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Clinical Utility of Procalcitonin-Guided Antibiotic Discontinuation in Hospitalized Pneumonia Patients in Daily Clinical Practice

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Abstract

Background: The optimal duration of antibiotic treatment has not been established for pneumonia patients.

Methods: We retrospectively enrolled hospitalized community-acquired or healthcare-associated pneumonia patients in whom antibiotics were discontinued on the day or next day of procalcitonin (PCT) measurement between 2014 and 2017 (PCT-guided group, n=272). During the period, PCT was measured serially, and physicians were encouraged to discontinue antibiotics according to the predefined PCT levels. The remaining patients admitted during the same period were included as control 1 (n=133). Those admitted between 2010 and 2014, during which period PCT was not measured serially, were also included in the study as control 2 (n=287). Primary endpoints were duration of antibiotic treatment and recurrence of pneumonia within 30 days after antibiotic discontinuation.

Results: Though PCT-guided group included significantly more severe pneumonia patients than control 1 group ($p<0.001$), duration of antibiotic treatment of the former (median 8.0 days) was not significantly different from the latter (median 9.0 days, $p=0.9043$). While pneumonia severity was not different between the PCT-guided and control 2 groups, duration of antibiotic treatment of the former was significantly shorter than that of the latter (median 10.0 days, $p<0.001$). Multivariable regression analysis revealed that PCT-guided antibiotic discontinuation was significantly related to duration of antibiotic treatment in both of PCT-guided and control 1 groups ($p=0.0131$), and PCT-guided and control 2 groups ($p<0.001$). Pneumonia recurrence within 30 days after antibiotic discontinuation of PCT-guided group (6.6%) was not statistically different from control 1 (3.0%) and 2 (5.9%) groups, respectively. Analysis regarding pneumonia patients with low PCT levels on admission revealed similar results.

Conclusion: PCT-guided antibiotic discontinuation might be useful for shortening the duration of antibiotic treatment without increasing pneumonia recurrence in daily clinical practice irrespective of PCT levels on admission.

Keywords: Antibiotic guidance; Pneumonia; Procalcitonin; Pneumonia recurrence.

Introduction

Community-acquired pneumonia (CAP) is a significant cause of morbidity and mortality worldwide [1]. Respiratory infections, including CAP, are the most frequent indication of antibiotic use [2]. Proper antibiotic use is essential to reduce antibiotic-resistant bacteria and maintain antibacterial effects. Patients with CAP should be given the appropriate dose / duration of antibiotic treatment. However, the optimal period for antibiotic treatment has not been established.

The American Society for Infectious Diseases / American Thoracic Society guidelines recommend that antibiotics be administered for at least 5 days, but many people with CAP are actually treated for more than 7 to 10 days in clinical practice [1]. There are several reports that have helped PCT-guided use of antibacterial drugs in CAP [3-6].

Though some reported that PCT-guided antimicrobial management method reduces the duration of antibiotic use without increasing infection-related mortality [7-10], Huang et al. did not recognize the usefulness of the method [11]. Recently, we reported the usefulness of discontinuing antibiotics with PCT in patients with CAP or Nursing and healthcare-associated pneumonia(NHCAP) with increased PCT levels on admission [12].

However, only one-third of pneumonia patients hospitalized during the study period were enrolled in the study. Those without PCT elevation, patients with aspiration pneumonia or dementia were excluded according to the study design. Studies that reported the usefulness of discontinuing antimicrobials with PCT did not investigate antimicrobial discontinuation with PCT in patients with pneumonia without PCT elevation. It is unclear whether discontinuation of antibacterial drugs by PCT-guided is useful for patients with pneumonia hospitalized in daily clinical practice.

In this study, we investigated the duration of antibiotic treatment and the relapse of pneumonia within 30 days after discontinuation of antibiotics for all CAP or NHCAP for which antibiotics were discontinued on the PCT measurement day or the next day. We compared patients who discontinued antibiotics during the same period regardless of PCT measurements or were hospitalized during periods when PCT was not measured.

