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ARTICLE

Influence of procalcitonin on decision to start antibiotic treatment in patients with a lower respiratory tract infection: insight from the observational multicentric ProREAL surveillance

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Abstract Procalcitonin (PCT)-guided antibiotic stewardship is a successful strategy to decrease antibiotic use. We assessed if clinical judgement affected compliance with a PCT-algorithm for antibiotic prescribing in a multicenter surveillance of patients with lower respiratory tract infections (LRTI).

Initiation and duration of antibiotic therapy, adherence to a PCT algorithm and outcome were monitored in consecutive adults with LRTI who were enrolled in a prospective observational quality control. We correlated initial clinical judgment of the treating physician with algorithm compliance and assessed the influence of PCT on the final decision to initiate antibiotic therapy.

PCT levels correlated with physicians' estimates of the likelihood of bacterial infection (p for trend <0.02). PCT influenced the post-test probability of antibiotic initiation with a greater effect in patients with non-pneumonia LRTI (e.g., for bronchitis: −23 % if PCT≤0.25 μg/L and +31 % if PCT> 0.25 μg/L), in European centers (e.g., in France −22 % if PCT≤0.25 μg/L and +13 % if PCT>0.25 μg/L) and in

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centers, which had previous experience with the PCT-algorithm (−16 % if PCT≤0.25 μg/L and +19 % if PCT> 0.25 μg/L). Algorithm non-compliance, i.e. antibiotic prescribing despite low PCT-levels, was independently predicted by the likelihood of a bacterial infection as judged by the treating physician. Compliance was significantly associated with identification of a bacterial etiology (p=0.01).

Compliance with PCT-guided antibiotic stewardship was affected by geographically and culturally-influenced subjective clinical judgment. Initiation of antibiotic therapy was altered by PCT levels. Differential compliance with antibiotic stewardship efforts contributes to geographical differences in antibiotic prescribing habits and potentially influences antibiotic resistance rates.

Introduction

Antibiotic mis- and overuse is associated with a relevant risk for side effects [1], collateral damage to the resident microorganisms [2] and the incidence of *Clostridium difficile* associated diarrhea [3]. Antibiotic use is the major driver for antibiotic resistance [4–8]. Infections due to antibiotic resistant organisms have worse clinical outcomes, longer length of stay and higher healthcare costs than infections due to their susceptible counterparts [9–11]. Since antimicrobial development pipelines are running dry, this is of paramount public health importance [12].

It is increasingly obvious that socioeconomic, geographic and cultural factors are a major driver for antibiotic prescribing habits and stewardship programs [4, 6, 7, 13–17]. Consistently, the lowest antibiotic use is observed in Northern Europe, Germany and Switzerland with comparatively higher rates in France and the USA [6, 13, 18].

Procalcitonin (PCT)-guided antibiotic stewardship is a successfully validated and established strategy to decrease antibiotic use and battle antibiotic resistance in randomized controlled trials and clinical practice [19–24]. We recently confirmed the effectiveness and safety of PCT-guided antibiotic therapy in lower respiratory tract infections (LRTI) in "real life" outside of study conditions in the observational ProREAL surveillance including 14 centers in Switzerland, France and the United States [25] and demonstrated that pre-existing differences in antibiotic prescribing habits affect compliance with antibiotic stewardship efforts.

Herein, we analyze the correlations between clinical judgment, PCT levels and algorithm compliance and the influence of PCT-levels on the final decision to initiate antibiotic therapy.

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Materials and methods

The study design has been described in detail [25]. In brief, "ProREAL" was a prospective observational international multicenter quality control survey enrolling consecutive patients without exclusion criteria, who presented with community-acquired LRTI to general physician (GP) offices or hospital emergency departments in 14 centers in Switzerland (n=10), France (n=3) and the United States (n=1) between September 2009 and February 2011. For this sub-analysis, mainly adherence to the published PCT algorithm (Fig. 1) and outcome were monitored. Three of the Swiss hospitals had previously participated in the ProHOSP study [21, 26] and were considered algorithm-experienced, while all other centers had not used this algorithm previously and were considered algorithm-naïve.

PCT measurement was recommended in all patients with LRTI, while choice of antibiotics, diagnostic and therapeutic management were in accordance with local guidelines. Patients were registered on a password-secured website which displayed the algorithm including PCT cut-off ranges and predefined overruling criteria [20, 21]. PCT results became available within 60 minutes after the initial blood draw. Physicians and study personnel were instructed in initial 1-hour seminars with ongoing reminders by personal or e-mail contact.

