Smart Use of Novel Biomarkers in Emergency Care Settings

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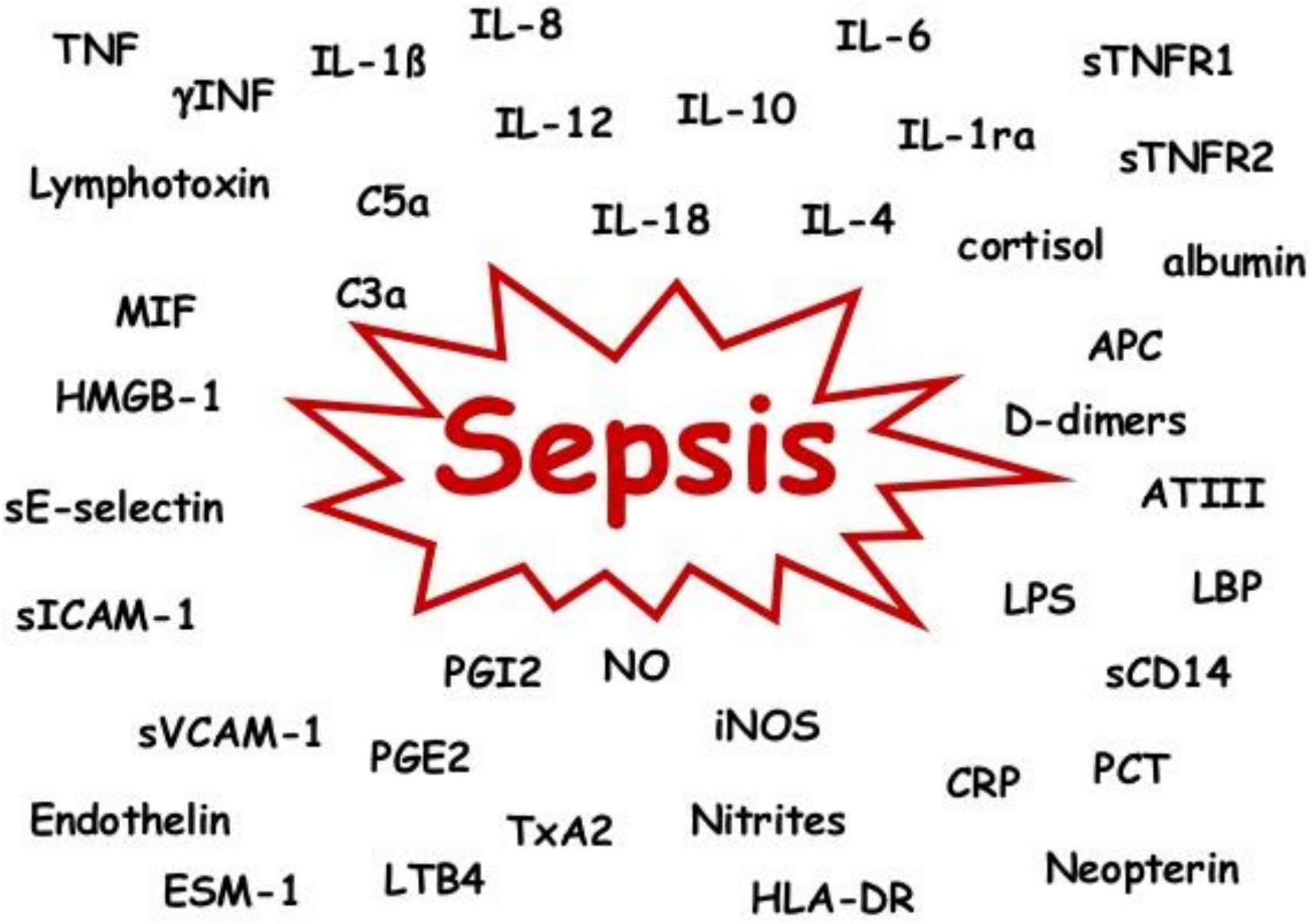
TNF
IL-1ß
IL-8
IL-6
sTNFR1
γINF
IL-12
IL-10
IL-1ra
sTNFR2
Lymphotoxin
C5a
IL-18
IL-4
cortisol
albumin
C3a
MIF
APC
HMGB-1
Sepsis
D-dimers
sE-selectin
ATIII
sICAM-1
LPS
LBP
PGI2
NO
sCD14
sVCAM-1
iNOS
PGE2
CRP
PCT
Endothelin
TxA2
Nitrites
Neopterin
ESM-1
LTB4
HLA-DR

OA Emergency Medicine
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Critical review

Clinical scores and blood biomarkers for early risk assessment of patients presenting to the emergency department

AC Rast, B Mueller, P Schuetz*

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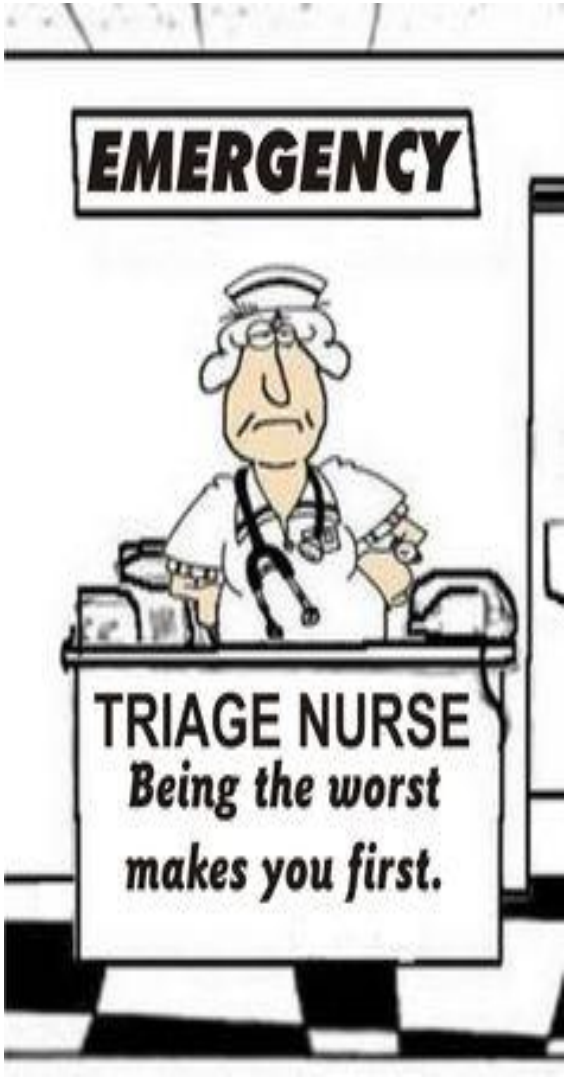
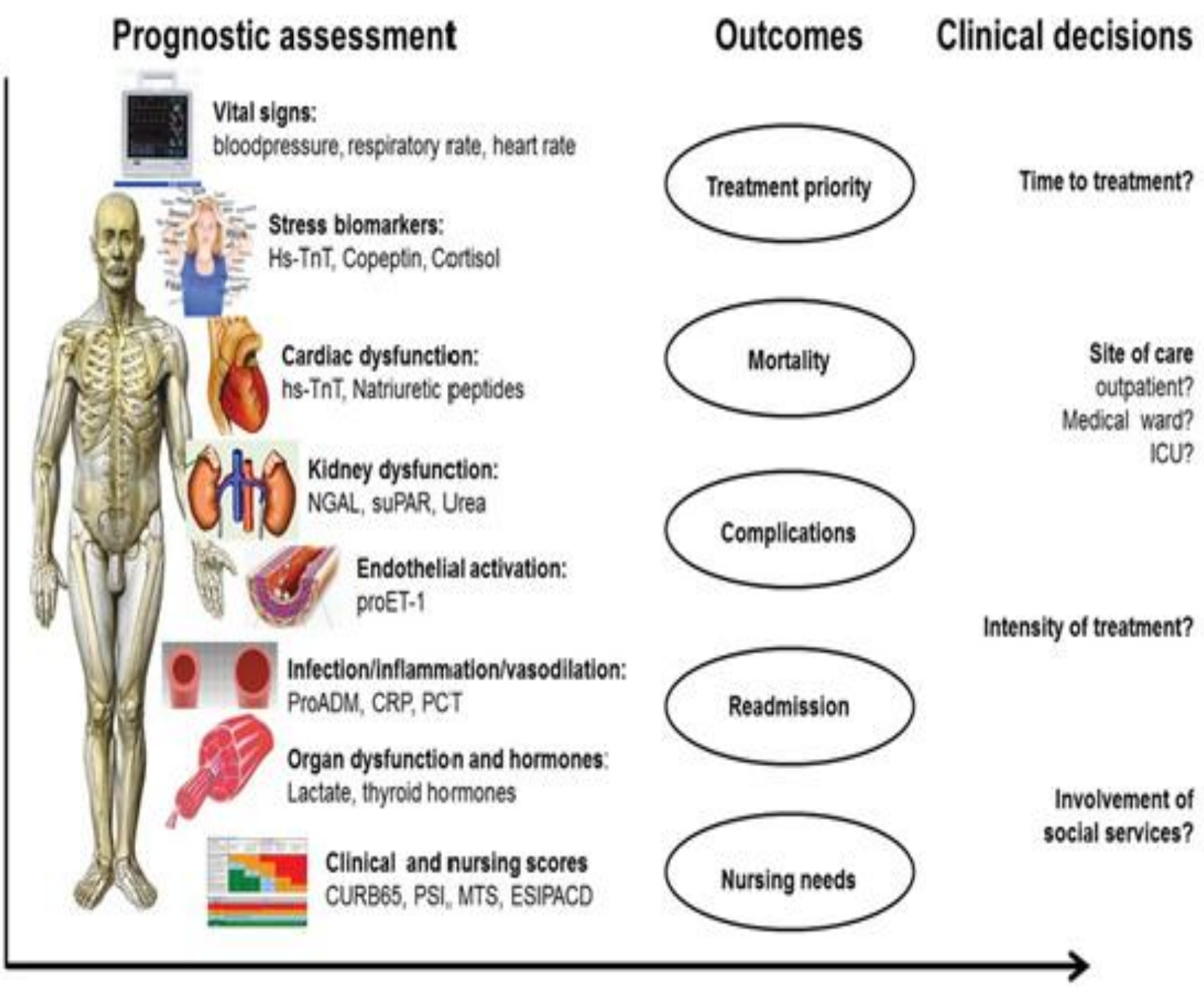
Usefulness of the biomarkers in ED settings

- Clinical scores for **early patient triage.**
- Clinical scores for **initial severity assessment** which may assist in **site-of-care decisions.**
- Scores for **early predicting nursing needs.**
- **Prognostic** biomarkers for triage and risk assessment.