Method

Since October 2010, our hospital has introduced quantitative measurement of PCT. During the period between October 2010 and September 2014, PCT was measured mainly on admission for the

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assessment of pathogen involved to assess the severity of pathogens (bacterial or not) and severity of pneumonia, and not used to determine antibiotic discontinuation. In clinical trials (October 2014 to December 2017), we started discontinuing antibacterial drugs by PCT in October 2014. During this period, antibiotics were discontinued based on predefined PCT levels in CAP / NHCAP hospitalized patients who agreed to participate. Antibiotic withdrawal by PCT was also applied to some patients who were not enrolled in the trial at the discretion of the attending physician during the trial period. All inpatients with CAP / NHCAP who were admitted to our hospital from October 2014 to December 2017 were enrolled in this study. Patients whose antibiotics were discontinued on the day of PCT measurement or on the next day were defined as PCT-guided antibiotic discontinuation groups. Patients who were not in the PCT guide group were defined as control 1 if the antibiotic was discontinued regardless of PCT measurement. The patients with pneumonia who were hospitalized between October 2010 and September 2014 were definend as control 2 group. We included the following pneumonia patients, that is, (1) outpatient onset (2) acute disease including new cough with or without fever or chills, pleurisy, dyspnea, and (3) X-ray showing acute infiltrative shadow. Pneumonia was diagnosed by two respiratory physicians. Antibacterial drugs were selected based on the Japanese Respiratory Society Guidelines [13]. PCT levels were examined on day 5 (± 1 day), day 8 (± 1 day), and day 11 (± 1 day) as needed in the PCT-guided group. When PCT decreased to <0.20 ng / mL, we encouraged discontinuation of antibiotics. Discontinuation was strongly recommended at less than 0.10 ng / mL of PCT levels. The following data were examined at admission: age, gender, pneumonia category (CAP or NHCAP [14]), pneumonia severity index (PSI) class [15], age, dehydration (blood urea nitrogen ≥ 21 mg / dL), respiratory failure (percutaneous oxygen saturation ≤90% or arterial oxygen tension ≤60 torr), orientation disturbance, pressure (A-DROP) score [16], comorbidities, body mass index (BMI), serum albumin, white blood cell (WBC), C-reactive protein (CRP), PCT levels, degree of pneumonia on chest x-ray, number of segments with pneumonia shadows on computed tomography (CT) images. We also examined recurrence of pneumonia during hospitalization, or readmission due to pneumonia, within 30 days after antibiotic discontinuation. Microbiological examinations, measurement of serum PCT levels, assessment of degree of pneumonia on chest x-ray were the same as our previous report [12, 17].

The primary end point was the period of antibiotic use and readmission due to recurrent pneumonia within 30 days after discontinuation of antibiotics. Secondary endpoints were death within 30 days of hospitalization and death from recurrent pneumonia. Factors associated with recurrence of pneumonia were also investigated.

Comparison between the PCT induction group and the control group was performed by the Mann-Whitney U test. Factors related to the duration of antibiotic use were subjected to multiple linear regression . Factors related to pneumonia recurrence during or after re-hospitalization within 30 days after discontinuation of antibiotics were examined by logistic regression analysis. Multivariate analysis was performed for variables with P <0.1 by univariate analysis. All statistical analyzes were performed at Excel Tokei 2015 (Social Survey Research Information Co., Ltd., Tokyo, Japan). P <0.05 was considered statistically significant.

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Fukuoka University Medical Ethics Review Board (IRB approval number: R18-034, approval date: 1/ Aug/ 2018). The committee was exempt from obtaining informed consent from patients.

Results

Study population

From October 2014 to December 2017, 444 CAP or NHCAP patients were hospitalized. Of these, 39 patients died of pneumonia without discontinuation of antibiotics, and the purpose of the study was to evaluate the clinical outcome of discontinuing antibiotics with a PCT guide. The study candidates were 405 patients. Of these, 272 patients with PCT measurement (PCT guide) were discontinued on the day of PCT measurements or the next day, and 133 patients (control 1) were discontinued regardless of PCT measurement. Between October 2010 and September 2014, 315 patients with CAP or NHCAP were hospitalized. Of these, 26 patients died of pneumonia without discontinuing antibiotics and were excluded from the study. As a result, the remaining 287 patients were used as control 2 group. There were 75, 93, and 111 patients with low PCT (less than 0.2 ng / mL) at admission in the PCT guide group, Control 1 and Control 2 groups. The main clinical features are shown in Tables 1 and 2. The PCT guide group included more severe pneumonia patients than the control 1 group, but as shown in the table, there was no significant difference in the severity of pneumonia between the PCT guide group and the control 2 group. In contrast, there was no significant difference in the severity of pneumonia between the PCT guide group with lower PCT levels on admission and the control 1 group, but the PCT guide group with lower PCT levels on admission had more severe pneumonia than the control 2 group. Chronic lung disease, diabetes, and dementia were the most frequently associated comorbidities in all groups. In all groups, the main pathogen was Streptococcus pneumonia (Table 1 & 2).

