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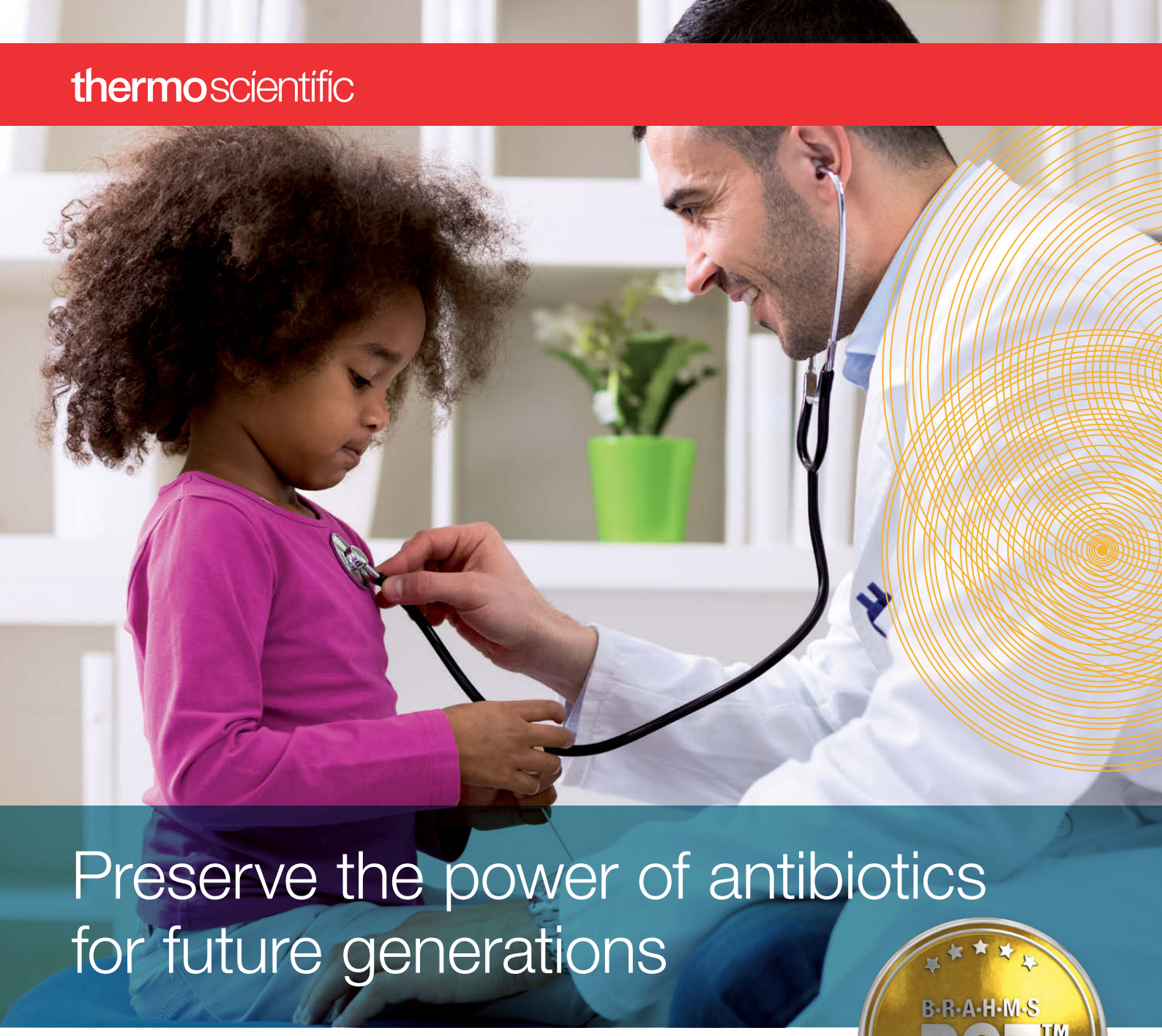

Preserve the power of antibiotics for future generations

B·R·A·H·M·S PCT: Early infection diagnosis and targeted antibiotic guidance

Procalcitonin (PCT) in PEDIATRICS

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Suspicion of bacterial infection?

