The Role Of Procalcitonin In The Management Of Sepsis

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Introduction

- **Sepsis** is a global healthcare problem, characterized by whole body inflammation in response to microbial infection, which leads to organ dysfunction.
- Crucial for a successful treatment and positive outcomes, is an early diagnosis and differentiation from non-infectious causes, in order to rapidly start with antimicrobial therapy and fluid resuscitation .

- To date, **no gold standard exists for the detection of sepsis caused by bloodstream infections .**

Blood biomarkers

- The use of **conventional diagnostic approaches** such as blood cultures and inflammatory blood markers [CPR, ESR, WBC] in patients with a clinical suspected infection or sepsis **is restricted by some limitations.**

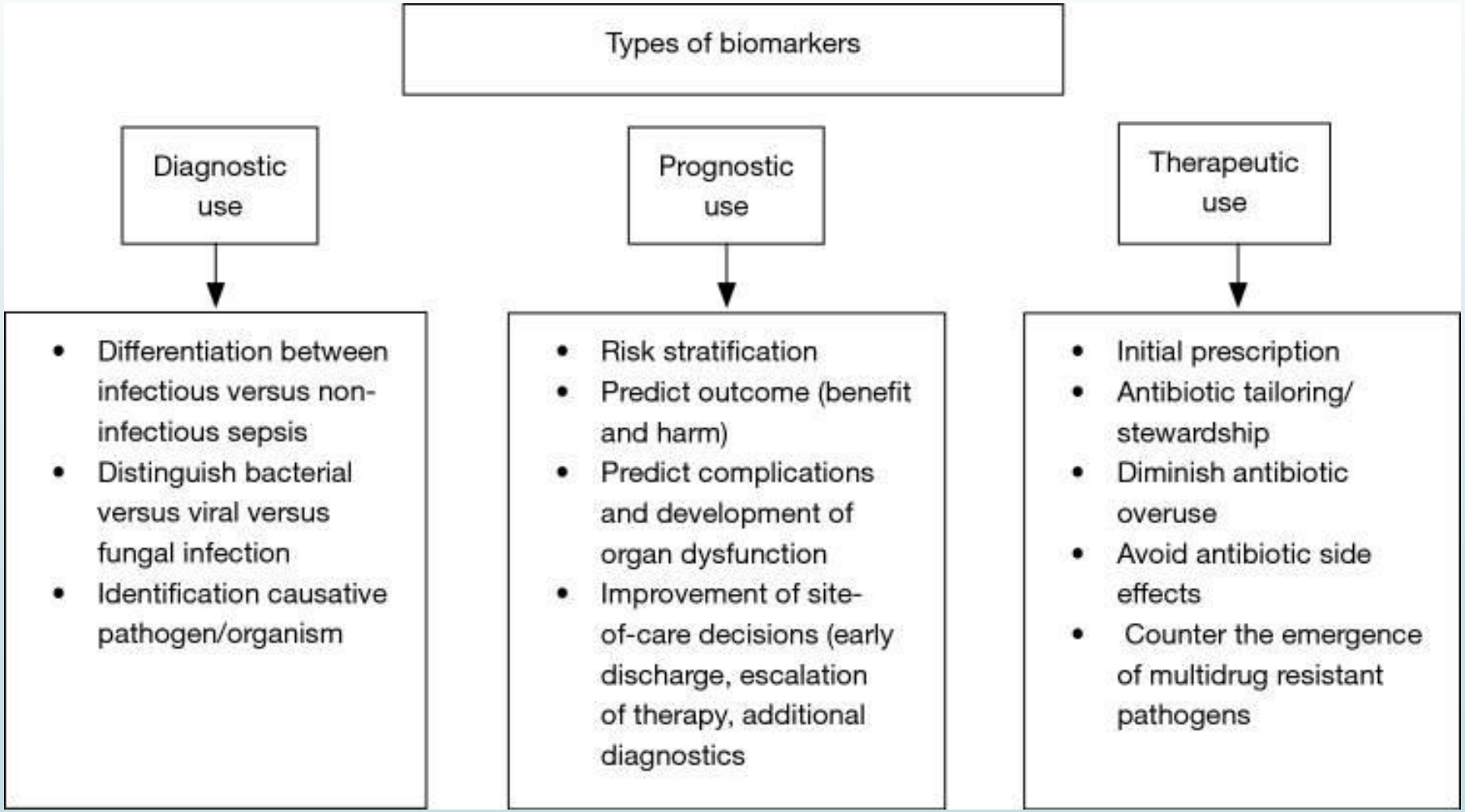
- In this regard, the use of **blood biomarkers** has great potential to improve sepsis care.
- Clinical management of critically ill patients with severe infection and sepsis can be improved by **shortening the time to diagnostic and treatment decision** (i.e., differentiation between bacterial *vs.* viral *vs.* fungal infection and *vs.* non-infectious etiologies).

Blood biomarkers

By biomarkers, site-of-care decisions can be improved (e.g., early discharge or escalation of care) by an **early risk stratification and the provision of prognostic information**

- **Repeatedly measured biomarkers also help monitoring patients** for tailoring therapy to individual needs of patients (antibiotic stewardship).