Definitions

LRTI, bronchitis, acute exacerbation of chronic obstructive pulmonary disease (AECOPD) and community acquired pneumonia (CAP) were diagnosed according to guidelines [21]. We defined "compliance" as initiation and discontinuation of antibiotic treatment in accordance with the PCT cut-off ranges or, if the PCT-levels suggested no antibiotic therapy, with the predefined overruling criteria. Conversely, "non-compliance" was defined if antibiotic therapy was initiated or not discontinued despite low PCT levels in the absence of any of the predefined criteria. Not giving an antibiotic in patients with high PCT levels was allowed if it was considered safe by the clinician. It was not considered "non-compliance" in order to avoid treating only abnormal laboratory values which might result in antibiotic overuse.

Endpoints

Herein, we focused on the initial subjective clinical judgment of the treating physician before the PCT value became

Procalcitonin (PCT) algorithm (ug/L = ng/ml)

<0.1 ug/L	0.1-0.25 ug/L	0.26-0.5 ug/L	>0.5 ug/L
Antibiotic therapy strongly discouraged	Antibiotic therapy discouraged	Antibiotic therapy recommended	Antibiotic therapy strongly recommended

If no antibiotic therapy initiated:

- Repeat PCT within 6-24 h (also in outpatients if symptoms persist or worsen)
- Differential diagnosis? E.g. pulmonary embolism, congestive heart failure, tumor, BOOP, viral, fungal
- Antibiotic therapy can be considered for:
  1. Admission to intensive care (ICU) or intermediate care unit (IMC):
     - Respiratory instability (respiratory rate >=30/min and/or oxygen saturation <90% with 6 L O2/min)
     - Hemodynamic instability (systolic blood pressure for at least 1h <90 mmHg despite adequate volume replacement or need for vasopressors)
  2. Life-threatening comorbidity: a) imminent death; b) severe immunosuppression (neutrophiles <500/uL; for HIV: CD4<350/uL); c) chronic infection or other non-respiratory infection requiring antibiotics (e.g. endocarditis, TB)
  3. Complications and difficult-to-treat-organisms: Legionella (antibiotics > 10d), abscess, empyema
  4. a) PCT <0.1ug/L: CAP PSI V (>130) or C(U)RB65 >3 points, COPD GOLD IV; b) PCT 0.1-0.25ug/L: CAP PSI IV&V (>90), C(U)RB65 >2 points, COPD GOLD III&IV, SaO2 <90% despite 30' intensive therapy
- Falsely low PCT: e.g. parapneumonic effusion, loculated infection (empyema), early phase of infection, fungal, most severe immunosuppression

If antibiotic therapy initiated:

- PCT control on day 2-3, 4-5, 6-8 and every 2 days after day 8 for guidance of antibiotic therapy
- To stop ongoing antibiotic therapy use the same cut-offs as above
- For outpatients duration of antibiotic therapy depends on last PCT-value (>=0.25 ug/L: 3d, >=0.5ug/L: 5d, >=1ug/L: 7d)
- For initially very high PCT (e.g. >5ug/L) follow the relative decline of PCT if there is good response: decline >=80% of peak: Stop recommended, decline >=90% of peak: Stop strongly recommended
- Persistently elevated PCT: suspect complicated course (resistant organism, MOF, abscess…)
- Falsely elevated PCT: e.g. severe SIRS & shock, ARDS, trauma, post-operative, tumor (e.g. medullary thyroid cancer, SCLC), fungal, malaria

Fig. 1 Procalcitonin (PCT) algorithm (ug/L=ng/ml)

available. For this purpose the treating physician was required to provide two related estimates: the likelihood that the LRTI was due to an underlying bacterial infection, and the likelihood of initiating antibiotic therapy if there had been no PCT-guidance. The estimated probabilities had to be entered on the website prior to the availability of the PCT result on a scale from 0–100 % with 10 % increments. Endpoints were the correlation between clinical judgment and PCT levels, the influence of the initial subjective judgment on algorithm compliance and the influence of PCT on the final decision to initiate antibiotic therapy.

