Safely reduce antibiotic exposure

B·R·A·H·M·S Procalcitonin (PCT):
An effective tool for antibiotic stewardship
Antibiotics (ABx) are a limited resource. At the current pace of injudicious use, all antibiotics will soon become ineffective. The WHO Global Action Plan on antimicrobial resistance, 2015, emphasizes that antimicrobial resistance is a crisis that must be managed with the utmost urgency.

The emergence and spread of antibiotic-resistant bacteria harm individuals and societies worldwide by causing:

- Prolonged illnesses
- Higher health care expenditures
- Greater risk of death

How does resistance to antibiotics develop?

1. Antibiotics
2. Large population of bacteria, only a few are drug-resistant
3. Susceptible bacteria are killed while the resistant bacteria survive
4. Only the drug-resistant bacteria continue to proliferate in the presence of the antibiotic and take over
5. Some bacteria give their drug-resistance to other bacteria, causing further increase in drug-resistance in the society

1/3 antibiotic prescriptions are unnecessary. 

2
A potential for change

B·R·A·H·M·S Procalcitonin (PCT) supports responsible use of antibiotics to prolong their effectiveness

We suggest the use of low procalcitonin levels … to assist the clinician in the discontinuation of empiric antibiotics in patients who appeared septic, but have no subsequent evidence of infection.³

Surviving Sepsis Campaign
International Guidelines for Management of Severe Sepsis and Septic Shock, 2012³

PCT-guidance of AB therapy has the potential to

- Reduce initial prescription rates
- Shorten treatment durations
- Save overall treatment costs
Use of B·R·A·H·M·S PCT reduces antibiotic exposure

Strong evidence supports safe reduction of antibiotics using PCT-guided antibiotic stewardship protocols

- Reproducible, randomized clinical trials with more than 10,000 patients included
- Proven utility across diverse clinical settings: ICU, ED, Pediatrics, Neonatology, Surgery

Proven efficacy: -16% to -74% antibiotic exposure
No adverse impact on outcome

Figure 1 Relative reduction in AB exposure with PCT-guidance
Benefits of reduced AB exposure achieved by PCT-guided antibiotic therapy

-85% AB related adverse effects
-72% initiation of ABx in primary care
-42% length of stay in ICU
-28% length of stay in hospital
-6% mortality at 1 year
-9% overall treatment costs
-85% initiation of ABx in primary care

Preserve the Power of ABx
When to start antibiotics?

B·R·A·H·M·S PCT enables rapid and reliable diagnosis of systemic bacterial infections

PCT levels increase 2-3 hours after bacterial challenge and return to normal as the infection is resolved (Figure 2) [19,20,21]

- High specificity and sensitivity for bacterial infection
- Indicator for disease severity and treatment response

Patients with LRTI symptoms in ED

- Bacterial infection likely
  - ABx recommended

- Bacterial infection unlikely
  - ABx NOT recommended**

PCT cut-off*

- 0.25μg/L

- 0.5μg/L

** PCT values should always be interpreted in context of the patient’s clinical condition.

* In high risk patients start empirical antibiotic therapy immediately.

Figure 2

Kinetics of PCT

Developing bacterial infection

Infection under control

Assess likelihood of infection and severity

Assess response to therapy, prognosis by declining PCT (ΔPCT)

Onset of infection

Time (h)

PCT [µg/L]
How long to give antibiotics?

B·R·A·H·M·S PCT algorithms help tailor therapy to individual patient needs

Daily monitoring of PCT course allows for customized ABx treatment duration, hence reduced ABx exposure

Ensure using the quality assay for SAFE clinical decision making

PCT cut-offs and clinical algorithms were established by use of the global reference standard Thermo Scientific™ B·R·A·H·M·S PCT™ sensitive KRYPTOR™ assay and are valid solely for all B·R·A·H·M·S PCT assays.
PCT-guidance for antibiotic therapy is a safe strategy

B·R·A·H·M·S PCT-guided reduction in antibiotic exposure could also reduce mortality rates

<table>
<thead>
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<th>PCT-guided group</th>
<th>OR (fixed) 95% CI</th>
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<td>Pooled Odds Ratio</td>
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<td>279</td>
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Odds Ratio

OR <1: lower risk in PCT-guided group
OR >1: higher risk in PCT-guided group

Figure 3 28-day mortality in PCT-guided group as compared to routine practice
Forest plot showing the comparison of PCT-guided algorithms vs. routine practice. The size of each square represents the proportion of information provided by each study. The vertical line depicts the point of “no difference” between the two groups, and the horizontal lines correspond to the 95% confidence intervals (CIs). Diamond represents the pooled odds ratio (OR) for all studies.
* 6-week follow-up
** 30-day follow-up

