Journal of Critical Care 53 (2019) 125–131

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.journals.elsevier.com/journal-of-critical-care

Adhering to the procalcitonin algorithm allows antibiotic therapy to be shortened in patients with ventilator-associated pneumonia

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ARTICLE INFO

Keywords:
Ventilator-associated pneumonia
Procalcitonin
Antibiotics stewardship

ABSTRACT

Purpose: Ventilator-associated pneumonia (VAP) increases exposure to antibiotics. Physicians are however reluctant to shorten treatment, arguing this could lead to failures and worse outcome. Monitoring procalcitonin (PCT) has proven effective for decreasing exposure to antibiotics in randomized controlled trials, but additional "real-life" studies are needed.
Materials and methods: All patients with VAP in whom ABT was stopped before death or discharge were included in this 5-year prospective cohort study. Patients in whom ABT was stopped in accordance with the algorithm ("PCT-guided" group: ABT withdrawal strongly encouraged if PCT < 0.5 ng/mL or < 80% peak value) were compared to those with ABT continuation despite PCT decrease ("not PCT-guided" group). The primary endpoint was ABT duration. The secondary endpoint was unfavorable VAP outcome (i.e. death or relapse).
Results: We included 157 of the 316 patients with microbiologically-proven VAP. The algorithm was overruled in 81 patients (51.6%). ABT duration was significantly longer in these patients than in the PCT-guided group (9.5 vs. 8.0 days; $p = .02$), although baseline and VAP characteristics did not differ. The rate of unfavorable outcomes was comparable (46.9% vs. 51.3%; $p = .69$).
Conclusions: PCT-guided ABT adherence appears safe for patients with VAP and is likely to reduce exposure to antibiotics.

1. Introduction

Ventilator-associated pneumonia (VAP) is the hospital-acquired infection most frequently seen in critically-ill patients. Treatment of this infection results in an increase in the consumption of antibiotics. In addition to cost and toxicity issues, prolonged antibiotic therapy (ABT) could promote the selection of multi-drug resistant (MDR) bacteria and in turn lead to secondary infections caused by difficult-to-treat bacteria [1]. Yet physicians are reluctant to administer short-course treatments, despite consistent published data demonstrating that ABT could be shortened in VAP patients, [1-4]. This reluctance may be the result of some reports suggesting that short ABT duration could lead to clinical and microbiological failure if VAP is caused by non-fermenting gram-negative bacilli (NF-GNB), even though recent guidelines do not raise this issue [4-7].

Given the impact of the host's condition and the virulence of the causative bacteria, a standard course of treatment probably does not fit all. Among the means used to assess infection, the serial measurement of biomarkers has been suggested in addition to clinical follow-up. It has been shown that a procalcitonin (PCT)-guided strategy could lead to substantial reduction in the use of antimicrobial agents in critically-ill patients with various sources of infection [8-11]. The same algorithm, tested for VAP in a multicenter randomized controlled trial (RCT), led to a significant reduction in the duration of ABT (27%) without worsening the outcome [12]. However, the results are difficult to interpret because ABT was prolonged far beyond the 7-day recommended course in control patients (i.e. standard therapy), since the median duration was 15 days in controls compared with 10 days in the PCT-guided group. In addition, it is well known that any extrapolation from RCTs should be done with caution since the included patients are selected and the management of such patients may differ from standard

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https://doi.org/10.1016/j.jcrc.2019.05.022
0883-9441/

practice [13]. The so-called "ProReal" study, which included patients with a broad spectrum of community-acquired respiratory infections, showed that although the reduction in ABT duration was less pronounced than in previous RCTs, it remained substantial and statistically significant in "real-life" conditions [14]. In addition, the authors reported a favorable impact on outcomes in PCT-guided patients compared with those who received a prolonged course of antibiotics.

