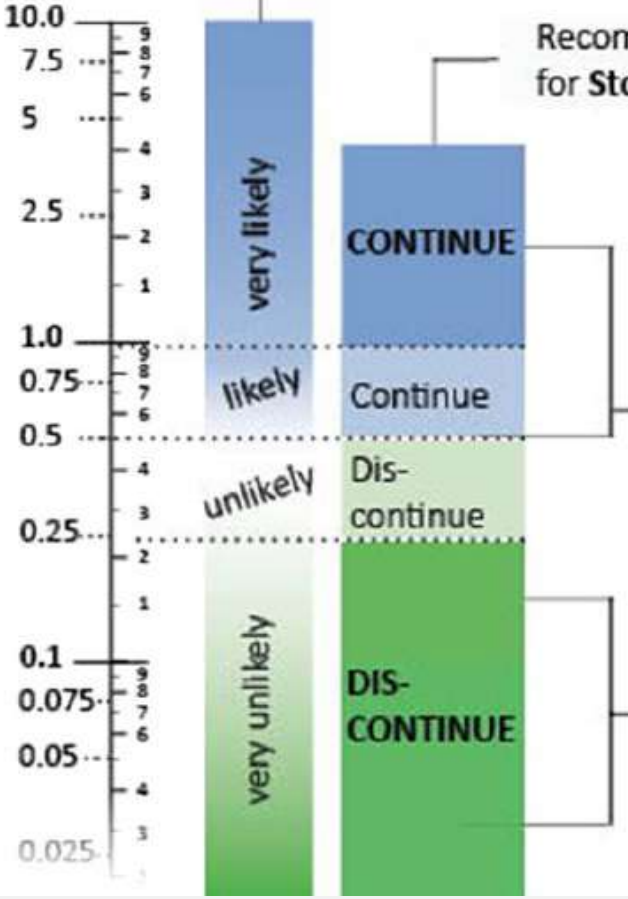
Wacker C., et al Procalcitonin as a diagnostic marker for sepsis: a systematic review and meta-analysis. *Lancet ID* 2013.

Prokalsitonin Artışı



Sager R, et al. BMC Med 2017

Yoğun Bakımda Sepsis



Ongoing **infection?**

Recommendation for **Stopping AB**

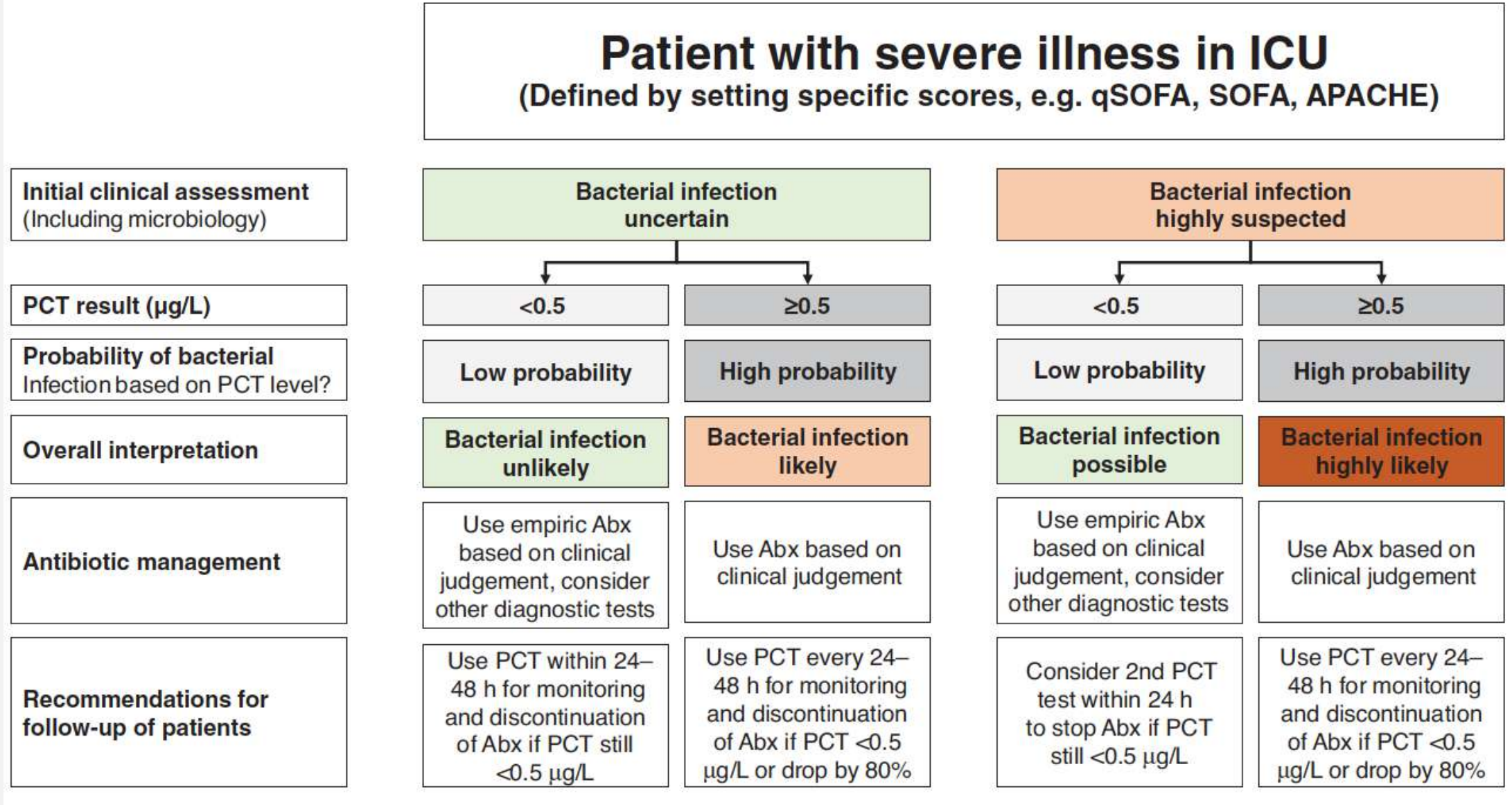
CONTINUE	Continue
	Dis-continue
DIS-CONTINUE	

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.

