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Accelerate treatment decisions with B·R·A·H·M·S Biomarkers

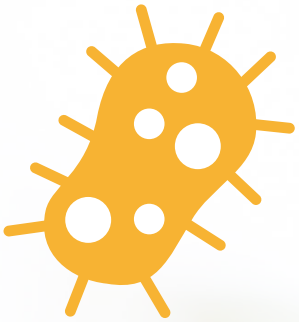
B·R·A·H·M·S PCT™ PROVEN CONFIDENCE

Early differential diagnosis and therapy decision in the emergency department

ThermoFisher SCIENTIFIC

The challenge ...

How to put the infected patient on the right therapy pathway



Is it bacterial infection?

Clinical symptoms like fever, cough, chest pain, shortness of breath, vertigo/dizziness, skin rash, laboured or difficult breathing, surgical and medical complications, abdominal pain, unspecific complaints may **overlap with other, non-infectious diseases. Fever or WBC may be in normal range in up to 50% of patients.**[1]

Are antibiotics required?

- **Rapid initiation of ABx is important for patients with true bacterial infection** to avoid progression to sepsis and shock and to improve survival.
- In contrast, **patients with other cause of clinical symptoms should** be put on the appropriate treatment pathway for the respective disease and **not get ABx unnecessarily**.

Is hospital admission required?

- What is the patient's risk level?
- Is hospital admission/specialized care required?

... and what biomarkers can contribute

Correct differential diagnosis and risk assessment already in the ED is important for optimal patient treatment and outcome. **Biomarkers may add an important piece of information for rapid clinical decision making in the ED.**

Procalcitonin (PCT)

Early confirmation/exclusion of suspected bacterial infection

→ **Decision on antibiotic treatment**

MR-proAdrenomedullin (MR-proADM)

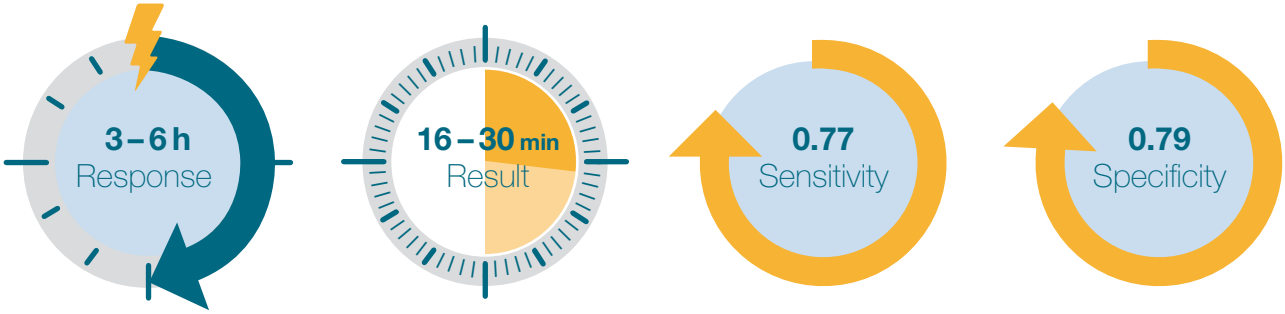
Early risk assessment

→ **Decision on in- or outpatient treatment**

Fast and precise

B·R·A·H·M·S PCT – the best marker for 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 clinically relevant bacterial infections and therapy control.



Early response

Levels increase within 3–6 hours after bacterial challenge [2]