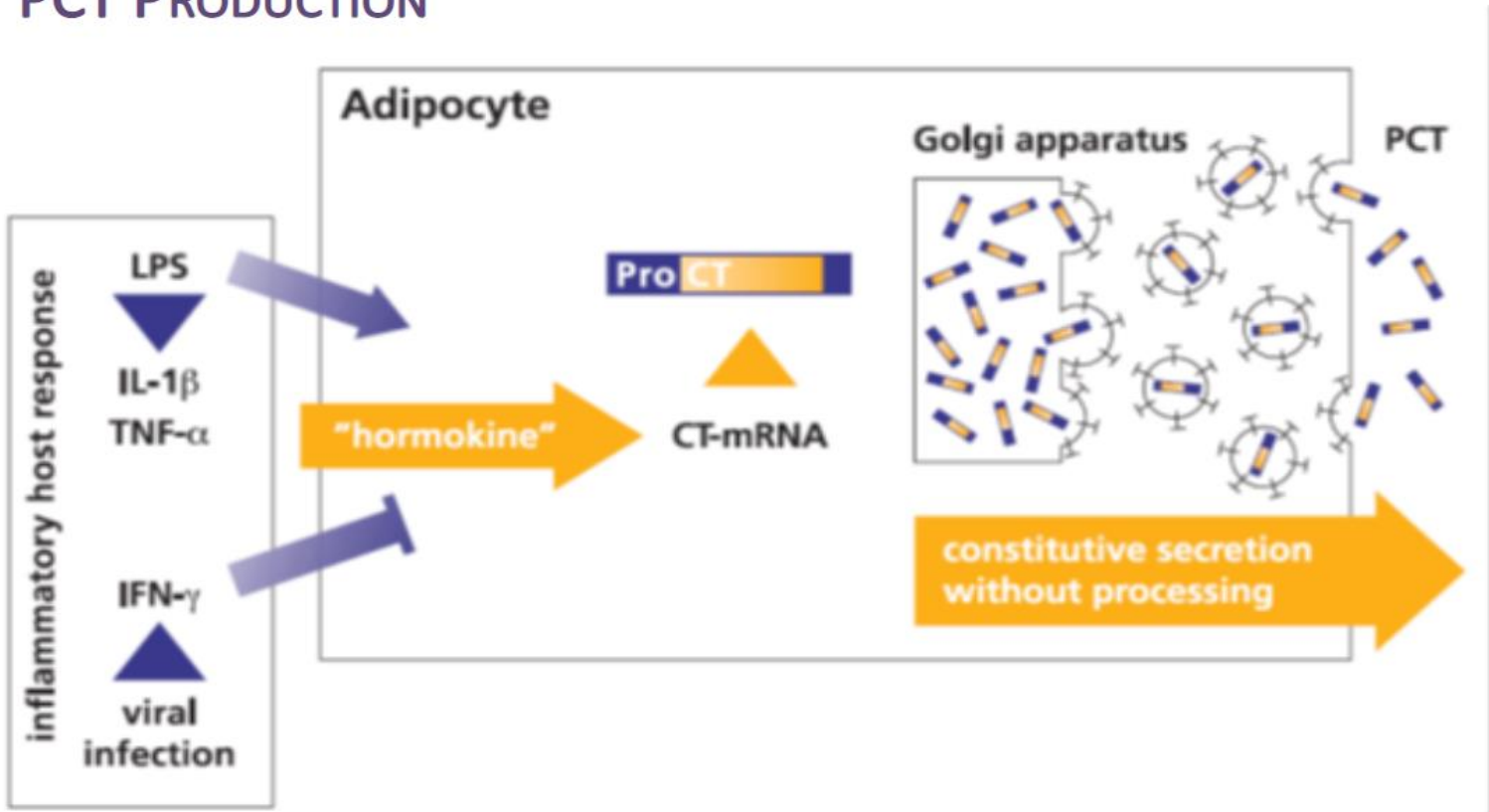
Role of biomarkers in sepsis management



Procalcitonin as a diagnostic biomarker for bacterial infection and sepsis

- One of the most investigated host-directed marker is **PCT.**
- PCT is a hormone that is synthesized by the **parafollicular C cells of the thyroid** and involved in calcium homeostasis.
- Its synthesis pathway can vary depending on different inflammatory states.
- **In healthy individuals, serum PCT is not detectable**, since the protein is not released into the blood in absence of systematic inflammation.
- **In case of a sepsis caused by bacterial infections**, however, PCT synthesis is induced in practically all tissues and therefore, detectable in the blood.

Procalcitonin – Presence of Bacterial Infection Stimulates PCT Production

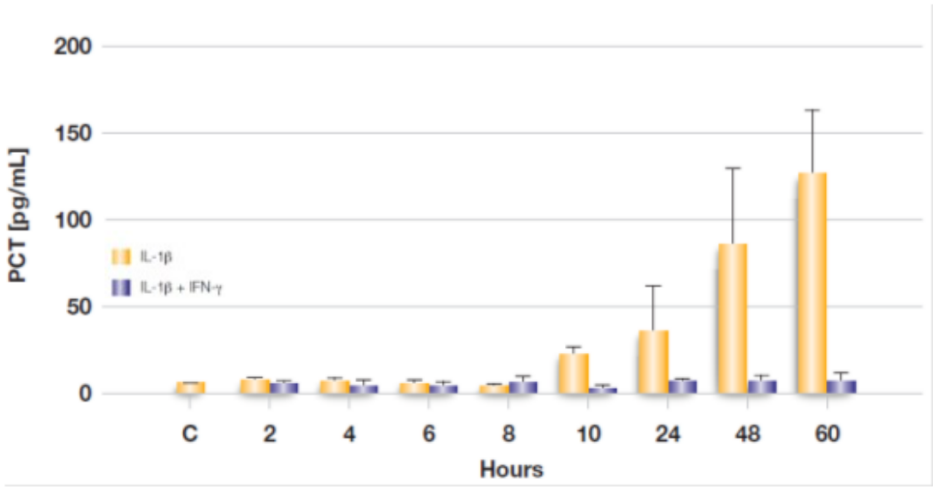


Alternative synthesis of PCT

- Bacterial toxins (gram+/-) and cytokines **stimulate production** of PCT in all parenchymal tissues
- PCT is **immediately released** into bloodstream
- This process can be **blocked** during viral infections

- Due to cytokines released during viral infections that inhibit the production of TNF-a, PCT synthesis is not induced in the most viral infections.