Duration of antibiotic treatment, pneumonia recurrence within 30 days after antibiotic discontinuation, death due to pneumonia recurrence, and death within 30 days after admission.

Although there was no statistically significant difference, the period of antibiotic use in the PCT guide group was shorter than that in the control 1 group. On the other hand, the period of antibiotic use was significantly shorter in the PCT induction group than in the control 2 group (P <0.001). The median PCT (interquartile range) the day before or on the day of antibiotic withdrawal was 0.08 (0.05 – 0.11) ng / mL in the PCT guide group. PCT was measured in 50.7% and 79.6% of patients hospitalized on days 5 and 8, respectively. There was no significant difference in pneumonia recurrence within 30 days after discontinuation of antibiotics between the PCT guide group and the control group. The number of patients who died of recurrent pneumonia and those who died within 30 days after admission were not statistically different between the PCT induction group and the control group (Table 3).

The duration of antibiotic use in the PCT-inducing group with low PCT levels on admission was significantly shorter than the control 1 group with low PCT levels on admission. On the other hand, there was no significant difference in the duration of antibiotic use between the PCT guide group with low PCT levels at admission and the two control groups with low PCT levels at admission. The number of patients who died of pneumonia within 30 days after discontinuation of antibiotics, the number of patients who died of pneumonia, and the number of patients who died within 30 days after hospitalization were not significantly different between the PCT guide group and the control group with low PCT level at the time of hospitalization. (Table 4).

Factors related to duration of antibiotic treatment:

