Procalcitonin Antibiotic Stewardship

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Objectives

Define and identify procalcitonin as a biomarker for sepsis

Understand how procalcitonin is used in diagnosis and treatment, particularly in antibiotic stewardship programs

Discuss the future use and challenges of procalcitonin

Definition

What is Procalcitonin (PCT)?

What is Procalcitonin?

PREDICTED TO EXIST IN THE 1960S, IT WAS LATER IDENTIFIED AROUND 1975

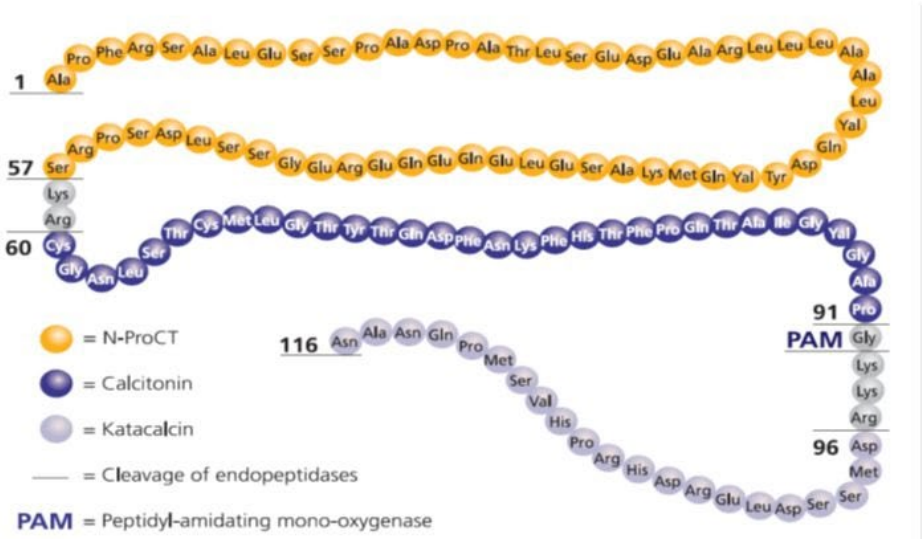
ACUTE PHASE REACTANT

PRODUCED BY THE CELLS OF THE LUNG AND THE INTESTINES, AMONG OTHER ORGANS AND TISSUES

What is Procalcitonin?

- Peptide precursor of calcitonin
- Composed of 116 amino acids and is 13 kDa in molecular weight

PROCALCITONIN – A BIOMARKER FOR THE ASSESSMENT OF CRITICALLY ILL PATIENTS AT RISK FOR SEVERE BACTERIAL INFECTION AND SEPSIS



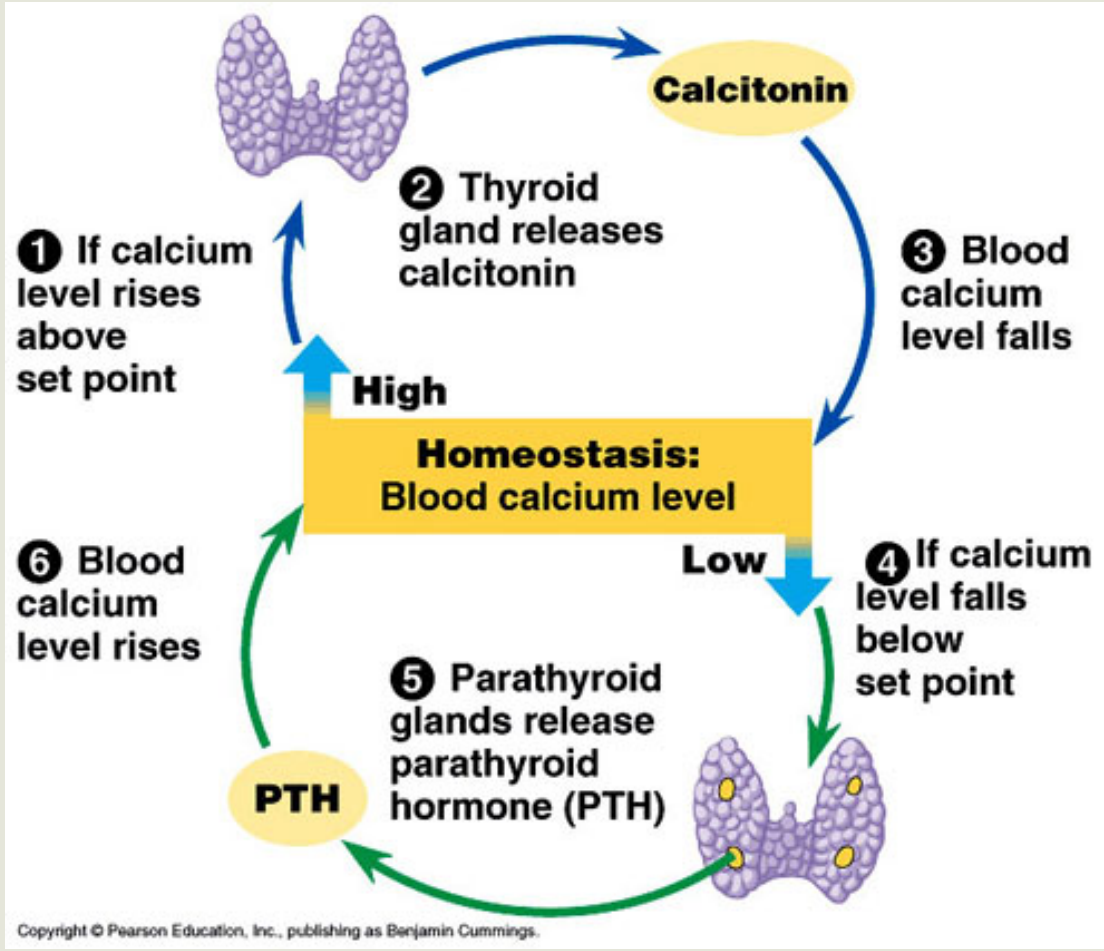
- **Simple blood test** specific for bacterial infection
- During severe bacterial infections and sepsis, **blood levels rise rapidly** (up to x100K) – no elevation from viral infections
- Is the **Standard of Care** for much of Europe in the management of infection and sepsis

Morgenthaler N. et al., Clin Lab 2002, 48: 263-270

(Maruna et al., 2000)

What is Procalcitonin?

- Normal Conditions:
  - Calcitonin is produced by the C-cells of the thyroid gland in response to hormonal stimuli – following cleavage of the procalcitonin molecule
- PCT is produced by the endocrine cells in response to elevated calcium levels (among other things) and is cleaved into calcitonin which is released into the bloodstream



(Deftos et al., 1975; Gregoriano et al., 2020; Maruna et al., 2000; Meisner, 2002; Vijayan et al., 2017)

What is Procalcitonin?

PCT is undetectable in healthy individuals (≤ 0.1 ug/L)

Production of PCT is controlled by the CALC-1 gene

Procalcitonin produced elsewhere does not undergo cleavage and is released into the bloodstream

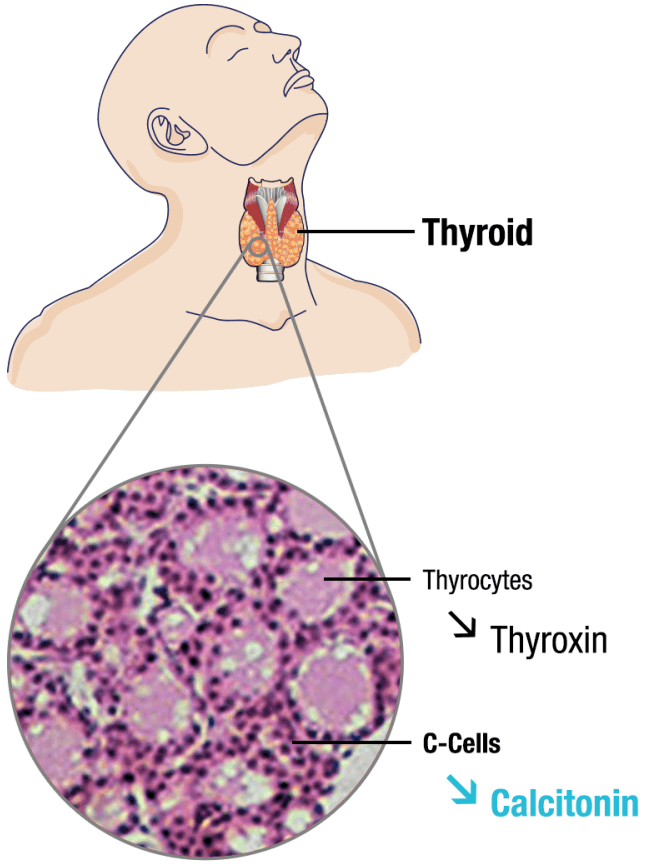
(Meisner, 2002)

What is Procalcitonin?

