



Procalcitonin in the
EMERGENCY DEPARTMENT

Early infection diagnosis

and risk assessment with Procalcitonin (PCT)

Early differential diagnosis and therapy decision in
the emergency department • Antibiotic stewardship
• Advanced risk stratification by MR-proADM

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Suspicion of infection?

Superior differentiation with PCT

Clinical symptoms of infection are frequently inconclusive

- Many emergency patients present with non-specific overlapping symptoms that may be caused by infection as well as other reasons: Fever, cough, chest pain, shortness of breath, vertigo/dizziness, skin rash, labored or difficult breathing, surgical and medical complications, abdominal pain, unspecific complaints.
- Up to 50% of bacteremic patients consulting in the emergency department are afebrile or have a normal white blood cell count.²⁰
- Nevertheless antibiotics are frequently prescribed – in the US up to 20% of patients discharged from the emergency department.⁸

PCT accelerates treatment decisions

Bacterial infections can neither be predicted nor ruled out by bedside-available clinical parameters. Nevertheless, PCT was a significantly better predictor for blood culture positivity than other clinical parameters (i.e. CRP): **A low PCT value ($\leq 0.25 \mu\text{g/L}$) sufficiently rules out bacteremia.**¹³

PCT measurement can confirm the initial suspicion of infection based on unspecific clinical symptoms and **reduce the total number of blood cultures or molecular tests** (Table 1). In case of disproval, refocusing on non-infectious diagnoses and more targeted allocation of limited health-care resources are possible.

	CAP blood culture		UTI blood culture		Febrile patients molecular testing	
PCT cut-off [$\mu\text{g/L}$]	>0.1	>0.25	>0.1	>0.25	>0.1	>0.25
Sensitivity	99	96	99	95	98	98
Specificity	13	40	24	50	36	51
Reduction in sample collection (%)	12.6	36.9	19	40	30.8	45.6
Missed pathogens	1.4	4.1	1	5	1.8	1.8
NPV (%)	98	97			99	99

Table 1 PCT for bacteremia prediction in CAP (n=925), UTI (n=581) and febrile patients (n=1009) ^{12,13,23}
NPV = negative predictive value

PCT – the best in early diagnosis of bacterial infection and sepsis

Procalcitonin (PCT) is a reliable blood parameter that supports earlier and better diagnosis and clinical decision-making for systemic bacterial infections⁷ and therapy control:

- **High sensitivity and specificity for bacterial infection** (Figure 1)
- **Fast increase after bacterial infection** within 3-6 hours (faster than CRP)
- **Available as point of care test (Thermo Scientific™ B-R-A-H-M-S PCT™ direct)** and on various lab-based platforms
- **Recommended for antibiotic stewardship by the Surviving Sepsis Guideline**⁴

PCT demonstrated superiority over routine parameters and novel biomarkers in the differentiation of bacterial from viral infections (Figure 2).²

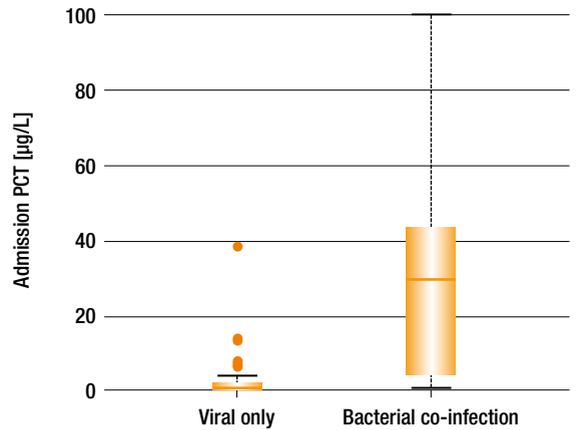


Figure 1 PCT levels discriminate between viral or mixed (bacterial and viral) pneumonia during a H1N1 influenza pandemic³