HIGHLY SPECIFIC INDUCTION AND RELEASE OF PCT DUE TO BACTERIAL INFECTION

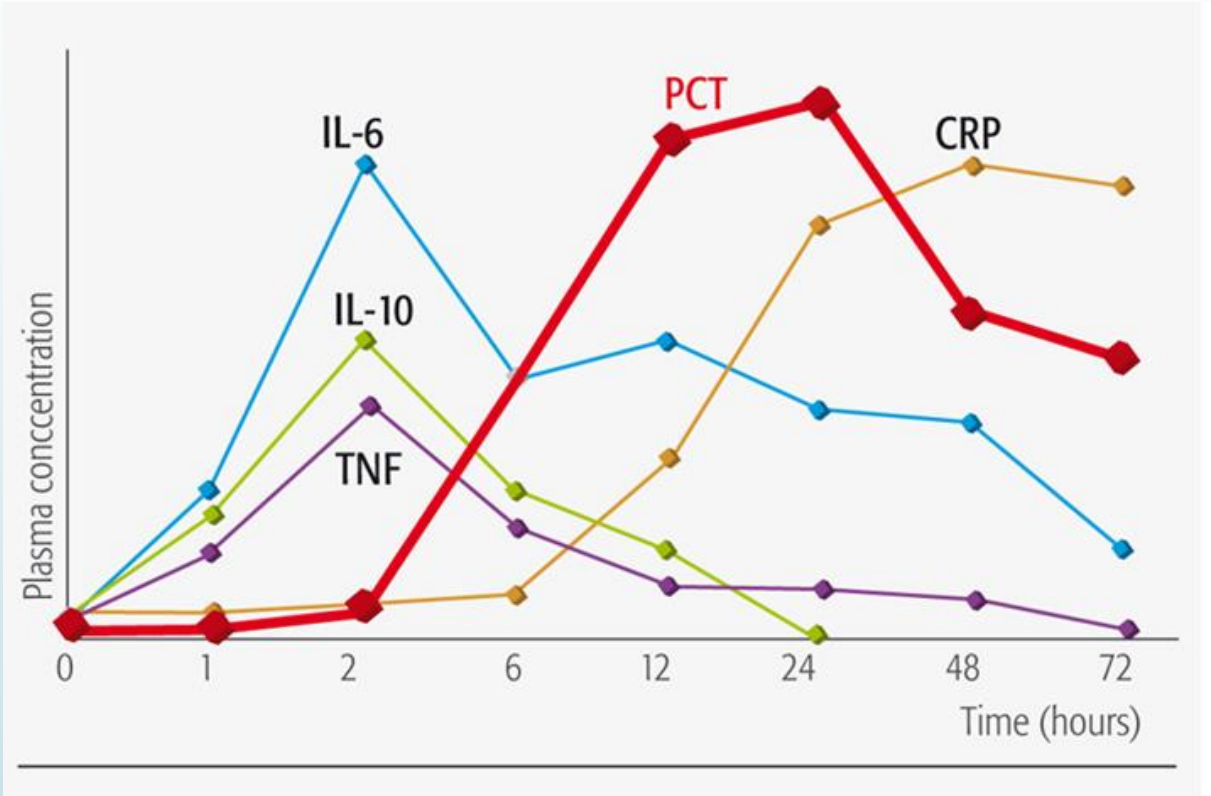


- **IFN-γ** released in viral infection, **blocks** the activation of **PCT** production, therefore in viral infection PCT levels **remain normally low**

- PCT has a wide biological range, a short time to induction after bacterial stimulation and a long half-life.
- Thus, PCT has good discriminatory properties for the **differentiation between bacterial and viral inflammations** with rapidly available results.

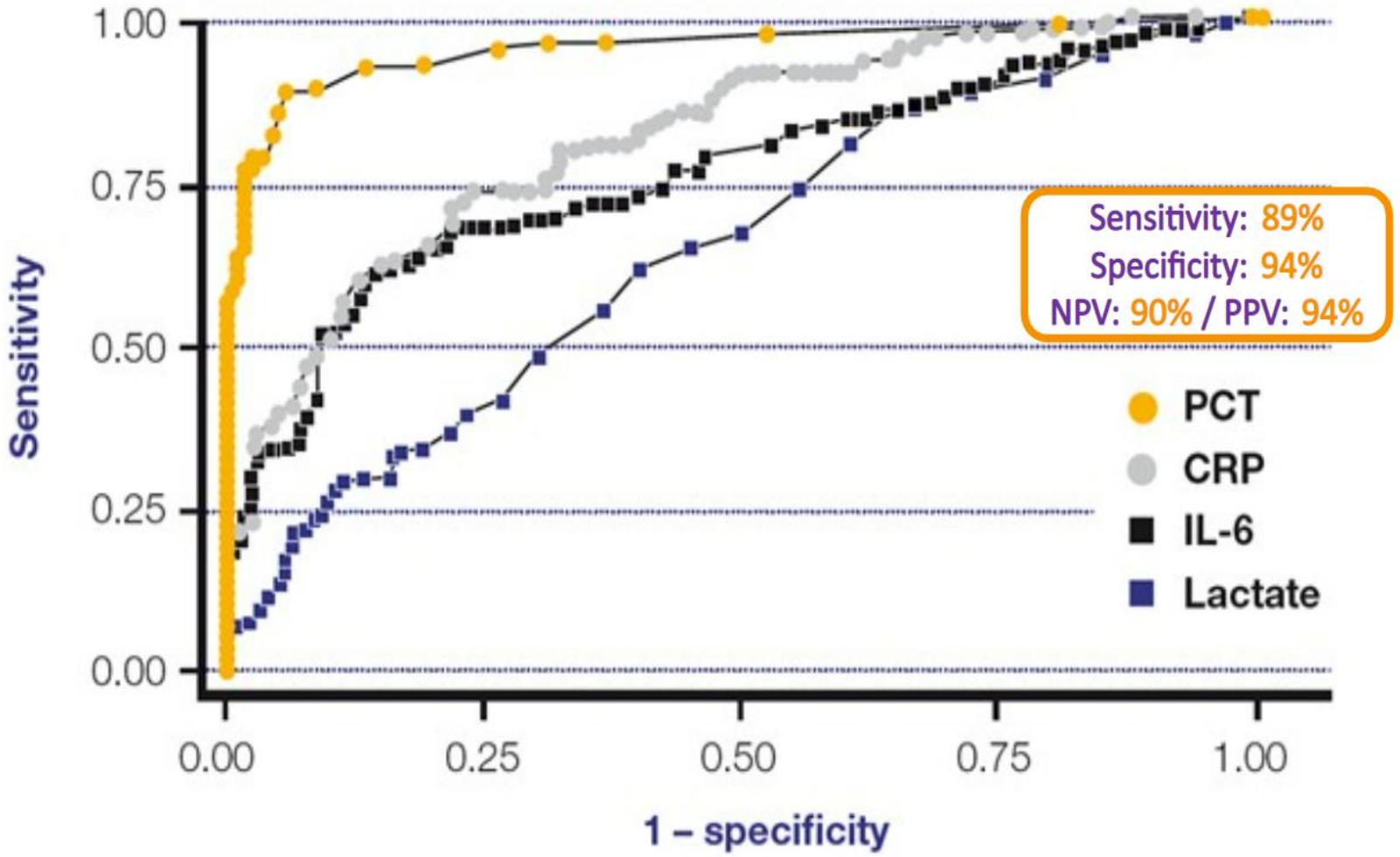
- PCT *per se* **cannot isolate or detect specific pathogens**, but the level of PCT may be useful to estimate the probability of a severe bacterial infection.

