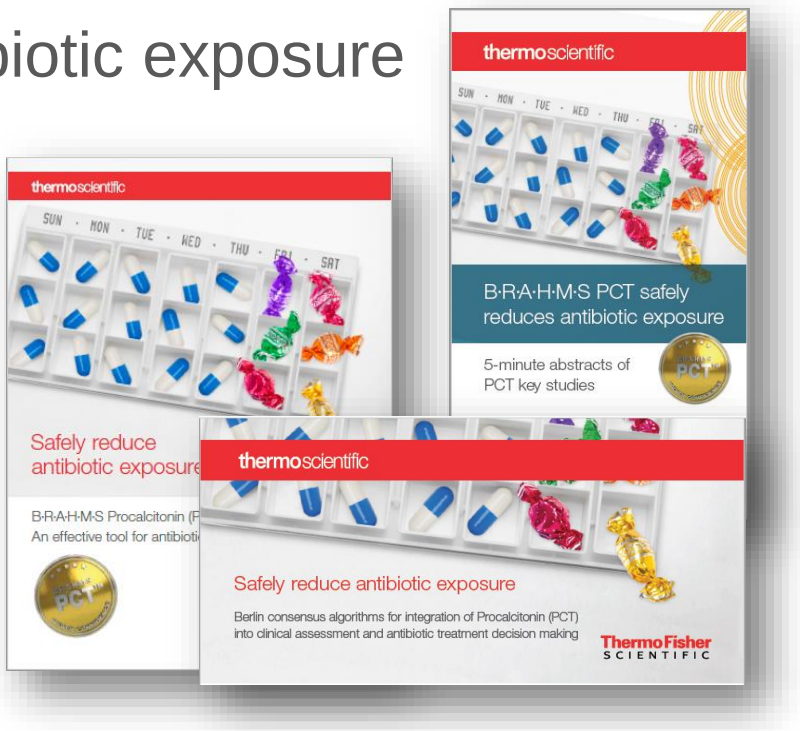
Content:

- Safely reduce antibiotic exposure



You can also order free copies of additional material at info.pct@thermofisher.com

- Berlin consensus algorithms
- 5-minute abstracts of PCT key studies

For more content and free on-demand webinars please visit: thermoscientific.com/procalcitonin

ThermoFisher SCIENTIFIC

thermo scientific

Safely reduce antibiotic exposure

B·R·A·H·M·S Procalcitonin (PCT):
An effective tool for antibiotic stewardship

B·R·A·H·M·S PCT™ PROVEN CONFIDENCE

ThermoFisher SCIENTIFIC

The challenge

Antibiotic resistance – an increasing threat to public health

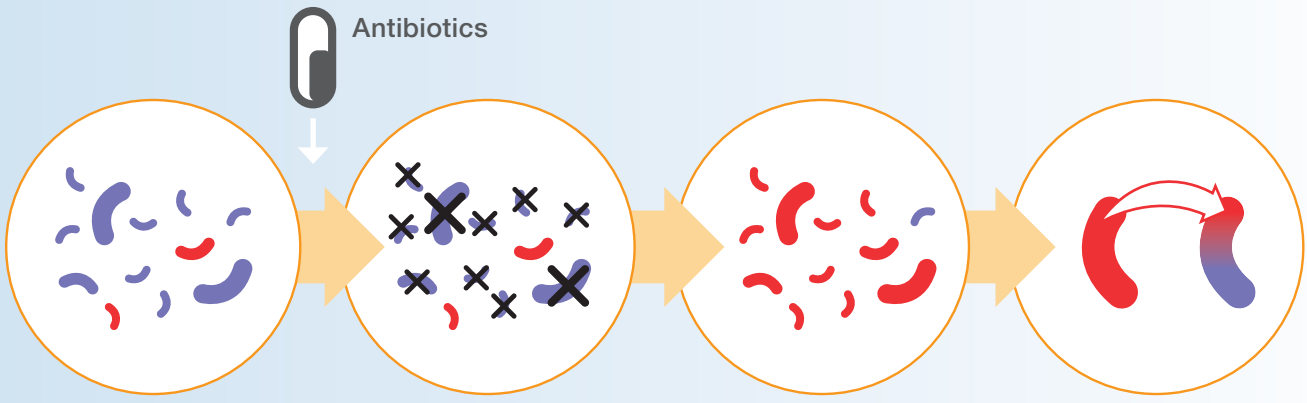
Antibiotics (ABx) are a limited resource. At the current pace of injudicious use, all antibiotics will soon become ineffective. The WHO Global Action Plan on antimicrobial resistance, 2015, emphasizes that antimicrobial resistance is a crisis that must be managed with the utmost urgency.[1]

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

1/3 antibiotic prescriptions are unnecessary[2]

How does resistance to antibiotics develop?



Large population of bacteria, only a few are drug-resistant

Susceptible bacteria are killed while the resistant bacteria survive

Only the drug-resistant bacteria continue to proliferate in the presence of the antibiotic and take over

Some bacteria give their drug-resistance to other bacteria, causing further increase in drug-resistance in the society

A potential for change

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

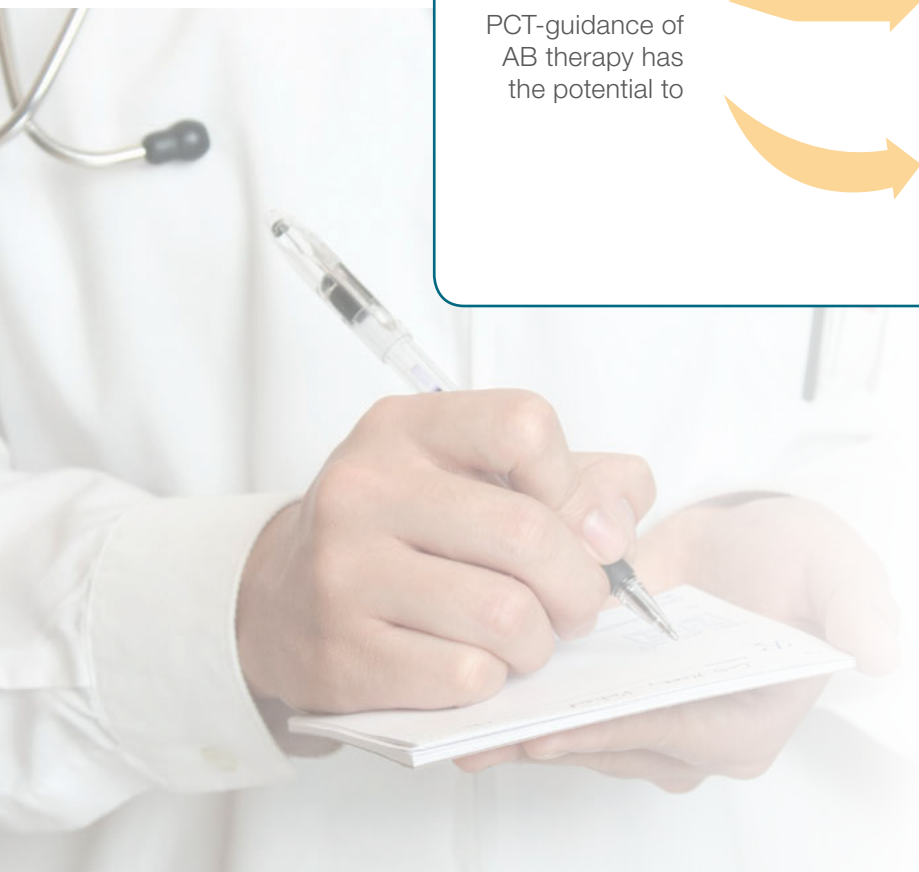
> We suggest that procalcitonin levels can be used to ...
>
> ... support **shortening the duration of antimicrobial therapy** in sepsis patients ...
>
> ... support the **discontinuation of empiric antibiotics** in patients who initially appeared to have sepsis, but subsequently have limited clinical evidence of infection.[3]