Abnormal Conditions:

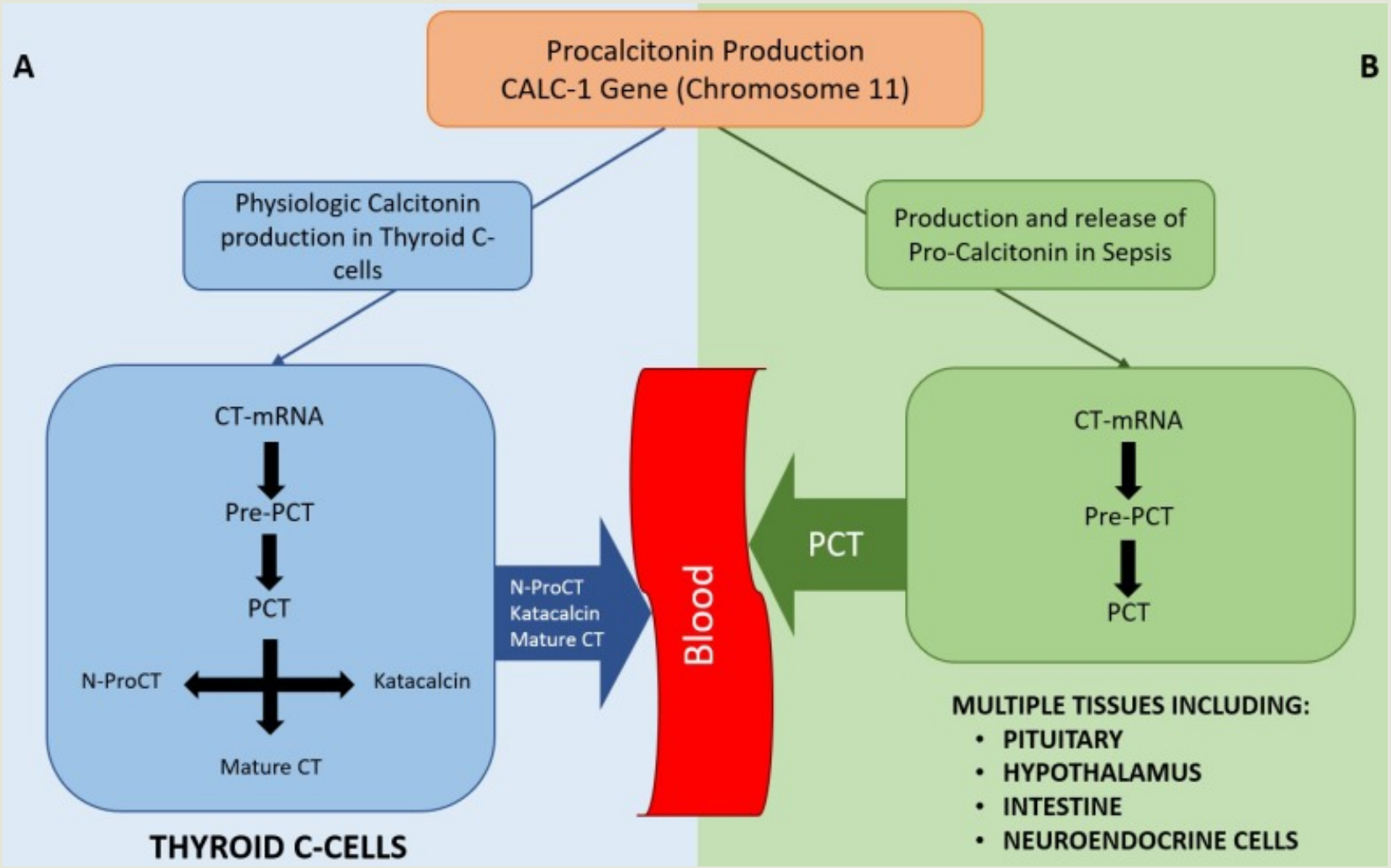
- CALC-1 gene is activated in adipose tissue and other locations such as the lungs or intestines such as during inflammatory events

Tissue	(pro)Calcitonin mRNA expression in healthy individuals
Thyroid	
White Blood Cells	
Perit. Makrophage	
Spleen	
Lung	
Liver	
Kidney	
Adrenal	
Brain	
Spine	
Pancreas	
Stomach	
Small intestine	
Colon	
Heart	
Muscle	
Skin	
Visceral Fat	
Testes	



(Gregoriano et al., 2020; Maruna et al., 2000; Meisner, 2002; Paudel et al., 2020; Vijayan et al., 2017)

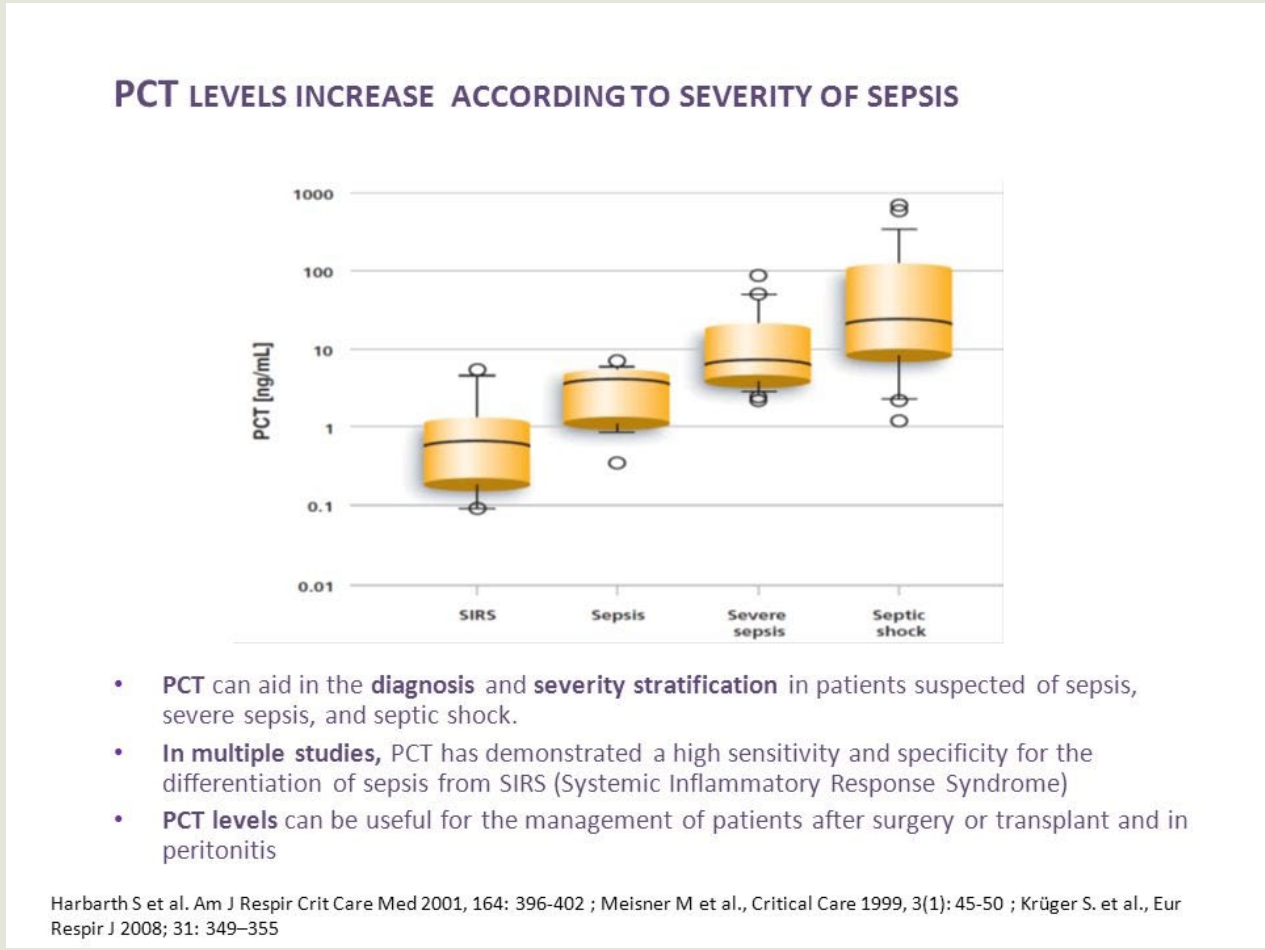
What is Procalcitonin?



(Paudel et al., 2020)

What is Procalcitonin?