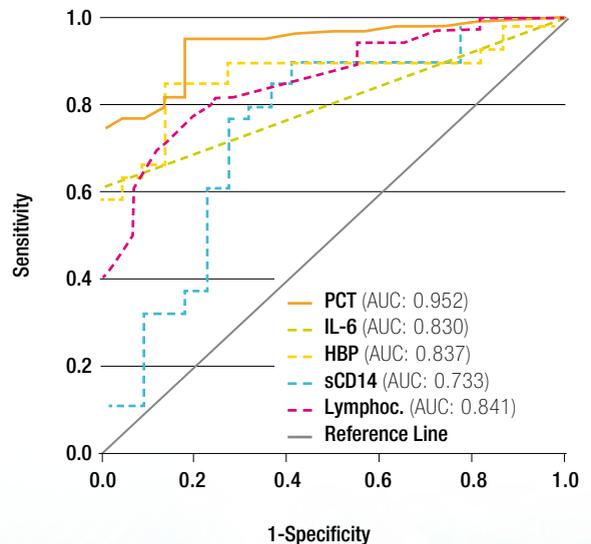


Figure 2 Receiver operating characteristic (ROC) curves for discrimination between bacterial and viral infection²

Early infection diagnosis in the emergency department

Sepsis diagnosis

PCT is a helpful biomarker for early diagnosis of sepsis and is useful in the emergency department for patients with suspected sepsis and/or patients with fever.

Metaanalysis of 30 studies including 3244 patients revealed a mean sensitivity of 0.77 and specificity of 0.79 for identification of bacterial infections (Figure 3).²⁵

Fever without source

Metaanalysis of 8 studies (n=1883) demonstrates the superior discriminative capability of PCT over conventional laboratory markers (i.e. CRP and leukocyte count) for detecting serious bacterial infection among children with fever without source.²⁶

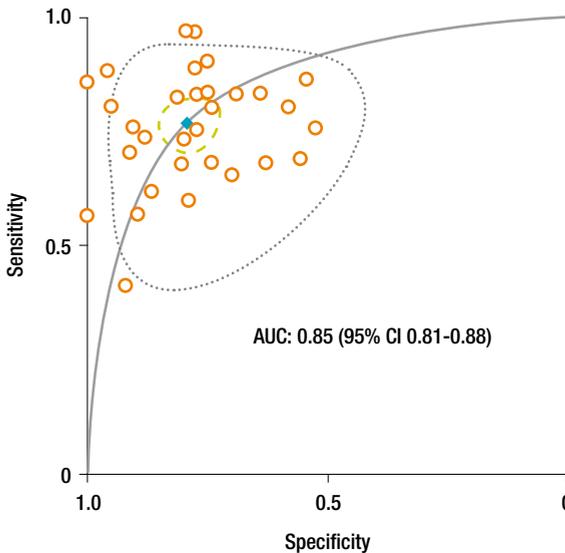


Figure 3 Summary receiver operating characteristic (ROC) curve for the diagnosis of sepsis in ICU and emergency department patients in 30 individual studies²⁵

- Individual studies
- ◆ Summary operating point
- Summary receiver operating characteristic (ROC) curve
- - 95% confidence contour
- 95% prediction contour

Urinary tract infection (UTI)

PCT appears to be the most useful marker in **differentiating lower urinary tract infection (cystitis) from upper tract infection (pyelonephritis).**⁹

Elevated PCT levels may also **predict subsequent vesicoureteral reflux and renal scarring** as well as avoiding unnecessary cystourethrographies in children.¹⁰

PCT accurately **predicts the presence of bacteremia and bacterial load** in adult patients with febrile UTI.²³

Meningitis

Acute bacterial meningitis is a rare but life-threatening infection requiring immediate antibiotic treatment.

Need for differential diagnosis!