Superior differentiation with PCT

Challenging infection diagnosis in children

- Fever is often the only symptom for an ongoing infection in infants and young children.
- In children with fever it is sometimes difficult to assess the source, type and severity of the infection correctly.
- This often results in an **overprescription of antibiotics**, with all the potential consequences of **resistance development**.
- In that situation biomarkers are a useful tool for early diagnosis as they are easy to measure and rapidly available for immediate clinical decision making.

PCT accelerates treatment decisions

- Bacterial infections can neither be predicted nor ruled out by bedside-available clinical parameters. However, pediatric patients with peripheral bacterial colonization, local infection without invasive sepsis, and most of those with viral infections were demonstrated to have low PCT levels.[1]
- Low PCT levels (≤0.25 µg/L) were also found to predict negative blood culture results, thereby sufficiently ruling out bacteremia at an early point in time.[2]
- Thus, **PCT can rapidly verify the initial clinical suspicion of bacterial infection**. This enables a more judicious use of empiric antibiotics and reduction of antibiotic exposure.

High usage of antibiotics in children

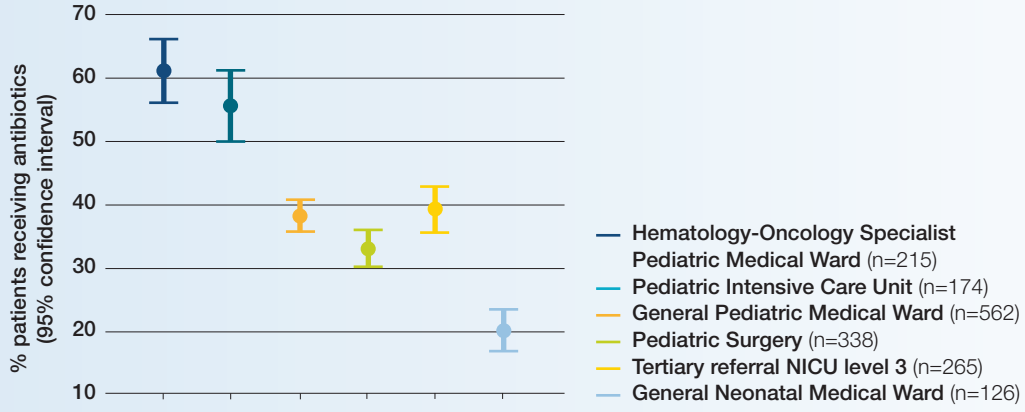

Figure 1 Antibiotic use in children by ward type (n=2172 children treated with at least 1 antibiotic, data from 50 European and 23 non-European hospitals)[3]

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 infections and therapy control:[4]

- **Fast increase after bacterial infection** within 3-6 hours (faster than CRP) (Figure 2)[5,6,7]
- **High sensitivity and specificity for bacterial infection**, improving clinical diagnosis (Figure 3)[4,7]
- **B·R·A·H·M·S PCT™ is available as point of care test (Samsung IB B·R·A·H·M·S PCT)** and on various lab-based platforms
- **Recommended for antibiotic stewardship by the Surviving Sepsis Campaign Guideline**[8]
- The **Experts of the European Medicines Agency (EMA) agreed to include PCT for neonatal and pediatric sepsis diagnosis**[9]

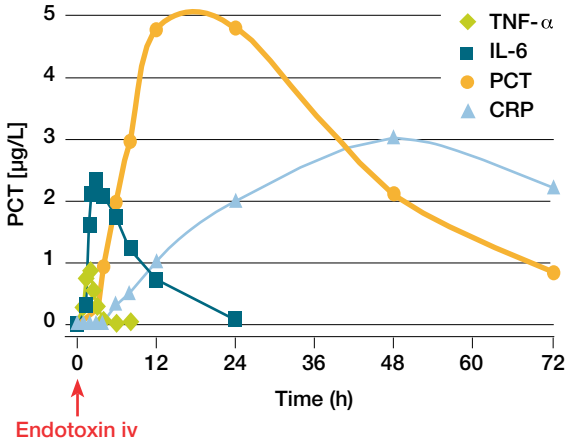

Figure 2 Kinetics of PCT compared to other inflammatory markers upon infection[5,6,7]