Sager R, et al. BMC Med 2017



Schuetz P, et al. PCT guided AS: An international expert consensus on optimized clinical use. Clin Chem Lab Med 2019

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Narrative review

How to: implement procalcitonin testing in my practice

O. Neeser [1], A. Branche [2], B. Mueller [1,3], P. Schuetz [1,3,*]

[1] Department of Internal Medicine, Kantonsspital Aarau, Switzerland
[2] Department of Medicine, University of Rochester Department of Medicine, Rochester General Hospital, Rochester, NY, USA
[3] University of Basel, Basel, Switzerland

Initial clinical assessment (including microbiology)	PCT (µg/L)	Probability of bacterial infection based on PCT level	PCT Interpretation	Antibiotic Management	PCT Monitoring
Bacterial infection uncertain	< 0.5	Low Probability	Bacterial infection unlikely	Initiate empiric antibiotic regimen consider other diagnostic tests	repeat PCT within 24-48h and discontinue antibiotics if PCT still <0.5 ug/L
Bacterial infection uncertain	≥ 0.5	High Probability	Bacterial infection likely	Initiate empiric antibiotic regimen consider other diagnostic tests	repeat PCT every 24-48h discontinue antibiotics when PCT <0.5 ug/L or decreases by 80%
Bacterial infection suspected	< 0.5	Low Probability	Bacterial infection possible	Initiate empiric antibiotic regimen consider other diagnostic tests	Repeat PCT test within 24-48h consider discontinuation of antibiotics if PCT still <0.5 ug/L
Bacterial infection suspected	≥ 0.5	High Probability	Bacterial infection highly likely	Initiate appropriate empiric or targeted antibiotic regimen	repeat PCT every 24-48h discontinue antibiotics when PCT <0.5 ug/L or decreases by 80%

Fig. 2. Suggested procalcitonin protocol in the intensive care unit.

Neeser O, et al. CMI 2019

Efficacy and safety of procalcitonin guidance in reducing the duration of antibiotic treatment in critically ill patients: a randomised, controlled, open-label trial

Evelien de Jong, Jos A van Oers, Albertus Beishuizen, Piet Vos, Wytze J Vermeijden, Lenneke E Haas, Bert G Loef, Tom Dormans, Gertrude C van Melsen, Yvette C Kluiters, Hans Kemperman, Maarten J van den Elsen, Jeroen A Schouten, Jörn O Streefkerk, Hans G Krabbe, Hans Kieft, Georg H Kluge, Veerle C van Dam, Joost van Pelt, Laura Bormans, Martine Bokelman Otten, Auke C Reidinga, Henrik Endeman, Jos W Twisk, Ewoudt M W van de Garde, Anne Marie G A de Smet, Jozef Kesecioglu, Armand R Girbes, Maarten W Nijsten, Dylan W de Lange

Jong, et al Lancet ID, 2016

Efficacy and safety of procalcitonin guidance in reducing the duration of antibiotic treatment in critically ill patients: a randomised, controlled, open-label trial

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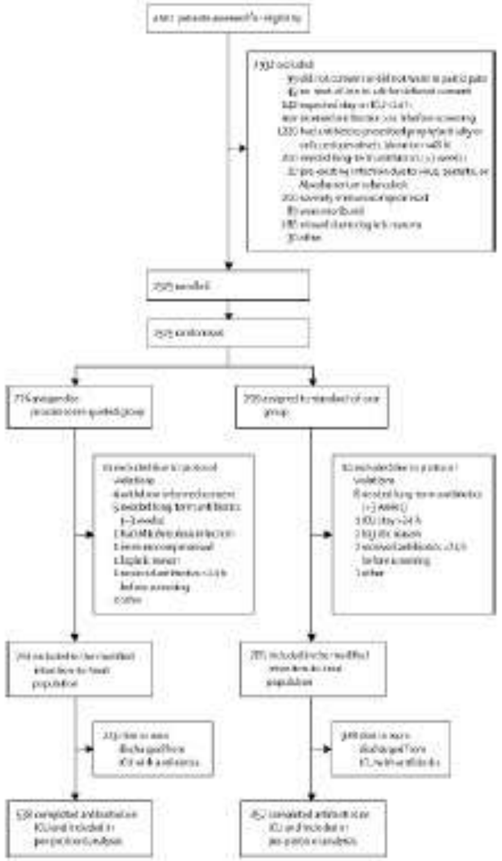
The Netherland, 15 ICUs

Primary endpoint: number of AB days

Secondary endpoint: mortality (28d, 1y)

February 29, 2016

THE LANCET Infectious Diseases



Screened: 4507

Enrolled: 1575 (35%)

776 PCT / 799 SOC

intention to treat: 761 / 785

per-protocol: 538 / 457

Jong, et al Lancet ID, 2016

	Procalcitonin-guided group (n=761)	Standard-of-care group (n=785)	Between-group absolute difference in means (95% CI)	p value
Antibiotic consumption (days)				
Daily defined doses in first 28 days	7·5 (4·0 to 12·8)	9·3 (5·0 to 16·5)	2·69 (1·26 to 4·12)	<0·0001
Duration of treatment	5·0 (3·0 to 9·0)	7·0 (4·0 to 11·0)	1·22 (0·65 to 1·78)	<0·0001
Antibiotic-free days in first 28 days	7·0 (0·0 to 14·5)	5·0 (0 to 13·0)	1·31 (0·52 to 2·09)	0·0016
Mortality (%)				
28-day mortality	149 (19·6%)	196 (25·0%)	5·4% (1·2 to 9·5)	0·0122
1-year mortality	265 (34·8%)	321 (40·9%)	6·1% (1·2 to 10·9)	0·0158
Adverse events				
Reinfection	38 (5·0)	23 (2·9)	−2·1% (−4·1 to −0·1)	0·0492
Repeated course of antibiotics	175 (23·0)	173 (22·0)	−1·0% (−5·1 to 3·2)	0·67
Time (days) between stop and reinstitution of antibiotics	4·0 (2·0 to 8·0)	4·0 (2·0 to 8·0)	−0·22 (−1·31 to 0·88)	0·96
Costs				
Total cumulative costs of antibiotics	€150 082	€181 263	NA	NA
Median cumulative costs antibiotics per patient	€107 (51 to 229)	€129 (66 to 273)	€33·6 (2·5 to 64·8)	0·0006
Length of stay (days)				
On the intensive care unit	8·5 (5·0 to 17·0)	9·0 (4·0 to 17·0)	−0·21 (−0·92 to 1·60)	0·56
In hospital	22·0 (13·0 to 39·3)	22·0 (12·0 to 40·0)	0·39 (−2·69 to 3·46)	0·77