As the PCT-guided withdrawal of antibiotics (in accordance with published algorithms) has been encouraged in our medical ICU since 2006, and as every suspected VAP is prospectively recorded (as previously detailed [15,16]), we decided to investigate: (i) the safety of PCT-guided decisions and their impact on ABT duration in a cohort of evaluable patients with VAP; (ii) adherence to the protocol and the factors associated with non-adherence. We hypothesized that PCT monitoring was possible in one ICU and likely to reduce ABT duration in patients with VAP without compromising the outcome.

2. Methods

2.1. Study population

Every patient admitted to our intensive care unit (ICU) between January 2006 and the end of December 2011 was eligible if they had undergone mechanical ventilation (MV) for >48 h. Each consecutive patient with suspected VAP (new and persistent (>48-h) or progressive radiographic infiltrate plus two of the following: temperature of >38 °C or < 36 °C, blood leukocyte count of >10,000 cells/ml or < 5000 cells/ml, purulent tracheal secretions, and abnormal gas exchange) was prospectively included by one of the investigators (PEC, JPQ, SP or RB) throughout the study period. For each patient, only the first episode of microbiologically-proven VAP (as defined below) was included, and, since ABT duration was our main clinical endpoint and PCT measurement was not routinely performed in the other wards, only patients who completed treatment in the ICU were analyzed. In addition, patients with a 'do not resuscitate' order and those who died while antibiotics were on-going were excluded. Collection of nominative data was approved by the national authority for the protection of privacy and personal data. In accordance with French law, all patients in this cohort were informed of the study and a statement of non-objection was collected.

2.2. Definitions

Suspected VAP were considered microbiologically-proven if quantitative cultures of tracheal aspirates or bronchoalveolar lavage fluid were positive for at least one potential bacterial pathogen. The currently established thresholds were applied to differentiate between airway colonization and pulmonary infection [6]. Only patients with microbiologically-proven VAP were considered since otherwise, ABT could be stopped independently from PCT value, once the negative culture result was brought to the attention of the physician in charge.

Bacteria were considered MDR as previously defined [17].

2.3. Data collection

The "modified" Clinical Pulmonary Infection Score (CPIS) was calculated as previously described [2,18] and recorded. Demographic data, the underlying disease, the baseline diagnosis and the usual risk factors for MDR bacteria were also prospectively recorded (i.e. time between suspected VAP and ICU admission, previous hospitalization, exposure to antibiotics defined as the administration of at least one 2-day course of antibiotics within the previous 30 days, residence in a nursing home, underlying chronic obstructive pulmonary disease). In addition, a PCT assay was systematically performed when sepsis was suspected so as to improve diagnosis and antimicrobial management [19]. Tracheal aspirate samples were obtained from every patient within a 24-h period following the clinical suspicion. Bacteriological cultures were grown on specific media and the results were used to calculate "day 3 CPIS" (1 point was added to the CPIS value obtained at day 1 if at least 10^6 colony forming units/mL were recovered). Another point was added if the direct examination showed the same germ.

2.4. VAP management and duration of PCT-guided antibiotic therapy

Antibiotic therapy was managed according to guidelines based on knowledge of local susceptibility patterns for the most frequently isolated bacteria and the clinical judgment of the attending physician. The first-line treatment (i.e. delivered within the first 24 h following clinical suspicion of VAP) was considered appropriate if the isolated pathogen(s) was (were) susceptible to at least one drug administered at the onset of sepsis according to the susceptibility testing report. The same definition was applied to the second-line treatment, which was given once the physician in charge obtained the bacteriological results.

The duration of ABT was dependent on PCT monitoring, which has been the standard of care in our ICU since 2006 [20]. Procalcitonin was measured daily in all patients with suspected VAP as long as they were taking ABT. Antibiotics were discouraged if PCT was lower than 0.5 μg/L on day 1. The withdrawal of antibiotics was strongly encouraged if the attending physician considered the patient clinically cured and there was a substantial decrease in the biomarker with respect to a predefined, published algorithm (i.e. recommended discontinuation of ABT if PCT < 0.5 μg/L, or ≥ 80% drop from the peak value if initial PCT ≥ 5 μg/L). This rule for clinical decision-making is included in our institutional guidelines and as such provided to all attending physicians and residents. Moreover, regular meetings were held to remind staff about the principles of the algorithm and its rationale. However, physicians were free to overrule the algorithm without any pre-specified criteria, similar to the Prorata study [9].