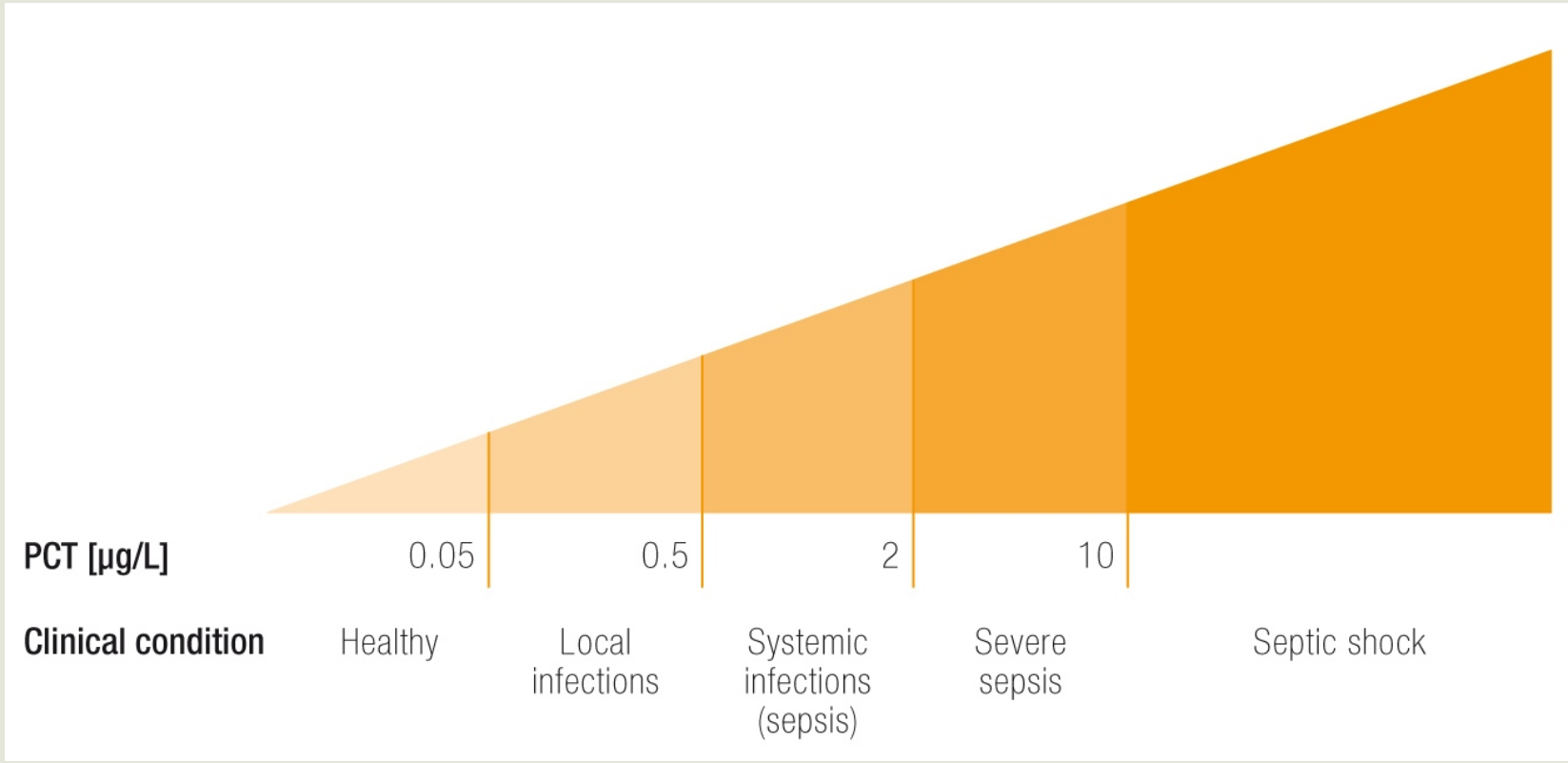
- PCT levels rise rapidly (within 6-12 hours) after bacterial infectious insult with systemic consequences
- The magnitude of the increase correlates with the severity of the bacterial infection



(Hamade & Huang, 2020; Meisner, 2002)

What is Procalcitonin?

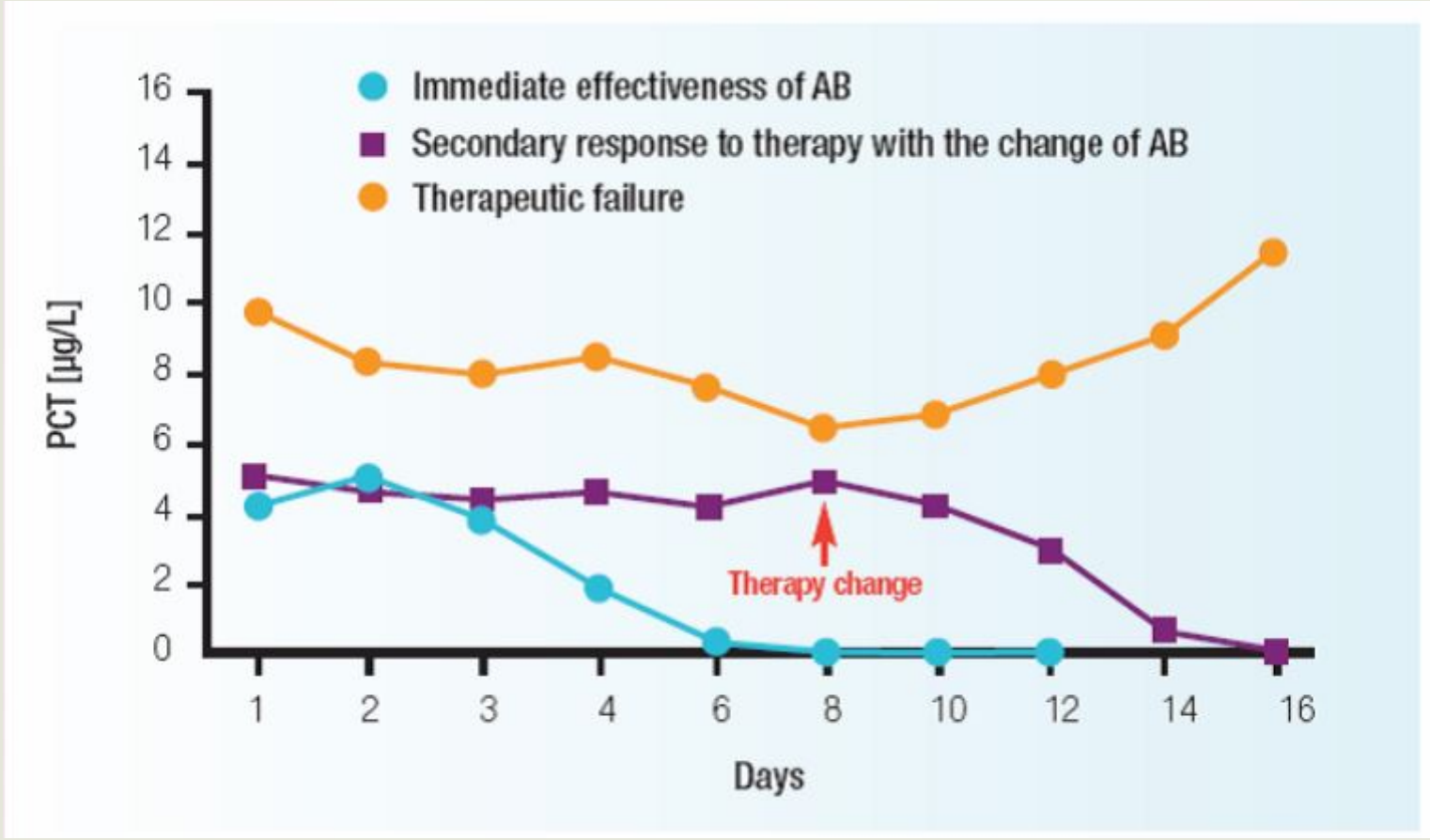
- A PCT concentration of >0.5ug/L should be considered a high risk for developing severe sepsis or septic shock



(Vijayan et al., 2017)

What is Procalcitonin?

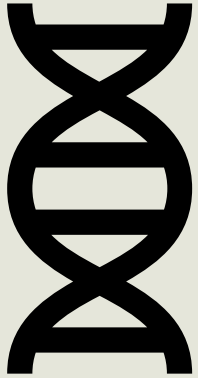
- Once the septic infection begins to clear, there is a subsequent decrease in circulating PCT
  - Half-life is 24 hours



(Pangalila, 2014)

What is Procalcitonin?