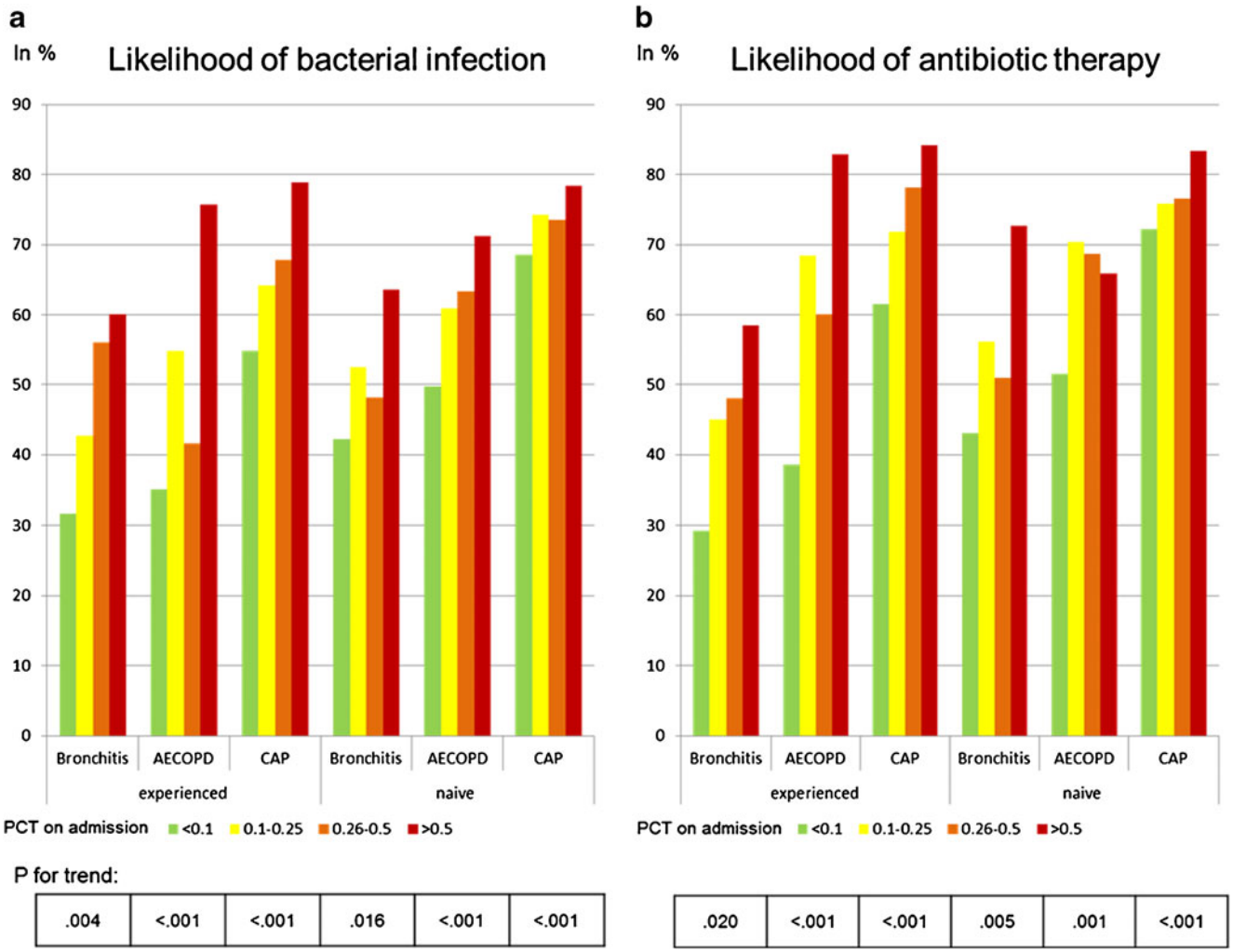
Statistical analysis

We used the Cochran-Armitage test for trend to assess the estimated likelihood of a bacterial infection and the likelihood of starting antibiotic therapy without knowledge of the PCT values (i.e. before PCT was available) as reported by the treating physicians over increasing PCT values. For correlation analyses we used the 2-tailed Spearman's correlation coefficient. Multivariable logistic regression was performed to assess for independent predictors of algorithm non-compliance. Analysis of variance (ANOVA) was used to assess the trend of the observed proportion of antibiotic initiation with increasing PCT values. All p values<0.05 were considered statistically significant. Analyses were made with SAS Software, version 9.2 (version 9.2, SAS Institute, Cary, NC) and OpenEpi (www.openepi.com).

Results

There were 1,810 patients enrolled in the ProREAL survey, and final diagnosis was an LRTI in 1,520 patients (86.2 %). A total of 1,425 had a final diagnosis of an LRTI and sufficient follow-up information at day 30.