- To avoid overuse of antibiotics and unnecessary hospitalization, decision rules have been proposed. The Meningitest includes PCT as the best biological marker to **distinguish between bacterial and aseptic meningitis in children.**⁵
- In adult patients (n=254) with meningitis with a negative direct cerebrospinal fluid (CSF) examination of serum PCT proved to be a highly discriminative parameter for the **differential diagnosis of bacterial versus viral meningitis** (Table 2).²⁴ According to the recommendation of the French Society of Infectiology **a concentration <0.5 µg/L is quite rarely associated with bacterial meningitis.**²¹

	Meningitis Children ⁵	Meningitis Adults ²⁴	FWS Children ²⁶	UTI Adults ²³
PCT cut-off	0.5 µg/L	0.28 µg/L	0.5 µg/L	0.25 µg/L
Sensitivity	0.99	0.95	0.78	0.95
Specificity	0.83	1.00	0.72	0.50
PPV (rule-in)	83%	97%	40%	36%
NPV (rule-out)	99%	100%	94%	97%

Table 2 Diagnostic value of PCT in children and adults with meningitis^{5,24}, children with fever without source (FWS)²⁶, and adults with urinary tract infection (UTI)²³

PPV = positive predictive value

NPV = negative predictive value

Lower respiratory tract infections (LRTI)

Reduction of antibiotics using PCT

Patients with lower respiratory tract infections represent a significant part of the emergency department patients. Despite the predominantly viral origin of their infection, as many as 75% of patients with LRTI are treated with antibiotics.¹⁶

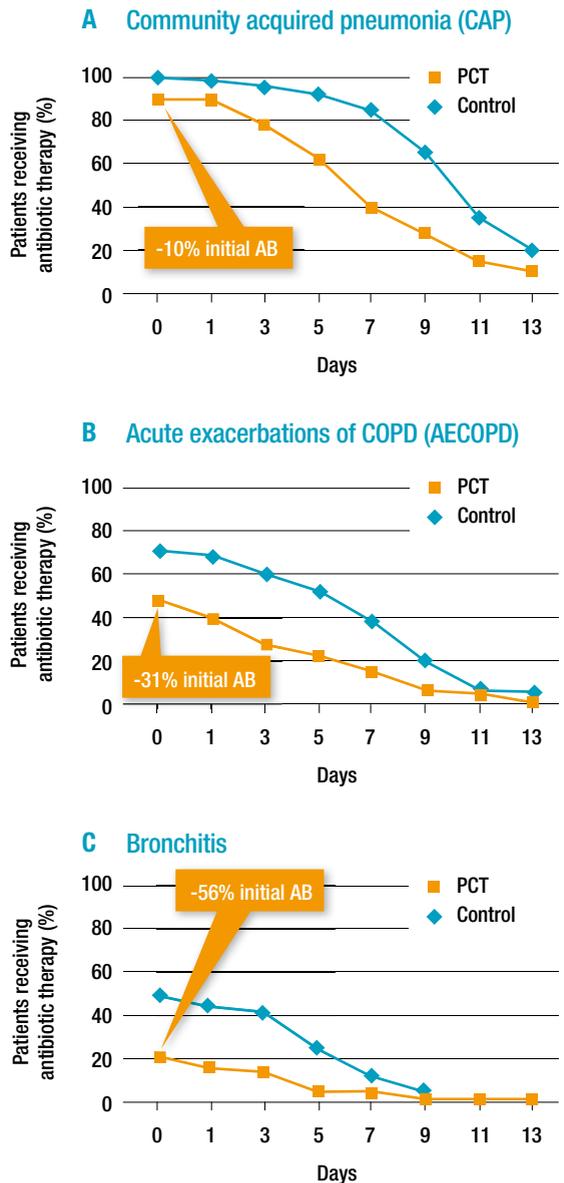
Antibiotic overuse contributes to

- increasing bacterial resistance
- rising medical costs
- raised risks of drug-related adverse events

PCT-guidance (Figure 4) in patients with respiratory tract infections of varying severity leads to a

- significant reduction of antibiotic prescription rate (COPD, bronchitis)
- strong reduction of duration of antibiotic exposure (CAP, COPD, bronchitis)

Figure 4 A-C Duration of antibiotic exposure and relative reduction of antibiotic prescription rates after diagnosis in the PCT group in comparison to the standard of care group for community acquired pneumonia (CAP) (n=925), acute exacerbations of COPD (n=228) and bronchitis (n=151) in the ProHosp trial¹⁶



Safe antibiotic guidance by PCT-based algorithm

A Cochrane review on randomized-controlled studies (14 studies with n=4221 hereof 7 studies with n=2605 coming from the emergency department) has proven the **safe use of PCT to assist in decisions about initiation and/or duration of antibiotic therapy** (Figure 5).¹⁸ Using a PCT-based algorithm has no influence on mortality or treatment failure.