Kinetic profiles of different biomarkers of bacterial infection



- **PCT levels**, can be observed within 3-6 hours after an infectious challenge with a peak - up to 1000 ng/ml - after 6-12 hrs. Half-life: ~24hrs
- **Specific** to bacterial origin of infection and **reflects** the **severity** of the infection

DIAGNOSTIC ACCURACY OF PCT COMPARED TO OTHER BIOMARKERS USED IN SEPSIS



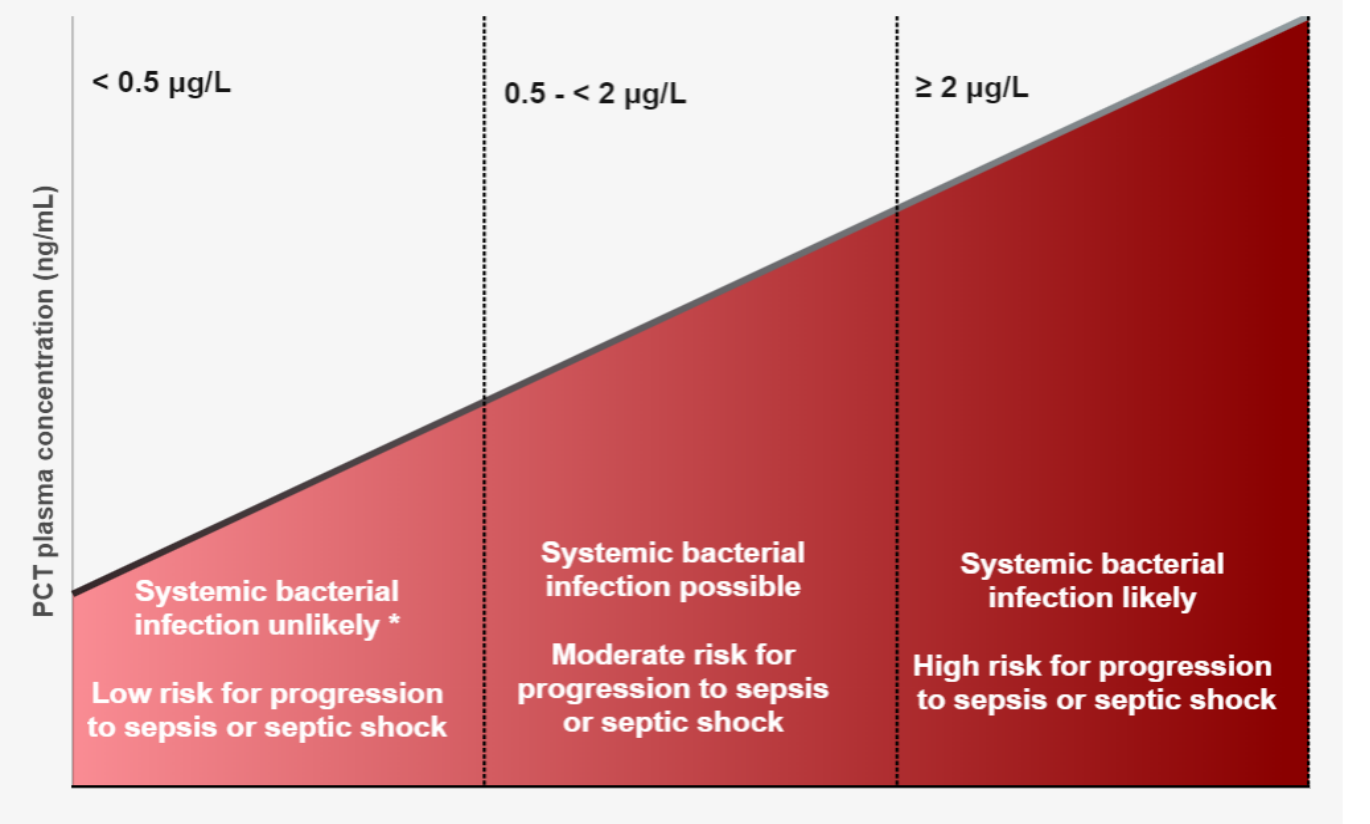
- **PCT levels accurately differentiate** sepsis from noninfectious inflammation*
- **PCT has been demonstrated** to be the best marker for **differentiating** patients with **sepsis** from those with systemic inflammatory reaction not related to infectious cause

Procalcitonin as a prognostic biomarker for the risk assessment in patients with severe infection and sepsis

- PCT kinetics over time has shown to improve the monitoring of critically ill patients with sepsis .
- Since **decreasing PCT values correlate with good outcomes** and increasing values are associated with adverse outcomes which also include mortality, **PCT kinetics have demonstrated prognostic implications**.
- PCT kinetics also showed a correlation with severity of illness.