There was a strong correlation between the estimated likelihood of a bacterial infection and the likelihood of starting antibiotic therapy without knowledge of the PCT values (i.e. before PCT values were available) as reported by the treating physicians (r=0.85; $p<$ 0.0001). Both the estimated likelihood of a bacterial infection and the likelihood of starting antibiotic therapy (before PCT values were available) increased with increasing PCT values in all patients, regardless of whether the center had experience with the algorithm or was algorithm-naïve (Fig. 2). If separated by country, the same effect was seen for Swiss centers. However, the estimated likelihood of a bacterial infection and of starting antibiotic therapy (before PCT values were available) did not vary significantly in relation to PCT values for US patients with bronchitis and AECOPD,



P for trend:

.004	<.001	<.001	.016	<.001	<.001

.020	<.001	<.001	.005	.001	<.001

Fig. 2 Correlation of estimated likelihood of bacterial infection (**a**) and estimated likelihood of antibiotic therapy (**b**) with initial PCT values (experienced–naïve)

and similarly, for French patients with AECOPD and CAP (Fig. 3).

In Switzerland, there was a significant, but weak correlation between the estimated likelihood of a bacterial infection before the PCT value was known and non-compliance with the PCT algorithm in patients with a low admission PCT value (Table 1). The same was found for the estimated likelihood of starting antibiotic therapy before PCT and non-compliance with the PCT algorithm if there was a low PCT value for bronchitis and AECOPD (Table 1). In the US and French sites, there were no significant correlations between either the estimated likelihood of a bacterial infection or the estimated likelihood of starting antibiotic therapy before the PCT values were available and non-compliance with the PCT algorithm if there was a low PCT value (Table 1). For bronchitis, AECOPD and CAP patients, the estimated likelihood of a bacterial infection was independently associated with algorithm non-compliance in multivariable models controlling for gender, CURB65 score, underlying comorbidities, treatment site (hospital vs. GP office) and algorithm experience ($p=0.02$, $p<0.001$ and $p=0.02$, respectively).

The observed proportion of antibiotic initiation on admission increased significantly with increasing PCT admission values for algorithm-experienced and algorithm-naïve centers for all diagnoses (Table 2a). The same correlation was found for patients in Switzerland (all diagnoses) and France (AECOPD and CAP), whereas initiation of antibiotics did not vary with PCT values for any diagnosis in the US site (Table 2b).

In Swiss and French sites, in patients with bronchitis and with AECOPD, and in experienced centers, PCT affected the post-test probability of antibiotic initiation by decreasing the likelihood of antibiotic therapy if PCT was ≤0.25 μg/l and by increasing the likelihood of antibiotic therapy if PCT was >0.25 μg/l (Fig. 4). If PCT levels were low, the