Procalcitonin differentiates between bacterial and viral/other causes of systemic infection – particularly respiratory infection



In viral infections, interferon gamma suppresses production of procalcitonin

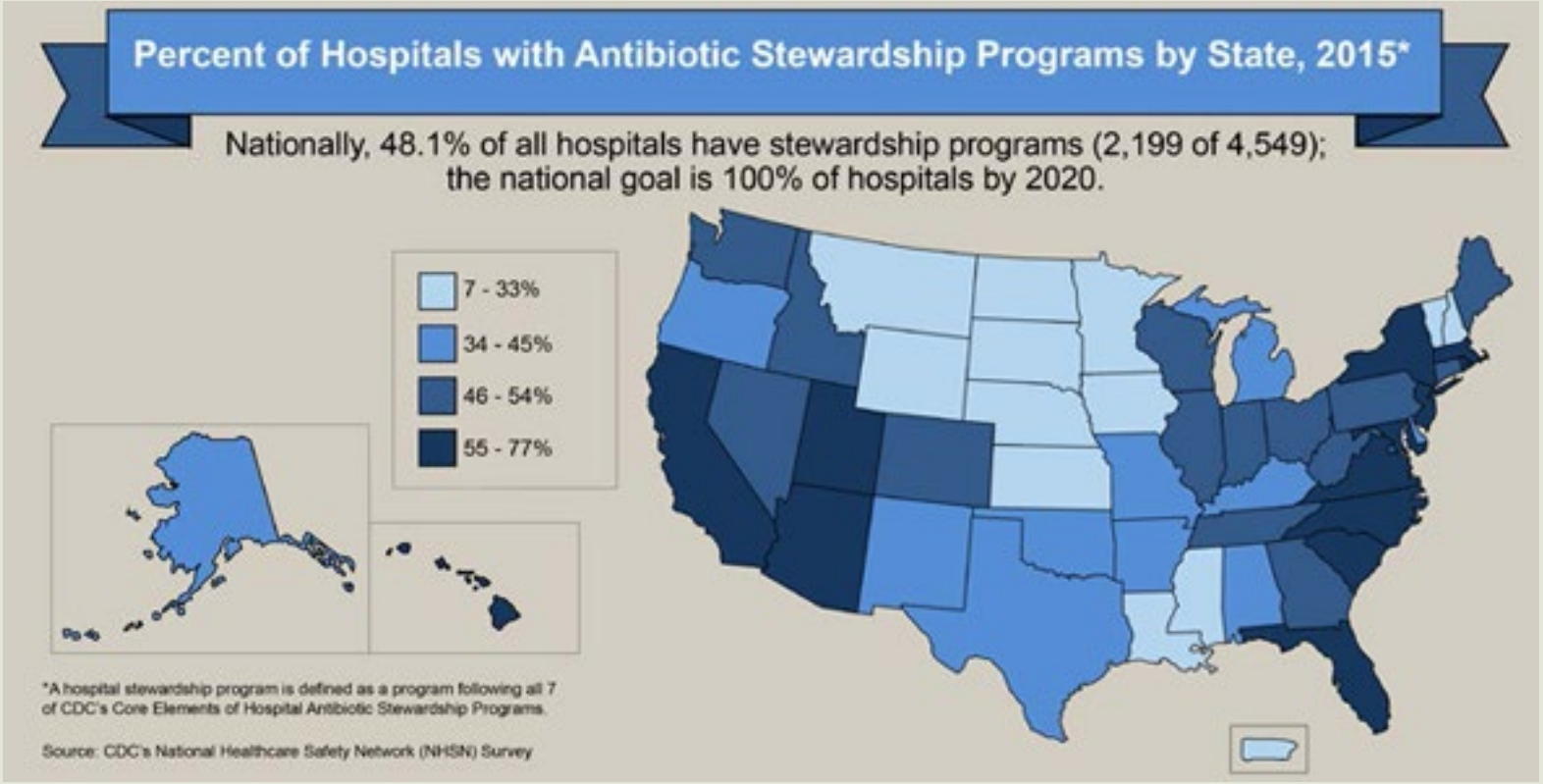
What is Procalcitonin?

- FDA Clearance
  - First cleared to help determine the risk of a seriously ill patient developing severe sepsis and septic shock
  - In 2016 the assay was cleared for use as a predictor of mortality due to severe sepsis
  - Finally in 2017 the FDA cleared the assay for use in antibiotic stewardship

(FDA, 2020)

What is Procalcitonin?

- Antibiotic Stewardship
  - Guided antibiotic therapy
  - Should an antibiotic be started?
  - Should it be discontinued?
  - Is the prescribed antibiotic working?



Diagnostic Utility

How do we use it?

Risk Assessment

Used to aid in the risk assessment of critically ill patients on their first day of ICU admission for progression to severe sepsis and septic shock

PCT >2.0ng/mL on the first day of ICU admission is associated with a high risk for progression to severe sepsis and/or septic shock

PCT <0.5ng/mL on the first day of ICU admission is associated with a low risk for progression to severe sepsis and/or septic shock

(Endo et al., 2008; *PCT - Clinical: Procalcitonin, Serum*, n.d.; *Sepsis Risk Assessment | Procalcitonin & Bacterial Infection*, n.d.; Rowland et al., 2015)

Risk Assessment

Important note: PCT levels below 0.5ng/mL do NOT exclude an infection – Localized infections may also be associated with low levels of PCT

Likewise, if PCT measurement is done very early after the systemic infection process has begun (usually <6 hours), these values may still be too low to trigger diagnostic thresholds

Various non-infectious conditions are known to induce changes in PCT levels

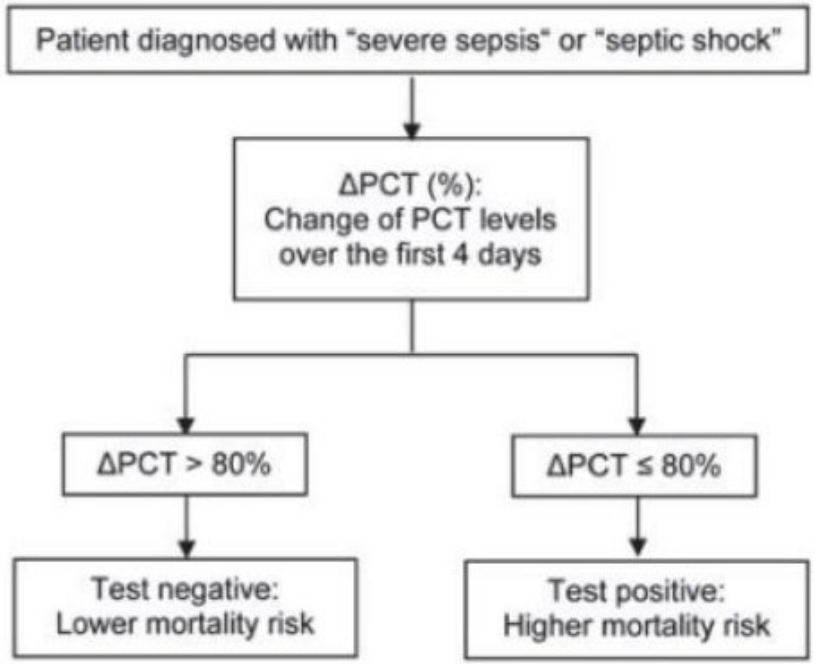
PCT levels between 0.5 ng/mL and 2.0 ng/mL should be interpreted in the context of specific clinical conditions – retest recommended within 6-24 hours

(*PCT - Clinical: Procalcitonin, Serum*, n.d.; *Sepsis Risk Assessment | Procalcitonin & Bacterial Infection*, n.d.)

Mortality

- Used as an aid in assessing the cumulative 28-day risk of all-cause mortality for patients diagnosed with severe sepsis or septic shock in the ICU or ED
- Change in PCT over time aids in the prediction of cumulative 28-day mortality
- PCT levels that decline ≤80% from the day that severe sepsis or septic shock is clinically diagnosed (Day 0) to four days after clinical diagnosis (Day 4) is associated with a higher cumulative 28-day risk of all-cause mortality than a decline of >80%

$$\Delta PCT = \frac{PCT_{\text{Day0 (or Day1)}} - PCT_{Day4}}{PCT_{Day0\ (or\ Day1)}} \times 100\%$$



(Gregoriano et al., 2020; *Sepsis Risk Assessment | Procalcitonin & Bacterial Infection*, n.d.)

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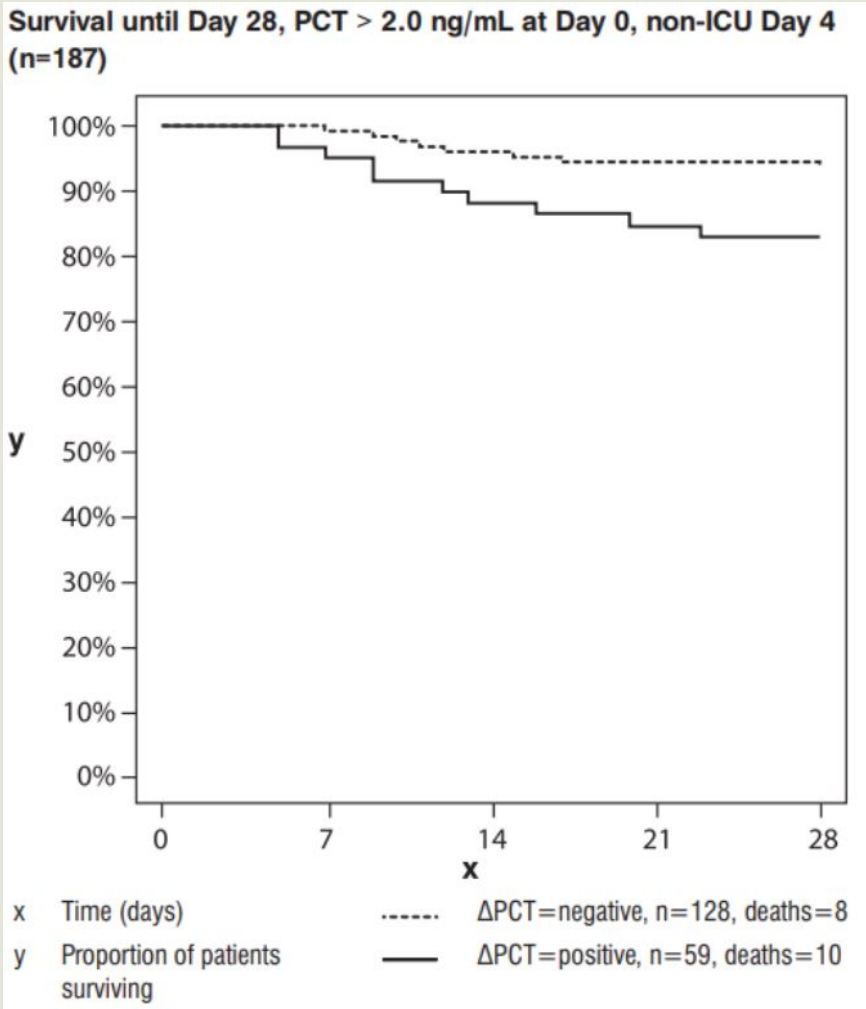

