MMTN
MEDICAL MYCOLOGY TRAINING NETWORK

How do I interpret …
Procalcitonin in suspected fungal sepsis?

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ASIA FUNGAL WORKING GROUP
an ISHAM working group

Procalcitonin in Suspected Fungal Sepsis

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Sepsis Biomarkers

- **Acute phase proteins**
  - CRP
  - Procalcitonin (PCT)***
  - Pentraxin3 (PTX3)
  - Lipopolysaccharide binding protein (LBP)
- **Cytokines & chemokines**
  - IL-1RA, IL-1b, IL-2, IL-6, MCP-1
  - TNF-a, TNFR1/2
  - HMGBP1

Inflammation

- **Cell surface markers**
  - Soluble CD14 (Presepsin)
  - Neutrophil CD64 index (CD64in)
  - mHLA-DR (monocyte HLA-DR levels)
  - CD-163
- **Receptor markers**
  - VEGF
  - Soluble VEGF-receptor 1 (sFLT)
  - Soluble urokinaseplasminogen activator (suPAR)
  - sTREM-1
  - RAGE (soluble receptor for advanced glycationend products)
- **Coagulation**
  - Activated partial thromboplastintime (aPTT) waveform analysis
  - Protein C receptor
  - Thrombomodulin

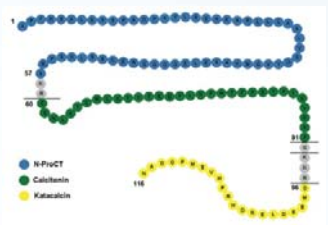
Coagulation

- **Endothelial damage**
  - Heparin binding protein
  - E-selectin
  - Neopterin
  - ICAM-1, VCAM-1
  - Angiopoietin-1 and -2
  - Syndecan-1 and -2
- **Vasodilation**
  - Copeptin (AVP precursor)
- **Cell damage**
  - MicroRNA
  - Microparticles
- **Cell repair**
  - Procollagen III amino propeptide