PCT guide and control 1 data were used to analyze factors related

Variables	POT-guided	Control 1	Control 2	p-value	
				vs. Control 1	*vs.* Control 2
No. of patients	272	133	287		
Age (years)	80 (72-86)	77 (67-85)	80 (71-86)	0.0219*	0.3581
Male /Female	169 (62.1%)/103 (37.9%)	77 (57.9%)/56 (42.1%)	188 (65.5%)/99 (34.5%)	0.4487	0.4286
CAP /NHCAP	161 (59.2%)/111 (40.8%)	85 (63.9%)/48 (36.1%)	180 (62.7%)/107 (37.3%)	0.3872	0.4350
Aspiration pneumonia	55 (20.2%)	27 (20.3%)	43 (15.0%)	0.6047	0.1193
ADROP score 0	32 (11.8%)	30 (22.6%)	34 (11 9%)		
1	54 (19.8%)	37 (27.8%)	64 (22.3%)		
2	87 (32.0%)	37 (27.8%)	109 (38.0%)		
3	74 (27.2%)	25 (18.8%)	67 (23.3%)	<0.001**	0.0786
4	18 (6.6%)	4 (3.0%)	9 (3.1%)		
5	7 (2.6%)	0 (0%)	4 (1.4%)		
PSI class I	13 (4.8%)	11 (8.3%)	15 (5.2%)		
II	36 (13.2%)	26 (19.5%)	32 (11.1%)		
III	57 (20.9%)	34 (25.6%)	78 (27.2%)	0.0029**	0.4910
IV	128 (47.1%)	51 (38.3%)	123 (42.9%)		
V	38 (14.0%)	11 (8.3%)	39 (13.6%)		
BMI (kg/mm^2)	20.3 (17.2-23.0)	20.1 (18.2-23.1)	20.0 (17.7-22.6)	0.7421	0.9662
Albumin (g/dL)	3.2 (2.9-3.7)	3.3 (2.9-3.7)	33 (2.8-3.6)	0.0488*	0.1990
POT (ng/mL)	0.52 (0.18-2.81)	0.10 (0.05-0.21)	0.35 (0.10-2.00)	<0.001**	0.0289*
ORP (mg/dL)	8.52 (3.50-16.93)	7.28 (3.52-12.69)	9.20 (4.03-16.55)	0.0757	0.4705
WBC (/mm^3)	11800 (8600-15600)	9900 (7200-12900)	10100 (7600-13500)	0.0020**	0.0013**
Extent of pneumonia shadow	1 (1-2)	1 (1-1)	1 (1-2)	0.0090**	0.5739
No. of involved segments	4 (3-7)	3 (2-5)	4 (3-7)	0.0031**	0.4721
Comorbidities					
Chronic lung disease	88	36	79	0.3028	0.2299
Diabetes mellitus	62	23	56	0.2424	0.3525
Dementia	50	23	46	0.2907	0.5015
Cerebrovascular disease	29	12	29	0.7264	0 2900
Chronic heart failure	23	7	25	0.3143	0.1198
Malignancy	15	8	12	0.8224	0.6912
Kidney diseas	12	5	13	1.0000	0.2958
Liver disease	6	3	5	1.0000	0.7670
Pathogens					
Streptococcus pneumoniae	59	21	53	0.1847	0.3441
Streptococcus agalactiae	6	2	1	1.0000	0.0621
MSSA	8	2	5	0.5085	0.4080
MRSA	1	0	3	1.0000	0.6242
Enterococcus faecalis	1	1	3	0 5495	0.6242
Haemophilus influenzae	19	4	17	0.1154	0.7308
Escherichia coli	17	3	11	0.0916	0.2446
Klebsiella pneumoniae	14	3	10	0.1993	0.4055
Moraxella catarrhalis	11	1	9	0.1140	0.6514
Pseudomonas aeruginosa	6	5	10	0.3516	0.4505
Serratia	8	4	2	1.0000	0.0571
Stenotrophmonas	3	0	2	0.5540	0.6784
Proteus mirabilis	2	0	3	1.0000	1.0000
Enterobacter cloaca	0	1	3	0.3284	0.2492
Legionella pneumophilia	1	1	2	0.5495	1.0000
Mycoplasma pneumoniae	4	10	13	0.0031**	0.0470*
Chlamydophila pneumoniae	2	1	6	1.0000	0.2870

PCT: Procalcitonin, CAP: Community-acquired pneumonia, NHCAP: Nursing- and healthcare-associated pneumonia, A-DROP: Age, dehydration, respiratory failure, orientation disturbance, pressure, PSI: Pneumonia severity index, BMI: Body mass index, CRP: C-reactive protein, WBC: White blood cell, MSSA: Methicillin- sensitive Staphylococccus aureus, MRSA: Methicillin-resistant Staphylococccus aureus. Data are presented as number (%) or median interquartile range). * p<0.05,** p<0.01

Table 1: Baseline characteristics.

to antimicrobial use. In multivariable linear regression analysis, PCT antimicrobial withdrawal (P = 0.0109), PCT on admission (P <0.001), and chronic heart failure (P = 0.0368) were significantly associated with duration of antibiotic use (Table 5). PCT guide and control 2 data were also analyzed. Antibiotic withdrawal due to PCT (P <0.001), PCT on admission (P = 0.0212), CRP on admission (p = 0.0176), degree of pneumonia (p <0.001) and aspiration pneumonia (p = 0.0139) The duration of drug use was significant (Table 6).