(Gregoriano et al., 2020)

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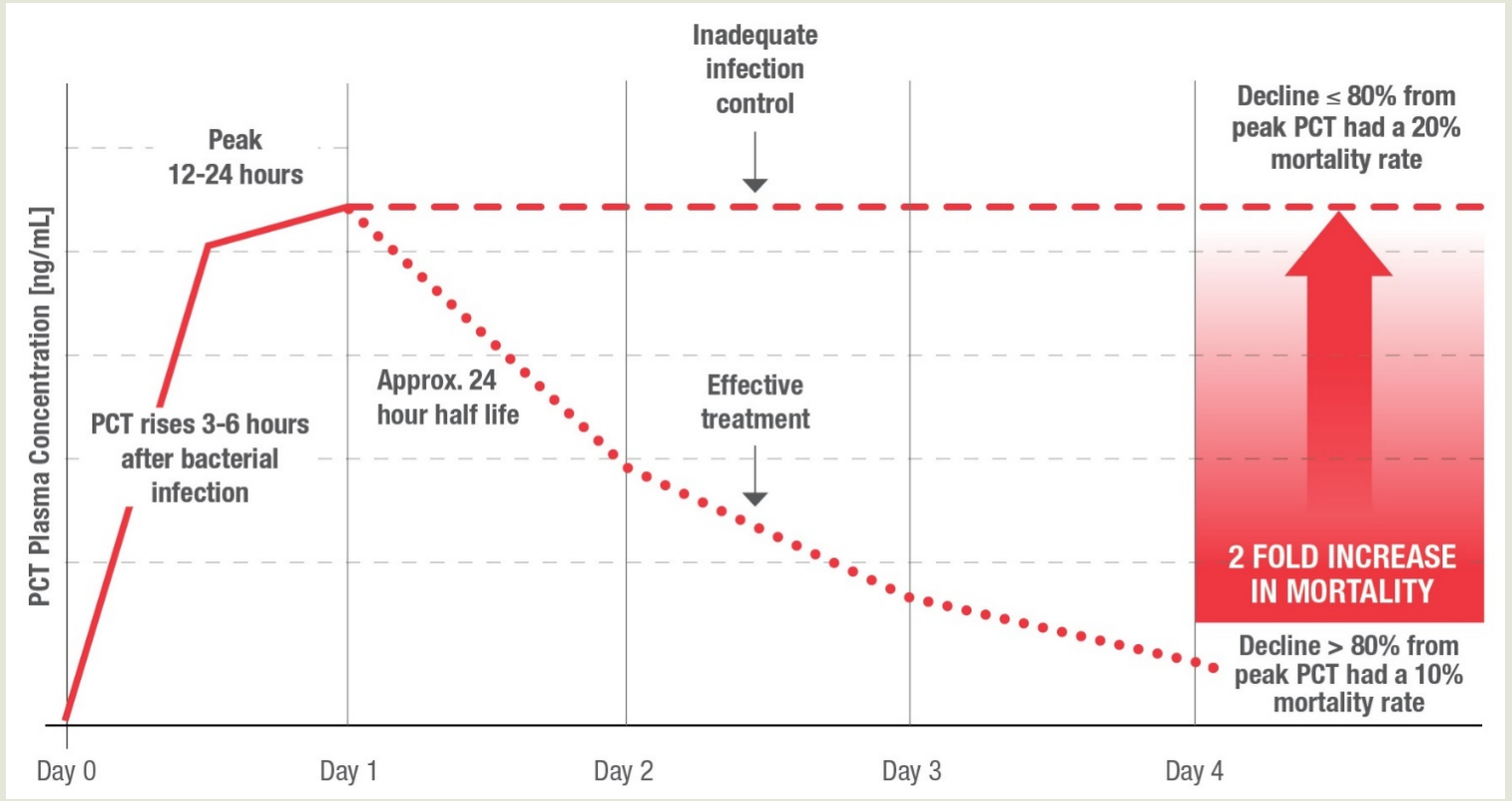
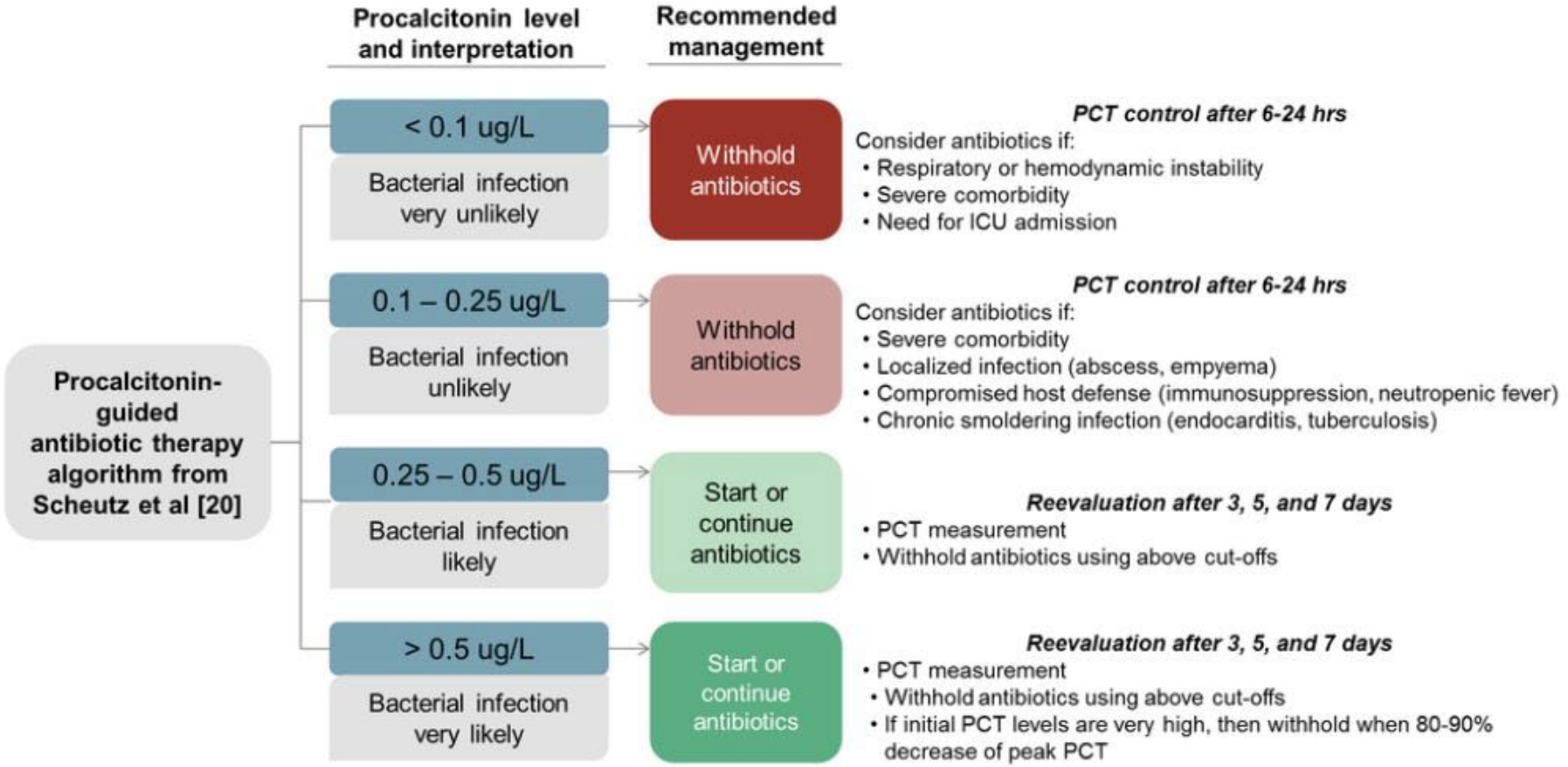


(*Sepsis Risk Assessment | Procalcitonin & Bacterial Infection*, n.d.)