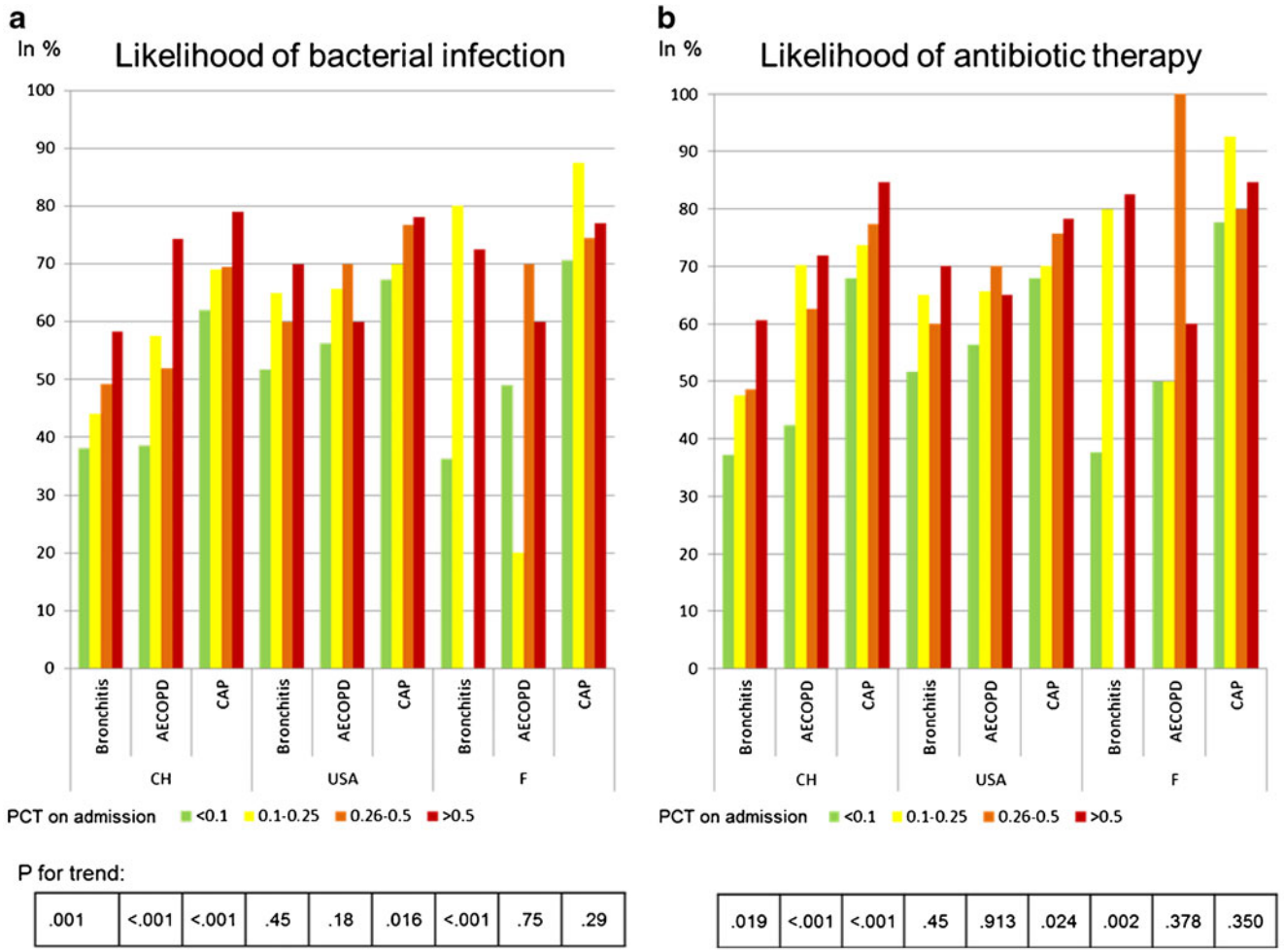


Fig. 3 Correlation of estimated likelihood of bacterial infection (**a**) and estimated likelihood of antibiotic therapy (**b**) with initial PCT-values (countries)

post-test probabilities of prescribing antibiotics were not reduced in algorithm-naïve centers, in patients with CAP and in the US site (Fig. 4).

Algorithm compliance according to etiology is listed in Table 3. Compliance was significantly higher if an etiology was subsequently identified than if no organism was detected (OR 1.497; 95 % CI 1.093–2.071; P=0.01).

Discussion

The five key findings of this study are as follows. First, physicians' estimates of the likelihood of bacterial infection correlate with PCT levels regardless of algorithm-experience, particularly for Swiss centers. Second, compliance with the algorithm was higher in patients in whom (subsequently) a bacterial etiology could be identified than in those without etiology. Third, the proportion of patients who received antibiotics on admission increased with rising PCT values independently of previous experience with the algorithm, with the strongest correlation for Swiss sites. Fourth, PCT levels did modify the post-test probability of antibiotic initiation, again most clearly in Swiss centers, in experienced centers and in patients with bronchitis and AECOPD. Finally, overruling of the algorithm was independently predicted by the likelihood of a bacterial infection as judged by the treating physician.

The positive correlation between physicians' compliance and subsequently identified bacterial etiology indicate a high quality of the initial clinical evaluation of the patient regardless whether there was previous experience with PCT or not, as had been shown in pediatricians' ability to predict bacteraemia previously [27]. Not surprisingly, the estimated likelihood of a bacterial infection was lowest for patients with bronchitis and highest for patients with CAP. Of note, the relatively low proportion of confirmed etiologies is at the lower range of the published literature [28] but reflects the reality of decreasing emphasis on and yield of diagnostic

Table 1 Correlation of estimated likelihood of bacterial infection and of estimated likelihood of starting antibiotic therapy (before PCT value is known) with overruling of the PCT algorithm

According to countries						
Diagnosis	Switzerland		USA		France	
	r	*p*	*r*	*p*	*r*	*p*
Estimated likelihood of bacterial infection						
Bronchitis	0.25	**0.003**	−0.03	0.91	0.09	0.61
AECOPD	0.33	**<0.001**	0.07	0.55	0.41	0.07
CAP	0.19	**0.003**	−0.17	0.142	−0.12	0.569
Estimated likelihood of starting antibiotic therapy						
Bronchitis	0.25	**0.004**	−0.03	0.907	0.06	0.718
AECOPD	0.36	**<0.001**	0.09	0.460	0.31	0.166
CAP	0.09	0.164	−0.17	0.146	−0.36	0.081
According to algorithm experience						
Diagnosis	Experienced		Naive			
	r	*p*	*r*	*p*		
Estimated likelihood of bacterial infection						
Bronchitis	0.32	**0.009**	0.20	0.025		
AECOPD	0.30	**0.010**	0.30	**<0.001**		
CAP	0.13	0.165	−0.01	0.922		
Estimated likelihood of starting antibiotic therapy						
Bronchitis	0.30	0.015	0.17	0.06		
AECOPD	0.26	0.024	0.26	**0.001**		
CAP	0.09	0.317	−0.13	**0.048**		

AECOPD acute exacerbation of chronic obstructive pulmonary disease, *CAP* community acquired pneumonia

Values in bold are statistically significant

tests in respiratory tract infections. In this study, the diagnostic evaluation was left at the discretion of the treating physicians.