Surviving Sepsis Campaign
International Guidelines for Management of Sepsis and Septic Shock, 2016[3]

B·R·A·H·M·S PCT

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

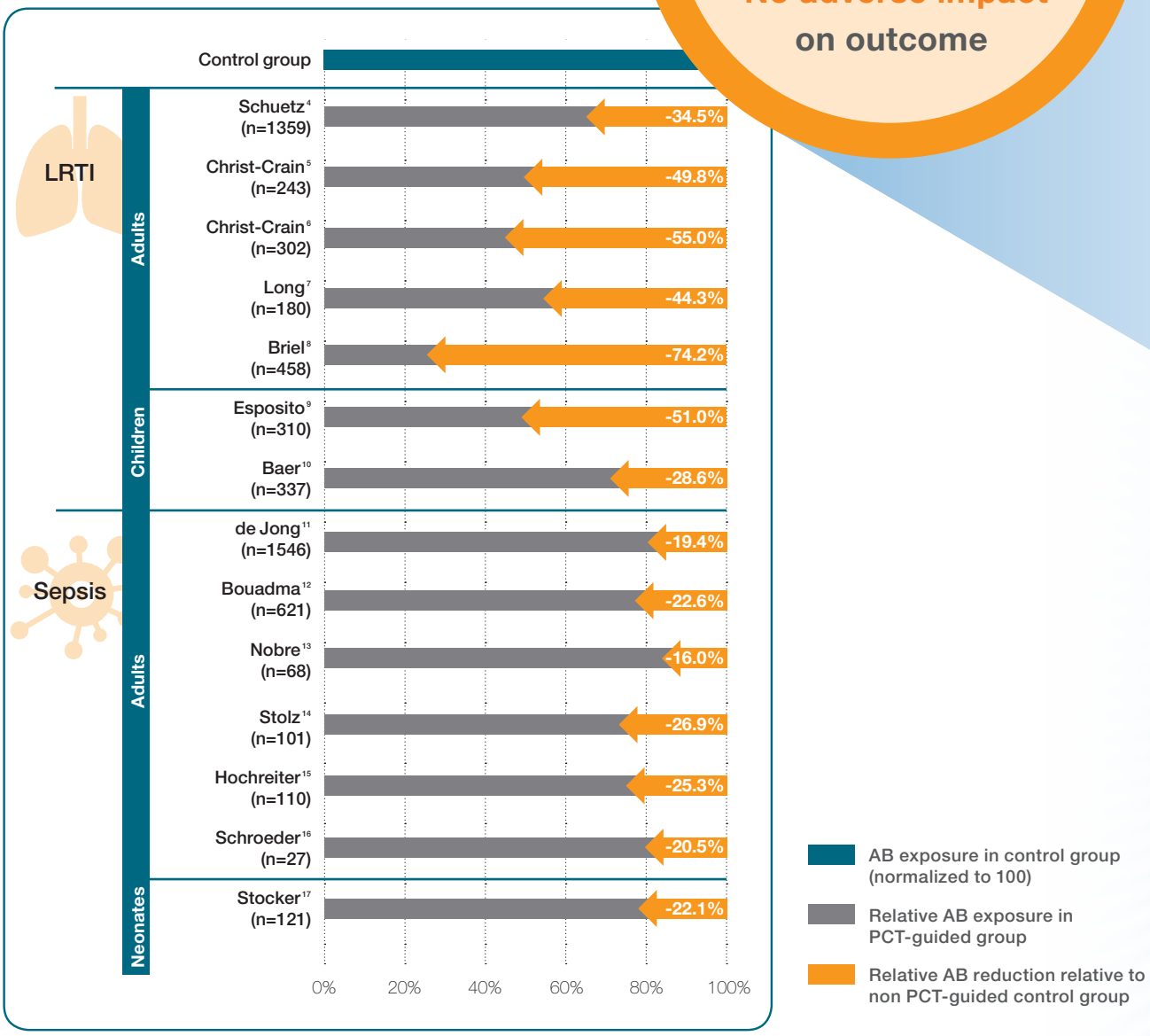
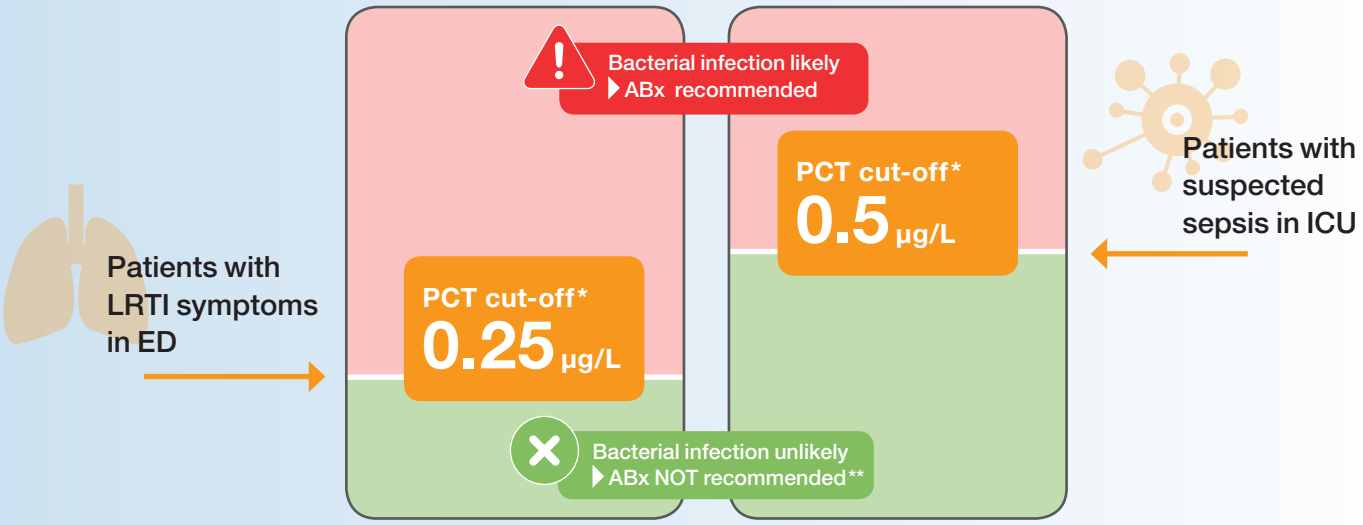


Figure 1 Relative reduction in AB exposure with PCT-guidance
AB exposure in control group is normalized to 100, shown by a blue bar at the top. The gray bar depicts the relative exposure in PCT group and the orange bar shows the relative AB exposure reduction. All studies reported significant reduction in AB exposure.