Fast results

Incubation time 16–30 minutes

Highly sensitive and specific

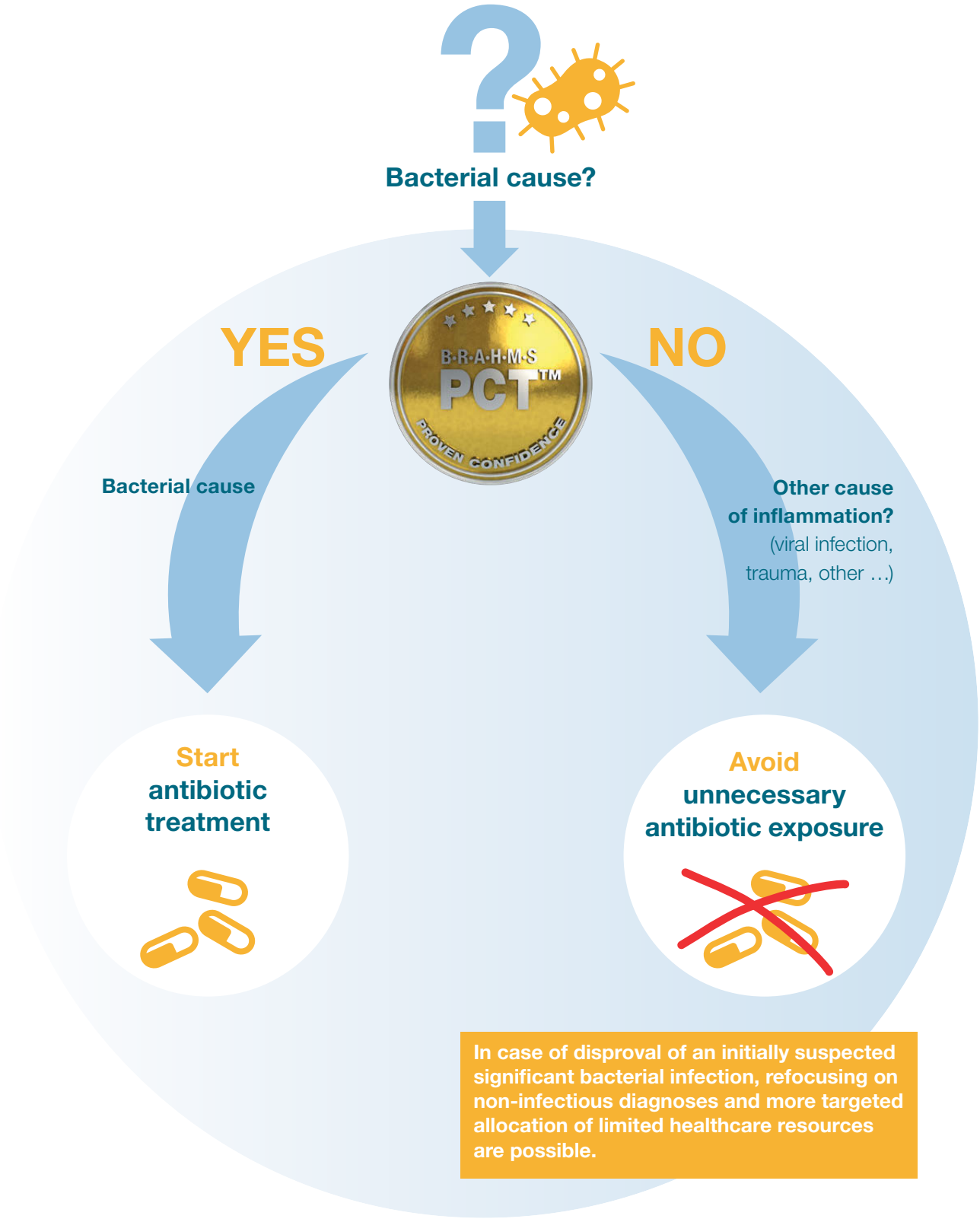
A mean sensitivity of 0.77 and a mean specificity of 0.79 to discriminate sepsis from SIRS of non-infectious origin – based on meta-analysis of 3244 patients [3]

Early rule out of bacteremia

Bacterial infections can neither be predicted nor ruled out completely by bedside-available clinical parameters. Nevertheless, PCT measurement on admission to ED could provide information on the likelihood of blood culture positivity. A low PCT value (≤0.25 µg/L) sufficiently rules out bacteremia.[4,5,6]

	CAP [4] Blood culture		UTI [5] Blood culture		Febrile patients [6] Molecular testing	
PCT cut-off	>0.1 µg/L	>0.25 µg/L	>0.1 µg/L	>0.25 µg/L	>0.1 µg/L	>0.25 µg/L
Sensitivity	0.99	0.96	0.99	0.95	0.98	0.98
Specificity	0.13	0.40	0.24	0.50	0.36	0.51
Missed pathogenes	1.4	4.1	1	5	1.8	1.8
NPV	98%	97%	n.a.	n.a.	99%	99%

Table 1 PCT for bacteremia prediction in CAP (n=925) [4], UTI (n=581) [5] and febrile patients (n=1009) [6]
NPV = negative predictive value



PCT-supported differential diagnosis in the ED enables
targeted treatment from the beginning

Is it bacterial infection?