Physicians in algorithm-experienced centers estimated the likelihood of bacterial etiology lower in patients with low PCT-values compared to their counterparts without algorithm experience. This suggests a learning curve probably in relation to previous experiences of having successfully withheld antibiotics without detrimental effect [21, 23]. It also correlates with lower actually observed proportions of antibiotic therapy in sites with previous algorithm experience. Teaching medicine residents both clinical judgment and the integration with the available technical diagnostics [29] to create an overall picture of the patient seems a laudable goal given the improvement in algorithm-experienced centers. Importantly, we predefined several overruling criteria, which allowed antibiotic therapy also in patients with low PCT values. This was done as any biomarker should only be used in combination with rather than instead of the clinical assessment.

Even in patients with bronchitis, physicians considered a bacterial etiology likely in 30–50 % with the highest values in the US site. This is considerably higher than what is usually reported as <10 % of cases [30]. Likewise, highest estimates in the US site are in accordance with previous reports that up to two thirds of US patients with bronchitis receive antibiotic therapy [31], which is in agreement with proportions observed in the US and French sites as well as in this study, but in marked contrast to considerably lower values for Swiss patients with bronchitis and, notably, recommendations of current guidelines [32].

The estimated likelihood of starting antibiotic therapy before PCT correlated with algorithm non-compliance in patients with bronchitis and AECOPD, but not for CAP. An explanation is that patients with CAP are generally the sickest at the time of presentation and most frequently receive antibiotics, there are more overruling criteria present and, therefore, the probability of being non-compliant with the algorithm decreases. Since there was no correlation between the estimated likelihood of starting AB therapy in these patients and non-compliance with the algorithm, the likelihood of bacterial infection alone was not responsible for algorithm non-compliance in CAP patients. Similar effects of not only medical factors might have been responsible for antibiotic prescribing in the French and US centers. Despite considering a bacterial etiology likely in <80 % of CAP patients, US physicians initiated antibiotic therapy almost uniformly in these patients regardless of PCT values. This discrepancy between clinical judgment and actual decision making has been explained by medico-legal pressures, patients' demands, peer pressure and traditional behaviour in the US healthcare system [14]. It however confirms our observations from previous studies [19, 21, 24] that the effect of PCT for patients with CAP even in Swiss centers is less due to restricting initiation of antibiotics—as is the main effect for patients with bronchitis and AECOPD—but rather an effect of reducing antibiotic duration. We only obtained information at the initial encounter and therefore were unfortunately unable to analyse subsequent effects of PCT. Comparatively lower AB prescription rates in the French than the US sites might be an effect of the recent successful antibiotic awareness campaigns in France [33, 34].

For the Swiss centers, we could find a significant, albeit weak correlation between the estimated likelihood of a bacterial infection and non-compliance with the PCT algorithm. This probably indicates that clinicians still rather confide in their own judgment than in objective clinical scores [35] or apparative parameters like PCT levels, even if their validity has been demonstrated well in randomized controlled trials [27]. It may take time until evidence-based criteria are being introduced into clinical care and probably a systematic and structured strategy on different levels of health care is necessary to be successful in this aim [33, 34, 36–39], particularly since inclusion criteria in studies