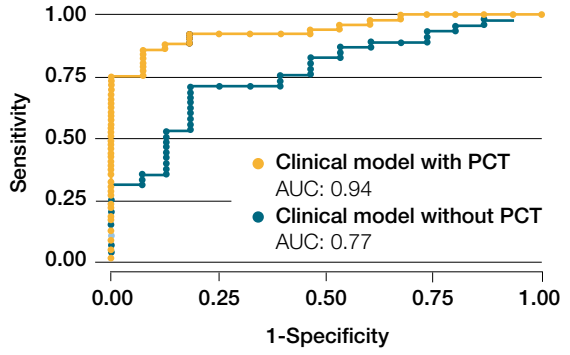

Figure 3 Accuracy of sepsis diagnosis based on a clinical model with and without PCT[7]

Integration of PCT into clinical algorithm improved the quality of sepsis diagnosis[7]

Rapid decision making

PCT supports differential diagnosis in pediatric emergency department

Meningitis

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

➔ **Need for differential diagnosis!**

A European multicenter case-cohort study (6 study centers, n=198) identified **PCT as the best bio-marker, with an odds ratio of 139 to distinguish between bacterial and aseptic meningitis in children** (Figure 4).[10] PCT was therefore also included into a clinical decision rule for meningitis in children[10] and clinical guidelines.[11,12]

Fever without source

Although most of children presenting with fever have a benign and self-limiting illness, a few are at **risk of developing a severe bacterial infection** which requires rapid therapeutic intervention with antibiotic therapy.

In a multicentric study on 1112 febrile pediatric patients <3 months of age admitted to 7 European emergency departments **PCT was the only independent risk factor for invasive bacterial infection with an odds ratio of 21.69 for PCT ≥0.5 µg/L.**[13]

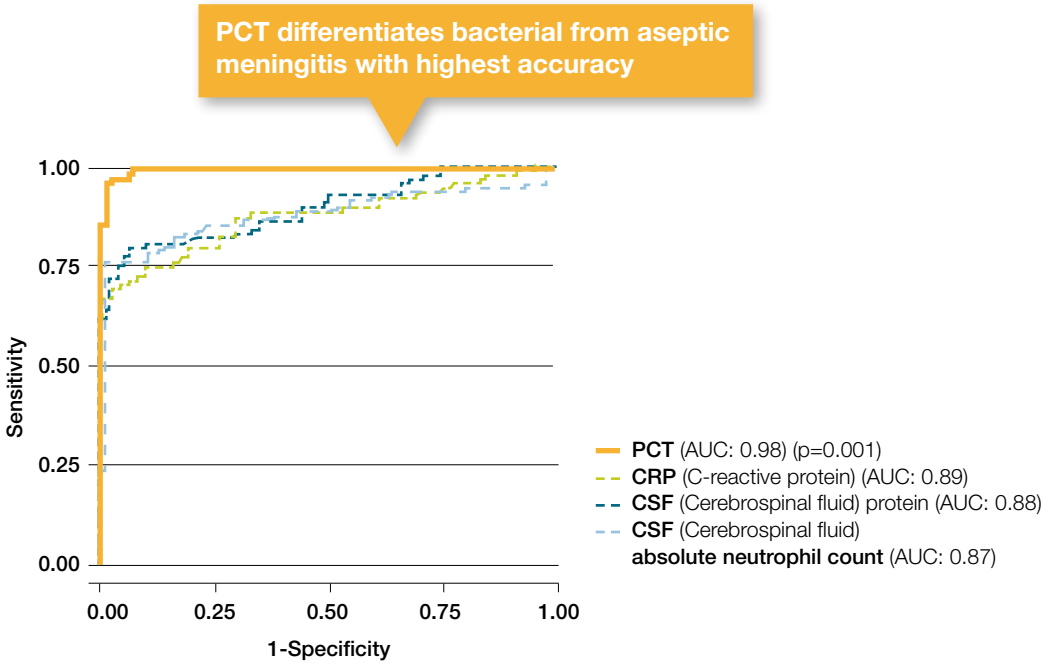

Figure 4 Receiver operating characteristics curves of the best predictors differentiating bacterial from aseptic meningitis (n=198)[10]