	POT-guided	Control 1	Control 2	P value	
				vs Control 1	vs Control 2
No. of patients	75	93	11 1		
Age (years)	80 (73-86)	77 (62-85)	77 (66-86)	0.1326	0.1623
Male / female	53 (70.7%)/ 22 (29.3%)	51 (54.8%)/ 42 (45.2%)	73 (65.8%)/ 38 (34.2%)	0.0363*	0.4842
CAP /NHCAP	41 (54.7%)/ 34 (45.3%)	61 (65.6%)/ 32 (34.4%)	76 (68.5%)/ 35 (31 .5%)	0.1507	0.0756
Aspiration pneumonia	16(21.3%)	17 (18.3%)	14 (12.6%)	0.6215	0.1136
ADROP score 0	11 (14.7%)	25 (26.9%)	22 (19.8%)		
1	18 (24%)	23 (24.7%)	35 (22.3%)		
2	25 (33.3%)	24 (25.8%)	38 (34.3%)		
3	18 (24%)	19 (20.4%)	15 (13.5%)	0.0693	0.0312*
4	1 (1.3%)	2 (2.2%)	1 (0.9%)		
5	2 (2.7%)	0 (0%)	0 (0%)		
PSI class I	6 (8%)	10 (10.8%)	12 (10.8%)		
II	7 (9.3%)	21 (22.5%)	20 (18.0%)		
III	20 (26.7%)	20 (21.5%)	34 (30.6%)	0.0907	0.0236*
IV	33 (44%)	32 (34.4%)	38 (34.3%)		
V	9 (12%)	10 (10.8%)	7 (6.3%)		
BMI (kg/mm2)	20.2 (17.3-23.6)	20.1 (18.2-23.1)	20.0 (18.3-23.0)	0.8936	0.8985
Albumin (g/dL)	3.2 (2.9-3.7)	3.2 (2.9-3.7)	3.4 (2.9-3.7)	0.8086	0.5044
POT (ng/mL)	0.08 (0.05-0.12)	0.07 (0.05-0.12)	0.07 (0.05-0.13)	0.3238	0.2048
ORP (mg/dL)	5.26 (2.28-9.62)	7.58 (3.88-12.98)	6.15 (3.52-11.69)	0.0241*	0.0918
WBC (/mm3)	10200 (7950-13000)	9600 (6900-13000)	9200 (6950-1 1700)	0.4787	0.0284*
Extent of pneumonia shadow	1 (1-1)	1 (1-1)	1 (1-1)	0.7980	0.8374
No. of involved segments	2 (1-4)	3 (2-5)	3 (2-5)	0.5968	0.8358
Comorbiditie s					
Chronic lung disease	21	25	36	1.0000	0.6270
Diabetes mellitus	21	17	16	0.1423	0.0259*
Dementia	13	15	17	0.8384	0.8393
Cerebrovascular disease	7	6	9	0.5673	0.7945
Chronic heart failure	11	6	8	0.1208	0.1377
Malignancy	6	6	3	0.7684	0.1607
Kidney diseas	2	3	3	1.0000	1.0000
Liver disease	1	2	1	1.0000	1.0000
Pathogens					
Streptococcus pneumoniae	14	14	6	0.5404	0.0068**
Streptococcus agalactiae	2	3	0	1.0000	0.1613
MSSA	2	1	1	0.5866	0.5661
MRSA	0	0	1	1.0000	1.0000
Enterococcus faecalis	0	1	0	1.0000	1.0000
Haemophilus influenzae	2	3	7	1.0000	0.3170
Escherichia coli	2	2	2	1.0000	1.0000
Moraxella catarrhalis	1	0	2	0.4464	1.0000
Morsxella ostarrhalis	2	0	0	0.1978	0.1613
Pseudomonas aeruginosa	2	3	4	1.0000	1.0000
Serratia	2	3	1	1.0000	0.5661
Stenotrophmonas	1	0	1	0.4464	1.0000
Proteus mirabilis	0	0	0	1.0000	1.0000
Enterobacter cloaca	0	1	1	1.0000	1.0000
Legionella pneumophilia	0	1	1	1.0000	1.0000
Mycoplasma pneumoniae	2	9	11	0.1139	0.0782
Chlamydophila pneumoniae	0	1	4	1.0000	0.1492

PCT: Procalcitonin, CAP: Community-acquired pneumonia, NHCAP: Nursing- and healthcare-associated pneumonia, AD ROP: Age, dehydration, respiratory failure, orientation disturbance, pressure, PSI: Pneumonia severity index, BMI: Body mass index, CRP: C-reactive protein, WBC: White blood cell, MSSA: Methicillin- sensitive Staphylococccus aureus, MRSA: Methicillin-resistant Staphylococccus aureus. Data are presented as number (%) or median interquartile range). * p<0.05.

Table 2: Baseline characteristics of patients with Procalcitonin(PCT) levels on admission below 0.2.