Prognostic assessment
Outcomes
Clinical decisions
Vital signs:
bloodpressure, respiratory rate, heart rate
Stress biomarkers:
Hs-TnT, Copeptin, Cortisol
Cardiac dysfunction:
hs-TnT, Natriuretic peptides
Kidney dysfunction:
NGAL, suPAR, Urea
Endothelial activation:
proET-1
Infection/inflammation/vasodilation:
ProADM, CRP, PCT
Organ dysfunction and hormones:
Lactate, thyroid hormones
Clinical and nursing scores
CURB65, PSI, MTS, ESIPACD
Treatment priority
Mortality
Complications
Readmission
Nursing needs
Time to treatment?
Site of care
outpatient?
Medical ward?
ICU?
Intensity of treatment?
Involvement of social services?

Types of biomarkers

- Markers of inflammation, infection and vasodilatation.
- Markers of cardiac dysfunction.
- Markers of stress.
- Markers of kidney dysfunction.
- Thyroid hormones
- Markers of endothelial dysfunction and activation.
- Markers of organ dysfunction.

Table 1 Selected emergency department studies investigating biomarkers from different organ systems for improved prognostic and diagnostic patient assessment

Biomarker (s)	Author, year	Setting, patient population	*n*	Main findings	Limitations
Proadrenomedullin, PCT, copeptin	Schuetz et al.[21]	Medical patients, ED, prospective, observational, cohort study	Around 4500	Study ongoing, preliminary results suggest a high-predictive ability of all markers for 30 day mortality as well as complications and treatment priority	(1) Treatment priority is as adjudicated by the attending physicians (gold standard) and (2) no blinding for physicians and nurses
Copeptin, troponin	Balmelli et al.[29]	Patients presenting to the ED with symptoms suggestive of AMI of < 12 h	1247 (34% female, 66% male)	(1) Important gender differences regarding the final diagnoses underlying acute chest pain; (2) no significant difference in the diagnostic accuracy of cTnT, hs-cTnT and copeptin, alone or in combination, in women vs. men; (3) increased risk of death to a similar extent in both genders having elevated versus normal concentration of cTnT, hs-cTnT or copeptin and (4) similar prognostic accuracy by cTnT, hs-cTnT and copeptin in both genders	(1) Only patients with chest pain as predominate symptoms enrolled and (2) three limited number of markers under investigation
Troponin	Iversen et al.[27]	Consecutive medical and surgical patients aged > 40 years	1176 patients (59,2% female)	Elevated hs-TnT in 57.1% of the entire cohort and in 52.3% of patients with non-cardiac diagnoses. Hs-TnT above the median was associated in univariate analysis with a 3-fold higher mortality in the entire population. In patients without past or present ischaemic heart disease hs-TnT in the upper quartile was associated in univariate analysis with a 5-fold higher mortality risk	(1) No serial measurements of troponin, for further characterisation of the cause of elevation and (2) blood samples were stored for 12 years

Table 1 *(Contiued)*

Biomarker (s)	Author, year	Setting, patient population	*n*	Main findings	Limitations
Cortisol	Kolditz et al.[28]	Hospitalised CAP-patients	984	Cortisol levels were significantly elevated in both adverse outcomes ($P < 0.001$) and predicted mortality (Area under the curve (AUC) 0.70, cut off 795 nmol/L) and critical pneumonia (AUC 0.71) independently of all other measured variables after logistic regression analysis. Prognostic accuracy of CRB-65 was significantly improved by adding cortisol levels (combined AUC 0.81 for both endpoints)	(1) No correction for concomitant steroid medication; (2) no controlling for the time point of blood sampling and (3) no testing for adrenal insufficiency
SuPAR	Uusitalo-Seppälä et al.[31]	Patients in the ED with suspected infection	539	The suPAR concentrations in all five groups were 4.7, 5.0, 4.4, 4.8 and 7.9 ng mL-1, respectively ($P < 0.001$). The levels were significantly higher in non-survivors compared with survivors (8.3 vs. 4.9 ng mL-1, $P < 0.001$) and in patients with severe sepsis (group 5) compared with those in the other groups (7.9 vs. 4.8 ng mL-1, $P < 0.001$)	Only sepsis patients included
Triiodothyronine (T3), thyroxin (T4)	Meyer et al.[33]	Critically ill patients in the medical ICU of an University hospital	103	Plasma T3 levels were lower in patients with sepsis as compared with patients with SIRS; circulating thyroid hormone levels measured on admission were not different in survivors and non-survivors and thus, did not give helpful prognostic information	(1) Secondary analysis; (2) no measurement of TSH levels and (3) small sample
NGAL	Soto et al.[30]	Prospective cohort study, patients admitted from the ED	616	Plasma NGAL is an accurate biomarker for prediction of AKI in patients admitted from the ED. Proposal of a three-grade classification of AKI risk based on plasma NGAL levels	No measurement of other kidney markers

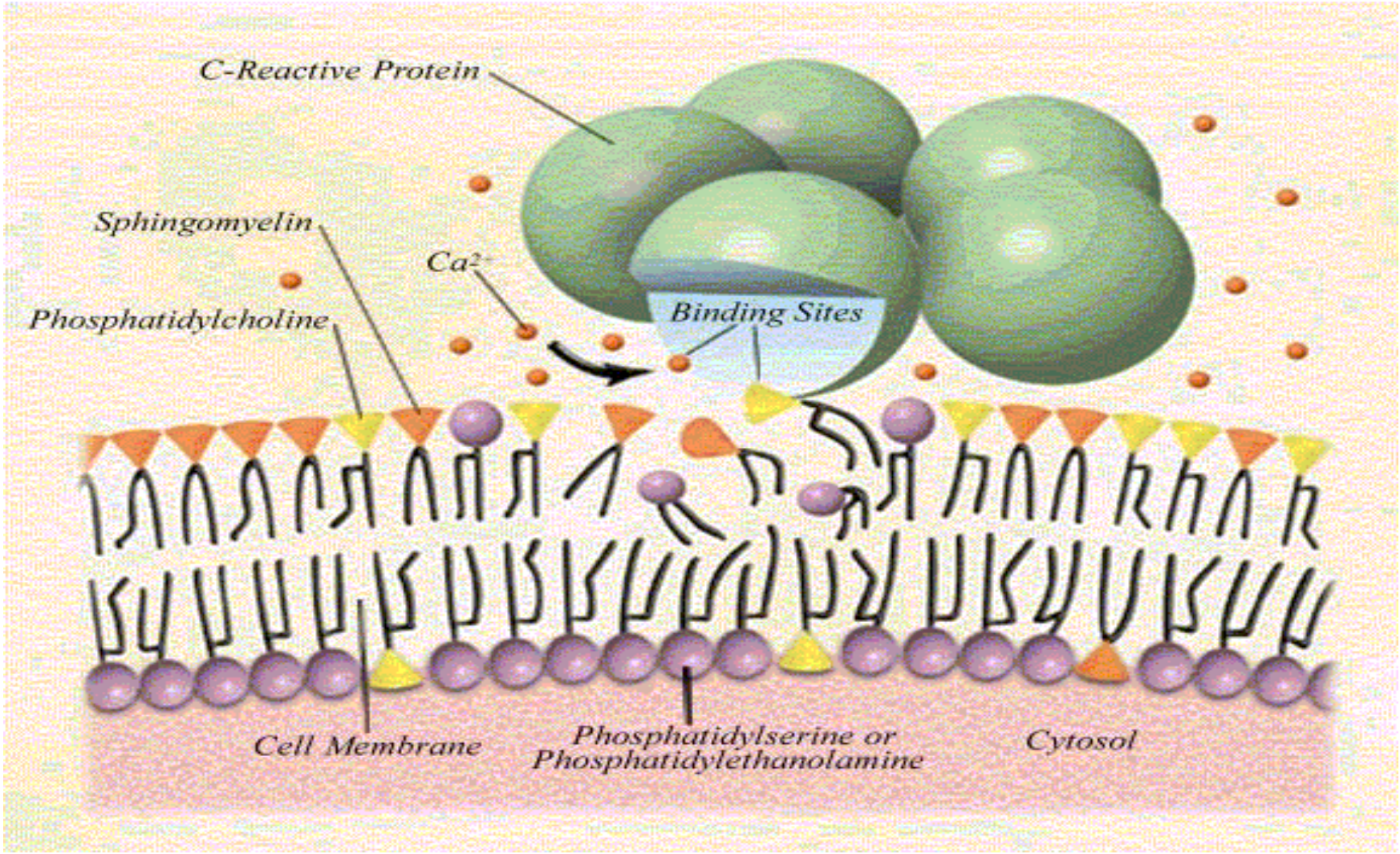
Table 1 *(Contiued)*

Biomarker (s)	Author, year	Setting, patient population	*n*	Main findings	Limitations
ProET-1	Schuetz et al.[35]	Consecutive patients with definite diagnosis of CAP	925	ProET-1 levels on admission and changes from baseline to day 3 were significant mortality predictors with adjusted hazard ratios of 10.5 and 28.4. Initial proET-1 levels improved the PSI in reclassification statistics and in c-statistics	(1) Exclusion of some patients with limiting diseases and (2) no assessment of pulmonary artery pressure, which may cause an increase in proET-1 levels independent from sepsis
Lactate	Trzeciak et al.[36]	Consecutive patients with primary or secondary diagnosis of infection and serum lactate	1177	Acute-phase deaths and in-hospital deaths increased linearly with lactate. Initial lactate ≥ 4 mmol/L was associated with 6-fold higher odds of acute-phase death; however, a lactate level less than 4 mmol/L had little impact on probability of death	(1) Timing of measuring lactate in relation to time that a clinician first identified the presence of an acute infection not available for all; (2) lactate measured by a clinician; (3) no comprehensive clinical information and (4) no estimations of clinicians for probability of death prior to obtaining the lactate measurement
PCT, CRP	Ruiz-Esteban et al.[24]	Patients admitted to a general internal medicine ward, > 18 and < 85 years of age, admitted for less than a week, temperature > 38°C the day before their inclusion	62	Neither PCT nor CRP was able to discriminate infectious (or bacterial) diseases from the other aetiologies as a group, with an AUC of 0.63 (95% CI 0.47–0.79, $P = 0.15$) for PCT and 0.61, (95% CI 0.44–0.78, $P = 0.23$) for CRP	(1) Issues concerning the cut-off point; (2) low-prognostic value in sepsis; (3) specifically selection of febrile patients and (4) small sample size
PCT	Hicks et al.[26]	Convenience sample, >18-years-old, signs and symptoms of infection, >38°C or blood culture acquisition	66	Higher PCT levels in patients with uncomplicated sepsis compared with patients with no sepsis. Better association with final diagnosis of sepsis when combination of SIRS criteria and PCT levels	(1) Low-risk sepsis cohort and (2) small sample size