-42%
length of stay in ICU[13]
-64%
hospital C. difficile infection[36]
-9%
overall treatment costs[18]
-6%
mortality at 1 year[11]
-72%
initiation of ABx in primary care[8]
-85%
AB related adverse effects[9]
Benefits of reduced AB exposure achieved by PCT-guided antibiotic therapy

When to start antibiotics?

B·R·A·H·M·S PCT enables rapid and reliable diagnosis of systemic bacterial infections[19]



* PCT values should always be interpreted in context of the patient's clinical condition.
** In high risk patients start empirical antibiotic therapy immediately.

PCT levels increase 3-6 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

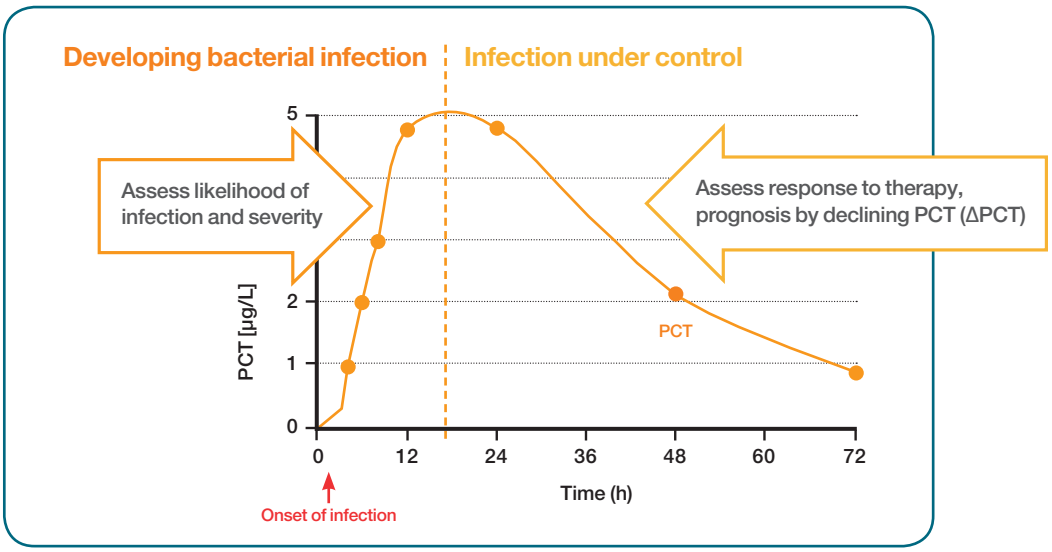
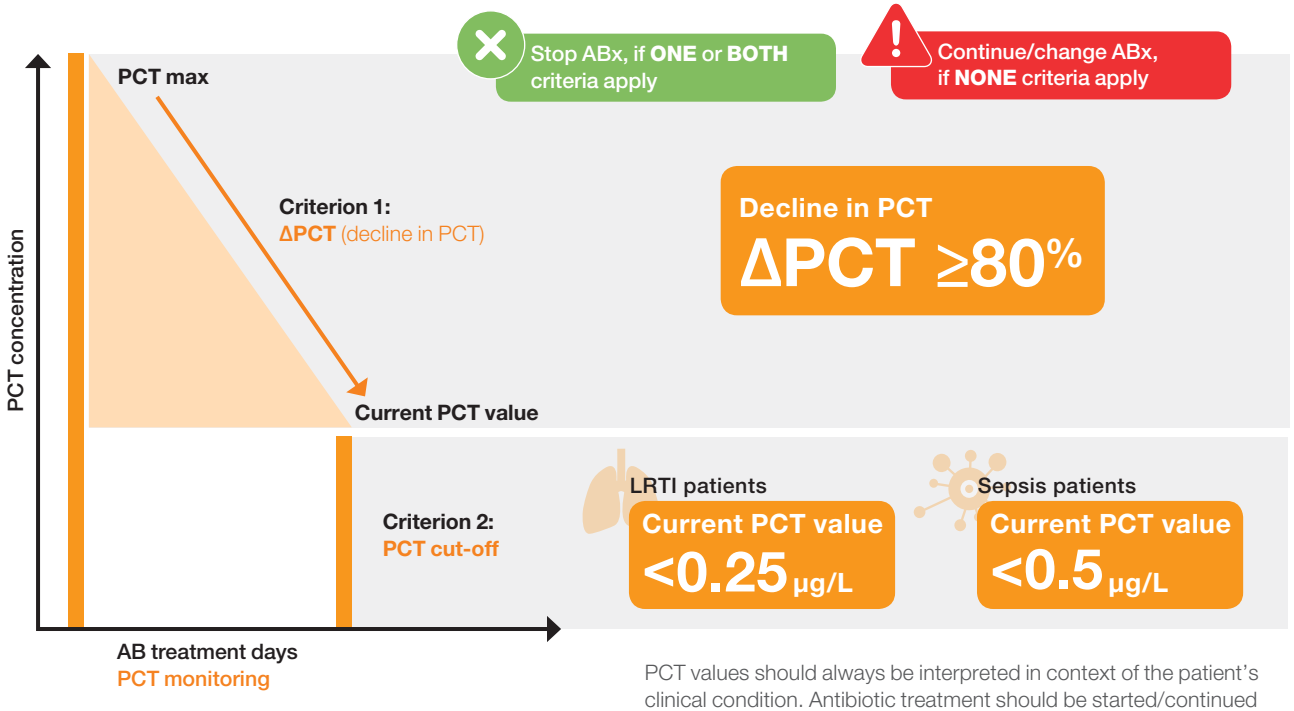


Figure 2
Kinetics of PCT[19,20]

How long to give antibiotics?

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



PCT values should always be interpreted in context of the patient's clinical condition. Antibiotic treatment should be started/continued on suspicion of infection.