The patients whose antibiotics were stopped in accordance with the algorithm were considered PCT-guided, and those whose treatments were continued in spite of the algorithm were classified as not PCT-guided.

In the not PCT-guided group, the time between the day the antibiotics should have been discontinued according to the PCT value and the day they were actually discontinued was recorded. In addition, the CPIS was calculated for all of the days the antibiotics were, or should have been stopped according to the PCT algorithm.

2.5. Clinical endpoints

The primary endpoint was the duration of ABT for the suspected VAP episode, expressed as the number of days under treatment.

We attempted to elucidate the reasons for which the PCT-guided algorithm was overruled by comparing the main clinical and biological features of the VAP, whether or not the protocol was followed.

Thirdly, we looked at outcomes according to the adherence to the algorithm described above. An unfavorable outcome was defined as either VAP recurrence during the ICU stay regardless of the bacteria involved (i.e. relapse or new infection), or death before ICU discharge, whichever occurred first. Otherwise, the outcome was considered favorable. The duration of mechanical ventilation and the ICU stay following the studied VAP episode and ventilator-free days were also used as secondary endpoints to assess outcomes.

2.6. Statistical analysis

Values are expressed as means and standard deviations (SD) unless otherwise stated. Continuous variables were compared using the Mann-Whitney *U* test. Categorical variables were compared using the chi-squared test. In the first set of analyses, the included patients were compared according to adherence to the PCT-guided ABT withdrawal rule. We then examined the independent contribution of factors that were

associated with protocol adherence through univariate analysis. The candidate variables were manually entered into a logistical regression model if the associated regression coefficient had a *P* value of <0.20 in univariate analysis, and then removed if a *P* value of >0.05 was obtained in multivariate analysis following a backward selection process. The validity of the model was assessed with the Hosmer-Lemeshow test for goodness-of-fit.

The aim of the second set of analyses was to assess the potential impact of adherence to the PCT-guided algorithm. In addition, every variable associated with an unfavorable outcome in univariate analysis was then entered into a logistical regression model using the rule described above.

Statistical significance was set at *P* value of <0.05, and STATA software was used for all analyses (College Station, Tex., USA).

3. Results

3.1. Study population

During the study period, 504 clinically-suspected VAP were recorded. As detailed in the flow chart (Fig. 1), we excluded 188 (37%) cases with negative microbiological results. Among the remaining 316 patients, 157 met the inclusion criteria and were retained for the final analysis. Only about half of the selected patients ($n = 76$) were treated according to the PCT algorithm. We compared these patients with their counterparts in whom the protocol was overruled ($n = 81$).

The baseline characteristics of the included patients are presented in Table 1. It is worth noting that except for diabetes mellitus, which was more frequent in the PCT-guided group, the two groups were comparable.

3.2. Duration of ABT and adherence to the PCT-guided algorithm

Patients in whom PCT-guided ABT withdrawal was followed received significantly shorter courses of antibiotics for the VAP episode than did the others (8.0 days [3.5] vs. 9.5 days [3.9], respectively; $P = .02$) (Table 2 & Fig. 2). The mean number of days of ABT beyond the withdrawal date determined by the PCT-guided algorithm was 4.1 (2.6).

3.3. Description of suspected VAP according to adherence to the PCT-guided algorithm

We also attempted to determine why the algorithm was overruled in certain cases by comparing the main features of the VAP episodes in the two groups of patients. We found that the main features of the VAP episodes were not significantly different whether the algorithm was followed or not (Table 2).

Enterobacteriaceae were the most frequently (35.7%) isolated pathogen overall (Table 2). It is worth noting that *P. aeruginosa* and other NF-GNB were found in the same proportions in both groups. The isolation of MDR bacteria as defined above was similar, as was the rate of appropriate first-line antibiotic therapy (73.7 vs. 65.4%; $p = .31$).