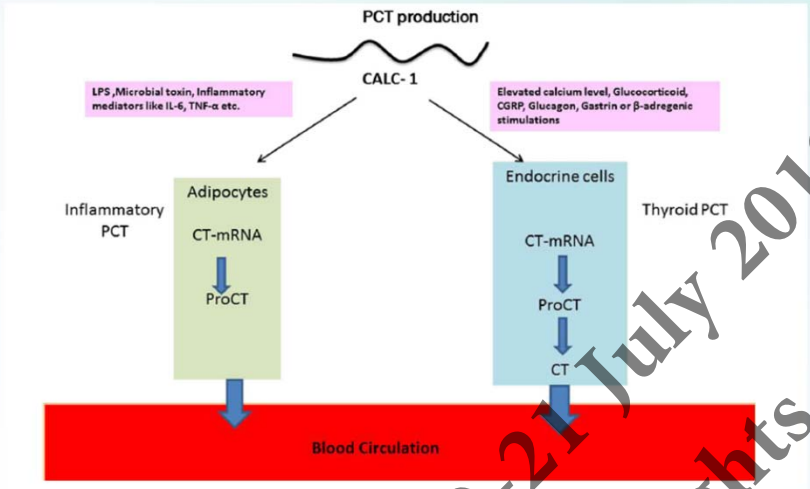
Tissue damage and repair

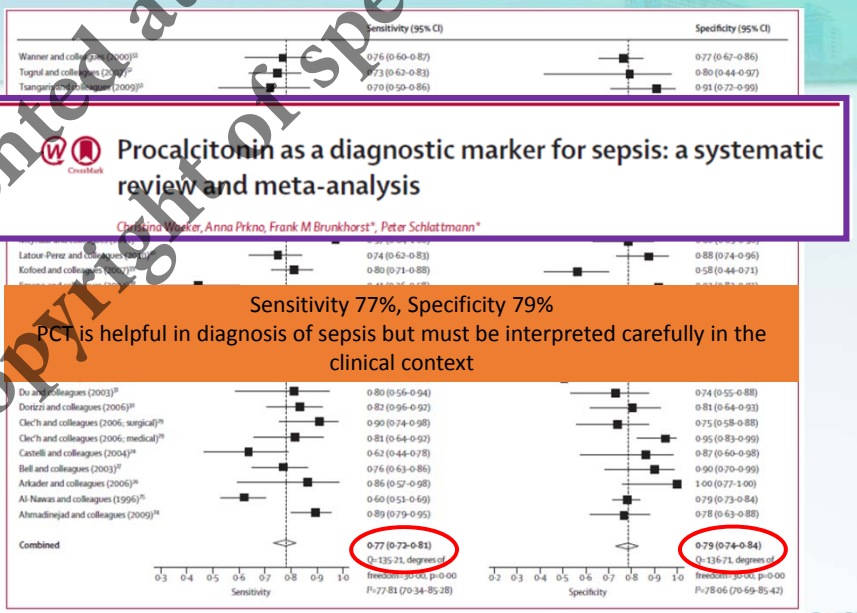
Procalcitonin (PCT)

- A peptide precursor of calcitonin
- 116 amino acids with a $T_{1/2}$ of 25 to 30 hours
- Produced by
  - Parafollicular cells (C cells) of thyroid
  - Neuroendocrine cells of lung and intestine
- Level in healthy individuals is below the limit of detection (10 pg/mL)
- Rises in a response to a pro-inflammatory stimulus, especially of bacterial origin.



Procalcitonin (PCT)

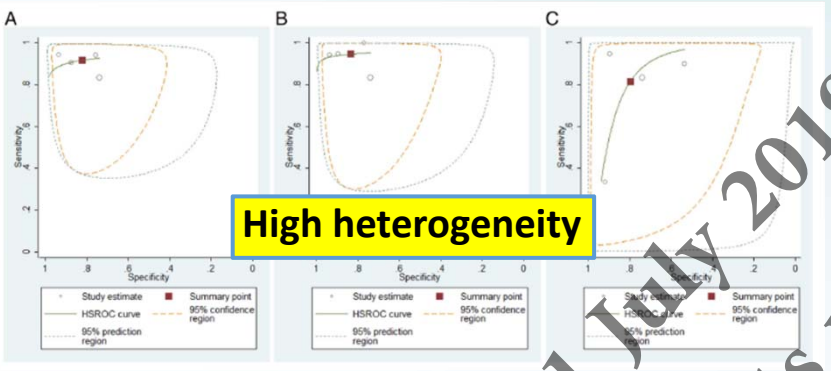




Wacker C., et al. Lancet Infect Dis 2013;13: 426–35

PCT and Fungal Infection: Systematic Review (8 studies before 2013)

PCT: Diagnosis of invasive candidiasis	PCT: Differentiate IFI vs. bacterial infection	PCT: Differentiate IFI vs. non-infection



High heterogeneity

Sensitivity 0.95	**Sensitivity 0.82**	**Sensitivity 0.88**
Specificity 0.83	**Specificity 0.80**	**Specificity 0.81**
LR+ 5.70	**LR+ 4.01**	**LR+ 4.65**
LR- 0.06	**LR- 0.23**	**LR- 0.15**

Dou TH, et al. Diagn Microbiol Infect Dis 2013;76:464-9

Procalcitonin in Invasive Fungal infections

- Observation in 20 patients

		BDG	GM	PCT (ng/mL)
8 hematologic malignancies	Aspergillosis = 5	+	+	< 0.5
	Candidemia = 3	+		< 0.5
6 Neonatal ICU	Candidemia = 6	+		4 children: 0.55-1.27 1 child: < 0.5 1 child: 17.1 (concomitant bacterial sepsis)
6 ICU	Aspergillosis = 1	+	+	1.91
	Candidemia = 5	+		0.05-0.33