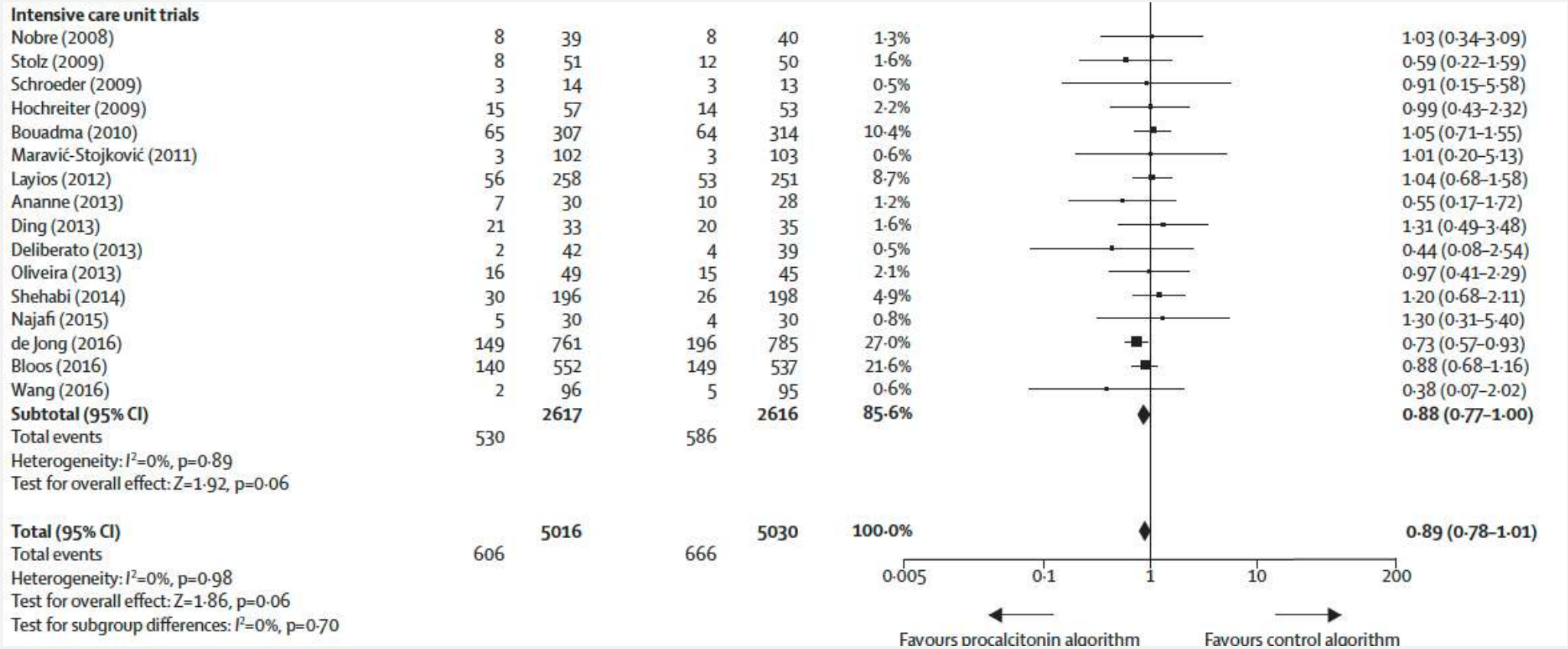
Data are median (IQR), n (%), or mean (95% CI). Between-group absolute differences were calculated using the mean values, percentage differences, and 95% CIs.
NA=not applicable.

Table 2: **Primary and secondary outcome measures**

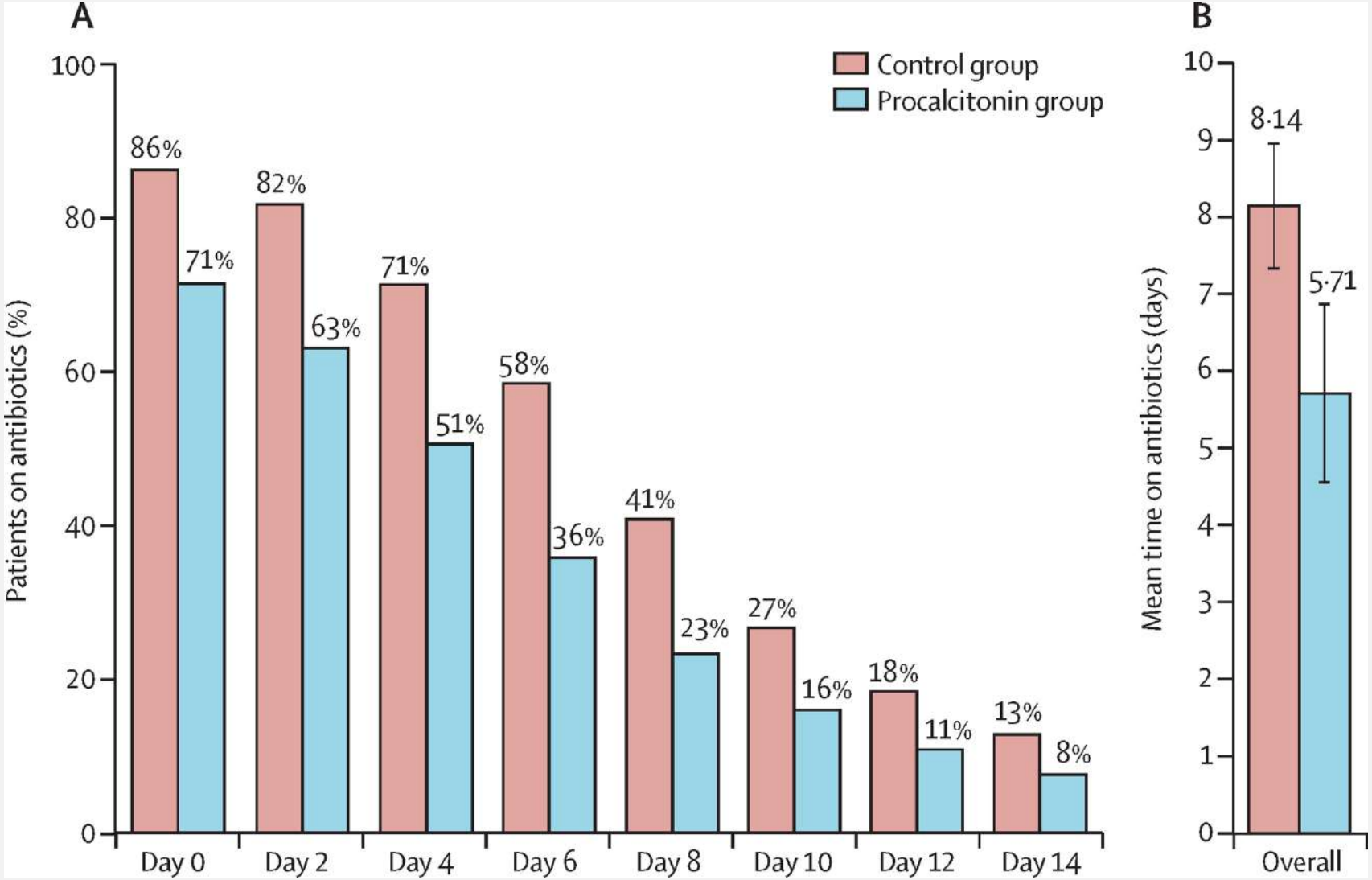
Jong, et al Lancet ID, 2016

Effect of procalcitonin-guided antibiotic treatment on mortality in acute respiratory infections: a patient level meta-analysis