For VAP severity, treatment according to the PCT-guided ABT withdrawal rule was not a significant influence on the occurrence of shock on day 1 (32.9 vs. 38.3%, respectively; $p = .99$), or the CPIS values (i.e. both day 1 and day 3). Similar conclusions can be drawn from the SOFA scores obtained on day 1 (8.3[2.9] vs. 8.1[3.0] points, respectively; $p = .69$) and on day 3.

In addition, CPIS values measured on the day antibiotics were, or should have been stopped according to PCT decline, were comparable (3.6 [2.0] vs. 3.9 [2.3] points, respectively; $p = .34$). Moreover, no difference was found when each CPIS criterion was considered separately.

Adherence to the PCT-guided ABT withdrawal rule seemed to be independently related to the PCT values themselves. Indeed, in the patients in the non PCT-guided group, the PCT value on the day ABT should have been stopped was 1.7 (2.7) μg/L compared with 1.6 (4.2) μg/L otherwise ($p = .89$). Thus, as expected, the PCT values measured on the day the antibiotics were actually stopped in the non PCT-guided group was significantly lower than in the PCT-guided group (Table 3). In addition, multivariate analysis indicated that the greater the PCT peak value, the lower the adherence to the algorithm (Table 4).

3.4. Outcome

No difference was found between the two groups for the main outcome, that is to say the composite criteria including death or relapse (i.e. unfavorable outcome) (Table 2). The similarity remained even after we adjusted for potential confounding variables such as disease

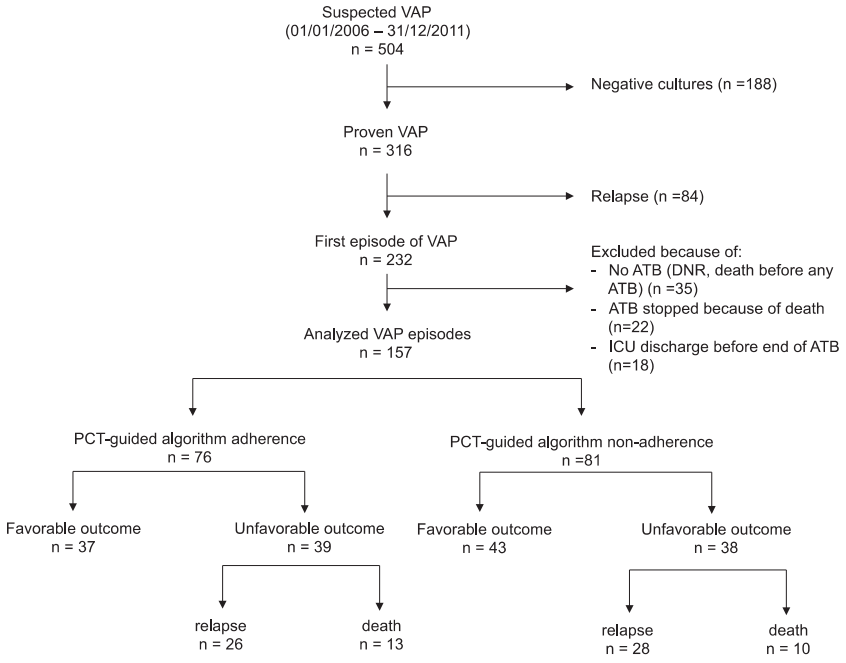

Fig. 1. Flowchart of selection of study patients. ICU: intensive care unit; ABT: antibiotic therapy; VAP: ventilator-associated pneumonia; DNR: do not resuscitate.

Table 1
Baseline characteristics of patients with VAP according to adherence to PCT-guided antibiotics withdrawal decision rule.