We also analyzed factors related to duration of antibiotic intreatment using data from patients with low PCT levels on admission. Multivariable linear regression analysis revealed that PCT-guided antibiotic discontinuation ($P \leq 0.001$) and albumin levels on admission ($P \equiv 0.0194$) were significantly related to duration of antibiotic treatment in patients with low PCT levels on admission of the PCT-guided and control 1 groups (Table 7). and that only antibiotic discontinuation ($P \equiv 0.0059$) was significantly associated with related to duration of

Variables	POT-guided	Control 1	Control 2	P-value	
				vs. Control 1	*vs.* Control 2
Number of patients	272	133	287		
Duration of antibiotics treatment (days)	8.0 (7.0 -11.0)	9.0 (7.0 -11.0)	10.0 (8.0 -13.0)	0.9043	<0.001 **
Number (%) of patients with pneumonia recurrence during admission and re-hospitalization due to pneumonia recurrence within 30 days after antibiotics discontinuation	18 (6.6%)	4 (3.0%)	17 (5.9%)	0.1642	0.6175
Number (%) of patients died of pneumonia recurrence	1 (0.4%)	0 (0%)	3 (1.0%)	1.0000	0.6944
Number (%) of patients died after discontinuation of antibiotics within 30 days after admission	4 (1.5%)	0 (0%)	4 (1.4%)	0.3076	0.6767
PCT levels on the day of antibiotics discontinuation (ng/mL)	0.08 (0.05 - 0.13)				
Number (%) of patients with PCT levels on the day before or the day of antibiotics discontinuation (ng/mL)					
> 0.40	2 (0 7%)				
0.31- 0.40	5 (1.8%)				
0.21- 0.30	8 (3 0%)				
0.11- 0.20	91 (33.5%)				
0.05- 0.10	166 (61.0%)				
Number of patients with POT measured /number of patients treated with antibiotics					
Day 5	138 /272 (50.7%)				
Day 8	211 /265 (79.6%)				
Data are presented as number (%) or median (interquartile range) **p<0.01					

Table 3: Outcome of procalcitonin (PCT)-guided antibiotic discontinuation and control groups.

Variables	POT-guided	Control 1	Control 2	P-value	
				vs. Control 1	*vs.* Control 2
Number of patients	75	93	111		
Duration of antibiotics treatment (days)	8.0 (7.0 - 10.0)	9.0 (7.0 - 1.0)	9.0 (7.0 - 1.0)	0.0190*	0.0734
Number (%) of patients with pneumonia recurrence during admission and re-hospitalization due to pneumonia recurrence within 30 days after antibiotics discontinuation	6 (8%)	2 (2.2%)	6 (5.4%)	0.0776	0.6175
Number (%) of patients died of pneumonia recurrence	0 (0%)	0 (0%)	0 (0%)	1.0000	1.0000
Number (%) of patients died after discontinuation of antibiotics within 30 days after admission	1 (1.3%)	0 (0%)	1 (0.9%)	0.4464	1.0000
PCT levels on the day of antibiotics discontinuation (ng/mL)	0.06 (0.05 - 0.10)				
Number (%) of patients with PCT levels on the day before or the day of antibiotics discontinuation (ng/mL)					
0.31- 0.40	1 (1.3%)				
0.21- 0.30	1 (1.3%)				
0.11- 0.20	17 (22.7%)				
0.05- 0.10	56 (74.7%)				
Number of patients with POT measured /number of patients treated with antibiotics (%)					
Day 5	46 /75 (61 3%)				
Day 8	47 /59 (79.7%)				
Data are presented as number (%) or median (interquartile range)					

Table 4: Outcome of procaloitonin (PCT)-guided antibiotic discontinuation and control groups with initial PCT levels below 0.2 ng/mL.

antibiotic treatment in patients with low PCT levels on admission of the PCT-guided and control 2 groups (Table 8).