Philipp Schuetz, Yannick Wirz*, Ramon Sager*, Mirjam Christ-Crain, Daiana Stolz, Michael Tamm, Lila Bouadma, Charles E Luyt, Michel Wolff, Jean Chastre, Florence Tubach, Kristina B Kristoffersen, Olaf Burkhardt, Tobias Welte, Stefan Schroeder, Vandack Nobre, Long Wei, Heiner C Bucher, Djillali Annane, Konrad Reinhart, Ann R Falsey, Angela Branche, Pierre Damas, Maarten Nijsten, Dylan W de Lange, Rodrigo O Deliberato, Carolina F Oliveira, Vera Maravić-Stojković, Alessia Verduri, Bianca Beghé, Bin Cao, Yahya Shehabi, Jens-Ulrik S Jensen, Caspar Corti, Jos A H van Oers, Albertus Beishuizen, Armand R J Girbes, Evelien de Jong, Matthias Briel*, Beat Mueller*



Prokalsitoninin Antibiyotik Kullanımı (A) ve Süresine (B) Etkisi:

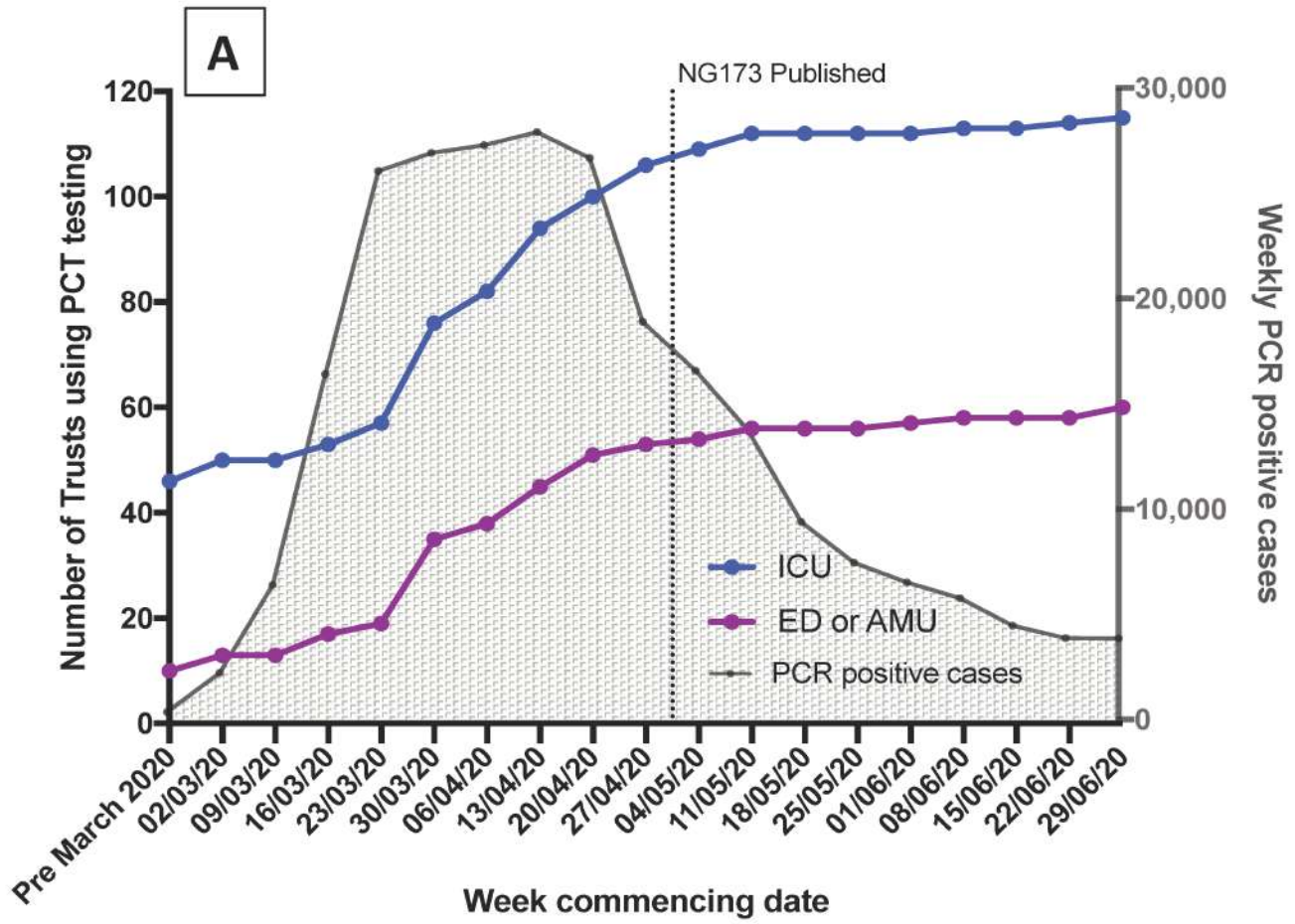


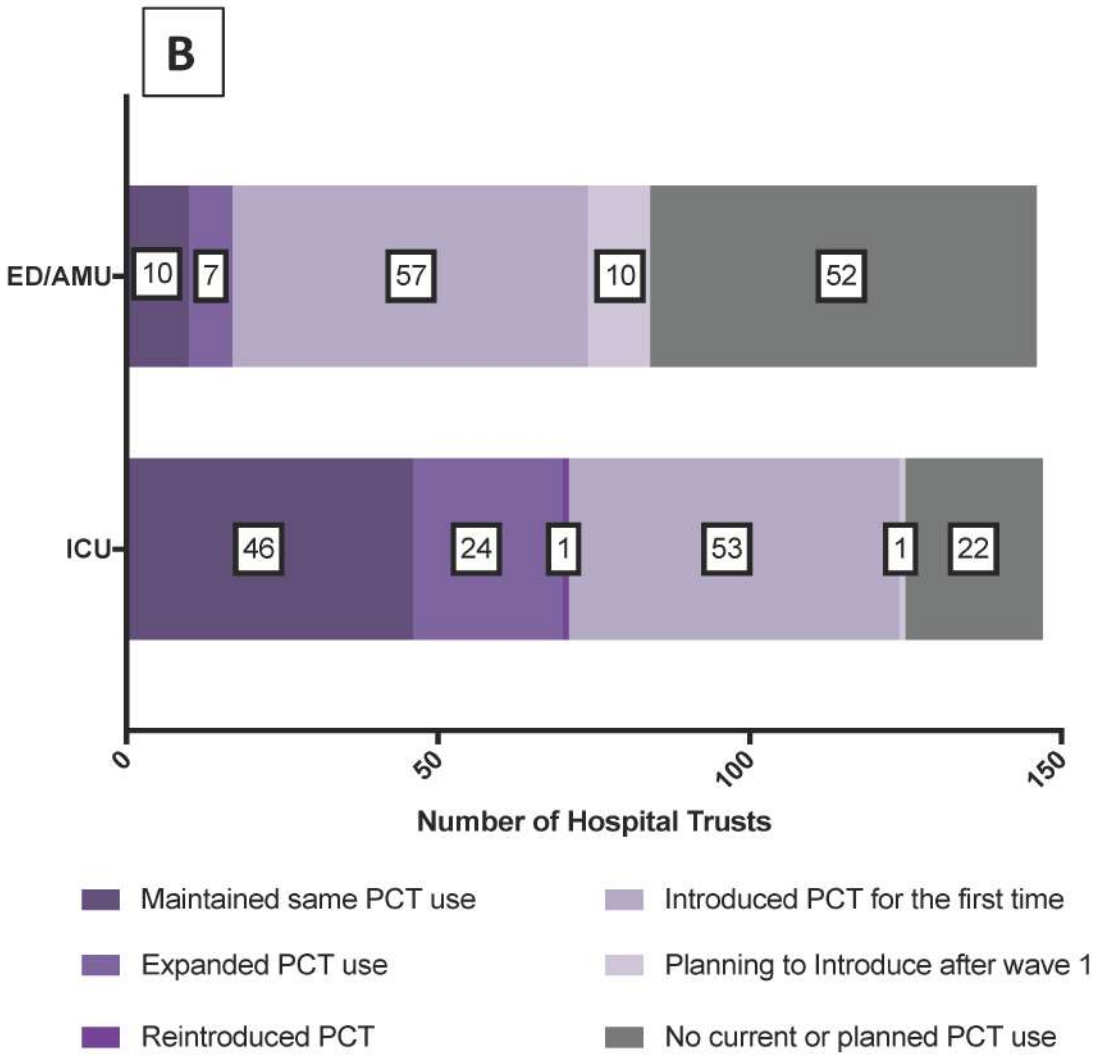
Schuetz, Lancet ID 2018

Sepsiste Procalcitonin ve CRP

	Procalcitonin	CRP
İlk yanıt	Erken	Geç (1 gün)
Özgüllük	Yüksek	Düşük
Takip	Azalması önemli	Uzun dönemde önemli
Steroid kullanımı	Etki yok	Etkilenir
Seri kullanım	Evet	evet

Pandemide Kullanım Arttı mı?





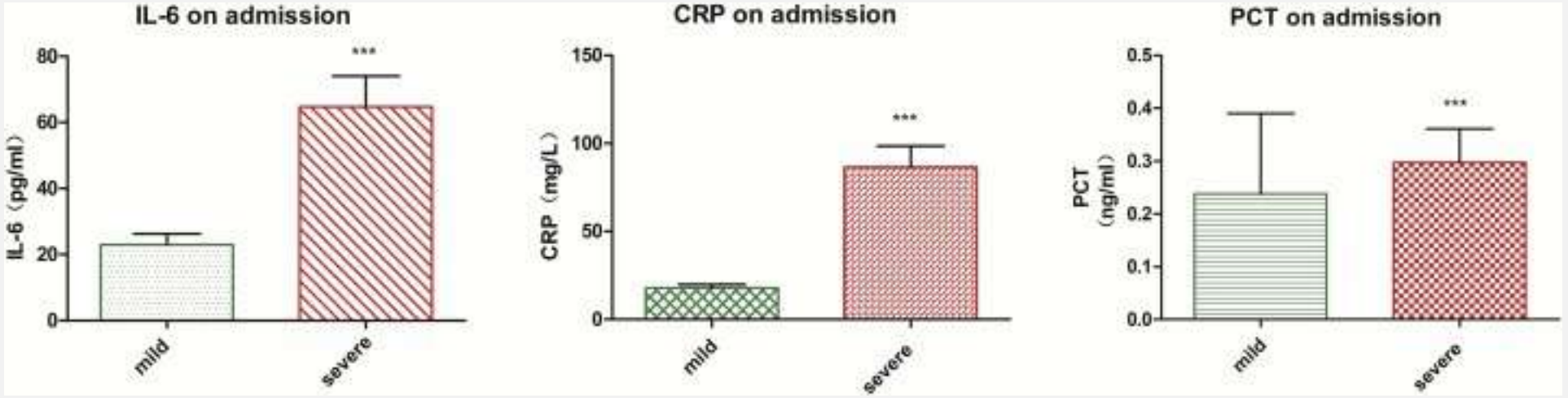
Powell N, et al. Use of Procalcitonin during the First Wave of COVID-19 in the Acute NHS Hospitals: A Retrospective Observational Study. Antibiotics (Basel). 2021.

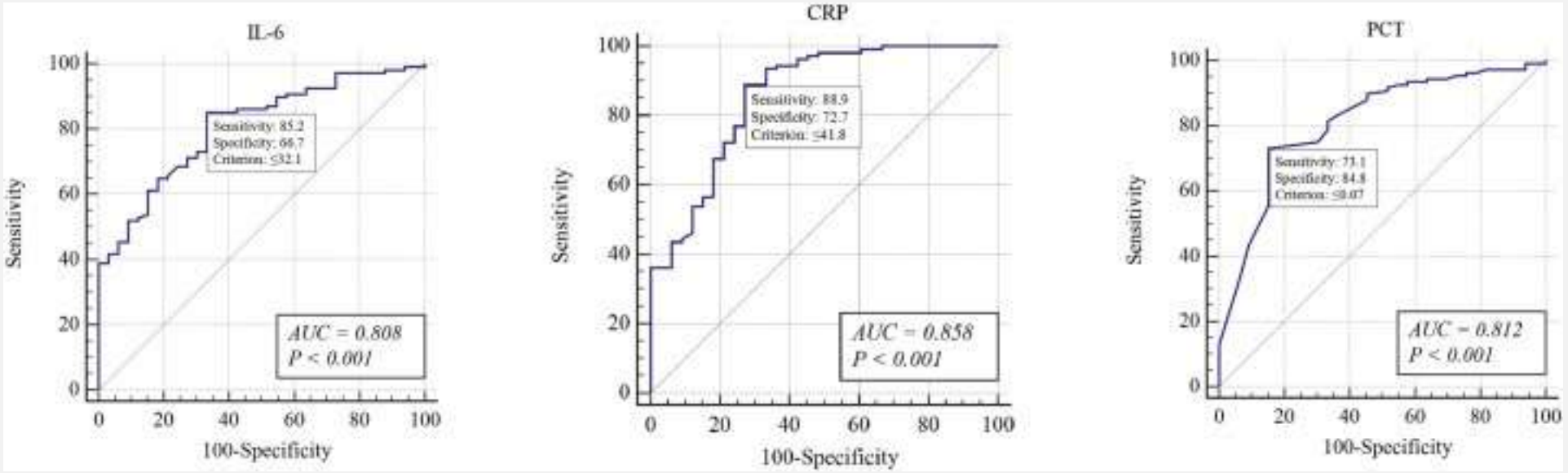
Table 1. Nature of procalcitonin (PCT) use to support antibiotic prescribing during first wave of COVID-19 pandemic in England and Wales.