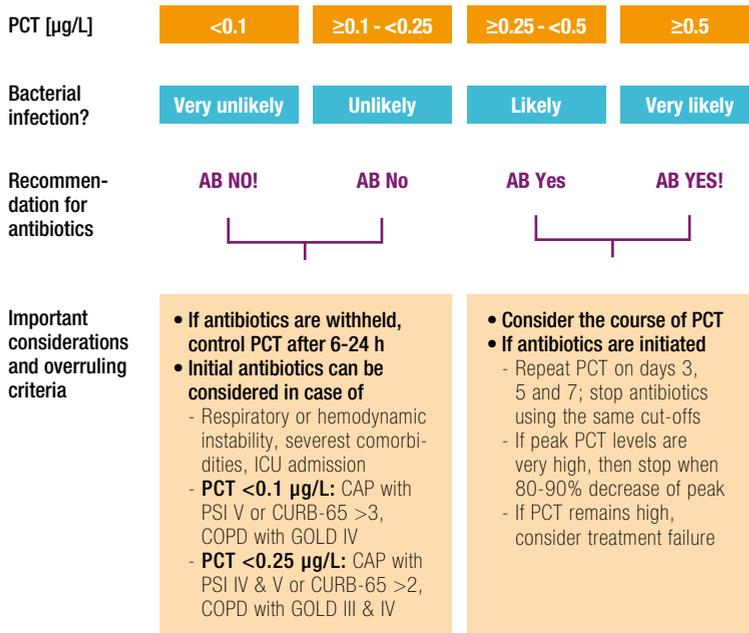


Figure 5 PCT algorithm for guidance of initiation and stopping of antibiotic (AB) treatment for patients with lower respiratory tract infections in the emergency department ¹⁷

PCT testing at time of admission to emergency department identifies patients that benefit from antibiotic therapy, enabling targeted use of antibiotic therapy and minimizing risk of resistance development.

Acute heart failure (AHF)

Superior infection management with PCT

Differentiating acute heart failure (AHF) from lower respiratory tract infection (LRTI) is challenging, due to the overlapping clinical picture and radiological findings.¹¹

- Infections cause 18% of hospitalizations for acute heart failure¹⁵
- Pneumonia independently associated with higher in-hospital mortality for hospitalized heart failure patients (Odds Ratio 1.60)⁶
- Pre-existing heart failure worsens pneumonia prognosis (14% vs. 24% mortality)²²

Including PCT in clinical diagnosis increases diagnostic certainty of pneumonia

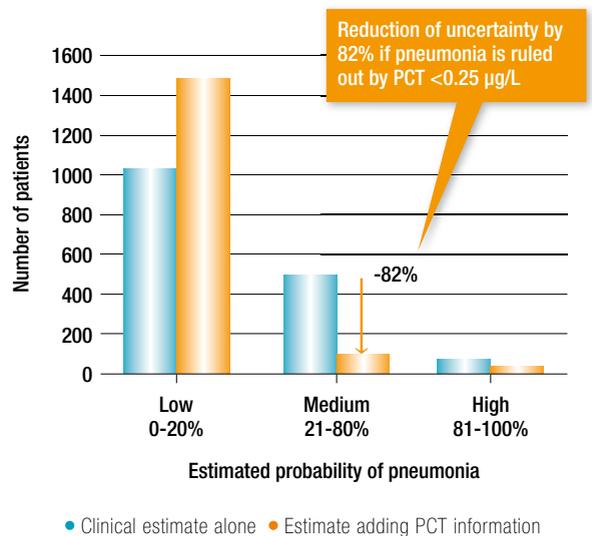


Figure 6 Estimated probability of pneumonia in patients (n=1641) in the emergency department presenting with shortness of breath¹¹

PCT supports diagnosis of concomitant pneumonia in patients with acute heart failure.