Factors related to pneumonia recurrence within 30 days after antibiotic discontinuation:

Using data from the PCT-guided and control 1 groups, we analyzed factors related to pneumonia recurrence within 30 days after antibiotic discontinuation. Univariable analysis revealed that male sex (p = 0.0274), PSI (p = 0.0222), aspiration pneumonia (p = 0.0093), and NHCAP (p = 0.0074) were significantly associated with pneumonia recurrence within 30 days after antibiotic discontinuation. Multivariable analysis revealed that only male sex (P = 0.0261) was significantly associated with pneumonia recurrence. Next, we analyzed factors related to pneumonia recurrence within 30 days after antibiotic discontinuation using data from the PCT-guided and control 2 groups. Univariable analysis revealed that male sex (p = 0.0089), albumin (p = 0.0018), duration of antibiotic use (p < 0.001), extent of pneumonia shadow (p = 0.0360), NHCAP (p < 0.001), and aspiration pneumonia (p < 0.001) were significantly associated with pneumonia recurrence within 30 days after antibiotic discontinuation. Multivariable analysis revealed that male sex (P = 0.0026) and NHCAP (P = 0.0348) were significantly associated with pneumonia recurrence.

Discussion

The use of appropriate antibacterial drugs in the treatment of pneumonia is essential to reduce resistant bacteria and maintain antibacterial effects. However, the optimal period of use of antibiotics for pneumonia patients is not clear. There is no objective standard for

Variables	PRC	95%CI		P-value
Age (years)	-0.0114	-0.0481	0.0253	0.5410
Sex (male *vs.* female)	-0.6315	-1.4998	0.2369	0.1535
Category of pneumonia (NHCAP *vs.* CAP)	0.4459	-0.6095	1.5014	0.4065
Aspiration pneumonia	0.9646	-0.1866	2.1158	0.1002
ADROP score	0.0836	-0.445	0.6121	0.7560
PSI class	0.7032	-0.0524	1.4589	0.0680
BMI (kg/mm^2)	-0.0549	-1500	0.0401	0.3811
Albumin on admission (g/dL)	-0.3887	-1.3098	0.5325	0.4071
PCT on admission (ng/mL)	0.0991	0.0464	0.1519	<0.001**
CRP on admission (mg/dL)	-0.0075	-0.0654	0.0503	0.7980
WBC on admission (/mm^3)	0.0000.	-0.0001	0.0001	0.9049
Number of involved segments	0.0681	-0.1031	0.2393	0.4344
Extent of pneumonia shadow	0.7180.	-0.3624	1.7983	0.1920
Malignancy	-0.1095	-2.9934	0.8028	0.2571
Diabetes mellitus	0.0850.	-0.8625	1.0335	0.8593
Dementia	-0 1252	-1.2357	0.9854	0.8247
Chronic heart failure	-1.8543	-3.4544	0.2542	0.0233*
Chronic lung disease	0.0717	-0.8067	0.9510	0.8725
Cerebrovascular disease	-0.0732	-1.4734	1.3269	0.9181
Kidney disease	1.4696	-0.5071	3.4463	0.1446
Liver disease	-0.7007	-3.3755	1.9741	0.6066
Antibiotics before admission (Yes *vs.* No	0.3706	-0.6301	1.3714	0.4668
PCT-guide (Yes *vs.* No)	-1.0914	-1.9518	-0.2310	0.0131*
Definition of extent of pneumonia shadow is described in the Patients and methods sections of the main text. ** p<0.01				

Table 5: Multivariable linear regression analysis of factors related to duration of antibiotic use in patients with procalcitonin-guided and control 1 groups.