ED, emergency department; PCT, procalcitonin; suPAR, soluble urokinase plasminogen activator receptor; AMI, acute myocardial infarction; hs-cTnT, high-sensitivity cardiac troponin T; cTnT, cardiac troponin T; hs-TnT, high-sensitivity troponin T; CAP, community-acquired pneumonia; TSH, thyroid stimulating hormone; NGAL, neutrophil gelatinase-associated lipocalin; AKI, acute kidney injury; PSI, pneumonia severity index; proET-1, proEndothelin-1; CRP; C-reactive protein; SIRS, systemic inflammatory response syndrome.

Types for the biomarkers	Biomarkers lab test
Markers of inflammation, infection and vasodilatation.	Proadrenomedulin (ProADM) C- reactive protein (CRP) Procalcitonin (PCT)
Markers of cardiac dysfunction.	High-sensitivity troponin-T assay (hs- Trop T) N-terminal pro-B-type natriuretic peptides (NT- pro BNP)
Markers of stress.	Serum cortisol Vasopressin and its precursor: copeptin
Markers of kidney dysfunction.	Creatinine, urea Neutrophil gelatinase-associated lipocalcin (NGAL), soluble-form of urokinase-plasminogen activator receptors (suPAR)
Thyroid hormones.	T3, T4
Markers of endothelial dysfunction and activation.	ProEndothelin-1 (ProET-1)
Markers of organ dysfunction.	Lactate

C- reactive protein (CRP)



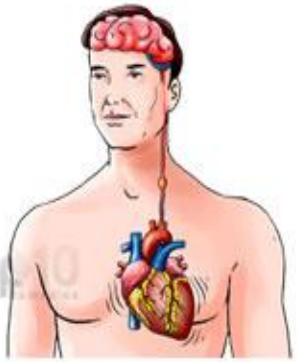
A Simple **BLOOD TEST** that Can Save Your Life

C-reactive protein (CRP) is a protein produced by the liver and found in the blood. The level of CRP rises when the body suffers inflammation.

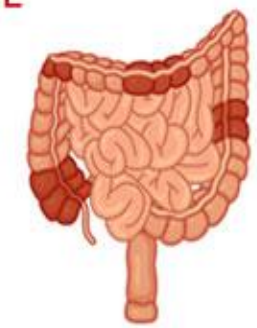
The American Heart Association categorizes the levels of CRP as follows:

- Low CRP – less than 1.0 mg/L
- Moderate CRP – between 1.0 mg/L – 3.0 mg/L
- High CRP – higher than 3.0 mg/L

DIABETES



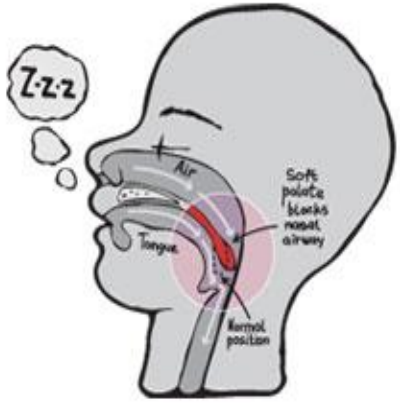
HEART DISEASE, ATTACKS & STROKES



CROHN'S DISEASE

CANCER

RHEUMATOID ARTHRITIS



OBSTRUCTIVE SLEEP APNEA

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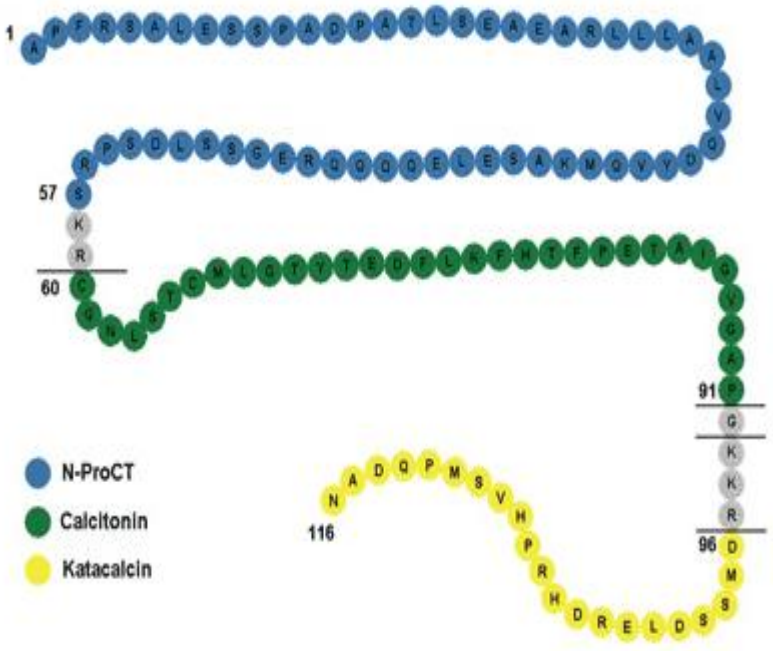
Procalcitonin (PCT)

Figure 1
Primary Structure 116-kD Precursor Polypeptide of Calcitonin



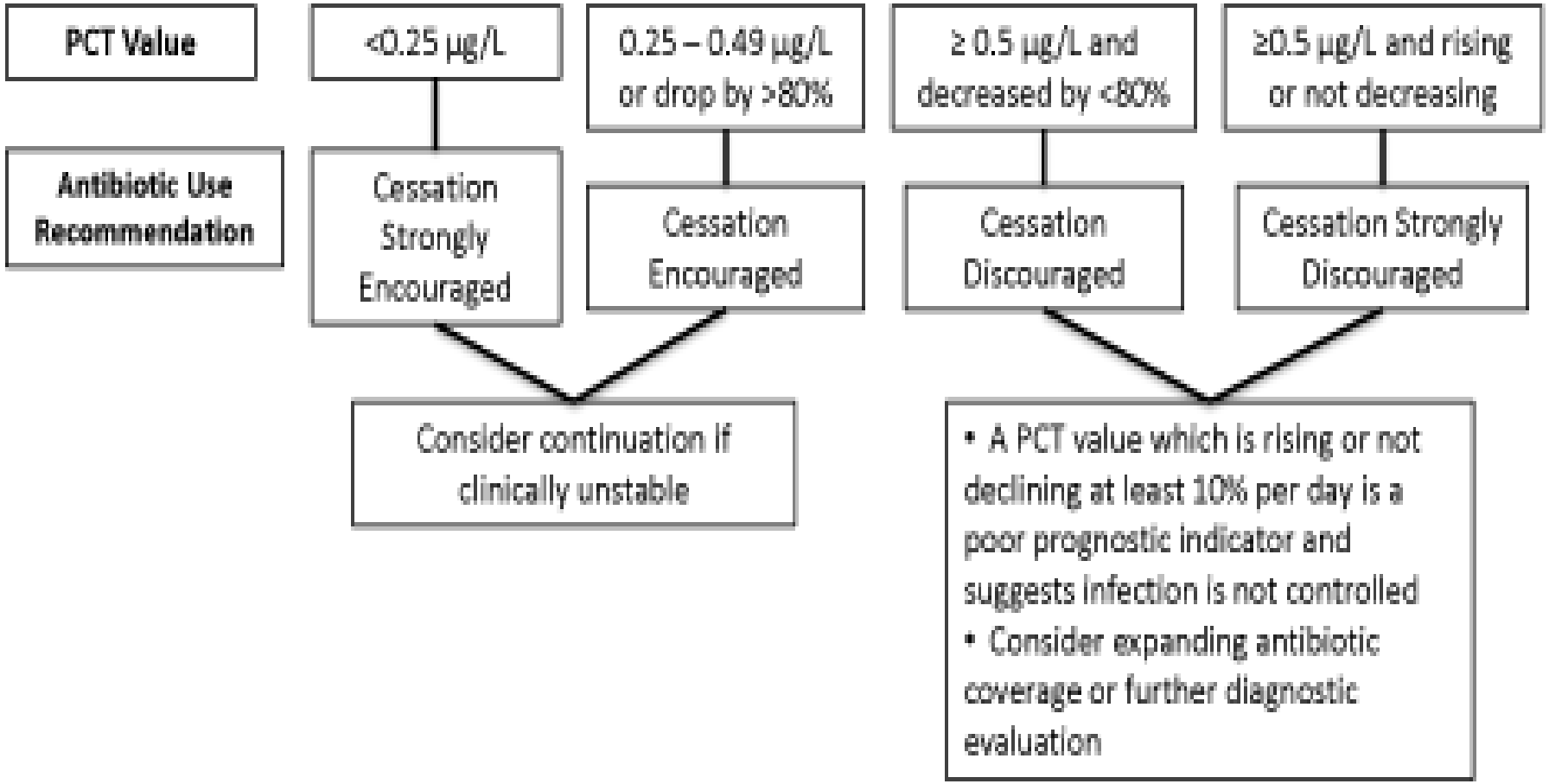
Procalcitonin is composed of three sections: the amino terminus (N-ProCT), immature calcitonin, and katacalcin