PCT-guided antibiotic therapy reduces unnecessary antibiotics...

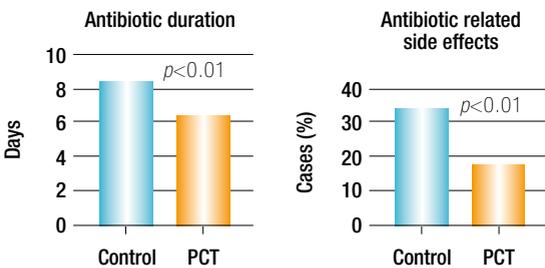


Figure 7 Antibiotic duration and side effects in the PCT and control groups of CHF patients presenting to the emergency department with respiratory symptoms and suspicion of respiratory infection (n=233) ¹⁹

...and may increase survival probability of heart failure patients

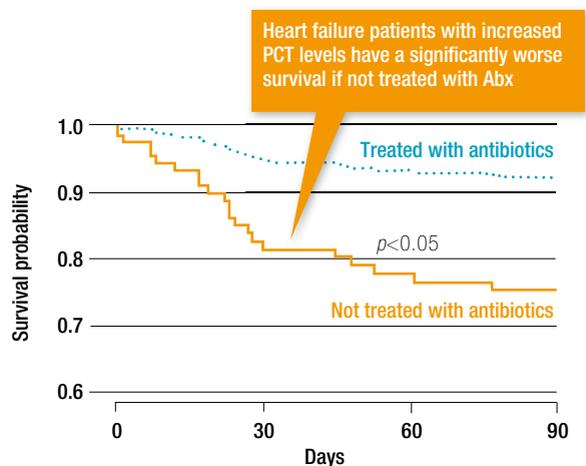


Figure 8 Survival and antibiotic treatment of heart failure patients with PCT > 0.21 µg/L (n=113) ¹¹

PCT-guided antibiotic therapy of AHF patients

Avoid unnecessary antibiotic therapy ^{11,19}

- Refocus on causal disease
- Reduce antibiotic associated side effects
- Prevent antibiotic resistance formation

Identify bacterial infected patients needing antibiotics ¹¹

- Patients are at increased mortality risk
- Missing treatment is associated with worse outcome
- Prolonged hospitalization

MR-proADM – a novel biomarker for advanced risk stratification

MR-proADM (ProAdrenomedullin)...

- ... adds an overall patient prognosis – on top of PCT and independent from infections
- ... secretion is upregulated by various forms of physiological stress and severe disease
- ... mean values are depending on individual disease conditions
- ... combined with the first clinical assessment of emergency department patients, offers advanced risk assessment and greater confidence in treatment site assignment

The use of specific MR-proADM cut-offs, in patients presenting to the ED with non-specific complaints (Figure 9) ¹⁴ or lower respiratory tract infections ¹, groups patients according to their prognosis.

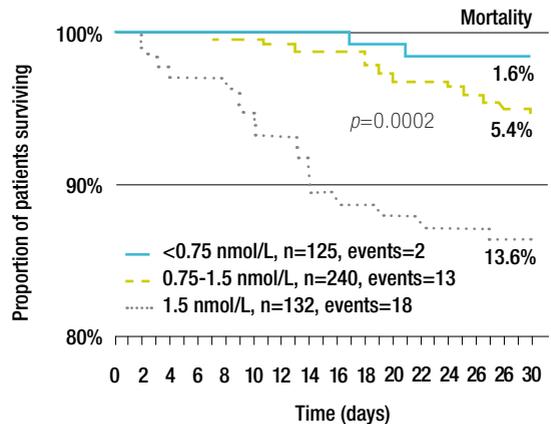


Figure 9 Kaplan-Meier survival curve for 30-day survival in patients presenting to the emergency department with non-specific complaints ¹⁴