Table 2 Observed proportion of antibiotic therapy at initial presentation

Stratified for algorithm experience									
PCT	Observed AB therapy at presentation (in %)								
	Experienced			Naive					
	Bronchitis (*n*=85)	AECOPD (*n*=89)	CAP (*n*=353)	Bronchitis (*n*=142)	AECOPD (*n*=191)	CAP (*n*=564)			
<0.1	7.32 (3/41)	11.63 (5/43)	55.77 (29/52)	19.1 (17/89)	45.31 (58/128)	83.19 (99/119)			
0.1–0.25	26.92 (7/26)	48.48 (16/33)	61.97 (44/71)	38.71 (12/31)	67.74 (21/31)	87.76 (86/98)			
0.26–0.5	100 (5/5)	100 (6/6)	98.18 (54/55)	81.82 (9/11)	100 (15/15)	100 (72/72)			
>0.5	100 (13/13)	100 (7/7)	99.43 (174/175)	81.82 (9/11)	94.12 (16/17)	99.64 (274/275)			
p for trend	**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**			
Stratified for country									
PCT	Observed AB therapy at presentation (in %)								
	CH			USA			F		
	Bronchitis (*n*=169)	AECOPD (*n*=182)	CAP (*n*=661)	Bronchitis (*n*=20)	AECOPD (*n*=75)	CAP (*n*=160)	Bronchitis (*n*=38)	AECOPD (*n*=23)	CAP (*n*=96)
<0.1	10.23 (9/88)	12.22 (11/90)	62.86 (66/105)	75 (9/12)	78.69 (48/61)	97.96 (48/49)	66.67 (2/30)	20 (4/20)	82.35 (14/17)
0.1–0.25	26.53 (13/49)	55.36 (31/56)	80.73 (101/138)	100 (4/4)	85.71 (6/7)	100 (23/23)	50 (/2/4)	0 (0/1)	75 (6/8)
0.26–0.5	92.86 (13/14)	100 (15/15)	98.97 (96/97)	50 (1/2)	100 (5/5)	100 (21/21)	–	100 (1/1)	100 (9/9)
>0.5	94.44 (17/18)	95.24 (20/21)	99.69 (320/321)	100 (2/2)	100 (2/2)	100 (67/67)	75 (3/4)	100 (1/1)	98.39 (61/62)
p for trend	**<0.0001**	**<0.0001**	**<0.0001**	0.391	0.591	0.523	0.997	**<0.0001**	**<0.0001**

Values in bold are statistically significant

frequently differ from real-life situations. This was an important impetus for us to perform an international multicenter real-life quality surveillance study [25] observing consecutive patients without exclusion criteria. The confirmatory results of this ProREAL surveillance might further increase acceptance of evidence-based PCT-guided antibiotic stewardship.

Maybe the most important indicator of the value of a biomarker is whether it affects decision making in real-life. This study confirms the hypothesis that the initiation of antibiotic therapy was altered by the availability of the PCT level with the strongest effect in Swiss centers, centers with algorithm experience and in patients with bronchitis and AECOPD. As stated above, restricting antibiotic initiation in CAP patients was less important also in the randomized controlled trials [19, 21, 24].

Strengths of our study are the "close-to-real-life" design and the large sample size of patients. As a limitation, some of the subgroup analyses were possibly underpowered. The multicenter international setting with implementation of an identical PCT-algorithm allowed a novel approach for international comparisons of the influence of different healthcare systems and antibiotic prescribing cultures.

It might be argued that the two estimates which the treating physicians had to provide online were closely related. However, we intentionally differentiated between the estimated likelihood of a bacterial infection and the estimated likelihood of starting antibiotic therapy. A physician might consider the risk of a bacterial infection low but still initiate antibiotic therapy in a patient who might be severely ill. The fact that we had no possibility to confirm that the two VAS (visual analog scale) questions were indeed answered before knowledge of the results of PCT testing could have created a Hawthorne effect, which is a potential limitation. The generally observed trends argue against a major contribution of this potential effect. We focused on qualitative trends given the many potential contributing factors affecting antibiotic prescribing.

One limitation might be that all "experienced" centers were centers in Switzerland. Therefore the comparison between "experienced" and "naïve" centers was confounded by a country effect. Furthermore, only one centre from the US participated in this study, limiting generalizibility to the whole country or region.

In conclusion, physicians' estimates of the likelihood of bacterial infection correlate with PCT levels. Compliance with the algorithm was influenced by physicians' opinion about the perceived likelihood of bacterial infections and was higher if a bacterial origin could be determined. PCT levels did affect decisions to initiate antibiotics, particularly for patients with bronchitis and AECOPD. Geographic differences were apparent for the likelihood of antibiotic prescribing and algorithm compliance.