	ICU	Non-ICU
PCT cut-off (ng/L)	n = 116	n = 78
0.1	1(1%)	0
0.2	1 (1%)	0
0.25	51 (44%)	41 (53%)
0.5	54 (47%)	27 (35%)
No cut off specified, cut-off varied dependent on clinical context	9 (8%)	10 (13%)
Timing of PCT testing	n = 114	n = 76
Single measurement	14 (12%)	39 (51%)
Two measurements	23 (20%)	21 (28%)
Serial	72 (63%)	9 (12%)
Other (i.e., varied dependent on clinical context)	5 (4%)	7 (9%)
PCT part of biochemistry order set	n = 122	n = 107
Yes	50 (41%)	33 (31%)
Hospital guideline	n = 114	
PCT part of a Hospital guideline for managing COVID-19	55 (48%)	

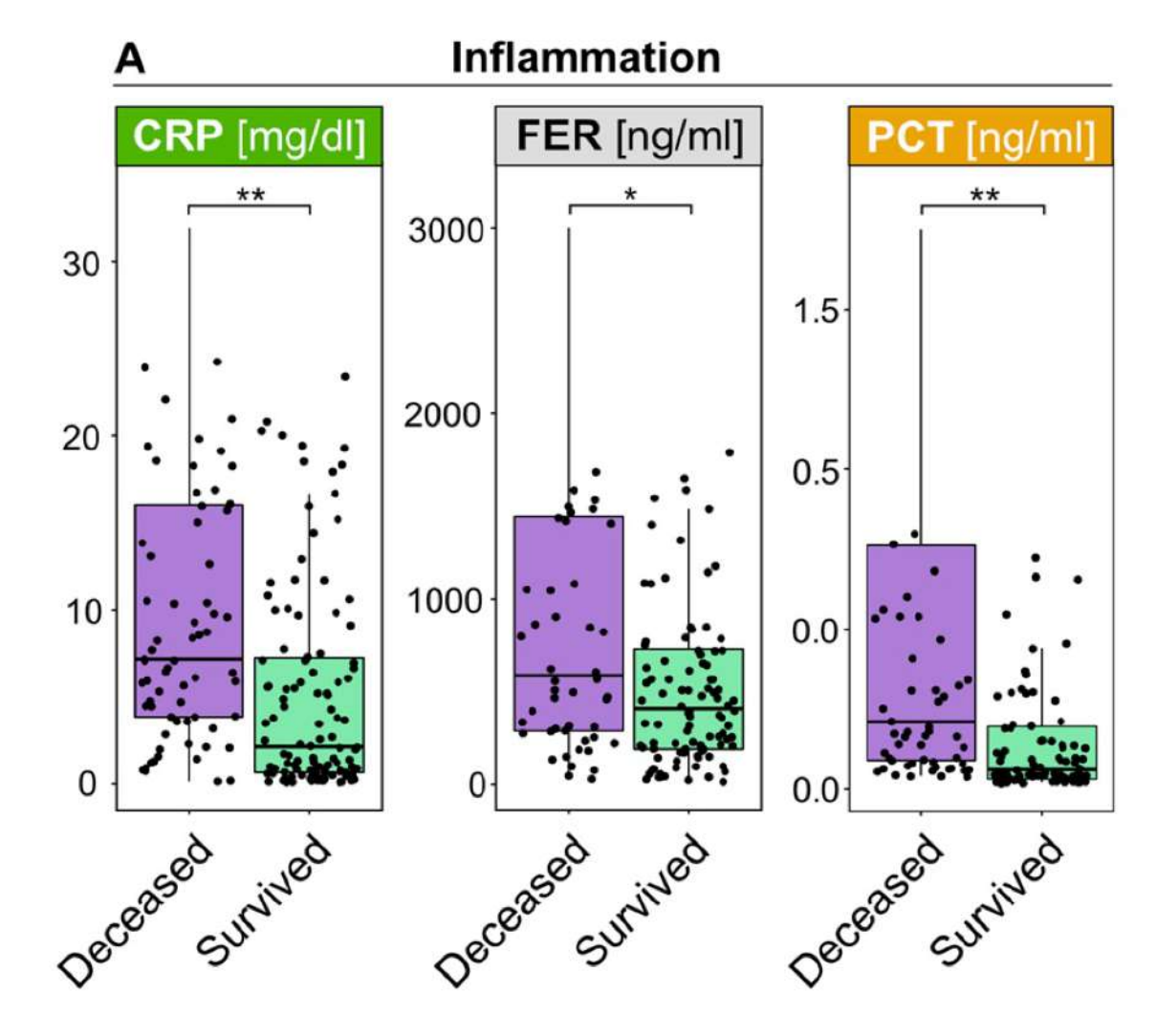
Powell N, et al. Use of Procalcitonin during the First Wave of COVID-19 in the Acute NHS Hospitals: A Retrospective Observational Study. Antibiotics (Basel). 2021.

CRP, Prokalsitonin ve IL-6 nın prognostik değerleri





JCV 2020



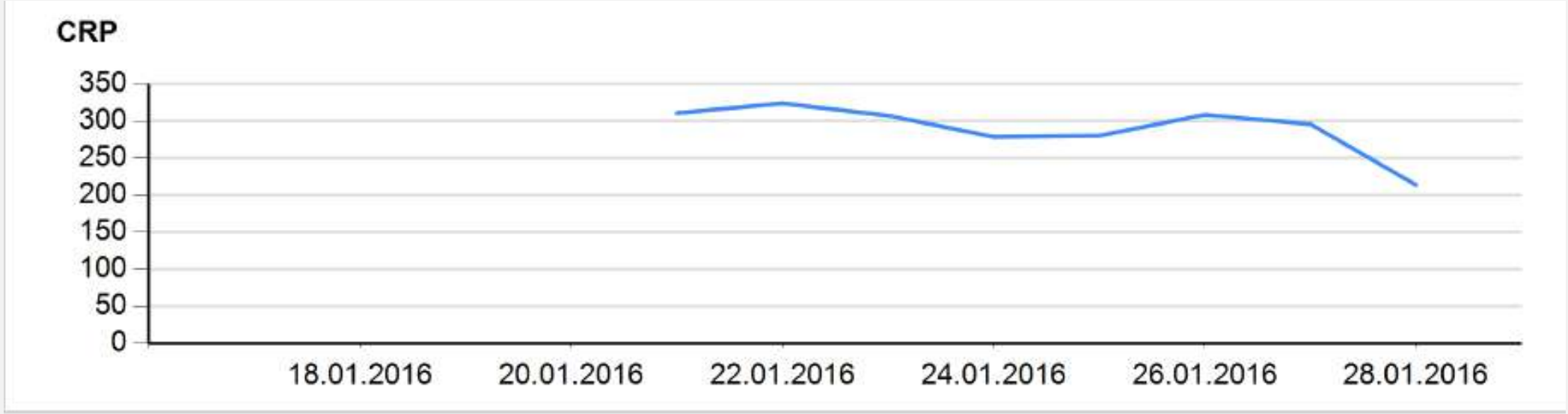
Styrzynski, F., Zhakparov, D., Schmid, M. *et al.* Machine Learning Successfully Detects Patients with COVID-19 Prior to PCR Results and Predicts Their Survival Based on Standard Laboratory Parameters in an Observational Study. *Infect Dis Ther* (2022)