PCT for early differential diagnosis in the ED

Fever without source (FWS)

- Fever without source is a common complaint in the ED, especially in pediatric patients. Distinction between self-limiting (viral) infection and severe bacterial infection remains a challenge even for experienced pediatricians.[7]
- A meta-analysis of 5 studies on 4692 children revealed that **PCT adds significantly to detect invasive bacterial infection in children with FWS**.[8]
- This discriminative capability of PCT was demonstrated to be superior compared to conventional biomarkers (e.g. CRP, leukocytes (meta-analysis of 8 studies, n=1883).[9]

Urinary tract infection (UTI)

- PCT accurately predicts the presence of bacteremia and bacterial load in adult patients with febrile UTI.[5]
- In children, PCT appears to be the most useful marker to **differentiate lower urinary tract infection (cystitis) from upper tract infection (pyelonephritis)**.[10,11]
- Elevated PCT levels may also predict subsequent vesicoureteral reflux and renal scarring thus helping to avoid unnecessary cystourethrographies in children.[12]

	FWS		UTI	
	Children[8]		Adults[5]	Children[10]
	Assess presence of invasive bacterial infection		Predict bacteremia in APN	Distinguish APN from cystitis
	Rule out	Rule in		
PCT cut-off	0.5 µg/L	2 µg/L	0.25 µg/L	0.5 µg/L
Sensitivity	0.82	0.61	0.95	0.97
Specificity	0.86	0.94	0.50	0.67
PPV	n.a.	94%	36%	84%
NPV	99%	n.a.	97%	91.7%

Table 2 Diagnostic performance of PCT in patients with fever without source (FWS; n=4692)[8] and urinary tract infection (UTI) in adults (n=581)[5] and children (n=136)[10]
APN = acute pyelonephritis; NPV = negative predictive value; PPV = positive predictive value

Meningitis

The global burden of meningitis is assessed with 2.82 million cases annually. Although vaccination programs have reduced the number of **bacterial meningitis** cases, it remains the most **life-threatening** form (up to 50% mortality if untreated) and requires immediate antibiotic treatment.[13]

Need for differential diagnosis!

To avoid overuse of antibiotics and unnecessary hospitalization, **decision rules** have been proposed to differentiate between bacterial and aseptic meningitis, with **PCT as the best biological marker** included.[14]

PCT was shown to be superior to other biomarkers for differential diagnosis of bacterial meningitis (Fig. 1 and 2).[15-17]

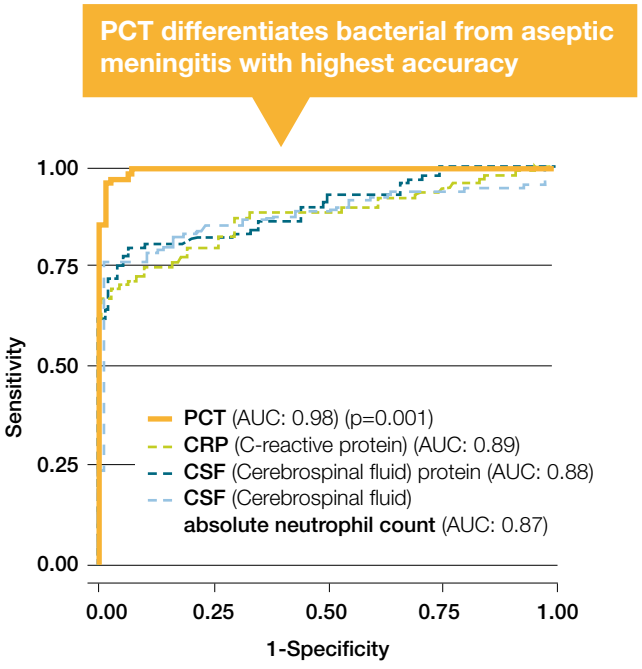


Figure 1 Receiver operating characteristics curves of the best predictors differentiating bacterial from aseptic meningitis (n=198) [15]