Montagna MT, et al. prev med hyg 2011; 52: 38-39

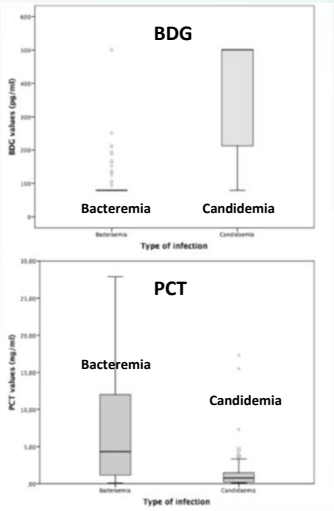
Studies of PCT in Fungal Infection

Year	Design	Patients	Population	Results	Comments
2006 (Charles et al.)	**Retrospective**	Bacteremia 35, Candidemia 15	Non-neutropenics	**For candidemia** PCT < 1: 9/15 PCT < 2: 12/15 PCT < 5.5: 15/15	**PCT > 5.5 ng/mL** 100% NPV for candidemia
2010 (Martini et al.)	**Prospective**	Bacteremia 16, Candidemia 17, Mixed 2	Surgical ICU with sepsis	**Candidemia:** PCT 0.71 (0.5-1.1) **Bacteremia:** PCT 12.9 (2.6-81.2)	**PCT < 2 ng/mL:** NPV = 94% for bacteremia **BUT** similar PPV for candidemia
2014 (Cortegiani et al.)	**Retrospective**	**N=260** Bacteremia=151 Candidemia=22 Mixed=31 Negative=56	Sepsis/ septic shock	**Candidemia:** PCT 0.99 (0.86-1.34) **Bacteremia:** PCT 16.7 (7.65-50.2) **Mixed:** 4.76 (2.98-6.08)	**Cut-off < 6.08 ng/mL** for Candidemia: Sensitivity 86.8% Specificity 87.4% PPV 63.9% NPV 96.3%

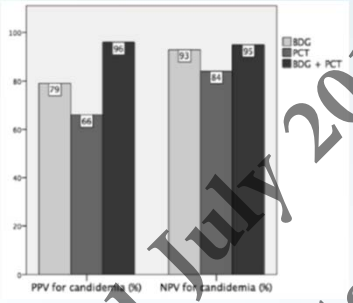
Studies of PCT in Fungal Infection

Year	Design	Patients	Population	Results	Comments
2015 (Leli C et al.)	**Prospective**	Gram-neg 345, Gram-pos 217 Candida 24	Blood stream infection	**Gram-negative:** PCT 13.8 (3.4-44.1) **Gram-positve:** PCT 2.1 (0.6-7.6) ***C. albicans*:** 0.5 (0.3-1.2)	Distinguish Gram-neg from Gram-pos and fungal infections
2017 (Pieralli et al.)	**Retrospective**	Bacteremia 128, Candidemia 64,	Septic patients with blood stream infection	**Candidemia:** PCT 0.73 (0.26-1.85) **Bacteremia:** PCT 4.48 (1.10-18.26)	**PCT > 2.5** NPV = 98.3% for candidemia **PCT < 2.5 OR 8.57** (3.09-3.70) for candidemia
2017 (Glacobbe et al.)	**Retrospective**	**N=166** Bacteremia=93 Candidemia=73	ICU patients with blood stream infection	BDG ≥ 80 and PCT < 2 **PPV 96% for Candidemia** BDG ≤ 80 and PCT ≥ 2 **NPV 95% for Candidemia**	PCT use in combination with BDG

BDG and PCT for Candidemia



Cut-off:
BDG 80 pg/mL
PCT 2 ng/mL



Giacobbe DR, et al. Crit Care 2017;21:176.

Summary

- Procalcitonin may be useful in diagnosis of candidemia and/or differentiate bacterial to fungal sepsis
- A low level of procalcitonin in septic non-neutropenic patients may be a clue for fungal etiology (especially when use in combination with BDG)
- Most of the studies were retrospective and performed in candidemia
- Large prospective study is needed before PCT can be recommended to use for diagnosis of fungal sepsis