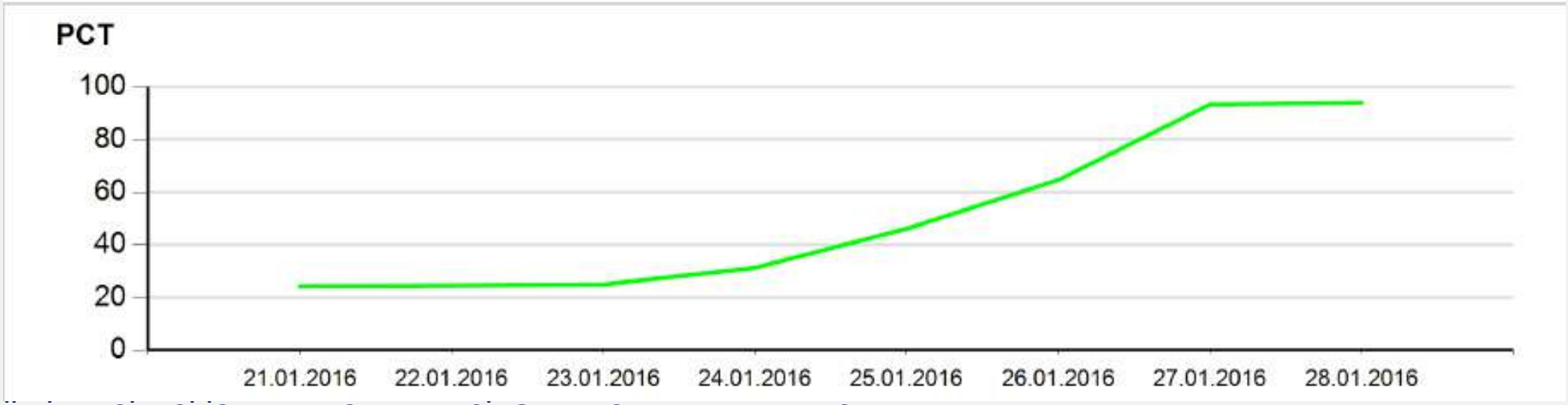
Beklenmeyen Artışlar

1. Akciğer hastalıkları
    1. Kanser
    2. diğer
2. Dissemine peritonit
3. Böbrek yetmezliği

4. Diğer enfeksiyonlar
    1. Tetanus
    2. Sıtma
    3. İnfluenza
    4. Covid-19 ?

MS ve Akciğer Kanseri





pathogens

Article

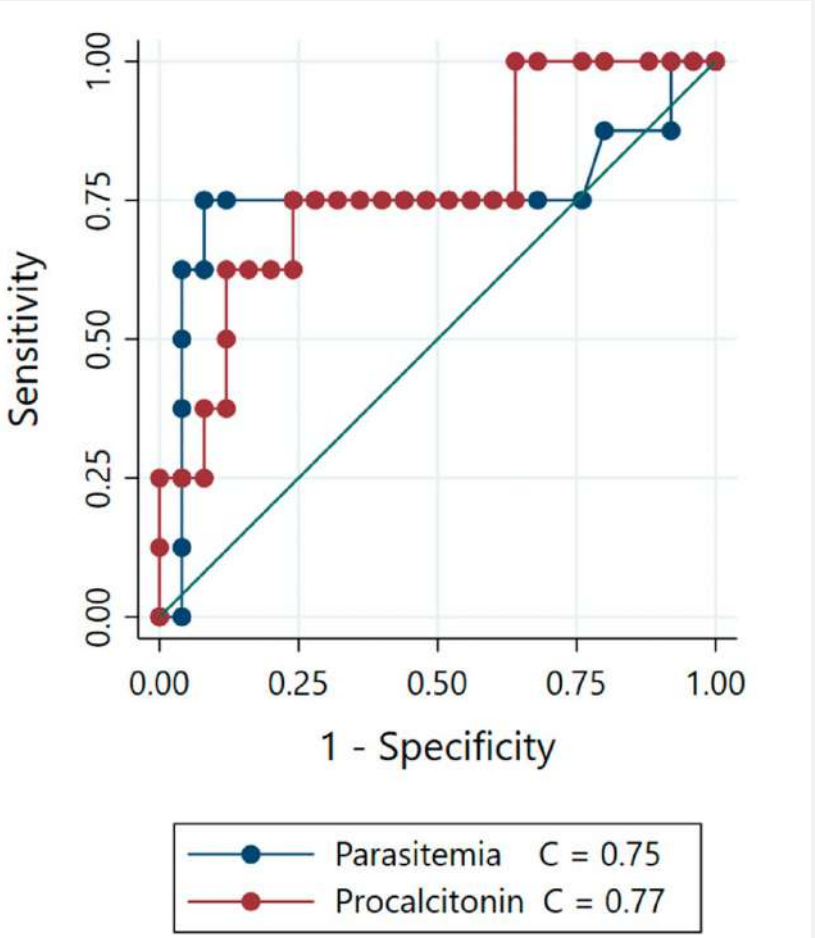
Procalcitonin as a Potential Biomarker in the Study of Babesiosis Caused by *B. microti*

Michael Lum [1,*], Caitlin Gauvin [2], Sophia K. Pham [3], Aikaterini Papamanoli [1], Eric D. Spitzer [4], Andreas P. Kalogeropoulos [5] and Luis A. Marcos [1]