	Overall ($n = 157$)	Adherence to the PCT-guided algorithm ($n = 76$)	Non adherence to the PCT-guided algorithm ($n = 81$)	p
Age, mean (SD)	62.1 (15.2)	63.4 (14.9)	60.9 (15.5)	0.31
SAPS II, mean (SD)	47.3 (15.0)	49.2 (15.2)	45.6 (14.6)	0.13
Gender (male %)	70.7	68.4	72.8	0.66
Hospitalization prior to ICU (Yes %)	84.7	85.5	83.9	0.96
Underlying disease, n (%)				
COPD	31 (19.7)	13 (17.1)	18 (22.2)	0.54
Chronic heart disease	45 (28.7)	20 (26.3)	25 (30.9)	0.65
Chronic renal insufficiency	7 (4.4)	4 (5.3)	3 (3.7)	0.92
Immunodepression	10 (6.4)	3 (3.9)	7 (8.6)	0.38
Steroids	7 (4.4)	3 (3.9)	4 (4.9)	0.99
Diabete mellitus	27 (17.2)	19 (25)	8 (9.9)	0.02
Cirrhosis	8 (5.1)	5 (6.6)	3 (3.7)	0.65
Evolutive cancer	15 (9.2)	7 (9.2)	8 (9.9)	0.99
Baseline diagnosis, n (%)				0.06
Acute respiratory failure	66 (42)	25 (32.9)	41 (50.6)	-
Septic shock	26 (16.6)	15 (19.7)	11 (13.6)	-
Acute heart failure	23 (14.6)	15 (19.7)	8 (9.9)	-
Neurological disturbance	34 (21.6)	15 (19.7)	19 (23.4)	-
Miscellaneous	8 (5.1)	6 (7.9)	2 (2.5)	-
MDR bacteria risk factors, n (%)				
Nursing home resident	8 (5.1)	5 (6.6)	3 (3.7)	0.65
Previous ABT administration	139 (88.5)	65 (85.5)	74 (91.3)	0.37

ICU: Intensive Care Unit; SAPS II: Simplified Acute Physiologic Score II; COPD: Chronic Obstructive Pulmonary disease; MDR: Multi-Drug Resistant; PCT: procalcitonin; ABT: antibiotic therapy.

Table 2
VAP episode description, microbiological data and outcome according to adherence to PCT-guided antibiotics withdrawal decision rule.