Neutropenic fever

Bacterial infections are life-threatening for neutropenic patients. Therefore rapid differentiation of bacterial infection from other causes of fever is essential for adequate decision making and patients' outcome.[1,14]

In a meta-analysis of 3585 febrile episodes in neutropenic children PCT was shown to be **superior to other biomarkers (e.g. CRP, IL6) for early prediction of bacterial infection** (see Table 1).[15]

Urinary tract infection (UTI)

PCT appears to be the most useful marker in differentiating lower urinary tract infection (cystitis) versus upper urinary tract infection (pyelonephritis).[16]

Elevated PCT levels may also predict vesicoureteral reflux and subsequent renal scarring[17,18] and can lead to **avoid 38% of unnecessary cystourethrographies** with DMSA (technetium-99m (99mTc)-dimercaptosuccinic acid) in children (Table 1), leading to a **cost reduction of about 30%**.[17]

	Meningitis [10]	FWS [19]	Neutropenic fever [15]	UTI [16]	UTI severity assessment [18]		
	Differentiate bacterial from viral meningitis	Identify invasive bacterial infection as the cause of fever	Identify bacterial infection as cause of neutropenic fever	Differentiate acute pyelonephritis from cystitis	Prediction of vesicoureteral reflux (VUR)		Prediction of renal scarring
					All grades (I-V)	Grades III-V	
PCT cut-off [µg/L]	0.5	0.5	0.2	0.5	0.5	0.5	0.5
Sensitivity	0.99	0.78	0.96	0.97	0.76	0.95	1.00
Specificity	0.83	0.72	0.85	0.67	0.51	0.54	0.57
PPV (%) (rule in)	83	40	n.a	84	47.2	42.3	46.0
NPV (%) (rule out)	99	94	n.a	91.7	79.1	96.5	100
Likelihood ratio +		2.69			1.56	2.06	2.31
Likelihood ratio –		0.25			0.46	0.1	0

Table 1 Diagnostic value of PCT in children with meningitis[10], children with fever without source (FWS)[19], children with neutropenic fever[15], and children with urinary tract infection (UTI)[16] and clinical performance characteristics of PCT for prediction of vesicoureteral reflux (VUR) and renal scarring in children with first febrile pyelonephritis[18]
PPV = positive predictive value
NPV = negative predictive value

Advanced diagnostic assessment

PCT in pediatric intensive care and pediatric surgery

Early identification of Sepsis

SIRS occurs in 82% of patients admitted to pediatric intensive care units (PICUs), including 23% with sepsis. However, it is difficult in the PICU to reliably distinguishing SIRS patients who are infected versus non-infected because clinical and laboratory signs are similar to those presented in different severities of SIRS caused by infectious or noninfectious disease.[1]

PCT has been demonstrated to be the most useful tool for early identification of sepsis in the PICU, superior to other markers like CRP or leukocyte count

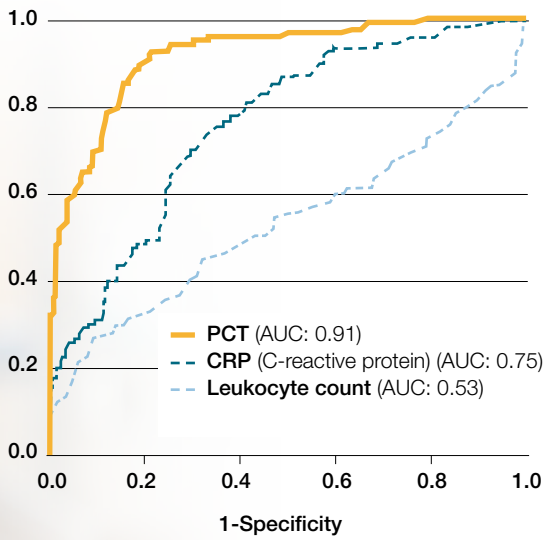

Figure 5 Receiver operating characteristics (ROC) curves for prediction of sepsis in patients admitted to the PICU; comparing PCT, CRP and leukocyte count (n=94)[20]