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

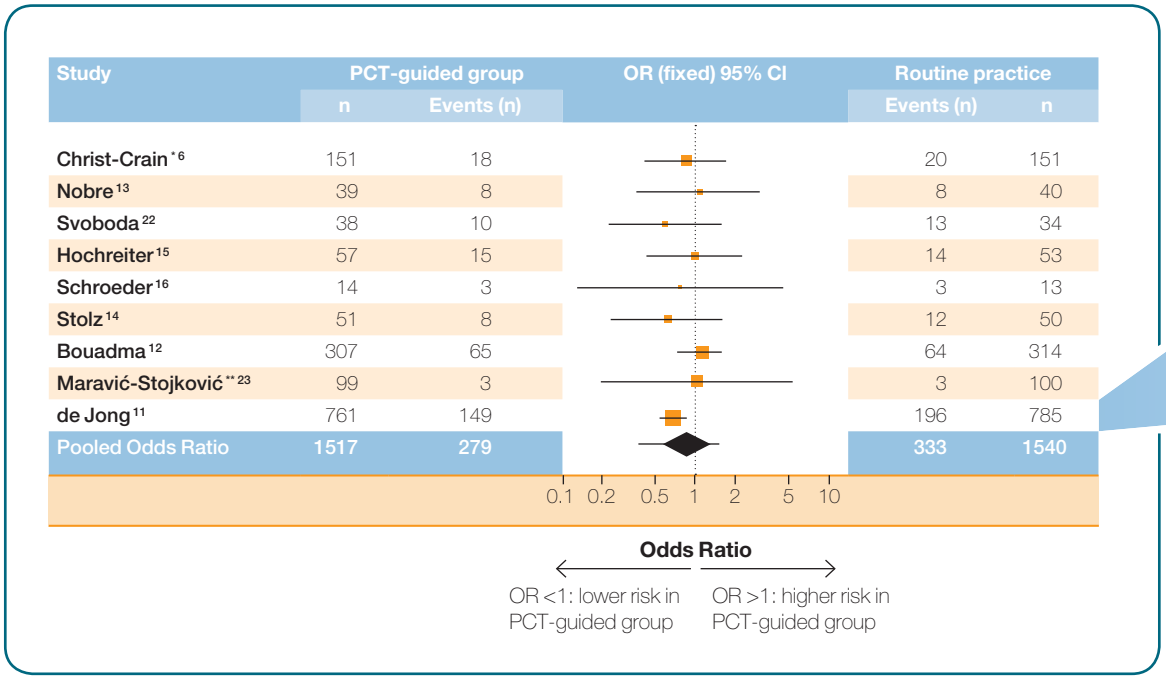


Figure 3 28-day mortality in PCT-guided group as compared to routine practice
Forest plot showing the comparison of PCT-guided algorithms vs. routine practice. The size of each square represents the proportion of information provided by each study. The vertical line depicts the point of "no difference" 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 [11]

- Randomized controlled interventional trial
- 1575 critically ill patients
- 15 centers

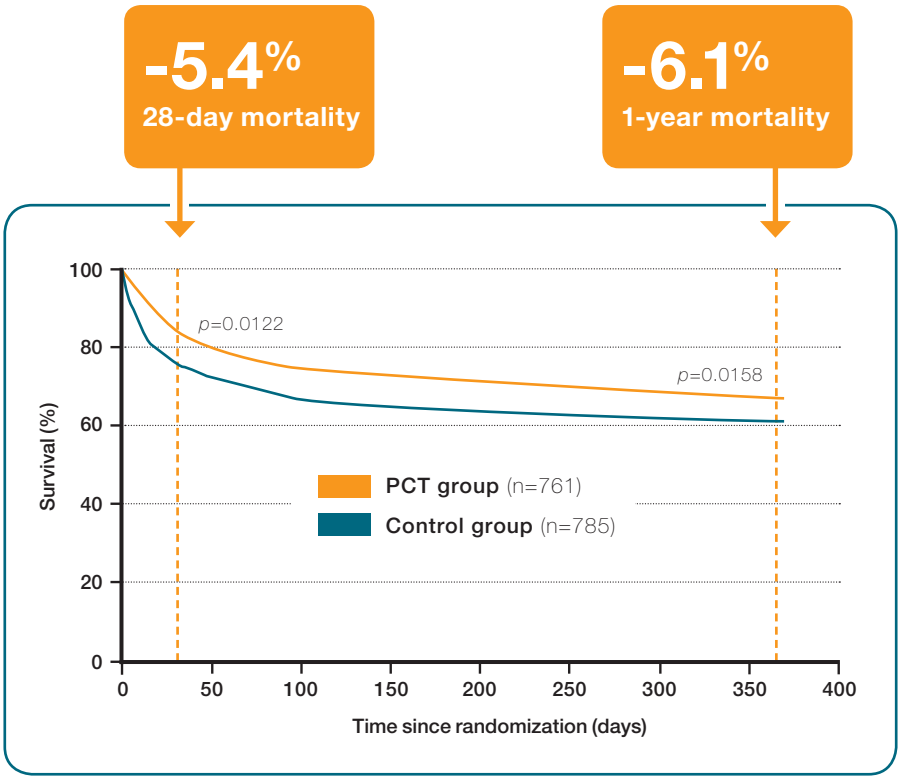


Figure 4 Probability of survival to day 365 in the PCT-guided group vs standard of care group[11]

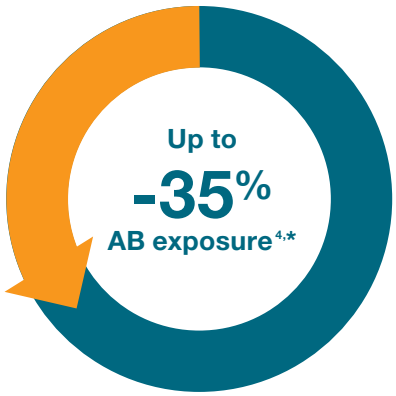
Antibiotics are a double-edged sword. Adequate dose helps, excess harms.

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.[5] PCT-guidance in such patients allows reduction in AB exposure without any adverse impact on outcome.[4]

-14%
initiation of ABx[4]