N (%) or mean (SD)	Overall (n = 157)	Adherence to PCT algorithm (n = 76)	Non adherence to PCT algorithm (n = 81)	p
VAP episode description				
Late-onset VAP	92 (58.6)	47 (61.8)	45 (55.6)	0.52
Time elapsed between ICU admission and VAP suspicion D1 (days)	11.8 (13.0)	12.3 (16.1)	11.4 (9.2)	0.67
Time elapsed between MV onset and VAP suspicion D1 (days)	10.8 (12.7)	11.6 (16.1)	10.0 (8.4)	0.44
CPIS D1	5.3 (1.9)	5.1 (1.9)	5.6 (1.8)	0.07
CPIS D3	7.2 (2.2)	7.0 (2.3)	7.4 (2.0)	0.23
CPIS the last day with ABT according to PCT-guided algorithm value	3.7 (2.2)	3.6 (2.0)	3.9 (2.3)	0.34
Temperature (°C)	37.1 (0.5)	37.2 (0.5)	37.1 (0.5)	0.82
PaO_2/FIO_2 (mmHg)	287.4 (140.3)	284.5 (147.6)	290.2 (133.9)	0.80
Abundant or purulent tracheal aspirates	44 (28.0)	21 (27.6)	23 (28.4)	0.93
WBC (cells/mm^3)	14,269 (7845)	14,136 (7724)	14,394 (8003)	0.84
Infiltrate on the chest X-ray	105 (73.4)	46 (67.6)	59 (78.7)	0.33
Positive culture	66 (42.0)	29 (38.1)	37 (45.7)	0.12
Peak PCT value (μg/L)	7.8 (17.7)	5.1 (17.7)	10.4 (17.4)	0.06
Median (IQR)	1.6 (5.6)	1.7 (2.8)	1.6 (11.6)	
PCT value the last ABT day (μg/L)	1.1 (3.1)	1.6 (4.2)	0.7 (1.2)	0.09
Median (IQR)	0.4 (0.9)	0.5 (1.3)	0.3 (0.7)	
Septic shock D1, n (%)	51 (32.5)	25 (32.9)	26 (32.1)	0.99
SOFA D1, mean (SD)	8.2 (3.0)	8.3 (2.9)	8.1 (3.0)	0.69
SOFA D3, mean (SD)	8.0 (3.0)	7.9 (3.0)	8.0 (3.0)	0.81
Isolated bacteria within the airway				0.02
Enterobacteriaceae	56 (35.7)	25 (32.9)	31 (38.3)	–
Pseudomonas aeruginosa	25 (15.9)	11 (14.5)	14 (17.3)	–
Staphylococcus aureus	26 (16.6)	21 (27.6)	5 (6.2)	–
Other GNB	11 (7.0)	3 (3.9)	8 (9.9)	–
Not pseudomonal NF-GNB	7 (4.5)	3 (3.9)	4 (4.9)	–
Other GP	16 (10.2)	6 (7.9)	10 (12.3)	–
Polymicrobial	16 (10.2)	7 (9.2)	9 (11.1)	–
MDR bacteria	65 (41.4)	33 (43.4)	32 (39.5)	0.74
VAP antimicrobial management				
Appropriate 1st-line ABT	109 (68.8)	56 (73.7)	53 (65.4)	0.31
Appropriate 2nd-line ABT	126 (80.2)	59 (77.6)	67 (82.7)	0.55
ABT duration (days)	8.8 (3.8)	8.0 (3.5)	9.5 (3.9)	0.02
ABT duration beyond the PCT threshold stop value (days)	-	-	4.1 (2.6)	-
Outcome				
Length of ICU stay after VAP (days)	25.1 (25.4)	21.6 (18.6)	28.3 (30.3)	0.10
MV duration after VAP (days)	16.0 (19.4)	13.7 (13.6)	18.1 (23.5)	0.16
Ventilator free-days (days)	24.3 (19.4)	23.7 (19.1)	25.2 (19.7)	0.48
Unfavorable	77 (49.0)	39 (51.3)	38 (46.9)	0.47
ICU mortality	23 (14.6)	13 (17.1)	10 (12.3)	0.69
VAP recurrence	54 (34.4)	26 (34.2)	28 (34.6)	0.68

ICU: Intensive Care Unit; D: day; CPIS: Clinical Pulmonary Infection Score; GNB: Gram Negative Bacilli; GP: Gram Positive; MV: Mechanical Ventilation; PCT: procalcitonin; VAP: Ventilator-Associated Pneumonia; MDR: Multi-Drug Resistant; ABT: antibiotics therapy; IQR: interquartile range; SOFA: sequential organ failure assessment.

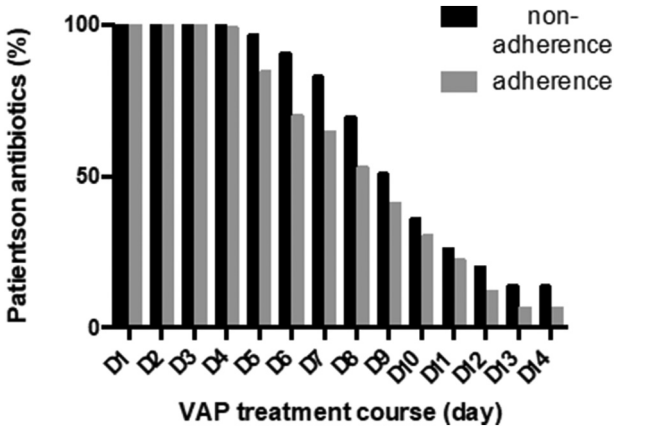

Fig. 2. Daily proportion of patients under antibiotics for VAP episode according to PCT-guided ABT withdrawal rule adherence. ICU: intensive care unit; ABT: antibiotic therapy; VAP: ventilator-associated pneumonia; PCT: procalcitonin.

severity and PCT peak-value (Table 5). Finally, the secondary outcomes such as MV duration or ventilator-free days after VAP onset were also found to be comparable in the two groups.