Early detection of post-surgical infection

Extensive surgical interventions induce systemic inflammatory reaction which makes it a challenge to detect potential infectious complications early after surgery. Also biomarkers can be temporarily nonspecifically induced due to pronounced post-surgical inflammation.[4]

As this transient increase lasts a relatively short time for PCT, serial testing of PCT can be used to assess the course of the patient's response and differentiate post-surgical infection from non-infection induced SIRS.[4,21]

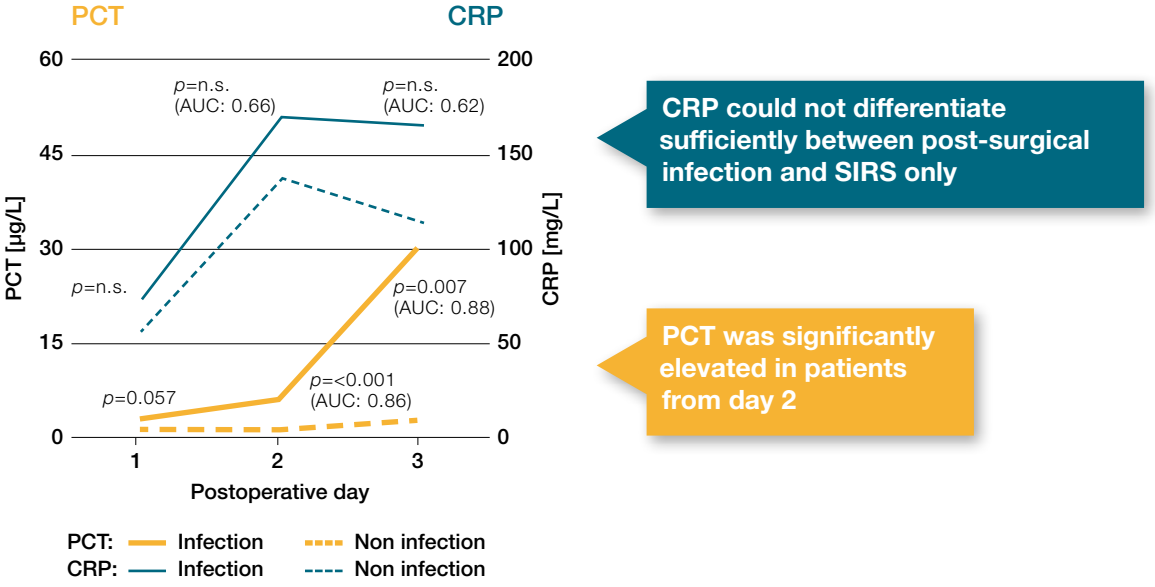

Figure 6 CRP and PCT course in children with and without infectious complication after cardiac surgery with cardiopulmonary bypass (CPB) (n=231)[21]

PCT has been proven to be superior to other markers for early sepsis diagnosis

Reduction of antibiotics

PCT-guided antibiotic stewardship

Lower respiratory tract infection

Lower respiratory tract infection (LRTI) is the most common infection in children. Etiologic diagnosis is not generally achieved and the pathogen eludes identification in most cases. Therefore overprescription of antibiotics (AB) is frequently observed in all hospital departments, especially in very young children (Figure 1).[3]

Antibiotic overuse contributes to

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

PCT has been proven to be a useful tool for efficient and safe guidance of AB treatment according to individual patient needs, both in adults and children.[22,23,24,25]