Procalcitonin (PCT)

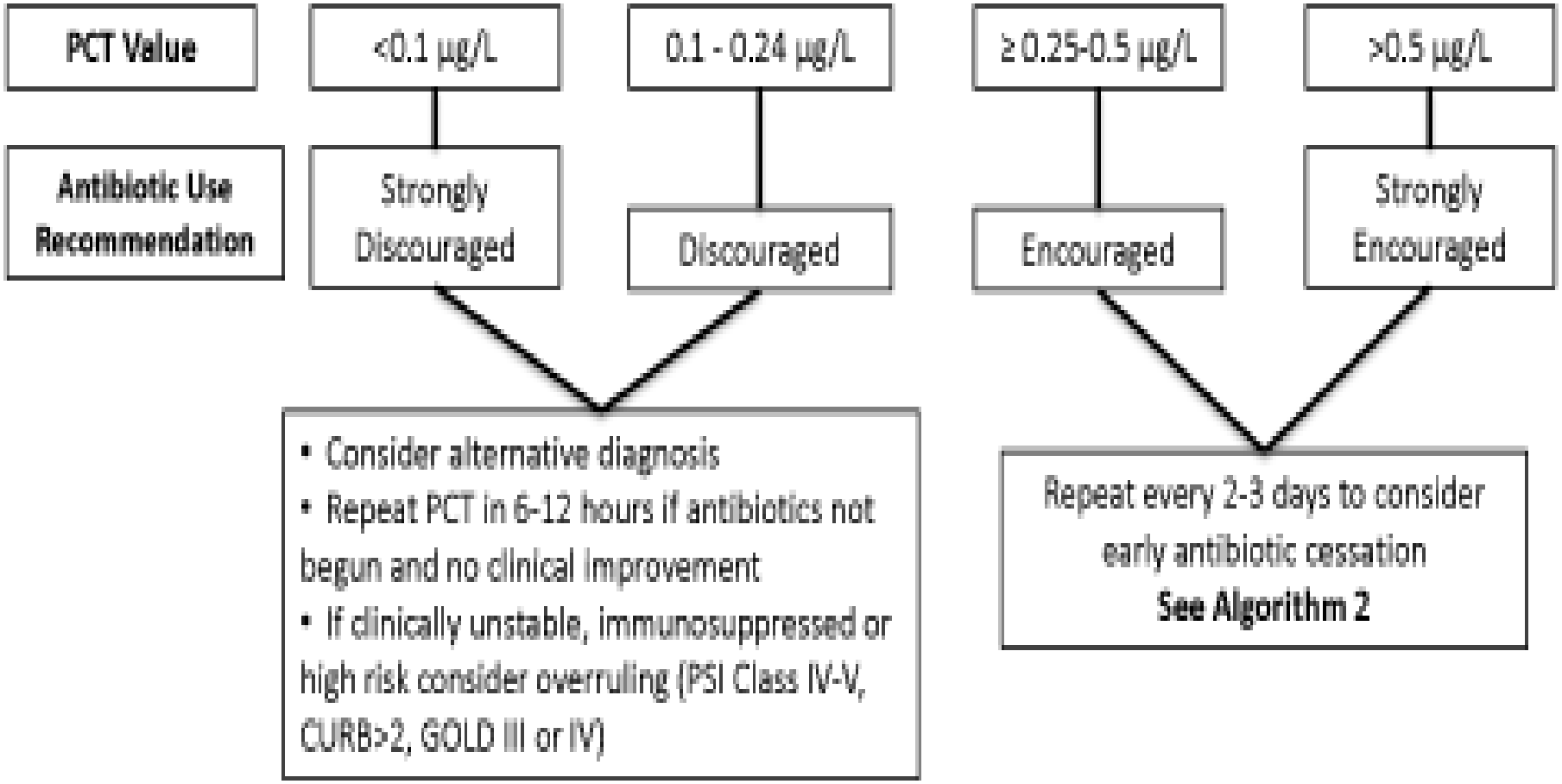
- Precursor peptide from the hormone calcitonin
- Has 2 differents type of metabolism depending on the presence of bacterial infection.
- PCT is released in response to bacterial toxins and pro-inflammatory mediators
- PCT is known as one of the most effective markers of bacterial sepsis
- Only few studies has evaluated the usefulness of PCT in LT patients

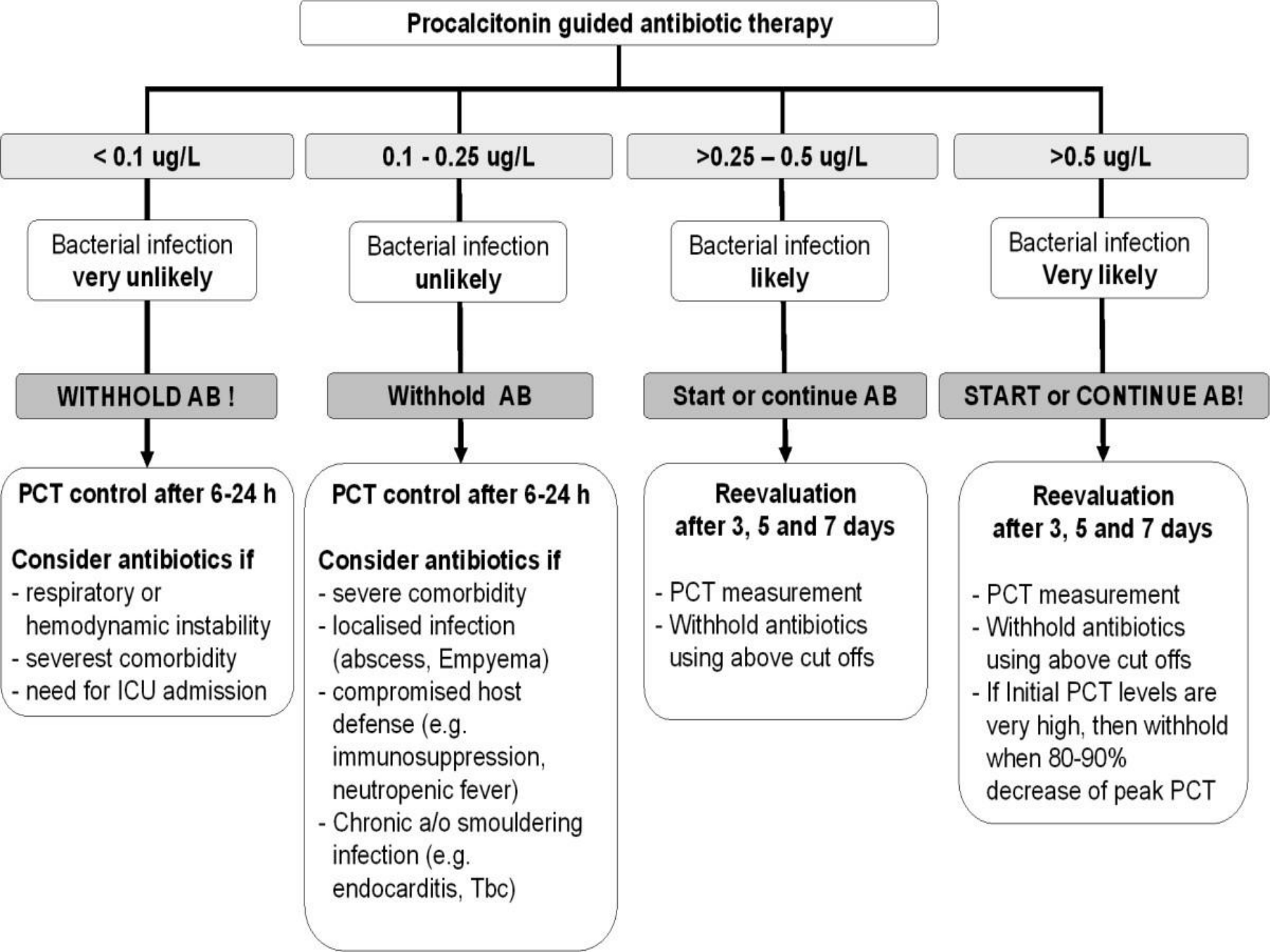
(Bloos et al, 2011)