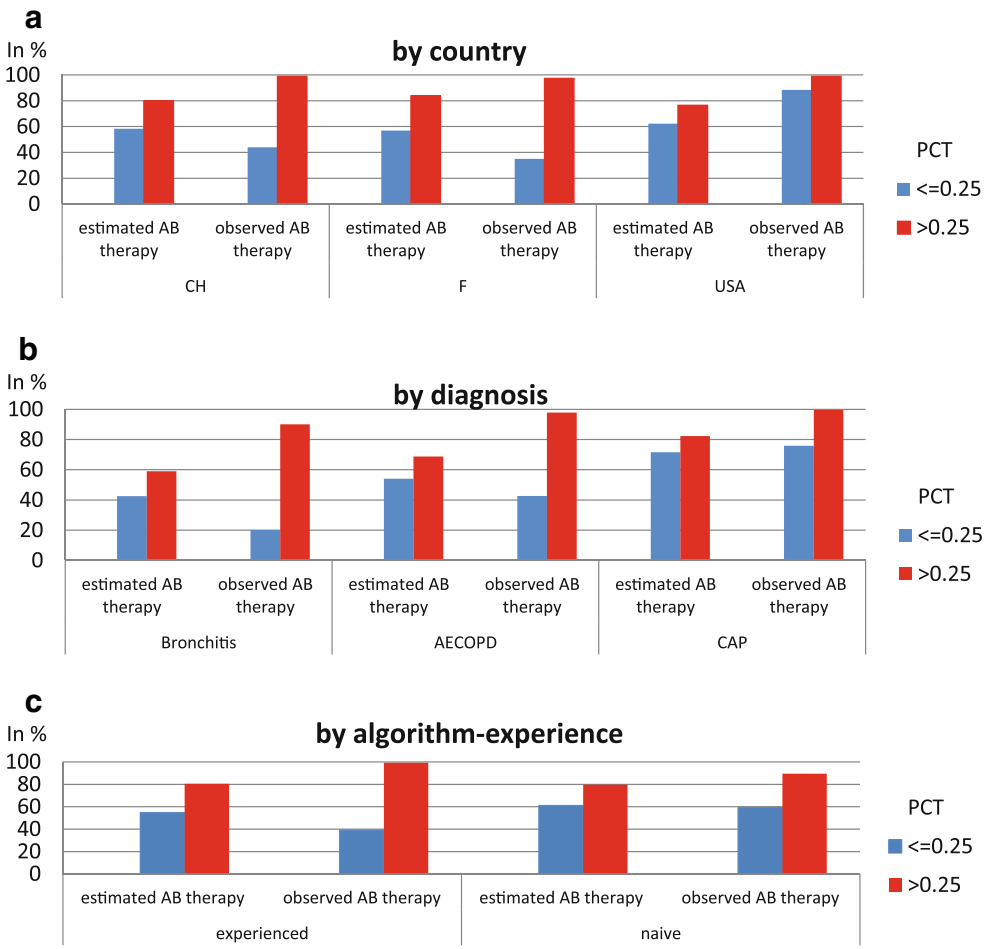


Fig. 4 Pre- and posttest probability of antibiotic therapy after PCT by country, for all LRTIs (**a**), by diagnosis, for all countries (**b**), and by algorithm-experience, for all LRTIs, all countries (**c**). Estimated likelihood of starting antibiotic (AB) therapy reflects pretest probability; observed antibiotic (AB) therapy reflects posttest probability

To encourage physicians to utilize and integrate both clinical and technical diagnostics and, in general, the implementation of evidence-based criteria into clinical routine seems a challenging but important goal to improve medical decision making. Probably specifically focused action plans and an intensified collaboration between scientists and clinicians are necessary to achieve this goal.

Table 3 Compliance with the procalcitonin-algorithm according to etiology

Pathogen	N (%)	PCT >0.25 µg/L (in %)	Compliance with algorithm
Streptococcus pneumoniae	88 (5.8 %)	86.2	65 (73.9 %)
Haemophilus influenzae	22 (1.4 %)	22.7	18 (81.8 %)
Legionella sp.	17 (1.2 %)	94.1	14 (82.4 %)
Influenza	14 (0.9 %)	21.4	12 (85.7 %)
Staphylococcus aureus	12 (0.8 %)	75.0	7 (58.3 %)
Escherichia coli	12 (0.8 %)	66.7	11 (91.7 %)
Klebsiella sp.	11 (0.7 %)	72.7	10 (90.9 %)
Haemophilus sp (other)	6 (0.4 %)	66.7	4 (66.7 %)
Streptococcus sp. (other)	6 (0.4 %)	83.3	4 (66.7 %)
Enterobacteriaceae (other)	6 (0.4 %)	60.0	3 (50.0 %)
Pseudomonas sp.	5 (0.3 %)	60.0	4 (80 %)
Mixed pathogens	17 (1.2 %)	76.5	13 (76.5 %)
Other	18 (1.2 %)	43.8	11 (61.1 %)
Any pathogen	234 (15.4 %)	41.6	176 (75.2 %)
No pathogen	1286 (84.6 %)	69.1	861 (67.0 %)

OR 1.497; 95 % CI 1.093–2.071; P=0.01146 (comparing any pathogen with no pathogen)

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