4. Discussion

We report herein that when a PCT-guided protocol was applied in patients with VAP, the duration of ABT was significantly reduced without altering death or relapse rates. However, the compliance rate was found to be rather low.

Reducing exposure to antibiotics in ICUs is an important part of any antimicrobial stewardship program. However, determining the best moment to stop ABT in critically-ill patients is still challenging, since clinical resolution remains hard to define. Monitoring PCT has been proposed as a reliable way to tailor ABT duration in patients with bacterial infections in various settings, including ICU. Accordingly, most RCTs report that PCT-guided algorithms reduce ABT duration without compromising outcome, even in subsets of VAP patients [9,11,21]. However, one can argue that following international guidelines is enough and costless since a 7-day course is currently recommended [6]. In addition, in the published RCTs where a PCT-guided algorithm was found to safely reduce ABT duration in VAP patients, treatment was markedly protracted in the control group, generally beyond 10 days [12]. It has been recently reported that implementing a PCT-guided protocol in patients with community-acquired pneumonia did not necessarily reduce ABT exposure if treatment duration was already short (i.e. close to the guidelines) in the control group [22]. One could argue that the included patients were not critically ill, but similar findings were reported in the ICU setting [23,24]. It is however worth noting that the PCT algorithms were different from those used in the Princeps studies (e.g., decreased magnitude allowing ABT interruption reaching 10% instead of 20% of peak value, leading to longer duration of treatment). Moreover, a recently published meta-analysis showed that VAP caused by NF-GNB are more likely to relapse with short-course than with prolonged-course therapy [1,25].

Table 3
Variables independently associated with adherence to PCT-guided antibiotics withdrawal decision rule.

	Odd ratio	95% CI	p
PCT the last day with ABT (μg/L)	6.1	[2.4–15.6]	<0.01
PCT peak value (μg/L)	0.8	[0.7–0.9]	<0.01
Staphylococcus aureus VAP	16.3	[2.6–101.7]	<0.01

C I: Confidence Interval. VAP: Ventilator associated pneumonia; PCT: procalcitonin; ABT: antibiotic therapy.

Table 4
Variables independently associated with unfavorable outcome in patients with VAP.

	Odd ratio	95% CI	p
PCT-guided ABT withdrawal rule adherence	1.4	[0.7–2.9]	0.33
PCT peak value (μg/L)	1.0	[1.0–1.1]	0.02
Chronic heart disease	2.5	[1.1–5.3]	0.02
SAPS II	1.0	[1.0–1.1]	<0.01

C I: Confidence Interval; VAP: Ventilator associated pneumonia; PCT: procalcitonin; ABT: antibiotic therapy; SAPS II: Simplified Acute Physiologic Score II.

We found that the PCT-guided ABT withdrawal rule was applied for almost half of VAP patients in our ICU. Although this rate is not optimal, it is near the 47% adherence reported in the Prorata and the SAPS study as well, underlining the reluctance of ICU physicians to comply with predefined rules [9,11]. Interestingly, the patients in whom the protocol was overruled was not found to be significantly different: the baseline characteristics and the severity of the VAP episode were comparable. Our findings suggest that the physician in charge was sometimes reluctant to stop ABT if PCT values remained "high" despite a favorable decline within the previous days (i.e. the 20% of peak value threshold was reached). Greater peak PCT values ($p = .06$) and in turn greater stop values were measured in the patients in whom the PCT-guided ABT withdrawal rule was not followed, signaling that physicians were more confident in absolute values than in biomarker kinetics. However, cumulative evidence supports the fact that a decrease in PCT magnitude is more reliable in predicting outcomes than peak value in critically ill patients, including those with VAP [26-28]. More education is perhaps needed to improve compliance to PCT-guided decision rules.