Sepsis Follow PCT Antibiotic Use Algorithm

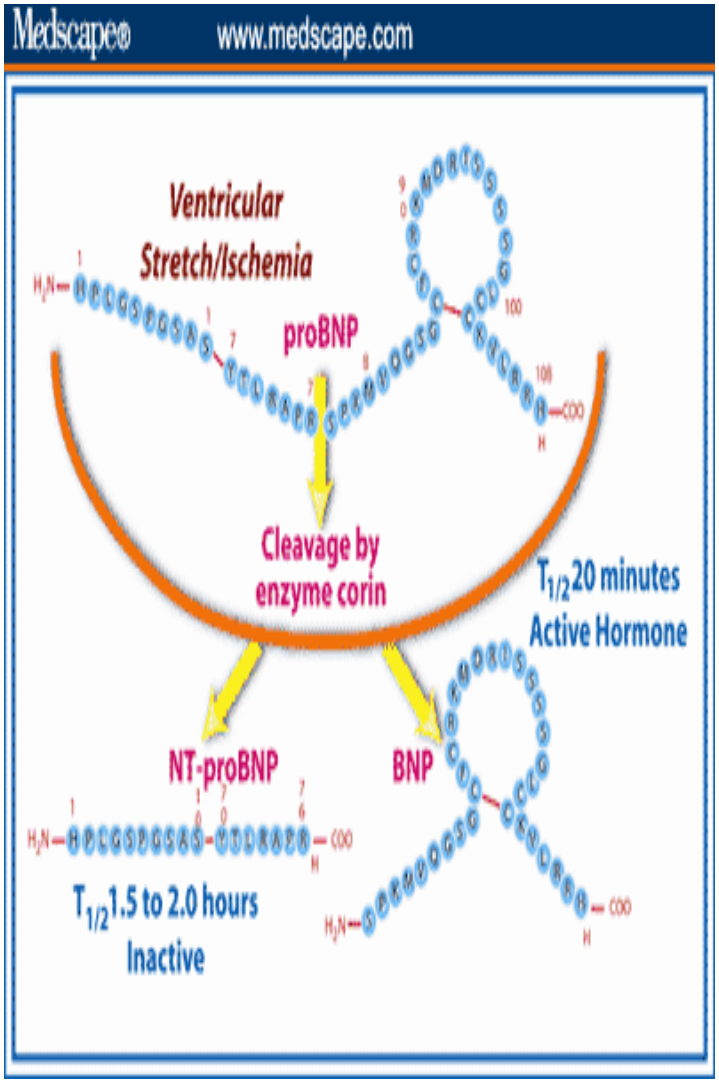


LRTI Initial Antibiotic Use Algorithm




Procalcitonin guided antibiotic therapy
< 0.1 ug/L
0.1 - 0.25 ug/L
>0.25 – 0.5 ug/L
>0.5 ug/L
Bacterial infection very unlikely
Bacterial infection unlikely
Bacterial infection likely
Bacterial infection Very likely
WITHHOLD AB !
Withhold AB
Start or continue AB
START or CONTINUE AB!
PCT control after 6-24 h
Consider antibiotics if
- respiratory or hemodynamic instability
- severest comorbidity
- need for ICU admission
PCT control after 6-24 h
Consider antibiotics if
- severe comorbidity
- localised infection (abscess, Empyema)
- compromised host defense (e.g. immunosuppression, neutropenic fever)
- Chronic a/o smouldering infection (e.g. endocarditis, Tbc)
Reevaluation after 3, 5 and 7 days
- PCT measurement
- Withhold antibiotics using above cut offs
Reevaluation after 3, 5 and 7 days
- PCT measurement
- Withhold antibiotics using above cut offs
- If Initial PCT levels are very high, then withhold when 80-90% decrease of peak PCT

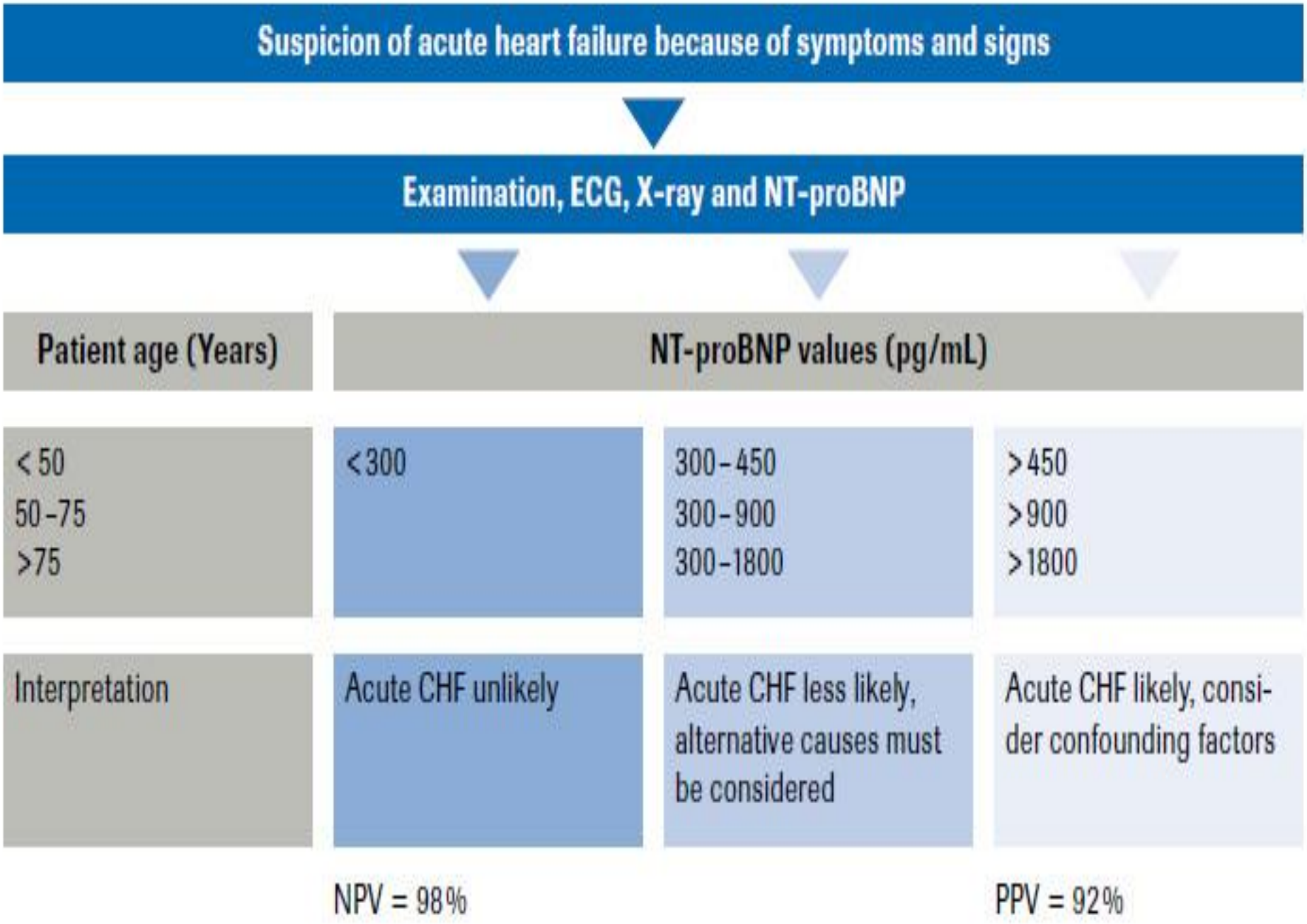
N-terminal pro-B-type natriuretic peptides (NT- pro BNP)



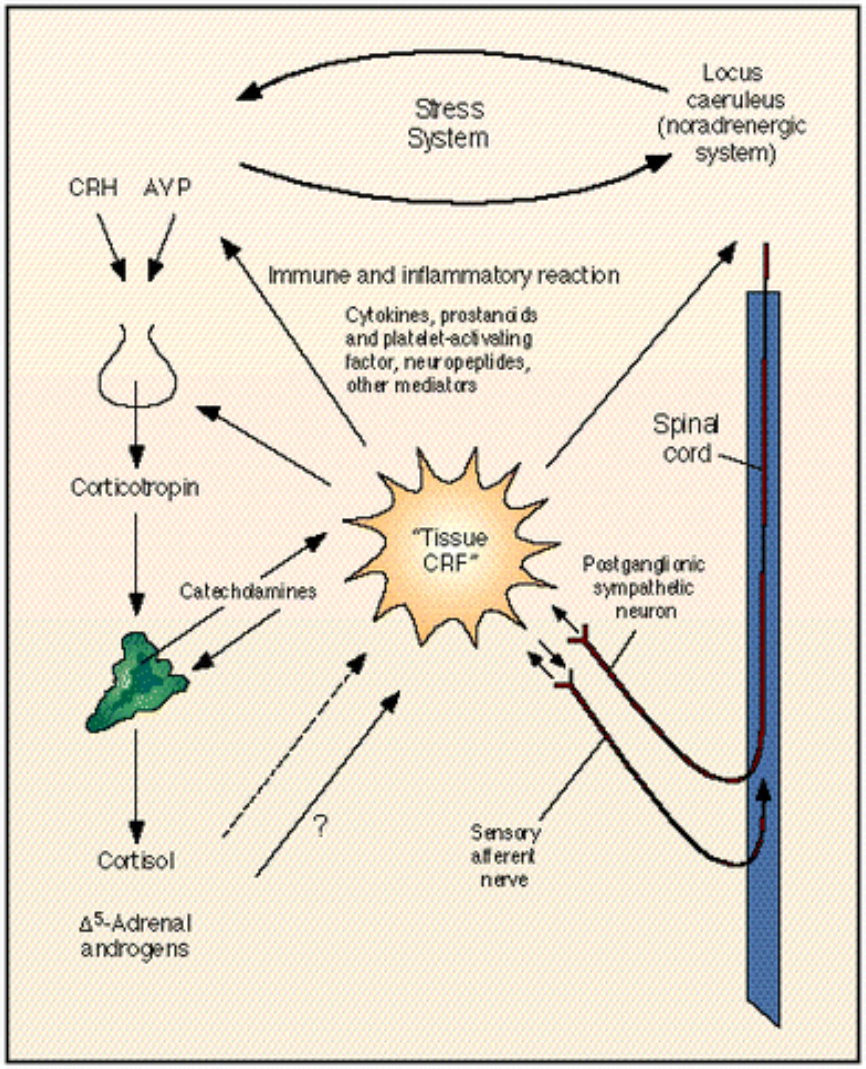
BNP vs NT-proBNP

Characteristic	BNP	NT-proBNP
Components	BNP molecule	NT fragment (1–76)
Molecular Weight	4 kilodaltons	8.5 kilodaltons
Genesis	Cleavage from proBNP	Cleavage from proBNP
Half-life	20 minutes	120 minutes
Clearance Mechanism	Neutral endopeptidase Clearance receptors	Renal clearance
Increases With Normal Aging	+	++++
Correlation With Estimated Glomerular Filtration Rate	–0.20	–0.60
Approved Cutoff(s) for CHF Diagnosis	100 pg/mL	Age <75: 125 pg/mL Age ≥75: 450 pg/mL
Studies Completed	1370	39
Entry on US Market	November 2000	December 2002