MR-proADM enables emergency department physicians to improve the initial risk assessment for a more efficient patient flow, by:

- Identifying patients at risk requiring hospitalisation ("red flag")
- Increasing the number of safely discharged patients
- Allocation of limited resources to patients at risk

Combined risk assessment with MR-proADM

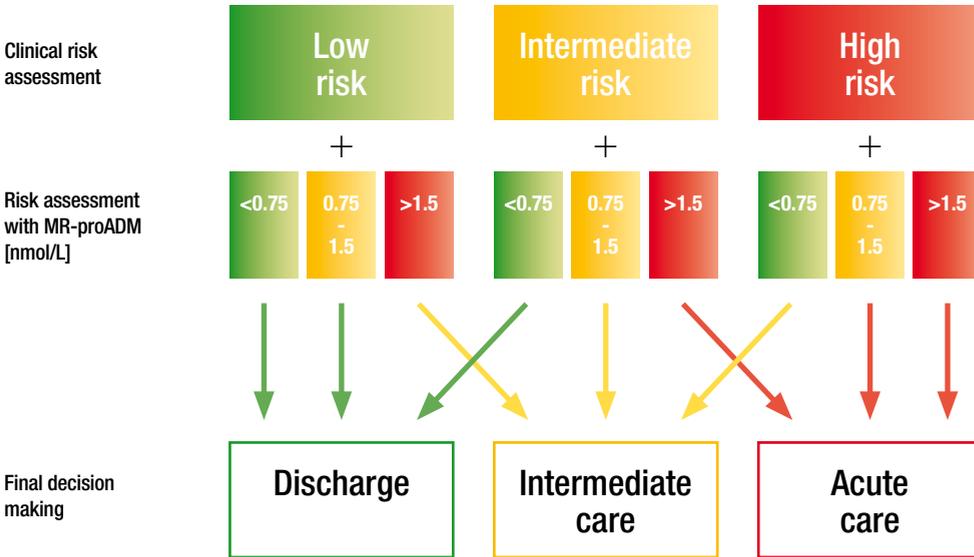


Figure 10 Combining clinical risk assessment with levels of MR-proADM for an advanced risk stratification and treatment assignment of patients with unspecific complaints: Based on the combined risk class, each patient is assigned an expected mortality risk and a recommendation for site-of-care decision (outpatient vs. intermediate care vs. acute care)¹⁴

Impact of MR-proADM

In one-fifth of patients with non-specific complaints the decision on level of care was modified based on additional impact of MR-proADM information. This was mainly a change to lower risk categories which allowed to treat more patients in intermediate care instead of ICU, or even at home (Figure 11).¹⁴

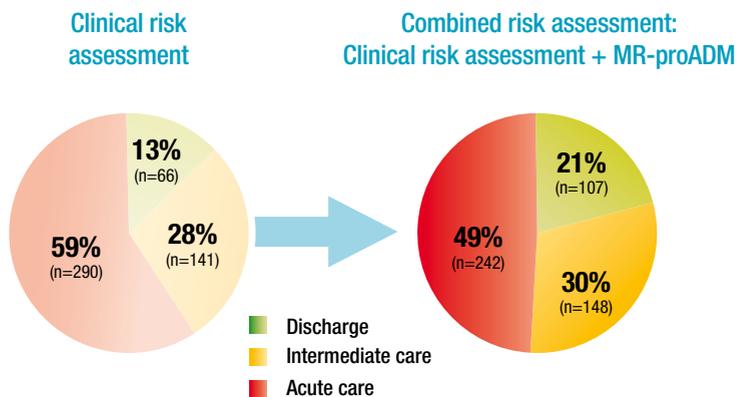


Figure 11 Treatment assignment based on clinical assessment alone or a clinical assessment combined with MR-proADM in patients with non-specific complaints¹⁴

Thermo Scientific

B·R·A·H·M·S PCT direct

Point of care testing

**Immediate and reliable decision-making:
Tailored for emergency use**

- Small sample volume (20 µL)
- Whole blood (capillary or venous EDTA)
- Time to result: 20 min



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