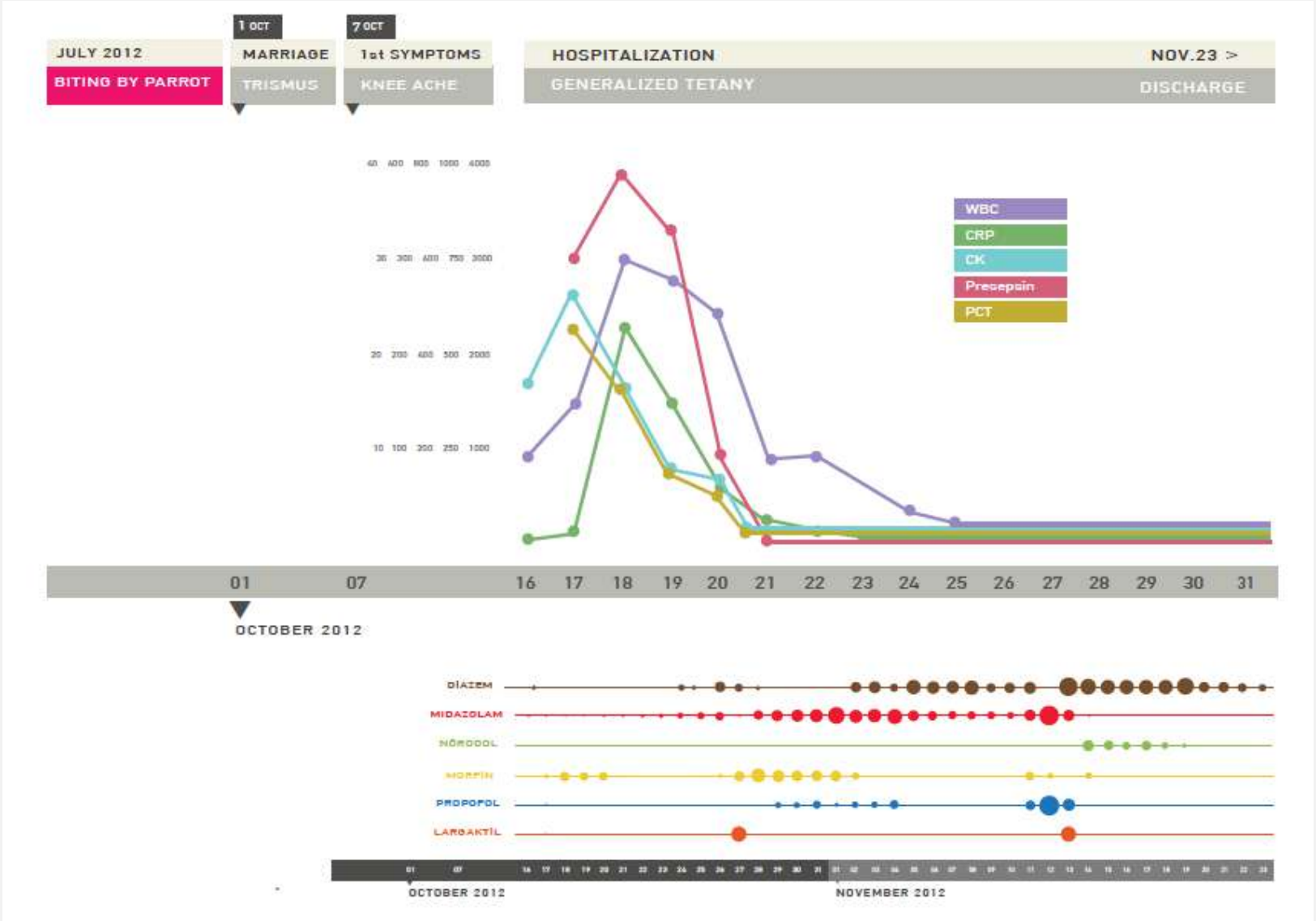
Babesia spp. veya P. falciparum tanılarında gecikmeler olabiliyor.

Oysa, Babesiosis ve Sıtmada prokalsitonin kullanılabilir.

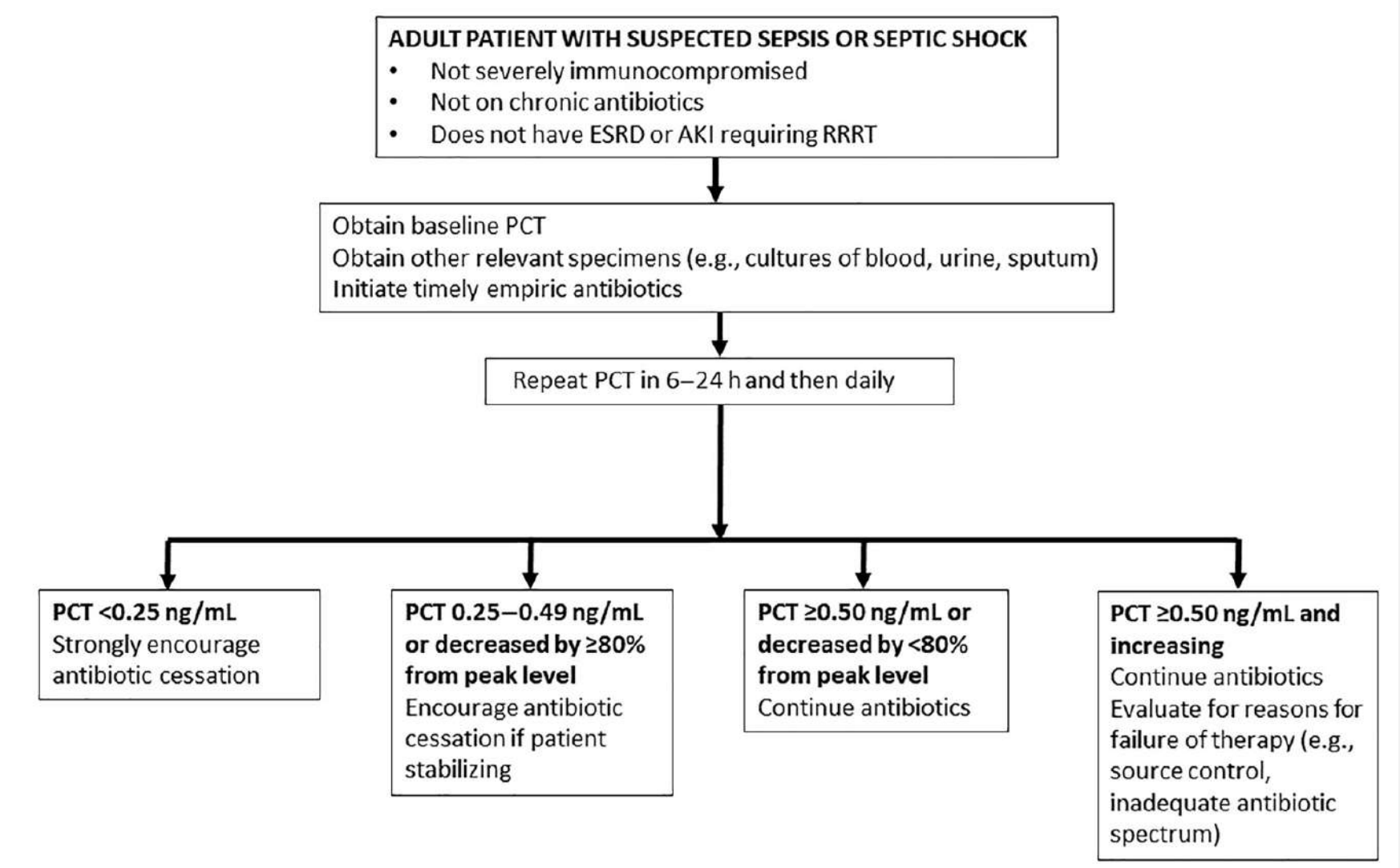
Lum M, et al. Pathogens 2022.



Tetanus and Prokalsitonin



Ergonul O, et al. Lancet ID, 2016



Maves RC, Enwezor CH. Uses of Procalcitonin as a Biomarker in Critical Care Medicine. Infect Dis Clin North Am. 2022

Özet

Sepsisi en iyi gösteren biyobelirteç.

Kullanımında zamanlama önemli.

Seri olarak ölçülmesi gerekir.

İmmunsüpresyondan etkilenmez

Steroid kullanımından etkilenmez

Böbrek yetmezliğinde ve Akciğer hastalıklarında yükselebilir

Teşekkürler

kuiscid@ku.edu.tr

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