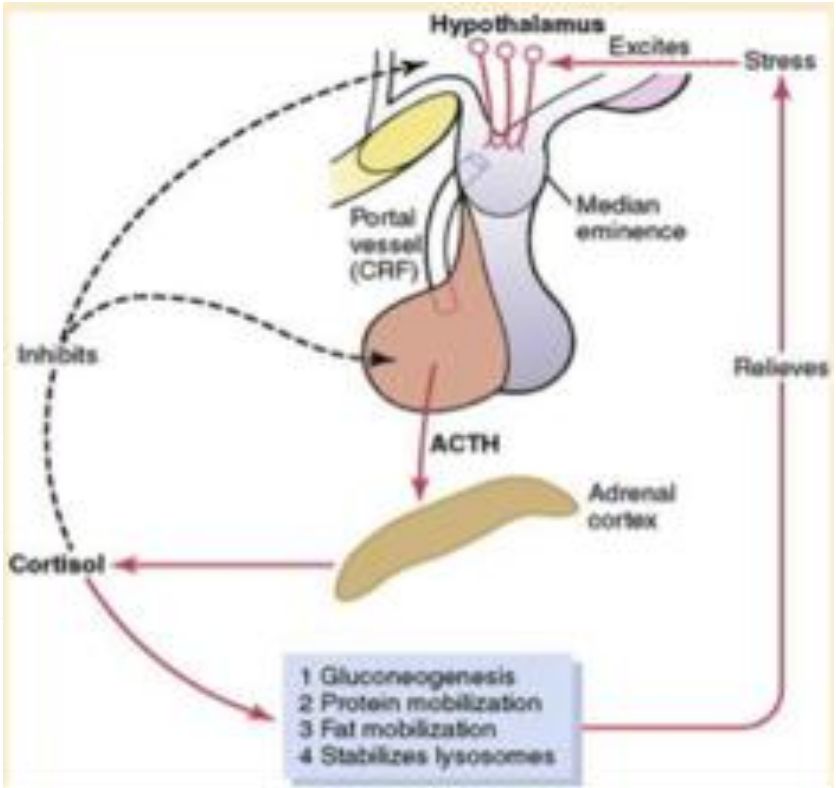
Adapted with permission from McCullough PA et al. *Rev Cardiovasc Med*. 2003;4:72


Suspicion of acute heart failure because of symptoms and signs
Examination, ECG, X-ray and NT-proBNP
Patient age (Years)
NT-proBNP values (pg/mL)
< 50
50–75
>75
<300
300–450
300–900
300–1800
>450
>900
>1800
Interpretation
Acute CHF unlikely
Acute CHF less likely, alternative causes must be considered
Acute CHF likely, consider confounding factors
NPV = 98%
PPV = 92%

Serum cortisol



- Relative adrenal insufficiency
- **CIRCI** : Critical illness induced corticotrophin insufficiency



Adrenal insufficiency and SEPSIS

- mech of dysfxn of HPA axis during acute illness are complex & poorly understood (prob. due to ↓ prod'n of CRH, ACTH & cortisol, & dysfxn of their receptors
- Corticosteroids
  - Consider IV hydrocortisone for adult septic pxs when hypotension responds poorly to adequate fluids and vasopressors (2C)
  - ACTH stimulation test is not recommended (2B)
  - HYDROCORTISONE DOSE SHOULD BE ≤ 300 MG/DAY (1A)
  - Dexamethasone should not be given (2B)
  - Corticosteroids should not be given in the absence of shock (1D)

Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock:

Neutrophil gelatinase-associated lipocalcin (NGAL)

NGAL – what is it?

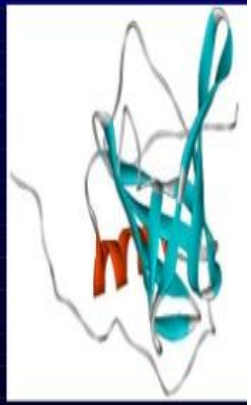
Cystatin-C

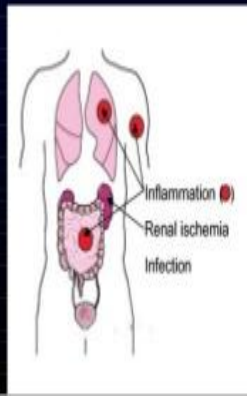
KIM-1

IL-18

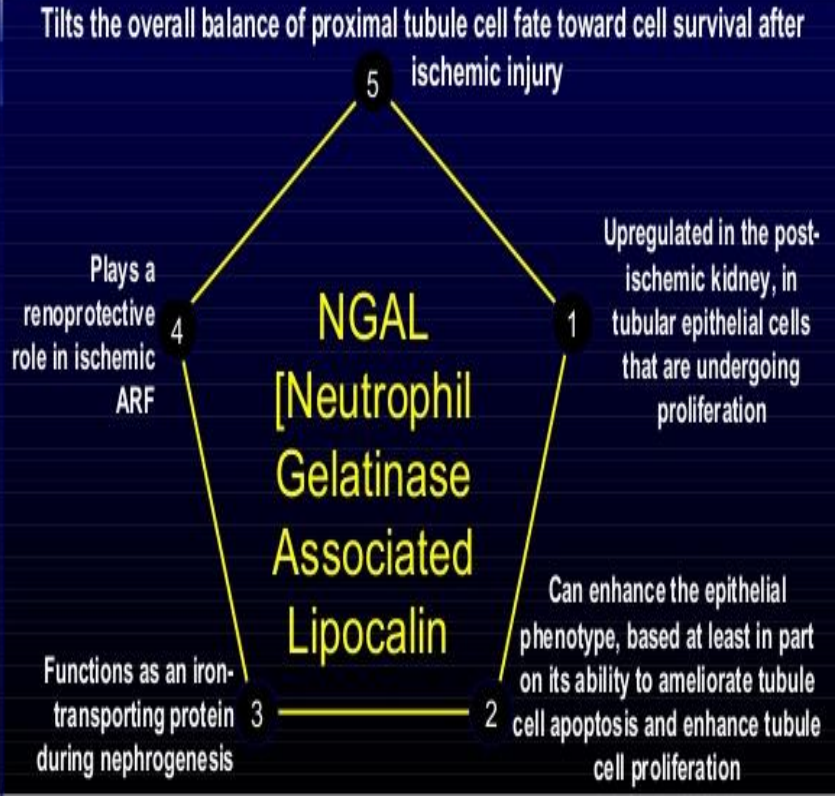
NGAL

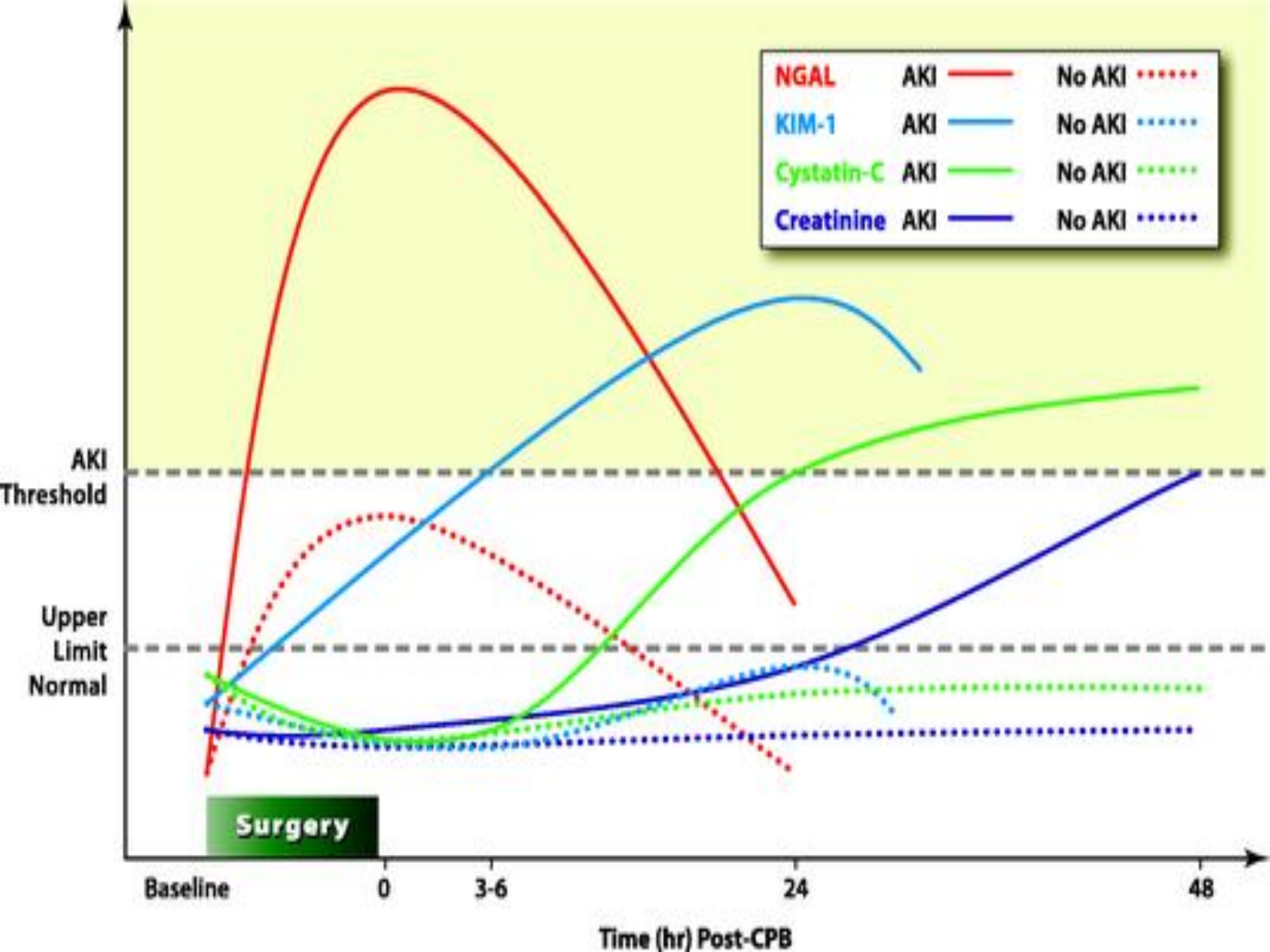
- Neutrophil gelatinase–associated lipocalin (NGAL) is a 25-kDa epithelial protein that is covalently bound to gelatinase from human neutrophils.
- 178 aa disulfide-bridged polypeptide chain
- Calculated molecular mass: 22 kDa
- Apparent molecular mass: 25 kDa (glycosylation)
- Forms complex with 92-kDa matrix metalloproteinase-9 (MMP-9; gelatinase B) **- capable of protecting from degradation by interacting with this protein.**