Antibiotic Stewardship

- Used as an aid in decision making for antibiotic stewardship



(Gregoriano et al., 2020; Hill & M.Ed, n.d.; Vijayan et al., 2017)

Antibiotic Stewardship – Lower Respiratory Tract Infection

- To aid in decision making for antibiotic therapy for inpatients or outpatients, with suspected or confirmed lower respiratory tract infections, defined as community-acquired pneumonia, acute bronchitis, and acute exacerbation of Chronic Obstructive Pulmonary Disease

Antibiotic therapy may be discontinued if the $PCT_{Current}$ is ≤ 0.25 ng/mL or if the ΔPCT is > 80%.

- PCT_{Peak}: Highest observed PCT concentration
- $PCT_{Current}$: Most recent PCT concentration
- Calculate ΔPCT using the following equation:

$$\Delta PCT = \frac{PCT_{Peak} \square - PCT_{Current} \square}{PCT_{Peak} \square} \times 100\%$$

(*Lower Respiratory Tract Infection Risk Assessment | Procalcitonin & Bacterial Infection*, n.d.)

Antibiotic Stewardship - Sepsis

- To aid in decision making for antibiotic discontinuation for patients with suspected or confirmed sepsis

Antibiotic therapy may be discontinued if the $PCT_{Current}$ is ≤ 0.50 ng/mL or if the ΔPCT is > 80%.

- PCT_{Peak}: Highest observed PCT concentration
- $PCT_{Current}$: Most recent PCT concentration
- Calculate ΔPCT using the following equation:

$$\Delta PCT = \frac{PCT_{Peak} \square - PCT_{Current} \square}{PCT_{Peak} \square} \times 100\%$$

(Goldberg, 2016)

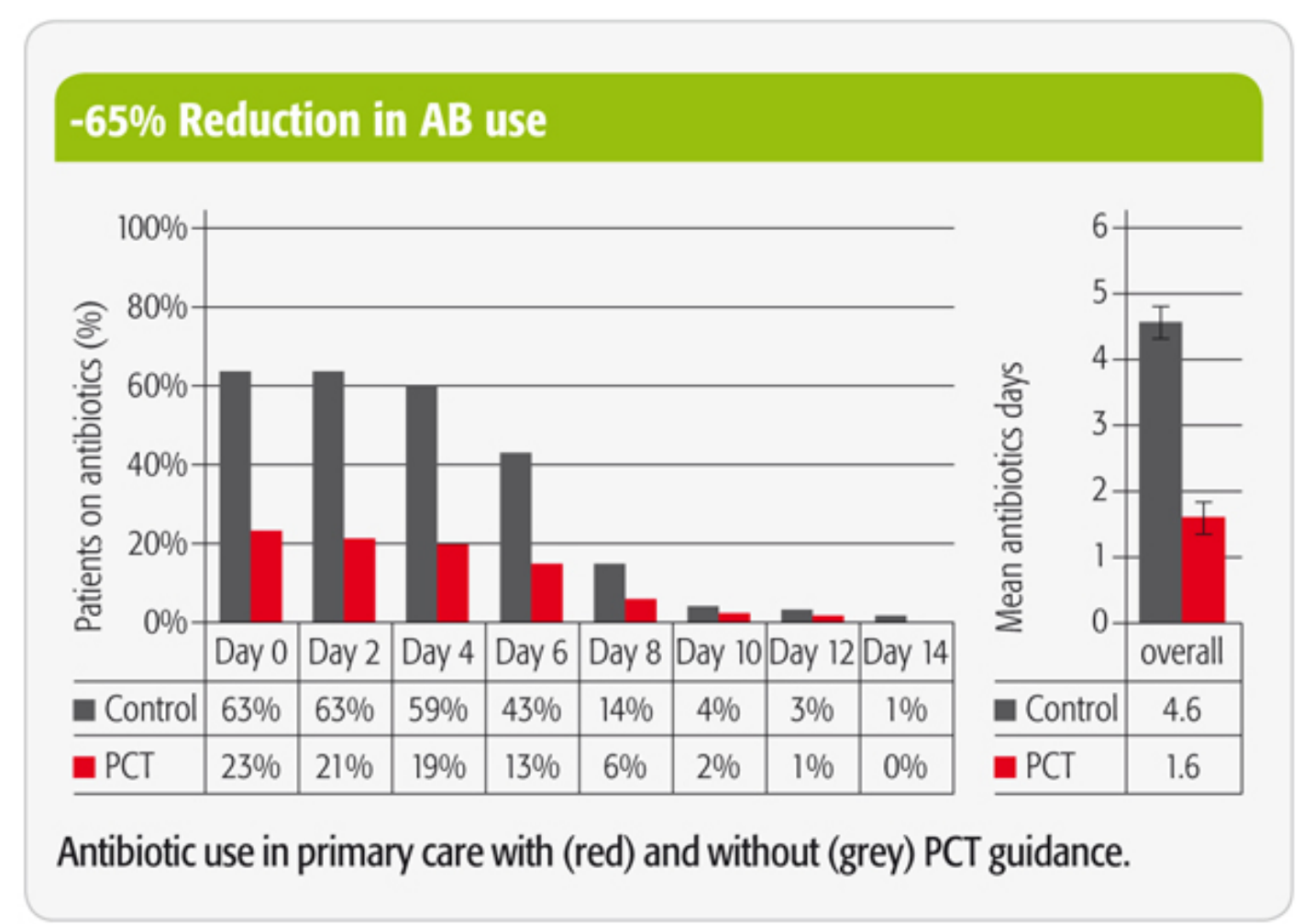
What are the benefits?

How does this aid in antibiotic stewardship?

Antibiotic Stewardship

What are the benefits?

- Decreased antibiotic duration
- Decreased antibiotic initiation
- Decreased antibiotic side effects
- Decreased antimicrobial resistance



	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.

(*Vidas-Brahms-Pct-Graph-Ab-Use.Jpg*, n.d.)

Benefits

ED physicians often prescribe broad-spectrum antibiotics early in the course of a suspected septic patient, before the source or illness severity if fully evaluated

Once patients move to the ICU or the floor, terminating antibiotics can be a challenging management decision

Benefits

For coagulase negative staph infections in pediatric patients, multiple blood cultures cause concern due to increased need for blood collections

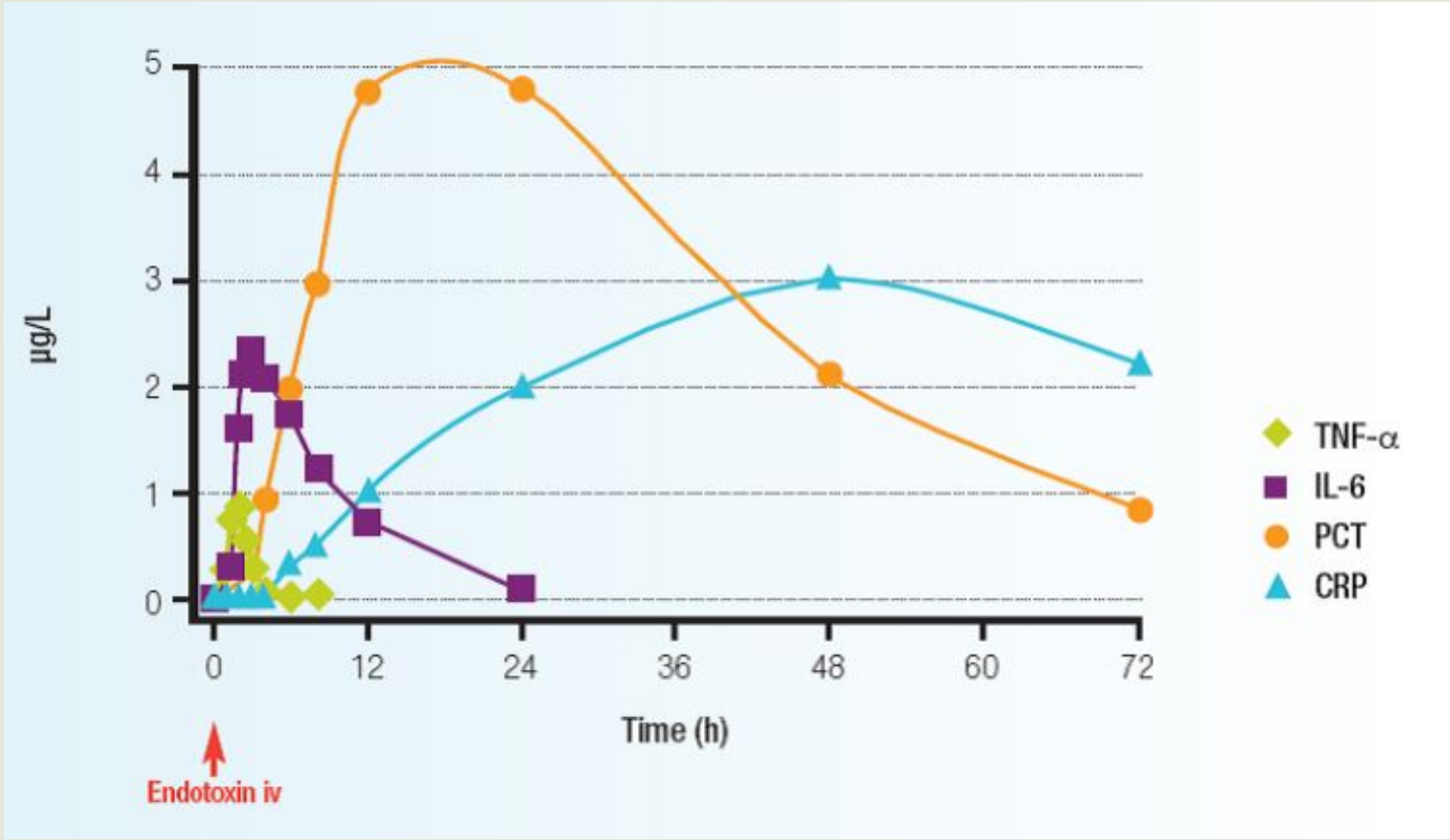
Utilizing PCT to confirm a positive culture, or event using prior to a blood culture to rule out sepsis and the need for additional collections may be of diagnostic utility