B·R·A·H·M·S PCT-guided antibiotic discontinuation
Higher probability of survival

The lower mortality in PCT-guided patients may be attributed to
- Adequacy of antibiotics
- More timely recognition of alternative diagnoses
- Lower toxicity of antibiotics

8
Antibiotics are a double-edged sword. Adequate dose helps, excess harms.

-5.4% 28-day mortality
-6.1% 1-year mortality

Figure 4 Probability of survival to day 365 in the PCT-guided group vs standard of care group

• Randomized controlled interventional trial
• 1575 critically ill patients
• 15 centers
Adults with LRTI symptoms

Patients in the ED
Is it bacterial infection?

As much as 75% of all antibiotic doses are prescribed for acute respiratory-tract infections, despite their mainly viral cause. PCT-guidance in such patients allows reduction in AB exposure without any adverse impact on outcome.

Data from: Effect of Procalcitonin-Based Guidelines vs Standard Guidelines on Antibiotic Use in Lower Respiratory Tract Infections (ProHOSP)
Largest prospective, multicentre, randomized controlled trial with PCT in LRTI patients presenting to EDs:
- 1359 LRTI patients, 6 centers
- PCT group (n=671), control group (n=688)

* % reduction related to non PCT-guided group

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**B·R·A·H·M·S PCT algorithm for LRTI patients**

**When to start ABx?**

- Bacterial infection likely ➤ ABx recommended
- Bacterial infection unlikely ➤ ABx NOT recommended

PCT LRTI cut-off 0.25 μg/L

**When to stop ABx?**

- Stop ABx, if ONE or BOTH criteria apply
- Continue/change ABx, if NONE criteria apply

Criterion 1
Decline in PCT
\[ \Delta \text{PCT} \geq 80\% \]

Criterion 2
Current PCT value
\[ <0.25 \mu \text{g/L} \]

PCT values should always be interpreted in context of the patient’s clinical condition. Antibiotic treatment should be started/continued on suspicion of infection.
Community-acquired pneumonia (CAP)
Tailor the treatment duration in hospitalized patients

Up to \(-40\%\) AB exposure\(^{24}\)

Acute COPD exacerbations
Does every exacerbation require ABx?

- Significant sustained reduction in total antibiotic exposure for up to 6 months\(^{25}\)
- No decrease in mean time to next exacerbation\(^{25}\)
- No increase in lung function decline\(^{25}\)

Up to \(-44\%\) AB exposure at index exacerbation\(^{25}\)

If it is viral, antibiotics will not help. PCT can quickly identify patients who will benefit from antibiotic therapy.
Effective antibiotic treatment is reflected by declining PCT values, consistent with its half-life time of about 20-24 hours. Serial determinations of PCT can be used to monitor the course of infection in sepsis patients. Appropriate empiric antibiotic therapy was associated with a significant decline in PCT from day 2 to day 3 (ΔPCT ≥30%).

Figure 6 Typical course of PCT serum level according to patient’s response to antibiotic treatment (n=109)

B·R·A·H·M·S PCT algorithm for sepsis patients

**When to start ABx?**
- **Bacterial infection likely**
  - ABx recommended
- **PCT sepsis cut-off**
  - 0.5 µg/L

**When to stop ABx?**
- **Stop ABx, if ONE or BOTH criteria apply**
  - **Criterion 1**
    - Decline in PCT
    - ΔPCT ≥80%
  - **Criterion 2**
    - Current PCT value
    - <0.5 µg/L
- **Continue/change ABx, if NONE criteria apply**
- **Bacterial infection unlikely**
  - ABx NOT recommended

PCT values should always be interpreted in context of the patient’s clinical condition. Antibiotic treatment should be started/continued on suspicion of infection.
Efficacy and safety in *critically ill patients*

**-2 days ABx in critically ill patients**

![PCT group (n=761)](image) ![Control group (n=785)](image)

**Figure 7** Median duration of AB treatment in PCT-guided group = 5 days, in control group = 7 days.\(^11\)

**-6% mortality at 1 year compared with control group**

Data from: The Stop Antibiotics on Procalcitonin Guidance Study\(^*\)

- Largest prospective, multicentre, randomized, controlled, open-label intervention trial with PCT in critically ill patients
- Conducted in the Netherlands – a healthcare system with comparatively low use of ABx\(^28\)
- 1575 critically ill patients, 15 centers

**Appropriate antibiotic use translates into survival benefit**

**Surgical ICU patients**

Intra-abdominal infections are a common cause of infectious mortality in surgical ICUs. The duration of antibiotic treatment for their management is controversial.\(^29,30\)

**-5 days ABx in adult surgical ICU patients**

![PCT group (n=52)](image) ![Control group (n=69)](image)

**Figure 8** Mean duration of AB treatment in PCT-guided group = 5 days, in control group = 10 days.\(^29\)

Excess of antibiotics is harmful. PCT indicates the right time to stop.