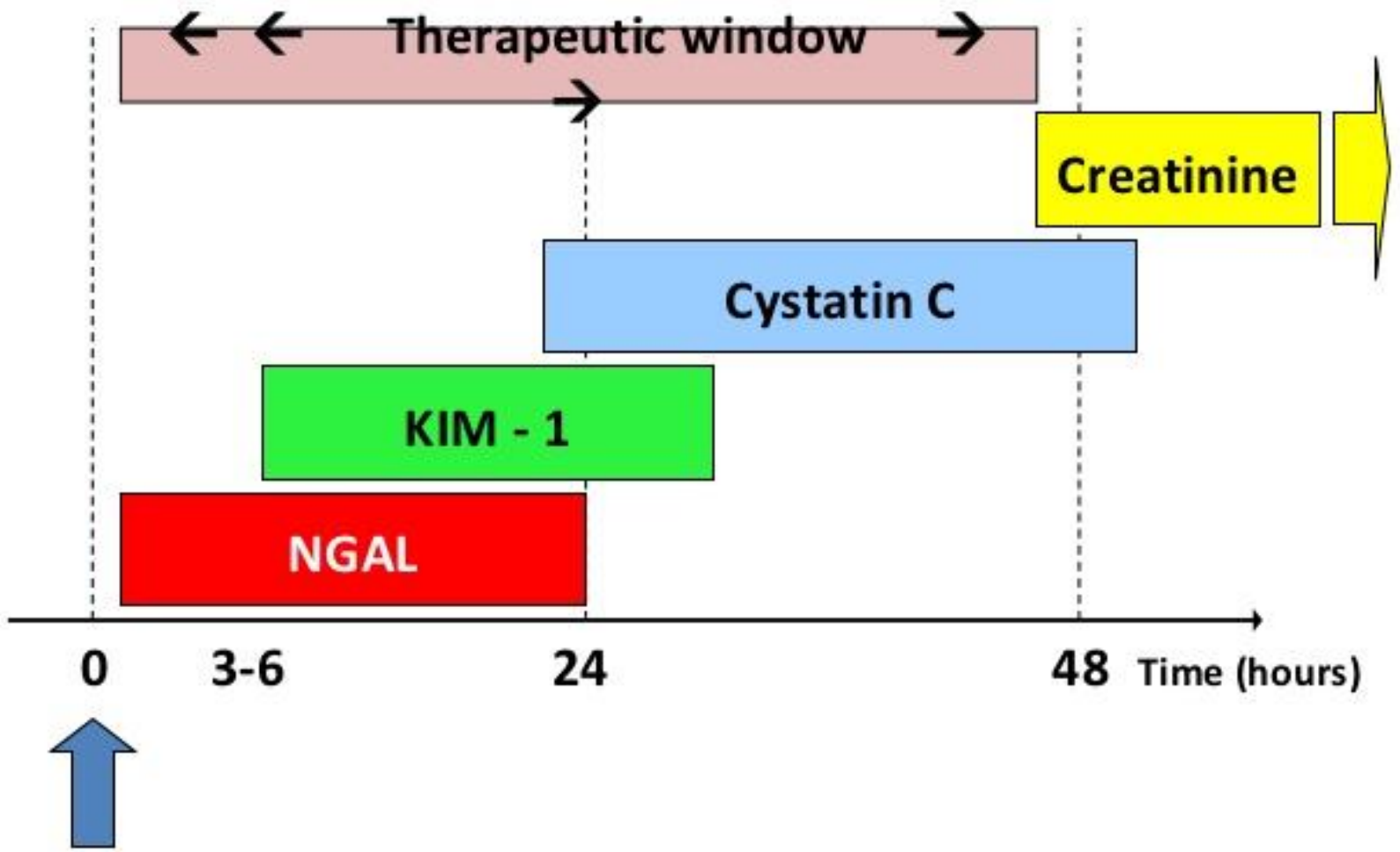


NGAL - Role



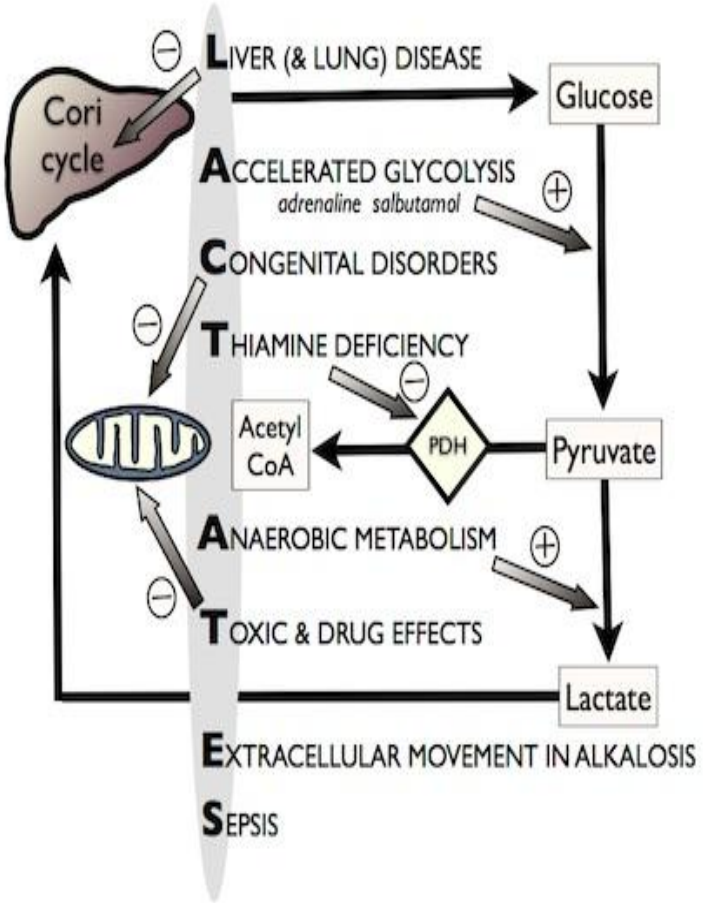

NGAL AKI No AKI
KIM-1 AKI No AKI
Cystatin-C AKI No AKI
Creatinine AKI No AKI
AKI Threshold
Upper Limit Normal
Surgery
Baseline
0
3-6
24
48
Time (hr) Post-CPB

Biomarker time-course



McIlroy DR, Wagener G, Lee HT. *Anesthesiology* 2010; **112**: 998-1004

Lactate


LIVER (& LUNG) DISEASE
Cori cycle
Glucose
ACCELERATED GLYCOLYSIS
adrenaline salbutamol
CONGENITAL DISORDERS
THIAMINE DEFICIENCY
Acetyl CoA
PDH
Pyruvate
ANAEROBIC METABOLISM
TOXIC & DRUG EFFECTS
Lactate
EXTRACELLULAR MOVEMENT IN ALKALOSIS
SEPSIS


Detection
Why We Should Measure Lactate
Monitoring
Prognosis

Nichol et al. Critical Care 2011, 15:R242
http://ccforum.com/content/15/5/R242

CRITICAL CARE

RESEARCH Open Access

Dynamic lactate indices as predictors of outcome in critically ill patients

Alistair Nichol[1,3], Michael Bailey[1], Moritoki Egi[2], Ville Pettila[1], Craig French[5,4], Edward Stachowski[6], Michael C Reade[4], David James Cooper[1,3] and Rinaldo Bellomo[1,4,7*]

Abstract

Introduction: Dynamic changes in lactate concentrations in the critically ill may predict patient outcome more accurately than static indices. We aimed to compare the predictive value of dynamic indices of lactatemia in the first 24 hours of intensive care unit (ICU) admission

Methods: This was a retrospective observational stu
consecutive critically ill patients from four Australian
dynamic lactate values collected in the first 24 hours

Results: We obtained 36,673 lactate measurements
the time weighted average lactate (LAC_{TW24}) and the
independently predictive of hospital mortality with b
one unit increase in LAC_{TW24} and $LAC_{\Delta 24}$ the risk of
0.0001) and by 15% (OR 1.15, 1.10 to 1.20; $P < 0.000$
Acute Physiology and Chronic Health Evaluation II (A
0.0001) achieving almost 90% accuracy. When all lac
combination of LAC_{TW24} and $LAC_{\Delta 24}$ significantly out
such as admission lactate, maximum lactate and mir

Conclusions: In the first 24 hours following ICU adn
independent predictive value, improve the performa
are superior to simple static indices of lactate conce

Keywords: lactate, hyperlactaemia, dynamic, intensiv

Introduction

In the critically ill, a higher admission blood lactate c
centration is associated with a higher risk of death [1
We recently reported that even within the current 'r
mal range' (< 2.00 mmol.L^{-1}) a higher admission bl
lactate concentration is associated with significa
increased hospital mortality [4], a finding which sugg
that even the subtle perturbations of lactate homeost
may be important.

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Road, Melbourne, VIC, Australia
Full list of author information is available at the end of the article

Bakker et al. Annals of Intensive Care 2013, 3:12
http://www.annalsofintensivecare.com/content/3/1/12

Annals of Intensive Care
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REVIEW Open Access

Clinical use of lactate monitoring in critically ill patients

Jan Bakker[1*], Maarten WN Nijsten[2] and Tim C Jansen[1]

Abstract

Increased blood lactate levels (hyperlactataemia) are common in critically ill patients. Although frequently used to diagnose inadequate tissue oxygenation, other processes not related to tissue oxygenation may increase lactate levels. Especially in critically ill patients, increased glycolysis may be an important cause of hyperlactataemia.
Nevertheless, the presence of increased lactate levels has important implications for the morbidity and mortality of

ationship
therefore more
adjust treatment
ne bedside from
s.

essen made an im-
our association of
e hypoxia. These
nterrupted oxygen
irds, lactic acid was
practice, lactate is
of patients, usually
xia. However, given
fect of acute illness
ctate levels can re-

e two main energy
wer life: glycolysis
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evolution (approxi-
s glucose into two
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Monitoring of serum lactate level during cardiopulmonary resuscitation in adult in-hospital cardiac arrest

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Abstract

Introduction: Serum lactate level may correlate with no-flow and low-flow status during cardiac arrest. Current guidelines have no recommended durations for cardiopulmonary resuscitation (CPR) before transition to the next strategy. We hypothesized that the lactate level measured during CPR could be associated with the survival probability and accordingly be useful in estimating the optimal duration for CPR.