Benefits

Unlike CRP and IL-6, PCT is not influenced by corticosteroid treatment

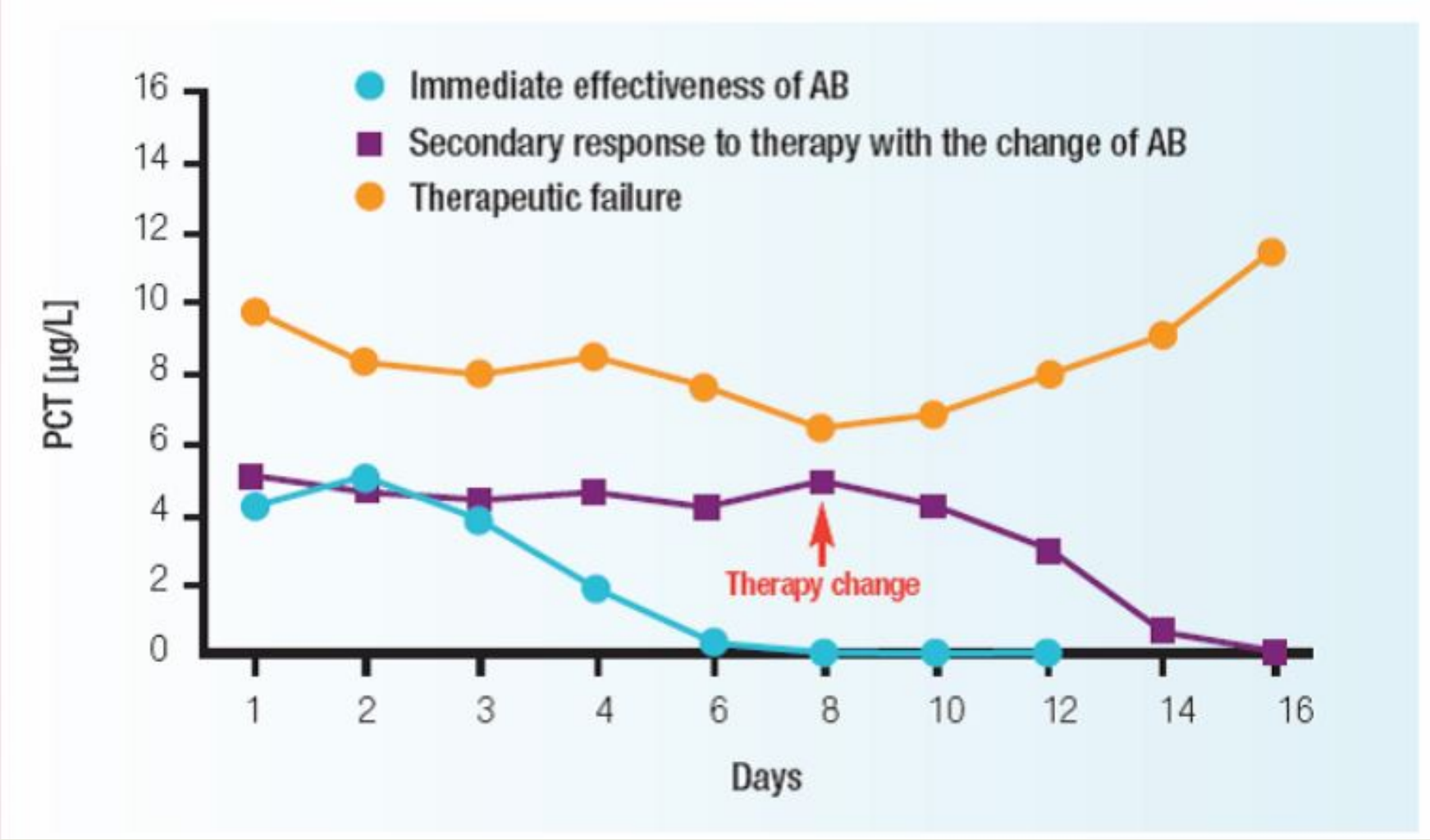
Early and high specific increase in PCT due to bacterial infection and sepsis

Other inflammatory markers, such as CRP and ESR, are non-specific



(Meisner, 2002)

Benefits



(Pangalila, 2014)

Challenges

What happens in the future?

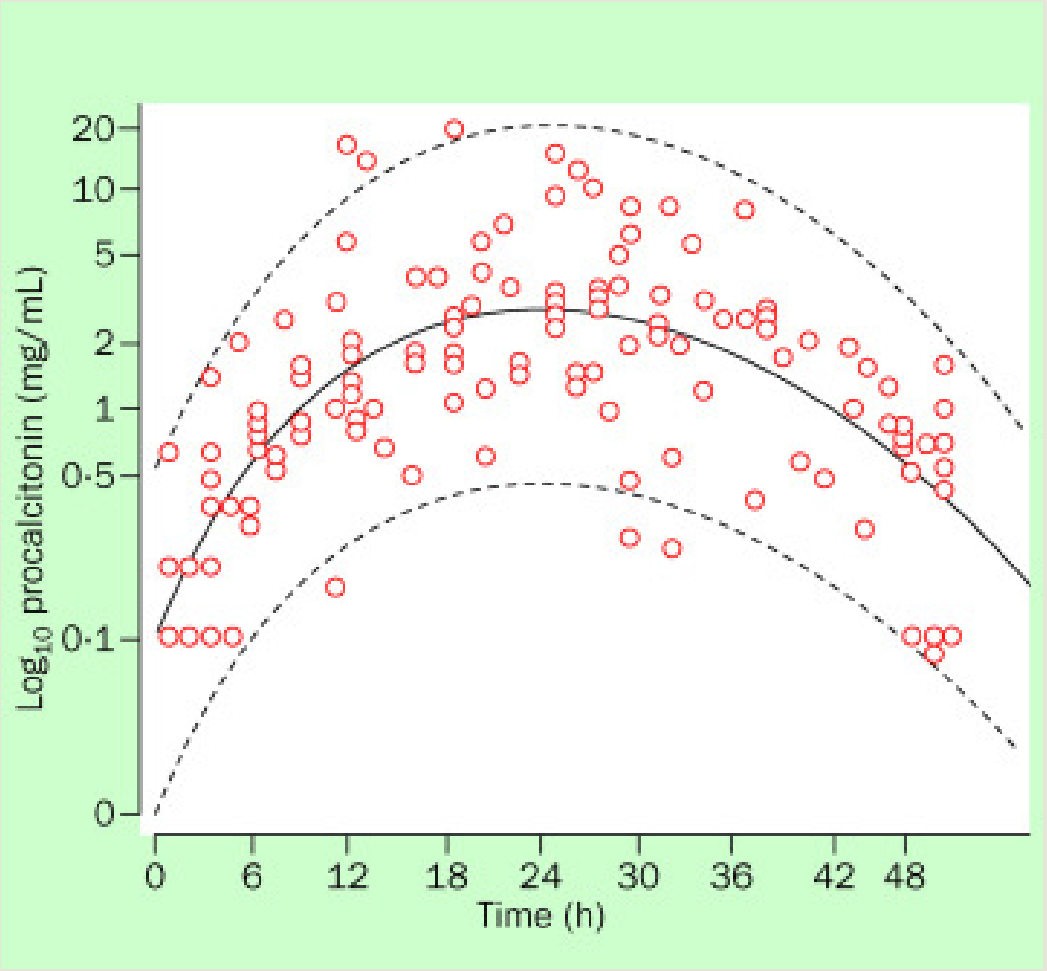
Other Causes of Increased PCT

- Neonates <48 hours of life
- Severe illness such as polytrauma, burns, major surgery, and prolonged or cardiogenic shock (PCT generally quickly returns to baseline, and a secondary increase in PCT can be viewed as an indication of sepsis development)
- treatment with OKT3 (murononab-CD3) antibodies and other drugs stimulating the release of pro-inflammatory cytokines
- Invasive fungal infections
- Acute attacks of Plasmodium falciparum malaria
- Patients receiving peritoneal dialysis or hemodialysis treatment
- Patients with biliary pancreatitis, chemical pneumonitis, or heat stroke
- Patients with small cell lung cancer, severe liver cirrhosis and acute or chronic viral hepatitis or medullary C-cell carcinoma of the thyroid

(Meisner, 2002)

Neonates

- Neonates <48hrs of life



(van Rossum et al., 2004)

Other Populations

Current guidelines establish adult cut-off values, and not enough information exists to identify efficacy in pediatric populations

What does this mean?