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\(^*\) Data from: The Stop Antibiotics on Procalcitonin Guidance Study

\(^1\)\(^11\) Reference numbers are not shown in the image. Please provide the complete list of references as per the original document.
Efficacy of PCT-guided AB therapy

Children with LRTI symptoms

Children presenting to ED with LRTI – need for a targeted use of ABx

Antibiotics are overused in children and adolescents with LRTI. PCT-guided treatment can markedly reduce ABx exposure in this patient group without any adverse impact on outcome.

-2 days ABx in children with LRTI symptoms

Figure 9 Mean duration of AB treatment in PCT-guided group = 4.5 days, in control group = 6.3 days

B·R·A·H·M·S PCT algorithm for children with LRTI symptoms

When to start ABx?

- Bacterial infection likely
  - ABx recommended

- PCT LRTI cut-off
  - 0.25 μg/L

When to stop ABx?

- Stop ABx, if ONE or BOTH criteria apply
- Continue/change ABx, if NONE criteria apply

Criterion 1
- Decline in PCT
  - ΔPCT ≥80%

Criterion 2
- Current PCT value
  - <0.25 μg/L

PCT values should always be interpreted in context of the patient’s clinical condition. Antibiotic treatment should be started/continued on suspicion of infection.
Pediatric community-acquired pneumonia (CAP)

Pediatric CAP, in many cases, despite viral etiology is treated with antibiotics, leading to considerable over-use and increase in

- Risk of bacterial resistance
- Incidence of drug related adverse events
- Therapeutic costs

PCT-guidance can help to avoid unnecessary antibiotics.

Figure 10 Duration of AB treatment in PCT-guided group = 5.37 days, in control group = 10.96 days

Figure 11 Antibiotic exposure according to disease severity and treatment group

-14% initiation of ABx

-85% adverse effects from ABx

-5 days ABx in children with CAP

PCT group (n=155)
Control group (n=155)
Neonates with suspected early-onset sepsis

Early detection of neonatal sepsis
Avoid unnecessary ABx

Early diagnosis of neonatal sepsis is vital to improve the outcome. In the absence of reliable infection markers during the first hours of life, AB treatment in newborn infants with risk factors for infection is started early, exposing a considerable number of patients to unnecessary treatment. PCT-guidance has been shown to significantly reduce antibiotic treatment duration in such cases (Figure 12).

-67% children treated

In healthy neonates, plasma PCT concentrations increase gradually after birth, reaching peak values at about 24 hours of age and then decrease to normal values below 0.5 μg/L by 48–72 hours of age.
Figure 12 PCT-guided treatment of suspected neonatal sepsis

-22.4 hours antibiotic therapy

PCT enables detection of neonatal sepsis from the first day of life.

-12% AB therapy in newborns

PCT group (n=60)
Control group (n=61)

$p=0.012$  $p=0.001$  $p=0.001$
The economic impact of PCT-guided treatment has been studied through health economic modeling in various settings:

- Sepsis patients – ICU
- Acute Respiratory Infections – inpatient, ICU, outpatient
- COPD exacerbation – inpatient

Treatment cost reductions ranging from 9% to 12% have been demonstrated across various countries.

The cost of testing for PCT is more than offset by downstream cost savings.
“PCT helps me to prescribe antibiotics rationally and thus to save their power for future generations.”

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## B·R·A·H·M·S PCT – Secured clinical decision making independent of platform

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Automated sensitive assay  | Point of care test  | * Available in Japan only

**Clinical Diagnostics**

- Thermo Fisher Scientific
  - B-R-A-H-M-S GmbH
  - Neuendorfrstr. 25
  - 16761 Hennigsdorf
  - Germany
  - +49 (0)3302 883 0
  - +49 (0)3302 883 100 fax
  - info.pct@thermofisher.com
  - www.thermoscientific.com/brahms

Find out more at [thermoscientific.com/procalcitonin](http://thermoscientific.com/procalcitonin)

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