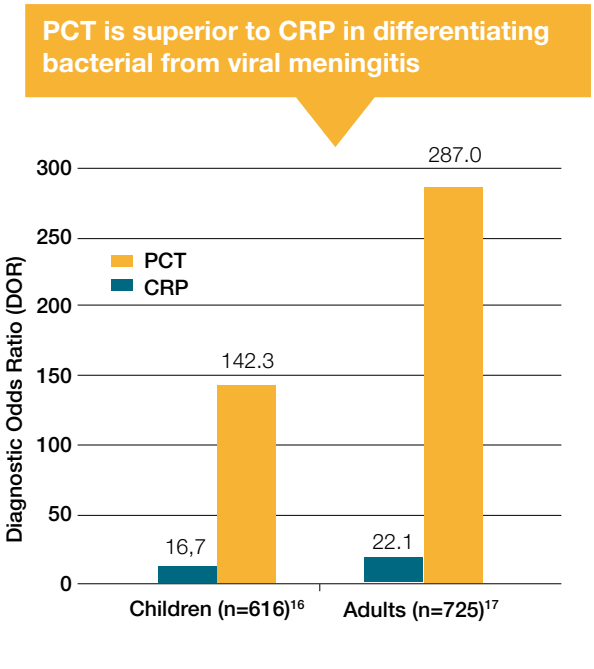


Figure 2 Diagnostic performance of PCT and CRP to differentiate bacterial meningitis from viral meningitis in children [16] and adults [17]

Are antibiotics required?

High efficacy of PCT-guided AB therapy in LRTI

As much as 75% of all antibiotic doses are prescribed for acute respiratory tract infections despite their mainly viral cause or other reasons of disease exacerbation (e.g. in COPD or asthma) patients. PCT guidance in such patients allows reduction of AB exposure without any adverse impact on outcome.[18]

-17%
initiation of AB in ED

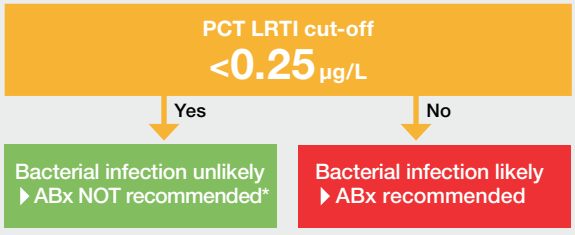
-10%
30d mortality rate

Data from: Effect of procalcitonin-guided antibiotic treatment on mortality in acute respiratory infections: a patient level meta-analysis[18]
Based on data of 6708 patients from 26 eligible trials in 12 countries.
PCT-guided patients:
3336 (thereof 1615 patients from ED)
Control patients:
3372 (thereof 1638 patients from ED)

* Effect of PCT-guided AB treatment in ED patients as % of reduction versus the control group

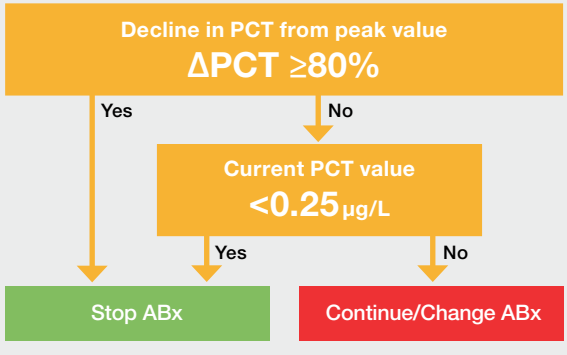
Thermo Scientific™ B·R·A·H·M·S PCT™ algorithm for LRTI patients

When to START antibiotics?



When to STOP antibiotics?