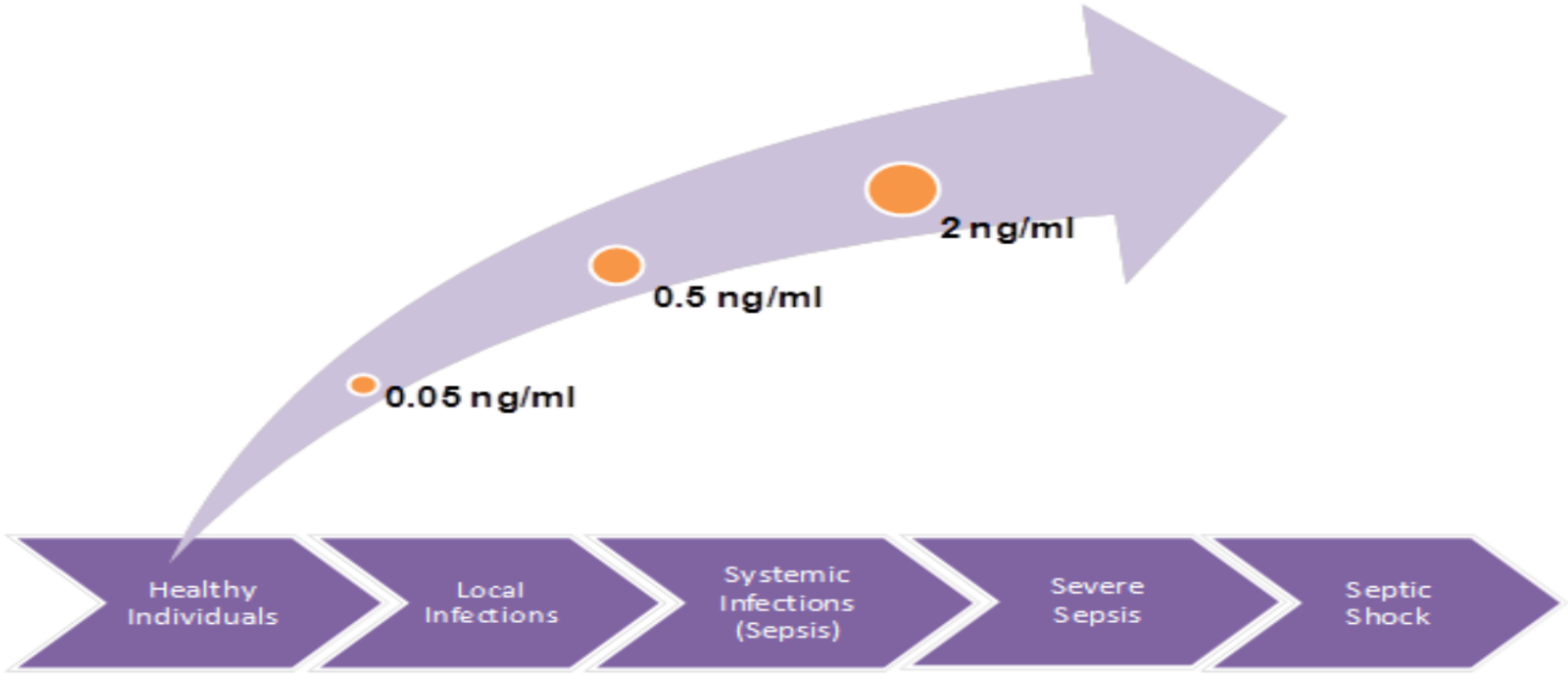
- Alan M, Grolimund E, Kutz A, et al. Clinical risk scores and blood biomarkers as predictors of long-term outcome in patients with community-acquired pneumonia: a 6-year prospective follow-up study. J Intern Med 2015;278:174-84.

- **An observational study identified PCT concentrations being higher in more severe cases of already advanced sepsis.**