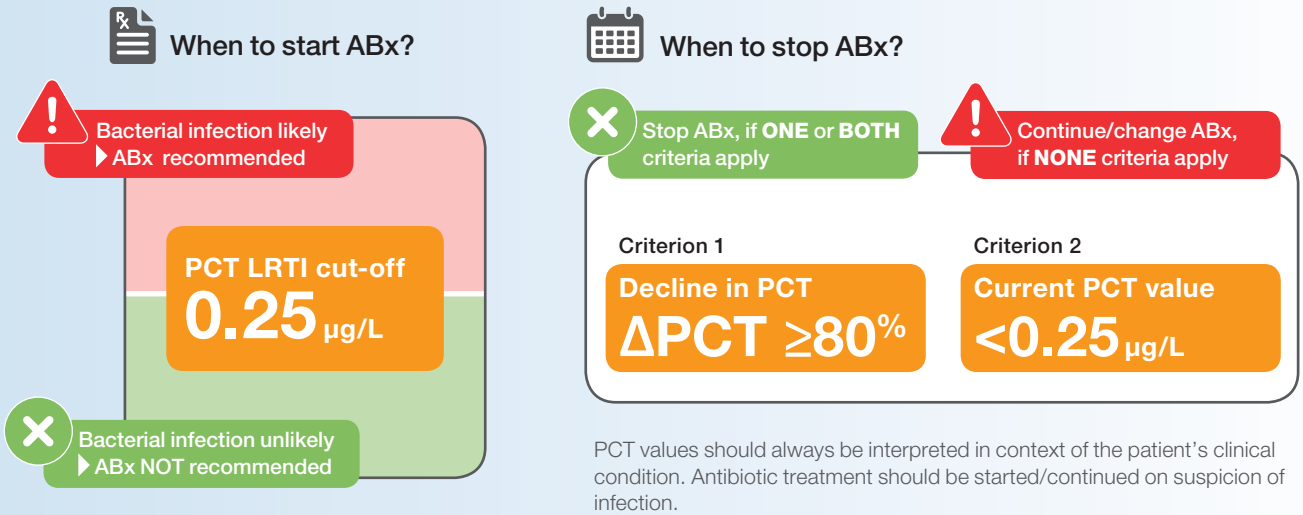


-30%
adverse effects from ABx[4]

Data from: Effect of Procalcitonin-Based Guidelines vs Standard Guidelines on Antibiotic Use in Lower Respiratory Tract Infections (ProHOSP)[4]
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

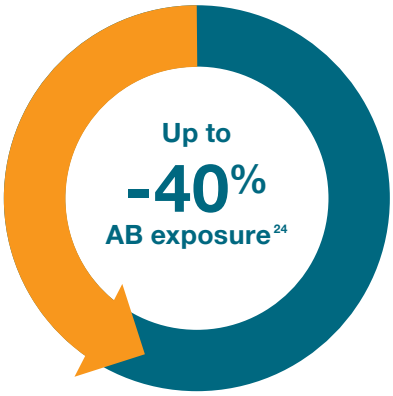
B·R·A·H·M·S PCT algorithm for LRTI patients



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



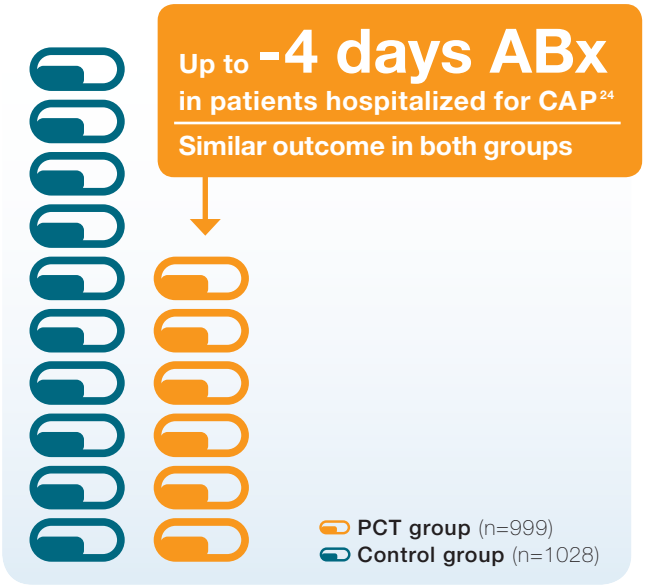
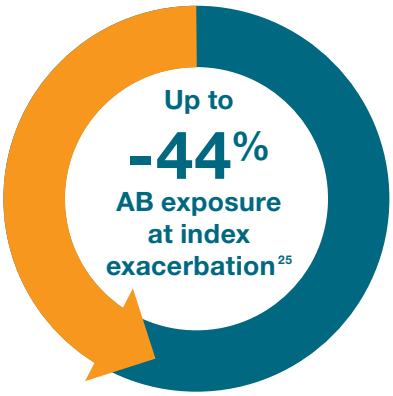


Figure 5 Meta-analysis data for 2027 patients hospitalized for CAP, total exposure of ABx in median days: PCT group = 6 days, control group = 10 days[24]

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]



If it is viral, antibiotics will not help. PCT can quickly identify patients who will benefit from antibiotic therapy.

Adults in Intensive Care Units

How to know the appropriateness of an empiric antibiotic?

Effective antibiotic treatment is reflected by declining PCT values,[26] consistent with its half-life time of about 20-24 hours.[20] 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%).[26]

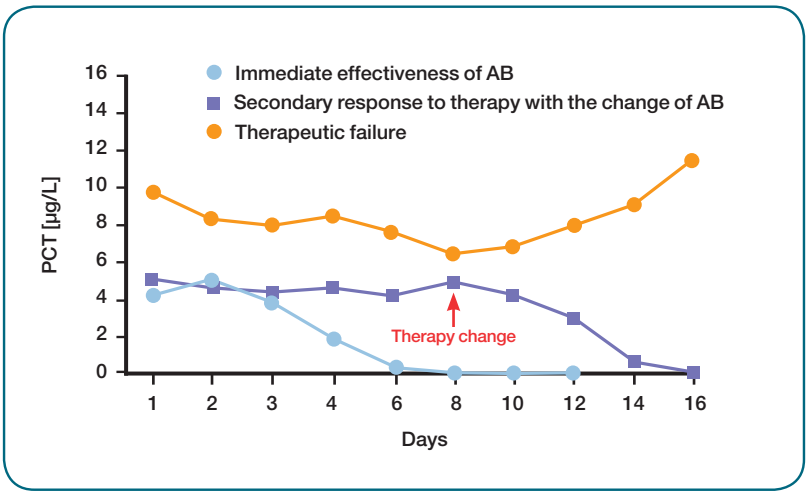
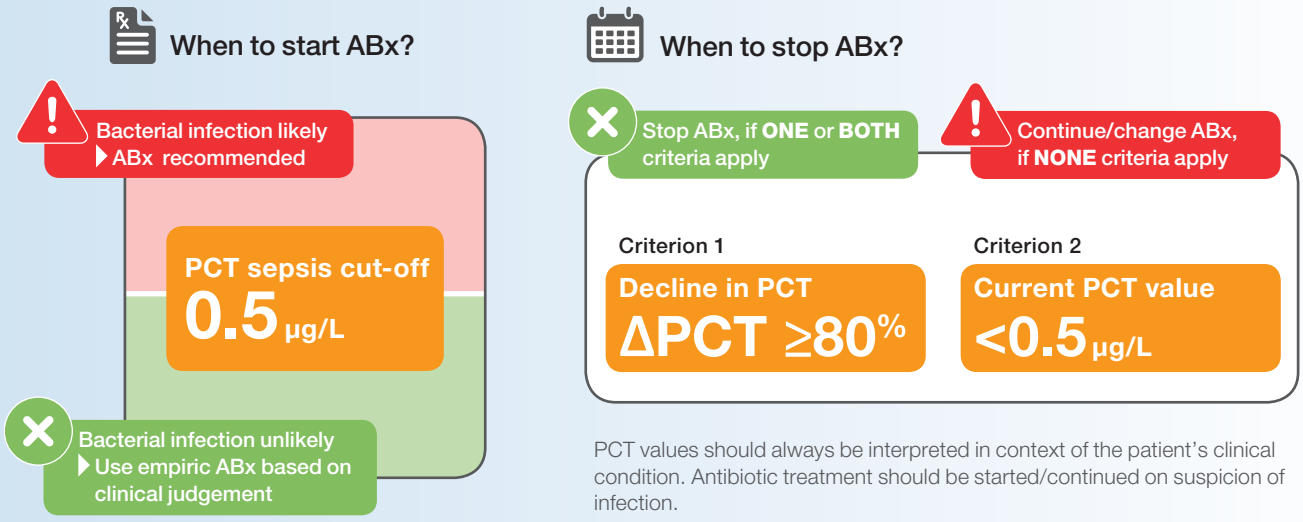