Repeat PCT measurement every alternate day



$$\Delta PCT = \frac{\text{Peak PCT} - \text{Current PCT}}{\text{Peak PCT}} \times 100\%$$

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

Detect pneumonia in patients with overlapping symptoms of acute heart failure

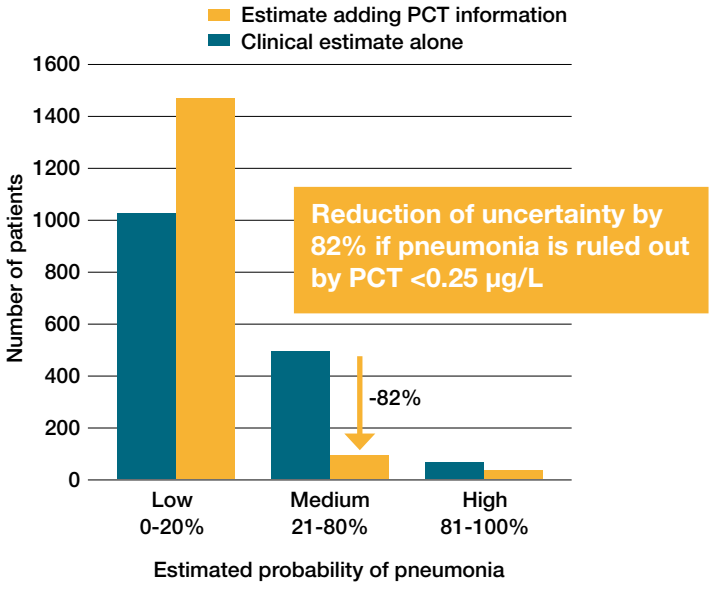


Figure 3 Estimated probability of pneumonia in patients (n=1641) in the emergency department presenting with shortness of breath [19]

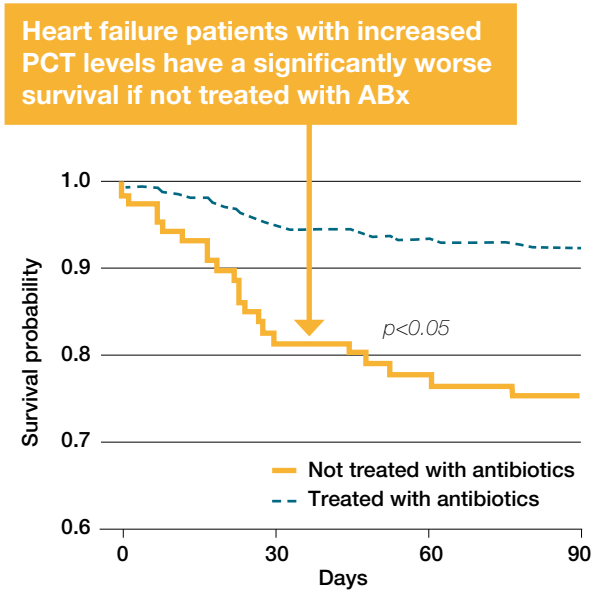


Figure 4 Survival and antibiotic treatment of heart failure patients with PCT >0.21 µg/L (n=113) [19]

Antibiotics?

Increase survival rate by improved diagnosis and targeted antibiotic treatment.

Hospital admission or treatment as out-patient?

Early risk assessment in the ED aided by MR-proADM*

Midregional pro-Adrenomedullin (MR-proADM) key facts

- Stable surrogate marker for the native adrenomedullin
- Reflects endothelial function and integrity
- Used to assess the risk for organ dysfunction development and prognosis

MR-proADM was demonstrated to be the best marker to identify patients at low and high risk, and to support decisions on adequate level of care.[20-22]

In the ED MR-proADM can help to rule-out severe conditions and potential disease progression early. This allows to

- identify patients at risk requiring hospitalization ("red flag")
- increase the number of safely discharged patients
- allocate limited resources to patients at risk[20,23]

High Risk
MR-proADM >0.87 nmol/L

Hospitalisation recommended

Low Risk
MR-proADM <0.87 nmol/L

Consider out-patient care

MR-proADM algorithm as an aid for risk assessment and decision on level of care

* Reference: Saeed et al., Crit Care 2019; 23(1): 40. doi: 10.1186/s13054-019-2329-5

MR-proADM for safe discharge of low risk patients from the ED

A recent observational multicentric study (n=1175) did reveal that based on the use of a MR-proADM decision rule, significantly more patients could be safely discharged from the ED and treated as out-patients without negative impact on mortality or re-admission rates (Fig. 5).[23]