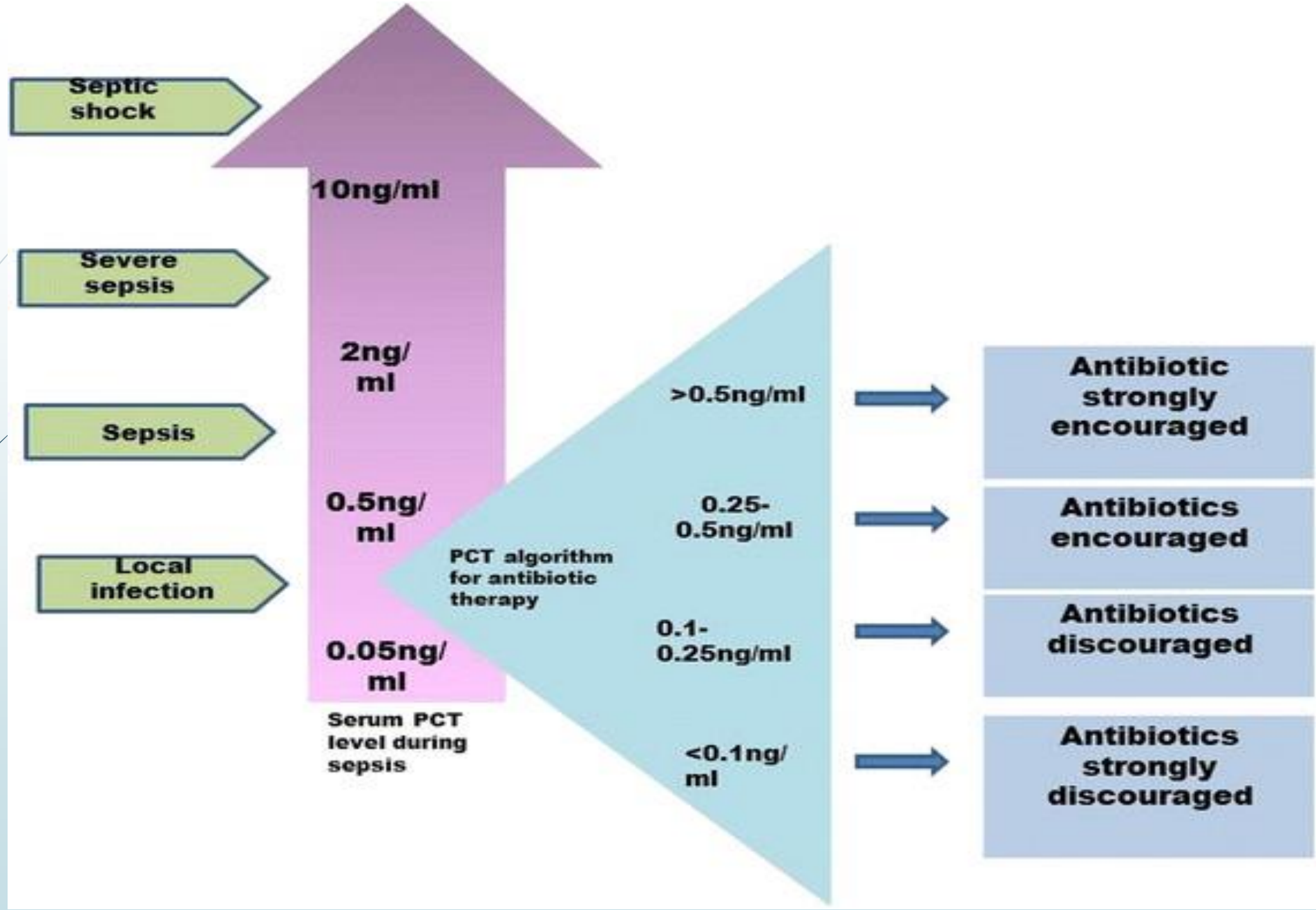


- Schuetz P, Kutz A, Grolimund E, et al. Excluding infection through procalcitonin testing improves outcomes of congestive heart failure patients presenting with acute respiratory symptoms: results from the randomized ProHOSP trial. Int J Cardiol 2014;175:464-72

PCT Level Increase = Increased Significance of Bacterial Infection



- In critically ill patients, **PCT levels** elevate in correlation to the severity of bacterial infection
- **In healthy people** , PCT concentration are found below 0.05ng/ml
- **Concentrations exceeding** 0.5ng/ml can be interpreted as abnormal


Septic shock
10ng/ml
Severe sepsis
2ng/ ml
Sepsis
0.5ng/ ml
Local infection
0.05ng/ ml
Serum PCT level during sepsis
PCT algorithm for antibiotic therapy
>0.5ng/ml
0.25-0.5ng/ml
0.1-0.25ng/ml
<0.1ng/ ml
Antibiotic strongly encouraged
Antibiotics encouraged
Antibiotics discouraged
Antibiotics strongly discouraged

Review of articles

- The analysis of retrospective data from two independent US critical care institutions indicated a high prognostic power for the 72-hour PCT kinetics for predicting sepsis mortality .
- A PCT **decrease >80% within 72 h after initial assessment had a negative predictive value of around 90% for the exclusion of ICU mortality**, which probably can help to identify patients with a reduced risk, for whom a therapy de-escalation or an early ICU discharge could be considered.
- In contrast, **no decrease or an increase of PCT** in the same timeframe had a **positive predictive value** of around 50%, indicating **patients at high risk who probably require treatment escalation.**

- Schuetz P, Maurer P, Punjabi V, et al. Procalcitonin decrease over 72 hours in US critical care units predicts fatal outcome in sepsis patients. Crit Care 2013;17:R115

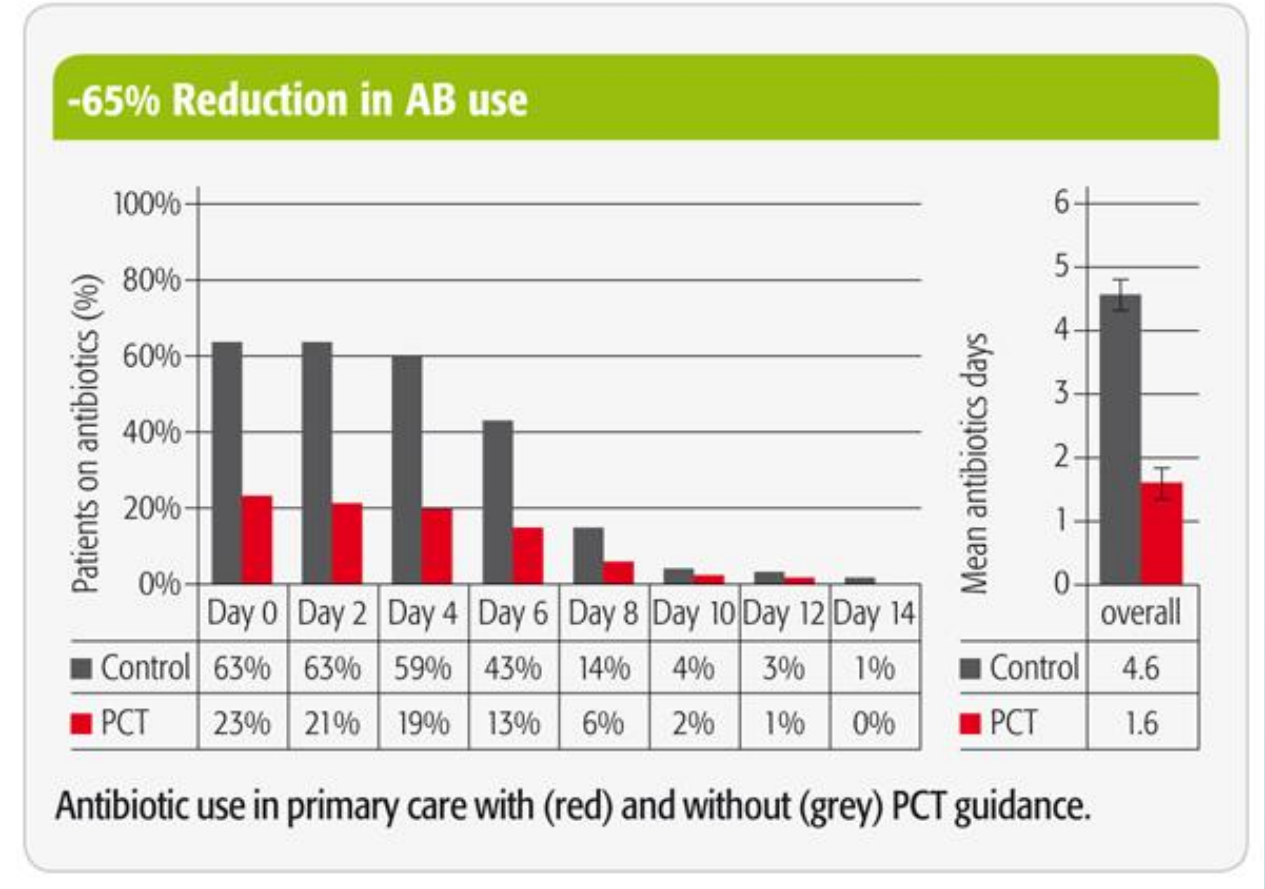
Procalcitonin as a therapeutic biomarker for antibiotic stewardship in patient with severe infection and sepsis