Figure 6 Typical course of PCT serum level according to patient's response to antibiotic treatment (n=109)[27]

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



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**

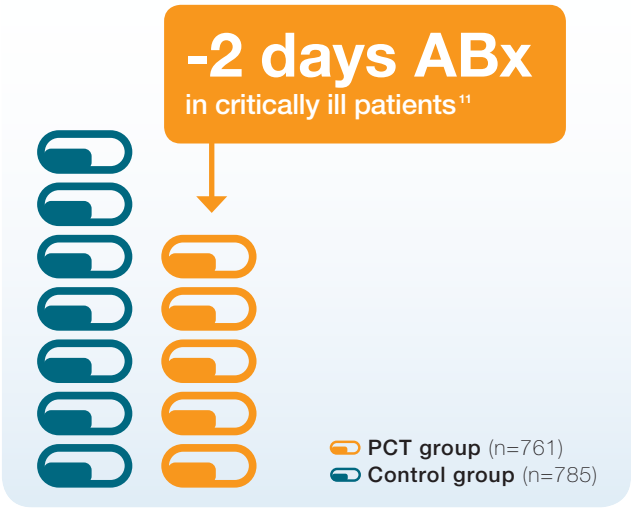


Figure 7 Median duration of AB treatment in PCT-guided group = 5 days, in control group = 7 days[11]

-6% mortality

at 1 year compared with control group[11]

Appropriate antibiotic use translates into survival benefit

Data from: The Stop Antibiotics on Procalcitonin Guidance Study[11]

- 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

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]

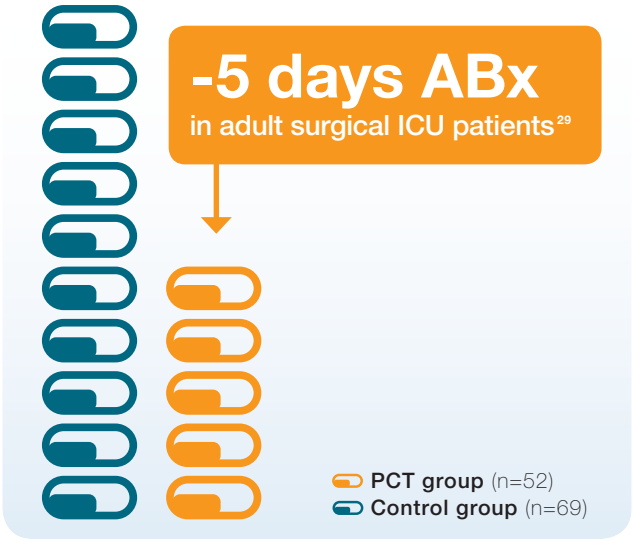


Figure 8 Mean duration of AB treatment in PCT-guided group = 5 days, in control group = 10 days[29]

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

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.[10] PCT-guided treatment can markedly reduce ABx exposure in this patient group without any adverse impact on outcome.

Figure 9 Mean duration of AB treatment in PCT-guided group = 4.5 days, in control group = 6.3 days[10]

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

Bacterial infection unlikely
▶ ABx NOT recommended

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[9]

PCT-guidance can help to avoid unnecessary antibiotics.

-14%
initiation of ABx[9]

-85%
adverse effects from ABx[9]

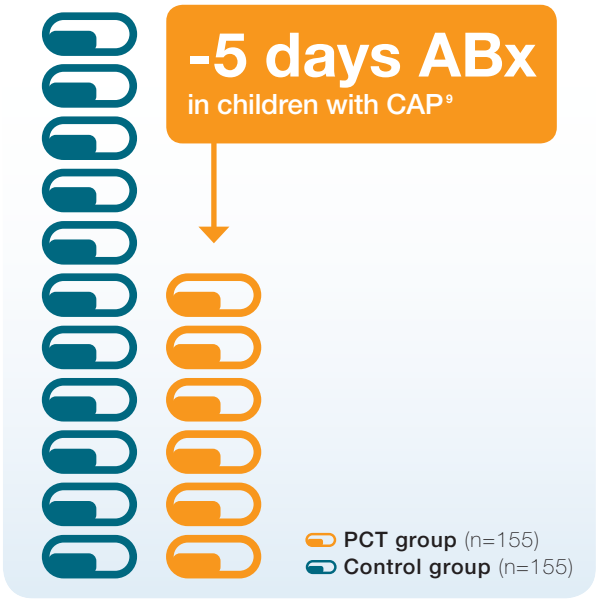


Figure 10 Duration of AB treatment in PCT-guided group = 5.37 days, in control group = 10.96 days[9]