PCT-guidance in children with respiratory tract infections of varying severity leads to a strong reduction of antibiotic exposure (Figure 7)[22,23] due to

- reduced prescription rate
- earlier discontinuation of antibiotics

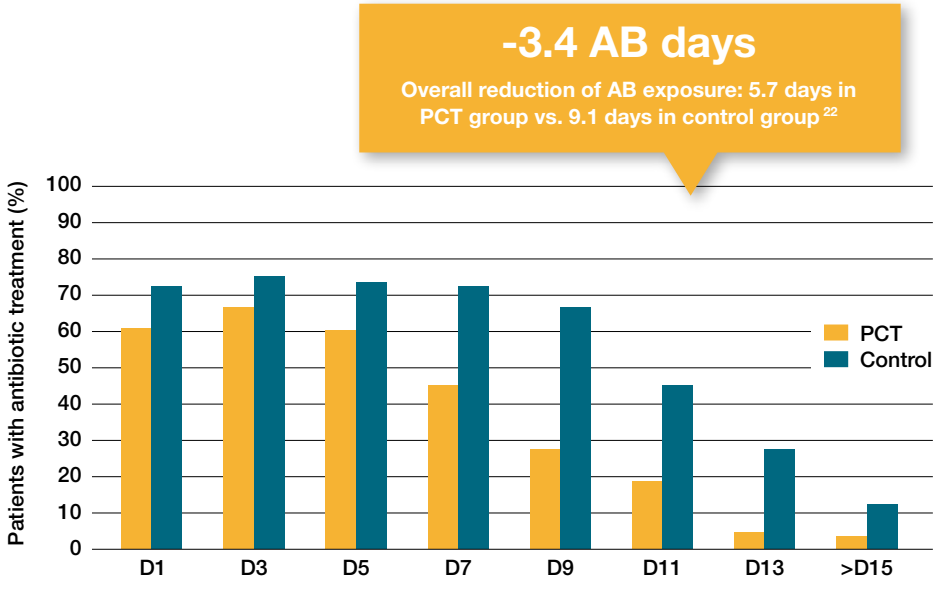

Figure 7 Antibiotic prescribing rate: Antibiotic treatment by day since randomization for pediatric patients with community-acquired pneumonia (CAP) (n=215)[22]
AB days = days of antibiotic therapy

PCT-based clinical algorithms facilitate a more targeted use of antibiotics

A Cochrane review on randomized-controlled studies (14 studies with n=4221 adult patients thereof 7 studies with n=2605 coming from the emergency department) has proven the safe use of PCT to assist decisions about initiation and/or duration of antibiotic therapy without influencing mortality or treatment failure.[26] Initiation, continuation or termination of antibiotic treatment in pediatric patients was also strictly guided by PCT cut-off levels used in previous trials in adults with LRTI (Figure 8). In the control group, antibiotic treatment was initiated based on physician assessment and clinical guidelines.[22]