- **Early empirical antibiotic therapy** has demonstrated to be highly effective for the reduction of mortality and morbidity in sepsis.
- However, **a prolonged and unnecessary ABs**, exposes patients to a high risk for **adverse drug reactions** without any additional therapeutic benefit.
- Furthermore, antibiotic overuse, still represents an important risk factor for the development of **antibiotic-resistant bacteria**.
- **Determining the duration of an antibiotic therapy is a challenging decision**, due to the fact that clinical signs and symptoms lack sensitivity and specificity to ensure differentiation between self-limited and mild viral infections from more severe bacterial infections.

- In recent years, there has been **great interest in biomarkers that are able to indicate the risk for bacterial infection in a short time** after admission and thus, can help to reduce antibiotic overuse and potentially diminish antibiotic associated side effects, mortality and treatment failure.
- The use of PCT for this propose has recently been approved by the US (FDA).
- This decision was based on several randomized controlled trials which have analyzed infections of different severity in various clinical settings and demonstrated the efficacy and safety of PCT-guided decision-making with regard to antibiotics.

- Schuetz P, Beishuizen A, Broyles M, et al. Procalcitonin (PCT)-guided antibiotic stewardship: an international experts consensus on optimized clinical use. Clin Chem Lab Med 2019;57:1308-18

Role of PCT in the reduction 0f AB use



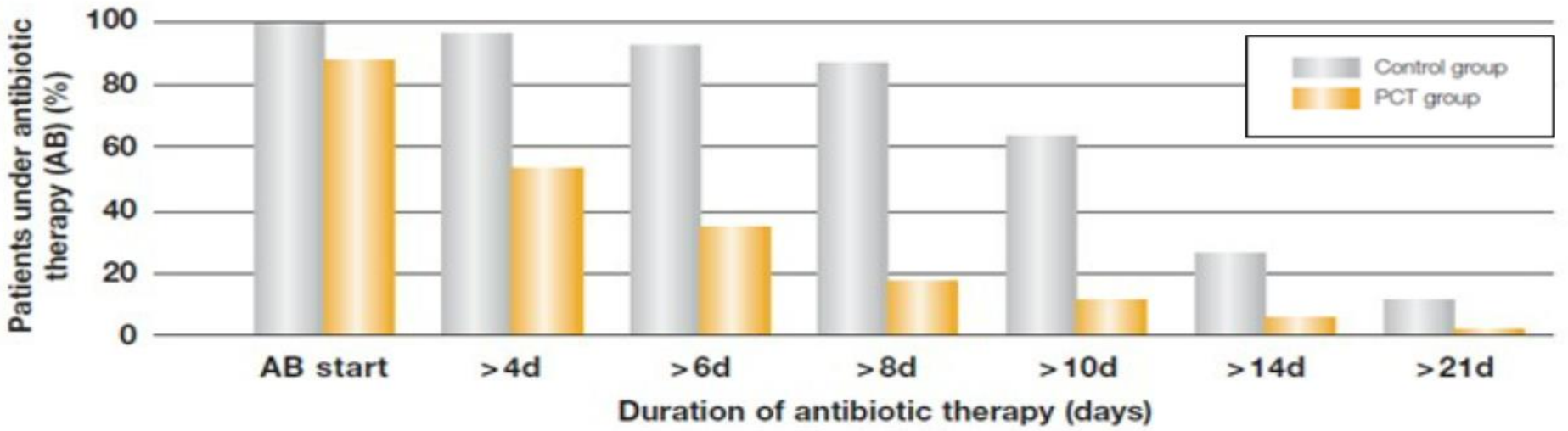
	Day 0	Day 2	Day 4	Day 6	Day 8	Day 10	Day 12	Day 14
Control	63%	63%	59%	43%	14%	4%	3%	1%
PCT	23%	21%	19%	13%	6%	2%	1%	0%

	overall
Control	4.6
PCT	1.6

Antibiotic use in primary care with (red) and without (grey) PCT guidance.