Since CPIS values, as well as each of its items, were comparable in the two groups on the day ABT should have been stopped according to the algorithm, a less favorable clinical outcome was unlikely [3]. However, one cannot exclude the possibility that some clinically relevant factors were not analyzed and may explain the differences in ABT duration. For example, some physicians reluctant to apply the PCT-guided rule in the SAPS trial claimed that the patient was still clinically "not stable" the day the target value was reached [11].

Use of the PCT-guided ABT withdrawal rule was apparently safe according to our end points; neither relapse nor death was more frequent when ABT was discontinued in accordance with the PCT algorithm. Since NF-GNB were responsible for only 20% of VAP, our study was underpowered to demonstrate any detrimental effect of a PCT-guided algorithm in this particular setting, as suggested elsewhere [1]. The reported rate of VAP relapse in our study could be considered high since clinical trials report 10 to 24% [29]. However, our population was composed of severely ill patients whose baseline characteristics were comparatively poor.

Taken together, our data suggest that the decision to discontinue ABT is challenging and does not necessarily rely on objective findings, hampering compliance to guidelines. These difficulties have been previously demonstrated in other settings such as long-term facilities [30].

This study does have several limitations. First, it was a single-center study, thereby limiting the external validity of our findings. For instance, our results should be interpreted cautiously since the bacterial ecology

Table 5
Safety of early ABT discontinuation according to PCT-guided algorithm in patients with VAP after adjustment for disease severity and PCT peak-value.

	Adjusted Odd ratio	95% CI	p
MV duration following VAP	0.9	[0.9–1.0]	0.21
Length of ICU stay following VAP	0.9	[0.9–1.0]	0.15
Ventilator free-days	0.9	[0.9–1.0]	0.37
Unfavorable outcome	1.3	[0.6–2.5]	0.48
ICU mortality	2.1	[0.8–5.6]	0.14
VAP recurrence	0.9	[0.4–1.8]	0.70

ICU: Intensive Care Unit; CI: Confidence Interval; VAP: Ventilator associated pneumonia; PCT: procalcitonin; ABT: antibiotic therapy.

of VAP is known to vary considerably from one location to another [31]. Second, our diagnostic criteria for VAP did not use invasive procedures in most cases to ascertain our microbiological findings [32]. However, it is worth noting that, in the current guidelines, bronchoscopic techniques and the culture of tracheal aspirates, as used in the present study, are also recommended [33]. Third, as was the case in the ProReal study and in the SAPS trial, no data were collected regarding physician behavior, and we therefore failed to determine why the algorithm was often overruled [11,34]. Physician behavior warrants study in future investigations, but has been addressed by some investigators [11]. Surprisingly, they found that most of the time, the physician failed to provide an explanation for overruling the algorithm. Fourth, the sample size was quite small. We cannot exclude that the trend toward a higher mortality rate in the patients in whom the PCT algorithm was followed would have reached a statistically significant level in a larger sample. However, our multivariate survival analysis model showed that compliance to the PCT-guided ABT withdrawal rule was not associated with a worse outcome, even after adjusting for other relevant factors. Finally, we did not perform a cost-effectiveness analysis. Nevertheless, previous studies have shown that the drug sparing that results from the implementation of a PCT-guided strategy leads to cost reductions despite the expenses related to PCT measurement [11,35].

5. Conclusions

We found that PCT monitoring is feasible in real life and could be used in patients with VAP as a way to reduce ABT duration without an obvious effect on outcomes. However, our results should be confirmed in a context where there is a strict compliance to current guidelines (i.e. 7-day treatment length), which was not the case in our cohort. Our findings suggest that PCT-guided protocols should be included in antibiotic stewardship programs, especially in the ICU. The overall unsolved issue of adherence to ABT protocols should be addressed in future prospective studies.

Funding sources

None.

Declaration of competing interests

None to declare.

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