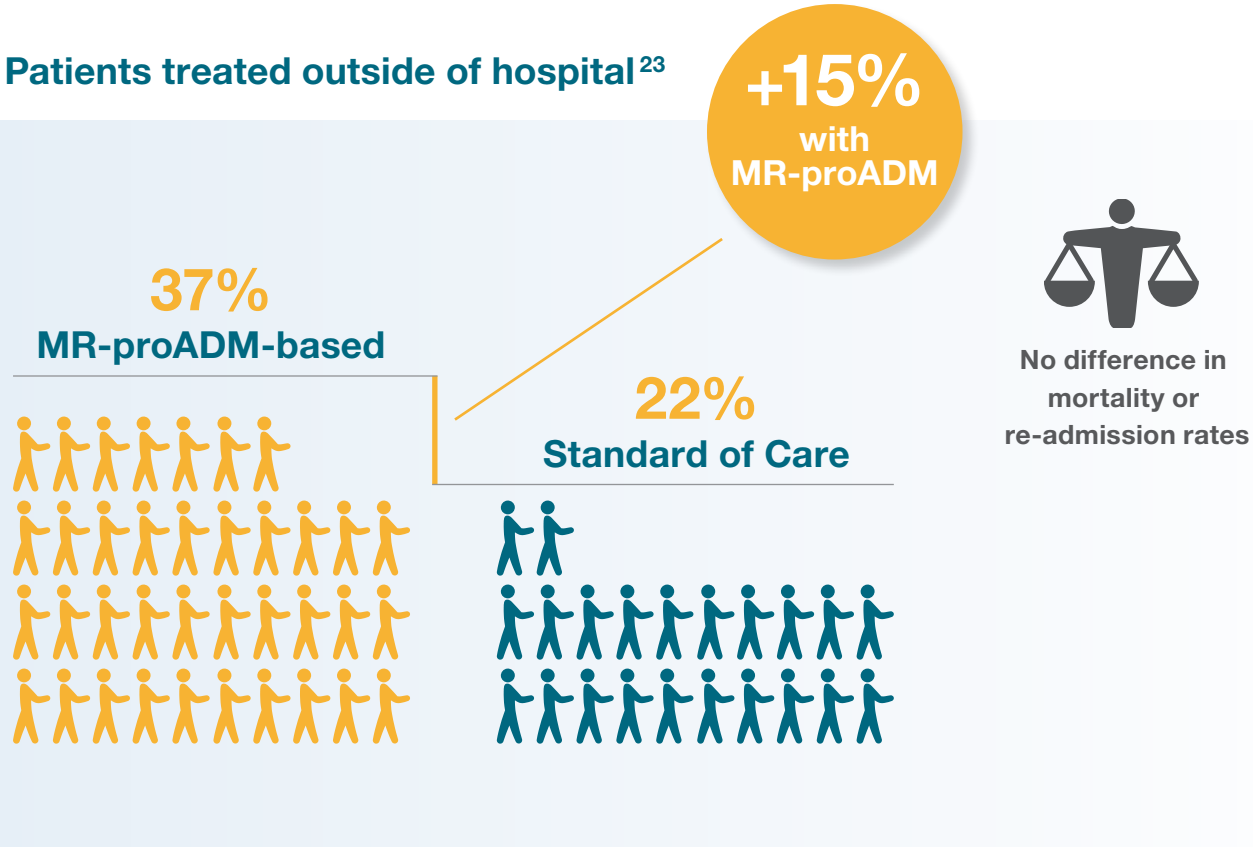


Figure 5 Number of patients (in %) admitted with signs of infection to ED, that could be discharged for out-patient treatment based on standard of care decision making or using MR-proADM cut-off <0.87 nmol/L (total patient cohort n=1175)
Mortality: 84 in-patients in both groups, zero out-patients in both groups
Re-admission: 10/260 discharged patients in standard-of-care group, 12/436 discharged patients in MR-proADM group[23]

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Just one drop of blood needed

PCT use at point of care in the ED

B·R·A·H·M·S PCT direct

- Quantitative results
- Only 20 µL whole blood (capillary or venous EDTA)
- Short total turn-around time
- Optimal fit to data management
- Independent from laboratory service

Thermo Scientific B·R·A·H·M·S direct Reader
The platform for B·R·A·H·M·S PCT direct

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