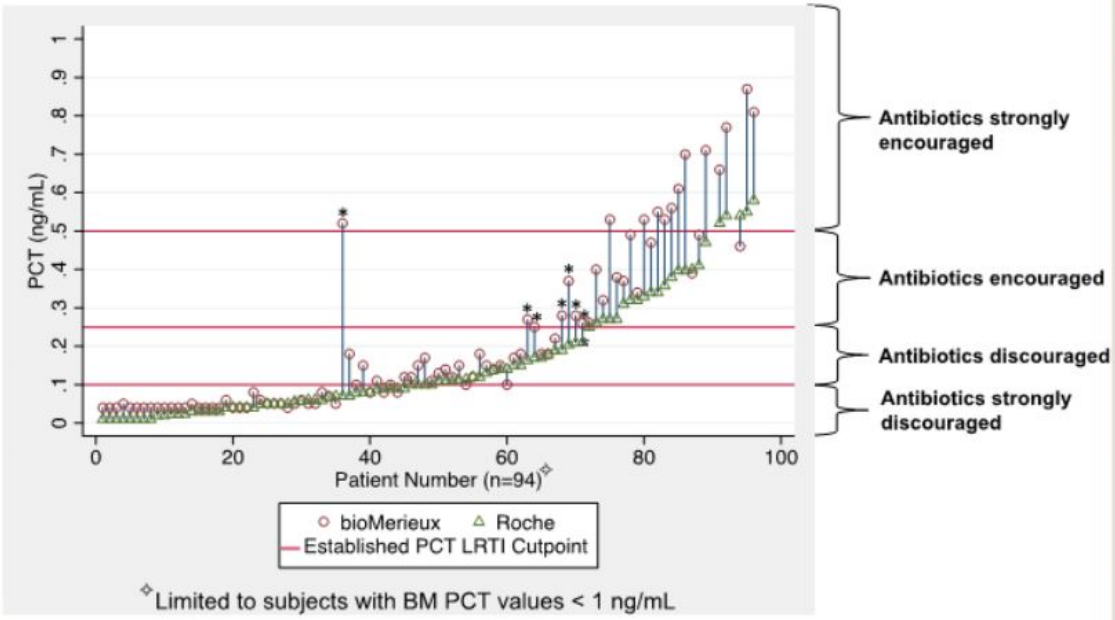
Do the same cut-points translate from adult to pediatric populations?

(Katz et al., 2021)

Platform Choice

- There are differences in values based upon the platform chosen in the laboratory
- NOTE: These are all run on the BRAHMS assay
- Serial patients should always be run on the same method for comparison

Figure 2. PAIRED PROCALCITONIN (PCT) TESTS USING BIOMÉRIEUX AND ROCHE PLATFORMS IN RELATION TO ESTABLISHED PCT CUT POINTS FOR LOWER RESPIRATORY TRACT INFECTION (LRTI)



PCT values were consistently lower using Roche than bioMérieux; mean difference of 0.15 ng/mL for PCT levels between clinically relevant range of 0 to 2.5 ng/mL (Bland-Altman r = 0.97, $p<0.001$).

*** 8/123 SUBJECTS (6.5%):**
Roche PCT, but not bioMérieux PCT value lower than the accepted cut point for LRTI of 0.25 ng/mL → potential to alter decision to start antibiotics.

(Katz et al., 2018)

Physician Education

As with any laboratory test, physician education is important on the use and limitations of the assay

Most often, laboratories have little control over how an assay is used once it is put into use

Are physicians ordering correctly?

In the appropriate situations?

Interpreting the results in the proper context?

Does the hospital have an effective Infectious Disease/Antibiotic Stewardship committee to aid in use?

What about new residents?

Future Use?

Researching the Changes of Serum Procalcitonin Levels in Ventilator-Associated Pneumonia Patients

goc Nguyen[2] and Quyet Do[3]
103, Hanoi, Vietnam

National Institute of Burns, Hanoi, Vietnam

versity, Hanoi, Vietnam

Dung Thai Pham
Intensive Care Unit, Hospital 103

, 2017; **Published Date:** July 24, 2017

Citation: Pham DT, Nguyen TN, Do Q (2017) Researching the Changes of Serum Procalcitonin Levels in Ventilator-Associated Pneumonia Patients. Mycobact Dis 7:246. doi:10.4172/2161-1068.1000246

Procalcitonin and Liver Disease: A Literature Review

Ruolin Dong [1], Bo Wan [2], Su Lin [2], Mingfang Wang [2], Jiaofeng Huang [2], Yinlian Wu [2], Yilong Wu [2], Nanwen Zhang [3] and Yueyong Zhu [*, 1]

Journal of Clinical and Translational Hepatology 2019;7(1):51-55 | **DOI:** 10.14218/JCTH.2018.00012

Received: February 20, 2018 | **Accepted:** October 23, 2018 | **Published online:** November 23, 2018

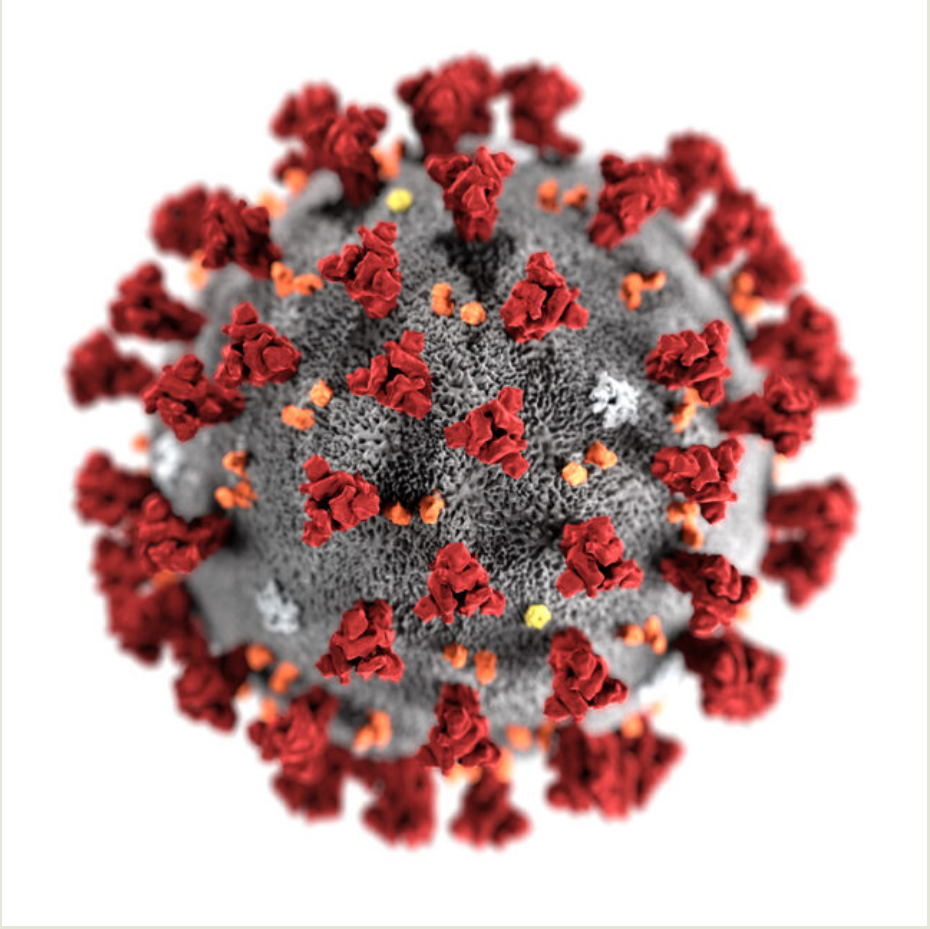
World J Gastroenterol. Dec 21, 2017; 23(47): 8283-8290
Published online Dec 21, 2017. doi: 10.3748/wjg.v23.i47.8283

Procalcitonin in inflammatory bowel disease: Drawbacks and opportunities

Giuseppe Lippi, Fabian Sanchis-Gomar

Future Use?

- The current SARS-COV-2 (“COVID-19”) has seen an increased interest in procalcitonin use as a marker for severe disease progression
- SARS is a viral pathogen, where PCT increases with bacterial infection and is inhibited by interferon gamma produced during a viral infection
- Increase in PCT due to COVID-19 would be indicative of bacterial co-infection and severe disease progression



(*COVID-19 Pneumonia | Procalcitonin & Bacterial Infection*, n.d.; Hu et al., 2020; Lippi & Plebani, 2020)

Resources

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Questions?

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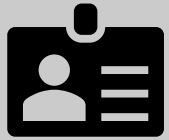

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