PCT GUIDANCE IN ANTIBIOTIC USAGE HAS BEEN SHOWN TO SIGNIFICANTLY SHORTEN THE TIME PATIENTS NEED TO BE ON ANTIBIOTICS

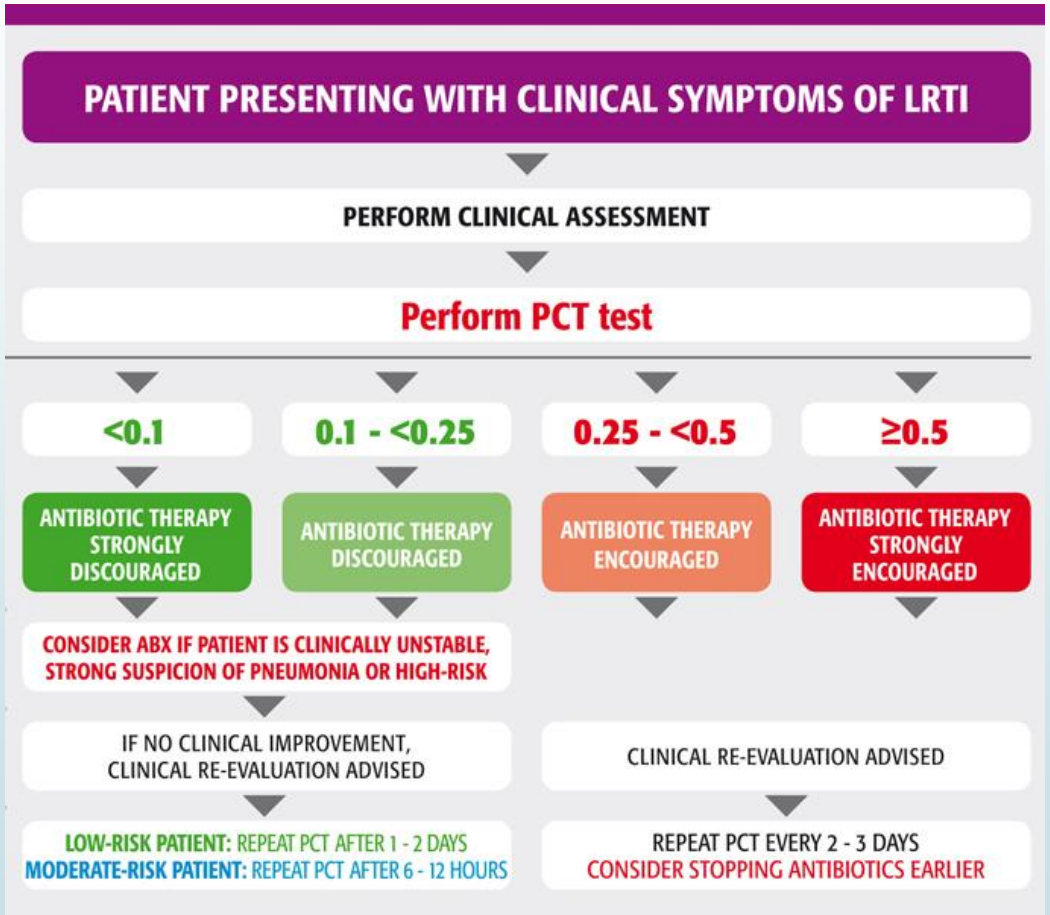
Duration of antibiotic therapy in the control group (n=151) and PCT group (n=151)



KEY TAKEAWAY:

Tailoring of AB treatment using **PCT** to the individual patient needs safely led to a **reduction** of average treatment duration from **12 to 5 days** with same outcome

Procalcitonin-based algorithm for the decision to start antibiotics for patients



PCT-guided therapy de-escalation

- Despite the available evidence regarding PCT-guided therapy de-escalation, the use of PCT-guided antibiotic therapy escalation **is not yet recommended.**
- A randomized trial analyzing 1,200 critically ill patients in nine multidisciplinary intensive care units in Denmark, demonstrated that therapy escalation did not improve outcome when PCT-algorithms were used.

- Jensen JU, Hein L, Lundgren B, et al. Procalcitoninguided interventions against infections to increase early appropriate antibiotics and improve survival in the intensive care unit: a randomized trial. Crit Care Med 2011;39:2048-58

Limitation of Procalcitonin

- PCT can be a better biomarker in detecting bacterial sepsis at initial stages. But the major limitations are to identify the causative bacteria.
- Moreover, it should be noted that **some non-infectious disorders**, such as C-cell **carcinoma or trauma**, can lead to a systemic inflammation resulting **in elevated PCT levels.**
- Further, the use of **PCT-guided stewardship is not recommended in patients** suffering from a **chronic infection such as osteomyelitis or endocarditis**, since observational studies were unable to identify any benefit and interventional investigations in this context are still lacking.

PCT release in the absence of infection

- Newborn < 48hr - increased PCT values (physiological peak)
  - On 3rd **day** after birth, **normal** adult reference ranges apply
- Primary inflammation syndrome following trauma: multiple trauma, extensive burns, major surgery (cardiac, transplant, abdominal)
  - **Rapid decrease** (half-life 24hr) in the absence of bacterial infection
- Medullary C-cell cancers of the thyroid, pulmonary small-cell carcinoma and bronchial carcinoma
- Prolonged circulatory failure (e.g.. cardiogenic shock, hemorrhagic shock, thermal shock)
- Treatments that can cause a cytokine storm e.g. OKT3, anti-lymphocyte globulins, etc.

Conditions of bacterial infection where PCT may be low in the presence of bacterial infection

- Early course of infection: re-measure in 6-12 hrs
- Subacute endocarditis
- Localized infections

Conclusion

- An **early diagnosis and the initiation of an appropriate antibiotic treatment** are still the cornerstones of effective sepsis care.
- In this respect, **PCT has shown promising results for the treatment of patients with sepsis**.
- However, it should be noted that **PCT values are not intended to replace good clinical practice**, but should be used as a **complementary tool** combined with available clinical and diagnostic parameters.

Conclusion

- In order to estimate the probability of bacterial infections, it is recommended to use **cut-off ranges with higher and lower positive and negative predictive values** for the identification of sepsis, **instead of one general cut-off.**
- A further important consideration is the quality of the used PCT assays.
- **The use of high-sensitive PCT assays should be preferred** in clinical practice since the use of semi-quantitative assays is not able to detect an increased PCT in lower ranges.

Conclusion

- **The prognostic information derived from PCT kinetics** can influence **further procedure** with regard to diagnostic testing, but also **therapeutic decisions** and **timing of patients discharge**.
- **In high risk situation the use of PCT should not delay or inhibit the start of empirical treatments**.
- Still, **further research is needed to understand optimal use of PCT**, also in combination with other remerging diagnostic tests for most efficient sepsis care.

Thank You For Your Kind Attention!