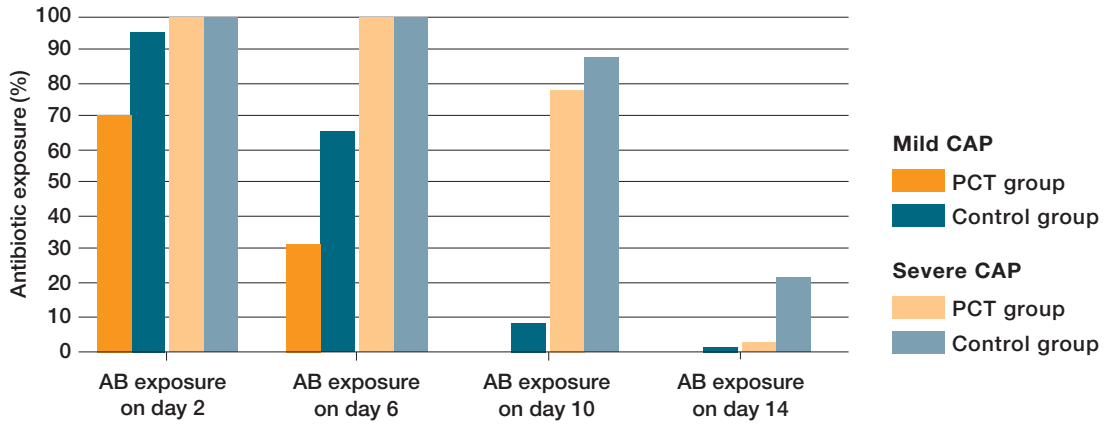


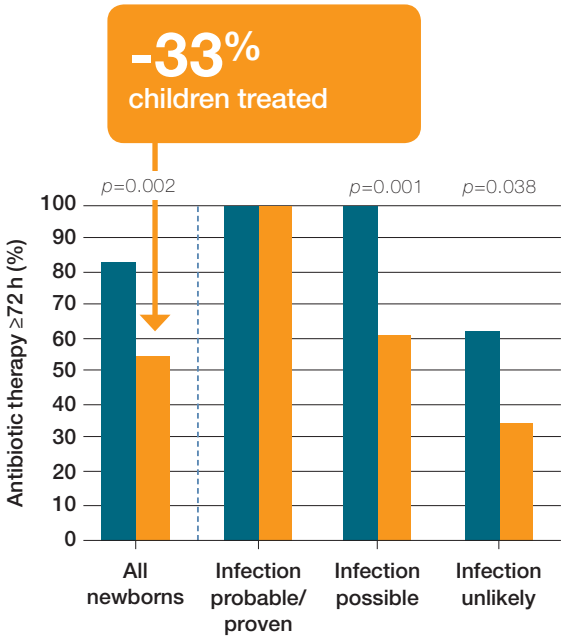
Figure 11 Antibiotic exposure according to disease severity and treatment group[9]

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.[31]

PCT-guidance has been shown to significantly reduce antibiotic treatment duration in such cases (Figure 12).[17]



B·R·A·H·M·S PCT cut-offs for neonates

To exclude maternal-fetal infection[32]	**PCT in cord blood <0.6 µg/L** Post-test probability of bacterial infection <0.001%
To reduce the duration of antibiotic treatment[17]	**2 consecutive normal PCT values:** **Stop antibiotic treatment for children born at term and prematurely** Consider PCT reference values according to children's age in hours (Figure 13)

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 72 hours of age.[17]

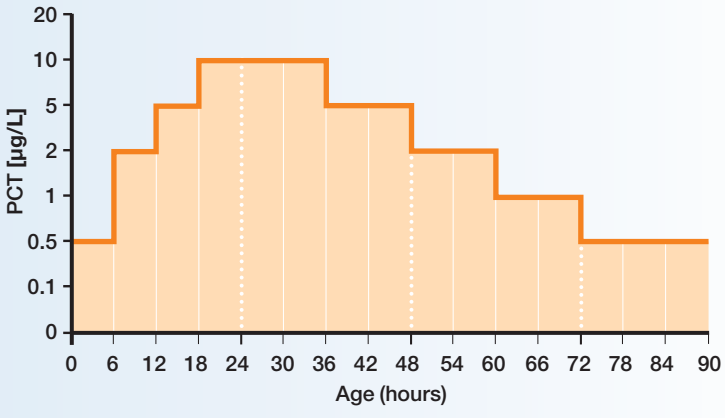
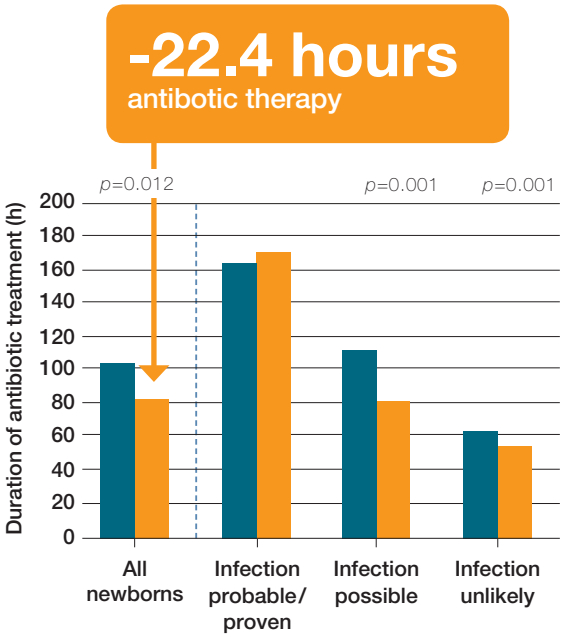
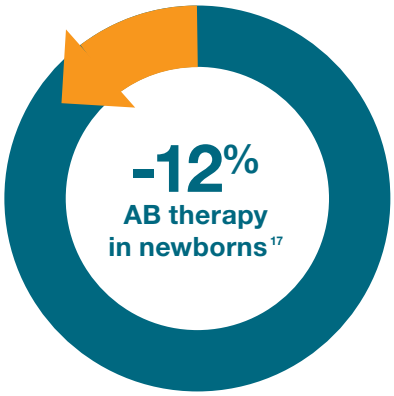


Figure 13 Age adjusted PCT cut-off values in newborns[17]