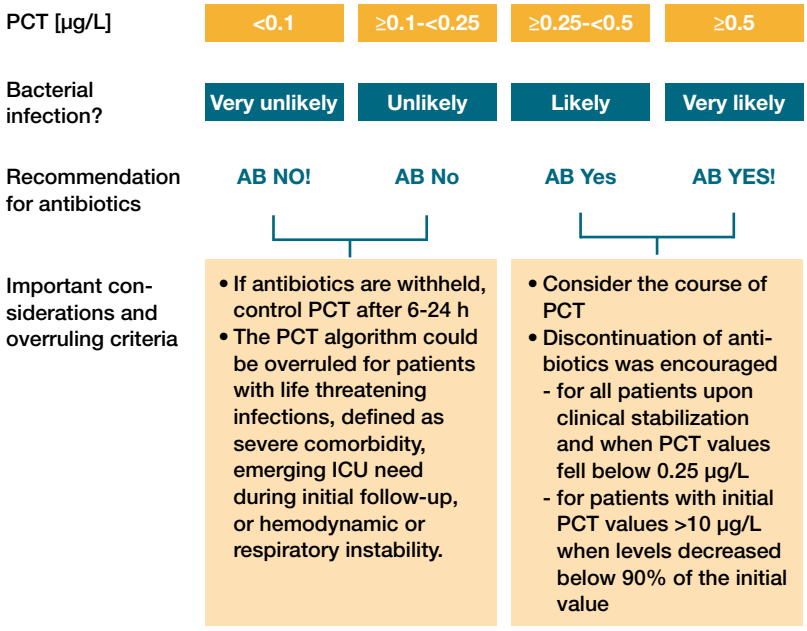

Figure 8 PCT-based clinical algorithm for guidance of antibiotic treatment in children with lower respiratory tract infections [22]

PCT testing from time of admission facilitates a more targeted use of antibiotics and contributes to minimize the risk of resistance development

How to manage PCT values in neonates

PCT allows rule out of sepsis from cord blood

PCT measurement from blood cord is an early and discriminating marker of early onset of neonatal infection and improves accuracy of clinical sepsis diagnosis significantly especially in comparison to CRP.

For detecting early onset neonatal sepsis, PCT can be measured in the venous blood including venous blood from the umbilical cord.[27]

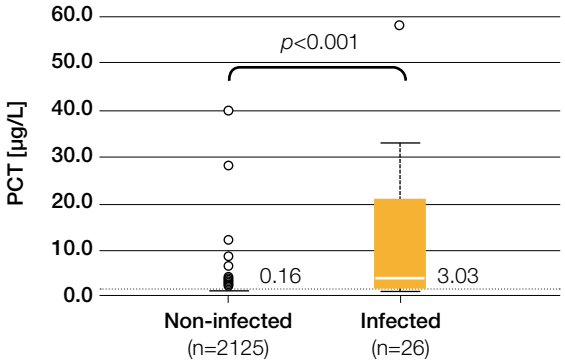

Figure 9 PCT measurements of 2151 newborns with an initial suspicion of infection. 1.2% (n=26) were probably or certainly infected judged by clinical signs, abnormal laboratory results (excluding PCT) or microbiology results and had a significantly increased PCT value. The negative predictive value was 99%.[28]

PCT reference ranges during the first 72 hours after birth

Normal birth and extrauterine adaptation stimulate an acute phase reaction in the newborn infant with release of PCT and other acute phase proteins. **In healthy neonates, plasma PCT concentrations increase gradually after birth, reach 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.**[29] After this period, the adult reference values apply.

In newborns admitted to the neonatal intensive care unit with clinical signs of respiratory distress without infection, peak plasma PCT concentrations at 48 hours of age have been reported to be higher (mean 3-4 µg/L) with large interindividual variations (range 0.2-20 µg/L).[29]

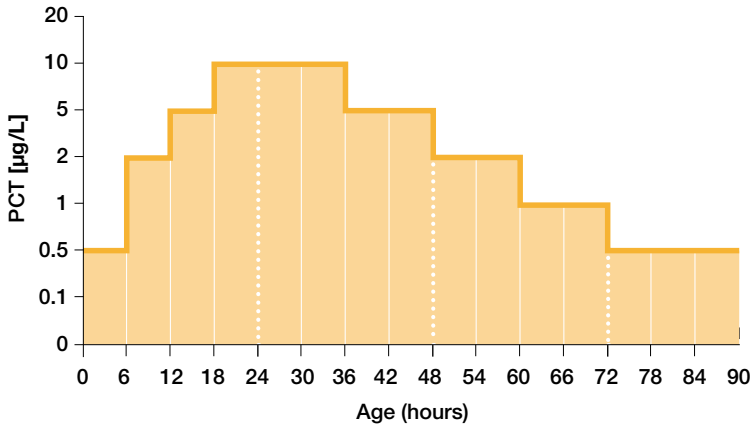

Figure 10 Age adjusted PCT cut-off values in newborns[29]

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PCT cut-offs and clinical algorithms were established by use of the global reference standard **B·R·A·H·M·S PCT™** sensitive KRYPTOR™

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