Methods: We conducted a retrospective observational study in a single medical centre and included adult patients who had suffered an in-hospital cardiac arrest between 2006 and 2012. We used multivariable logistic regression analysis to study the association of lactate level measured during CPR and outcomes. We used generalized additive models to examine the nonlinear effects of continuous variables and conditional effect plots to visualize the estimated survival probability against CPR duration.

Results: Of the 340 patients included in our analysis, 50 patients (14.7 %) survived to hospital discharge. The mean lactate level was 9.6 mmol/L and mean CPR duration was 28.8 min. There was an inverse near-linear relationship between lactate level and probability of survival to hospital discharge. A serum lactate level <9 mmol/L was positively associated with patient survival to hospital discharge (odds ratio 2.00, 95 % confidence interval 1.01–4.06). The optimal CPR duration may not be a fixed value but depend on other conditions.

Conclusions: Serum lactate level measured during CPR could correlate with survival outcomes. A lactate level threshold of 9 mmol/L may be used as a reference value to identify patients with different survival probabilities and determine the optimal CPR durations.

Introduction

More than 200,000 hospitalized adult patients experience in-hospital cardiac arrest (IHCA) annually in the USA with an estimated incidence of 1.6 per 1,000 hospital admissions [1]. The survival rate from IHCA has increased over the past decade [2], probably due to earlier recognition of cardiac arrest, higher quality of cardiopulmonary resuscitation (CPR), and improved post-resuscitation care [3, 4]. Despite this progress, mortality following IHCA remains high, with only about 18 % of patients surviving to hospital discharge [1].

The causes of high mortality could be due to the inability to establish rapid return of spontaneous circulation (ROSC) leading to subsequent multi-organ failure. Extracorporeal CPR (ECPR) has been advocated as a novel alternative for cardiac arrests that are considered refractory to initial conventional CPR [5, 6], especially for IHCA [7]. Nevertheless, the term, "refractory cardiac arrest," is ill-defined. Most studies on ECPR have used CPR duration as an indicator of futile resuscitation, which varied from 10 to 15 minutes [7–9] and led to initiation of ECPR within 30 to 60 minutes of CPR.

However, using CPR duration alone may not be an accurate indicator for estimating survival probability and determination of futile CPR. Matos et al. [10] reported

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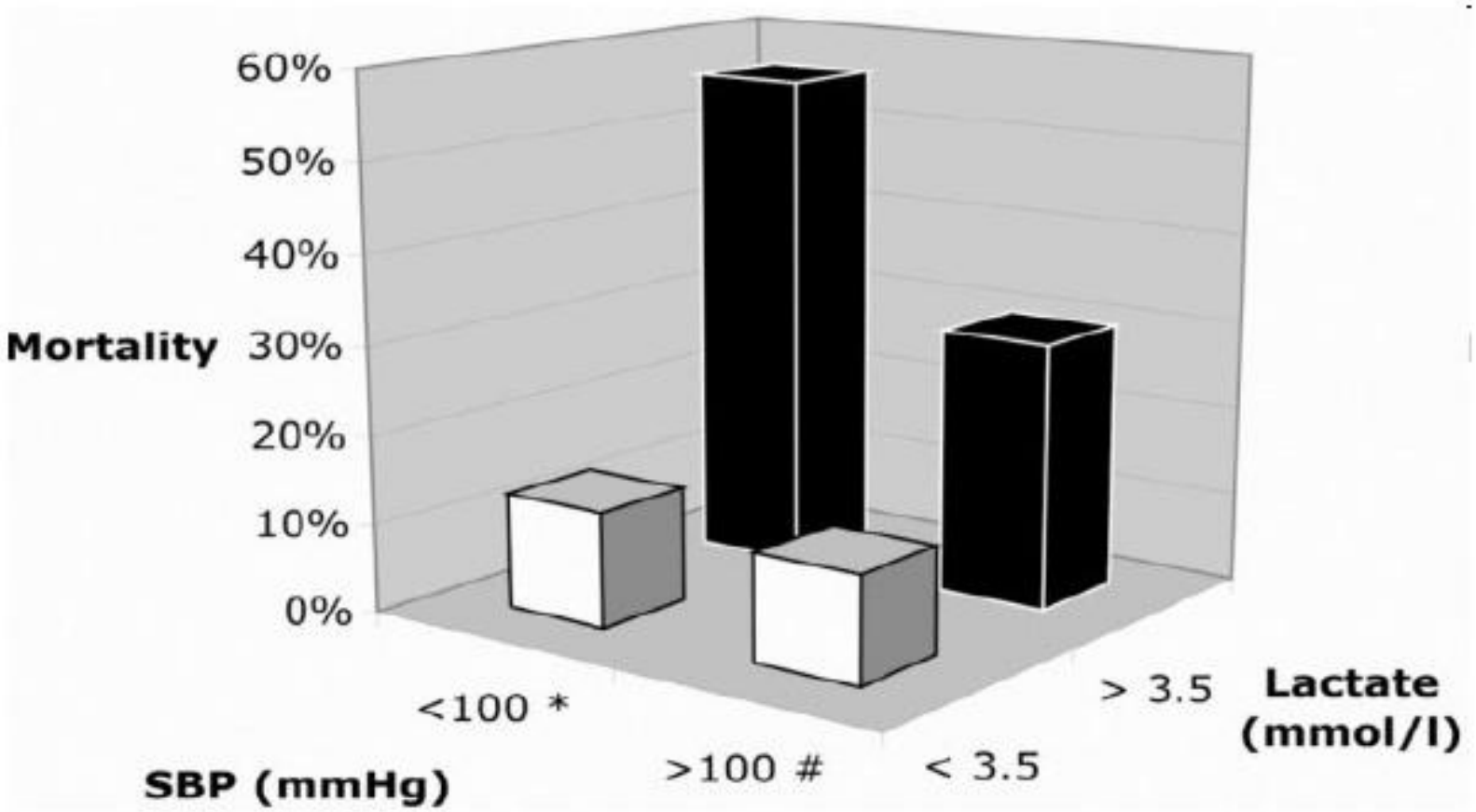
Pre-Hospital Lactate and Mortality



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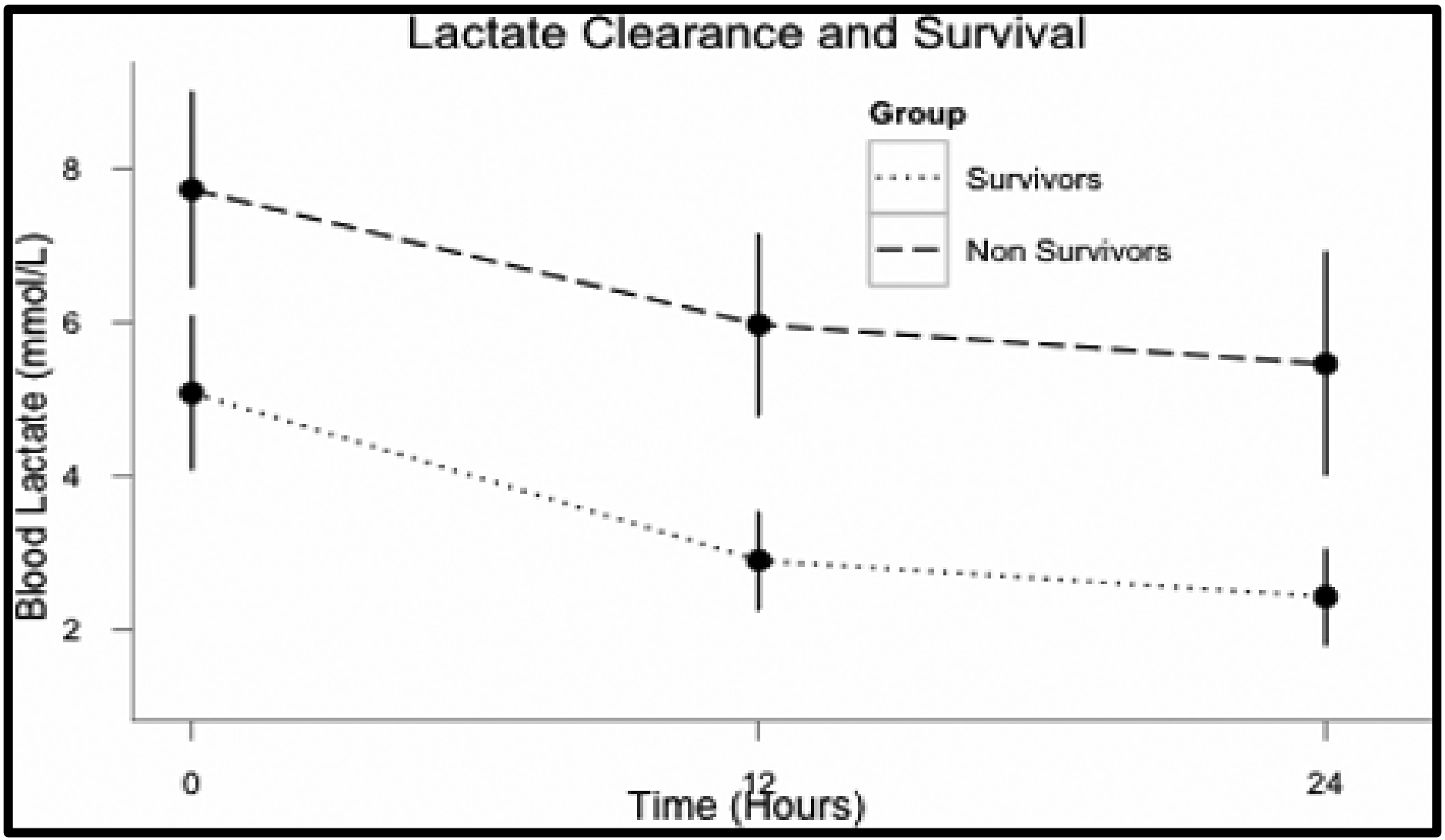
$$\text{Lactate clearance} = \frac{(\text{Lactate}^{\text{ED Presentation}} - \text{Lactate}^{\text{Hour 6}}) \times 100}{\text{Lactate}^{\text{ED Presentation}}}$$



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