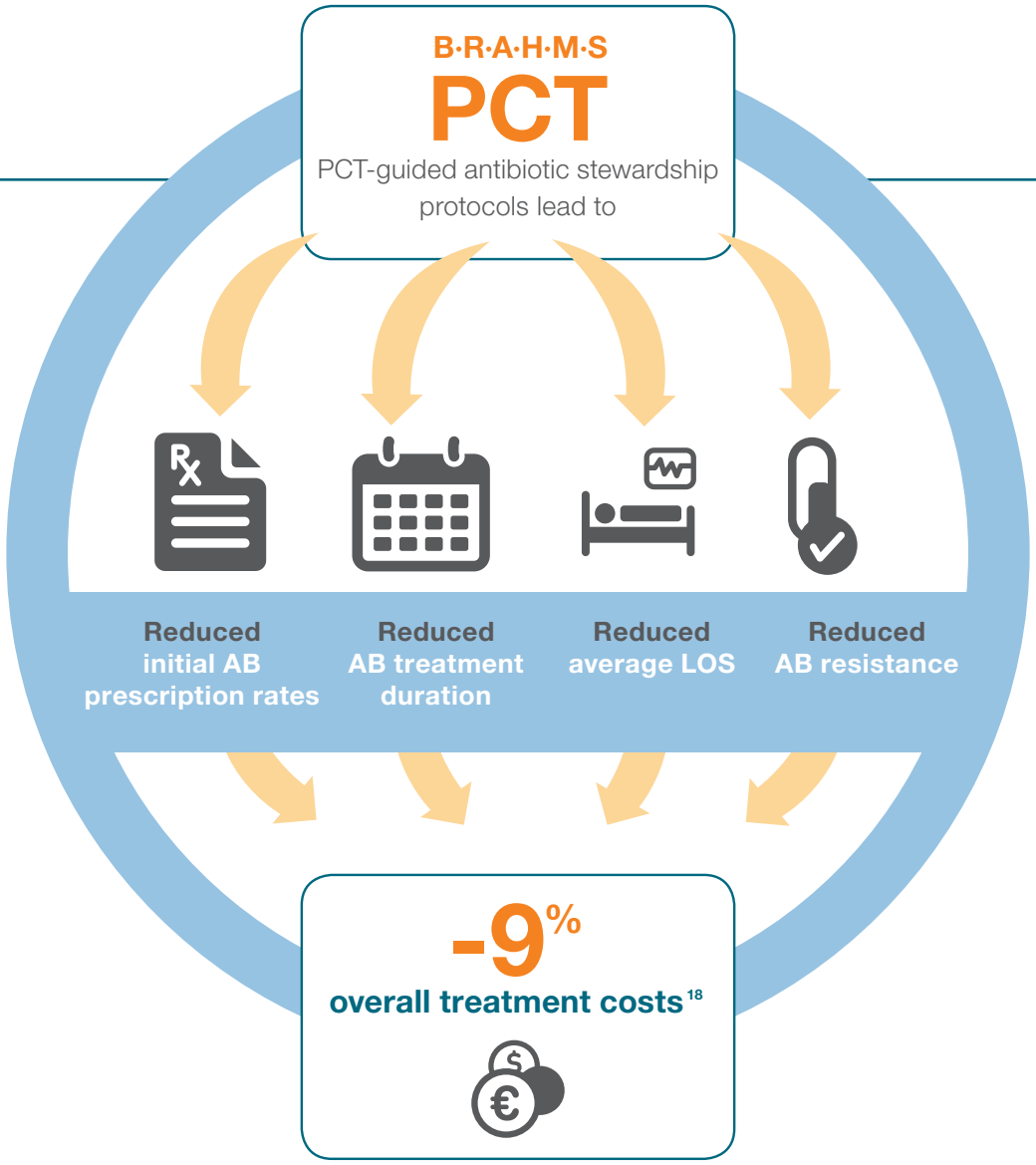




PCT group (n=60)
Control group (n=61)

Figure 12 PCT-guided treatment of suspected neonatal sepsis[17]

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



The economic impact of PCT-guided treatment has been studied through health economic modeling in various settings:

- Sepsis patients – ICU[18]
- Acute Respiratory Infections – inpatient, ICU, outpatient[33]
- COPD exacerbation – inpatient[34]

Treatment cost reductions ranging from 9% to 12% have been demonstrated across various countries.[35]

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."

PCT recognized by WHO

as an aid to fight antibiotic resistance:

PCT included on the Essential In Vitro Diagnostics List of the World Health Organization to aid in antibiotic stewardship[37]

References

1 WHO Global Action Plan Antimicrobial Resistance, 2015
2 Centers for Disease Control and Prevention (CDC), Press Release, May 3, 2016: http://www.cdc.gov/media/releases/2016/p0503-unnecessary-prescriptions.html
3 Rhodes et al., Intensive Care Med 2017; 43 (3): 304-377
4 Schuetz et al., JAMA 2009; 302: 1059-1066
5 Christ-Crain et al., Lancet 2004; 363: 600-607
6 Christ-Crain et al., Am J Respir Crit Care Med 2006; 174: 84-93
7 Long et al., Crit Care 2014; 18: 471
8 Briel et al., Arch Intern Med 2008; 168: 2000-7
9 Esposito et al., Respir Med 2011; 105: 1939-1945
10 Baer et al., PLoS One 2013; 8: e68419
11 de Jong et al., Lancet Infect Dis 2016; 3099: 1-9
12 Bouadma et al., Lancet 2010; 375: 463-474
13 Nobre et al., Am J Respir Crit Care Med 2008; 177: 498-505
14 Stolz et al., Eur Respir J 2009; 34: 1364-1375
15 Hochreiter et al., Crit Care 2009; 13: R83
16 Schroeder et al., Langenbecks Arch Surg 2009; 394: 221-226
17 Stocker et al., Neonatology 2010; 97: 165-174
18 Kip et al., J Med Econ 2015; 1-10
19 Harbarth et al., Am J Respir Crit Care Med 2001; 164: 396-402
20 Meisner M, Procalcitonin – Biochemistry and Clinical Diagnosis, ISBN 978-3-8374-1241-3, UNI-MED, Bremen 2010
21 Müller B et al., Crit Care Med 2000, 28 (4): 977-983
22 Svoboda et al., Hepatogasteroenterology 2007; 54: 359-363
23 Maravić-Stojković et al., Srp Arh Celok Lek 2011; 139: 736-742
24 Schuetz et al., Clin Infect Dis 2012; 55(5): 651-62
25 Stolz et al., Chest 2007; 131: 9-19
26 Charles et al., Crit Care 2009; 13: R38
27 Stüber, 21st Int. Congress of Intensive Care and Emergency Medicine (ISICEM), Brussels 2001
28 Filippini et al., Health Policy 2006; 78(1): 77-92
29 Maseda et al., J Crit Care 2015; 30: 537-542
30 Sartelli et al., Surg Infect (Larchmt) 2015; 17: 9-12
31 Joram et al., Arch Dis Child Fetal Neonatal Ed 2006; 91: F65-F66
32 Joram et al., Eur J Clin Microbiol Infect Dis 2011; 30(8): 1005-1013
33 Schuetz et al., Clin Chem Lab Med 2015; 53(4): 583-592
34 Maas et al., Poster, ISPOR 18th Annual European Congress, Milan, 2015
35 Steuten, Cost effectiveness of biomarker testing in sepsis patients; ISICEM Brussels, March 15-19, 2015
36 Broyles, Open Forum Infect Dis 2017; 4(4): ofx213
37 2nd WHO Model List of Essential In Vitro Diagnostics (WHO/MVP/EMP/2019.05)

thermo scientific

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

thermo scientific	B·R·A·H·M·S PCT sensitive KRYPTOR™ B·R·A·H·M·S PCT direct
Abbott	ALINITY i B·R·A·H·M·S PCT ARCHITECT B·R·A·H·M·S PCT
BIOMÉRIEUX	VIDAS® B·R·A·H·M·S PCT
DiaSorin	LIAISON® B·R·A·H·M·S PCT II GEN
FUJIREBIO Diagnostics, Inc.	Lumipulse® G B·R·A·H·M·S PCT
Ortho Clinical Diagnostics	VITROS® B·R·A·H·M·S PCT
Roche	ELECSYS® B·R·A·H·M·S PCT
SIEMENS	ADVIA Centaur® B·R·A·H·M·S PCT Atellica® IM B·R·A·H·M·S PCT

Automated sensitive assay

Point-of-Care-Test

Not all intended uses and applications mentioned in this printing are registered for every product in every country.

Clinical Diagnostics

Thermo Fisher Scientific
B·R·A·H·M·S GmbH
Neuendorfstr. 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**

Not all products are CE marked or have 510(k) clearance for sale in the U.S. Availability of products in each country depends on local regulatory marketing authorization status.

107528.5

ThermoFisher SCIENTIFIC