Variables	PRC	95% CI		P-value
Age (years)	0.0201	-0.0118	-0.520	0.1746
Sex (Male *vs.* Female)	0.3566	-0.3677	1.0810	0.3338
Category of pneumonia (NHCAP *vs.* CAP)	0.6245	-0.2104	1.4594	0.1423
Aspiration pneumonia	1.2321	0.2517	2.2125	0.0139*
ADROP score	0.1236	-0.3321	0.5793	0.5944
PSI class	0.1621	-0.4664	0.7906	0.6126
BMI (kg/mm^2)	-0.0374	-0.1213	0.0464	0 3811
Albumin on admission (g/dL)	-0.5231	-1.2156	0.1694	0.1384
PCT on admission (ng/mL)	0.0398	0.006	0.0737	0.0212*
CRP on admission (mg/dL)	0.0497	0.0087	0.0907	0.0176*
WBC on admission (/mm^3)	0.0000.	-0.0001	0.0001	0.9905
Number of involved segments	0.0407	-0.0927	0.1741	0.5489
Extent of pneumonia shadow	1.3775	0.5871	2.1678	<0.001**
Malignancy	0.9267	-0.753	2.6065	0.2789
Diabetes mellitus	0.4459	-0.3683	1.2602	0.2824
Dementia	-0.4151	-1.3687	0.5385	0.3928
Chronic heart failure	-0.8883	-2.0913	0.3148	0.1475
Chronic lung disease	-0.1313	-0.8987	0.6361	0.7369
Cerebrovascular disease	0.0254	-1.1457	1.1965	0.9660
Kidney disease	1.3696	-0.2365	2.9758	0.0945
Liver disease	-2.14	-4.5465	0.2665	0.0812
Antibiotics before admission (Yes *vs.* No	0.6247	-0.1890	1.4383	0.1321
PCT-guide (Yes *vs.* No)	-1.7875	-2.4422	-1.1328	<0 001**
PRC: Partial regression coefficient, CI: Confidence interval, NHCAP: Nursing and health-care associated pneumonia, CAP: Community - acquired pneumonia, A-DROP: age, dehydration, respiratory failure, orientation disturbance, pressure, PSI: Pneumonia severity index , BMI: Body mass index, PCT: Procalcitonin, CRP: C-reactive protein, WBC: White blood cell. Definition of extent of pneumonia shadow is described in the Patients and methods sections of the main text. ** p<0.01.				

Table 6: Multivariable linear regression analysis of factors related to duration of antibiotic use in patients with procalcitonin-guided and control 2 groups.

when to stop antibiotics. In Japan, antibacterial drugs are discontinued if the following criteria are met (or all but one).; (1) body temperature <37.0°C, (2) normalization of WBC, (3) less than 30% improvement in peak CRP levels, and (4) improvement of pneumonia shadow on chest x-ray [18].The American Society of Infectious Diseases / American Thoracic Society provides discontinuation criteria as follows, that is, no fever for 48 – 72 hours plus all (or all but one) of temperature <37.8°C, heart rate <100 beats / min, respiratory rate <24 breaths / min,

Variables	PRC	95% CI		P-value
Age (Years)	0.0172	-0.0261	0.0605	0.4332
Sex (Male *vs.* Female)	1.0521	-0.5651	2.6692	0.2003
Category of pneumonia (NHCAP *vs.* CAP)	-0.1014	-2.2036	2.0008	0.9241
Aspiration pneumonia	0.7043	-1.5135	2.9220	0.5309
ADROP score	0.6875	-0.4277	1.8028	0.2248
PSI class	-0.2702	-1.5488	1.0084	0.6766
BMI (kg/mm^2)	-0.0437	-0.2283	0.1409	0.6404
Albumin on admission (g/dL)	-2.0414	-3.7471	0.3356	0.0194*
PCT on admission (ng/mL)	0.8264	-16.0412	17.6940	0.9229
CRP on admission (mg/dL)	-0.0891	-0.2376	0.0595	0.2377
WBC on admission (/mm^3)	0.0002	0.0000.	0.0004	0.0818
Number of involved segments	-0.0043	-0.3849	0.3762	0.9821
Extent of pneumonia shadow	-0.1347	-2.4356	2.1663	0.9080
Malignancy	1.1100.	-2.1057	4.3256	0.4956
Diabetes mellitus	0.7886	-1.1582	2.7354	0.4243
Dementia	-1.0264	-3.1902	1.1374	0.3497
Chronic heart failure	0.3521	-2.3595	3.0638	0.7976
Chronic lung disease	0.6819	-1.1201	2.4838	0.4554
Cerebrovascular disease	0.9911	-1.9403	3.9225	0.5047
Kidney disease	-0.5546	-5.0732	3.9640	0.8085
Liver disease	2 9951	-2.8832	8.8734	0.3153
Antibiotics before admission (Yes *vs.* No)	-0.539	-2 4310	1.3529	0.5739
PCT-guide (Yes *vs.* No)	-2.6485	-4 1841	-1.1129	<0.001**

Definition of extent of pneumonia shadow is described in the Patients and methods sections of the main text.
**p<0.01

Table 7: Multivariable linear regression analysis of factors related to duration of antibiotic use in patients with procalcitonin-guided and control 1 group with low procalcitonin levels.

Variables	PRC	95% CI		P-value
Age (years)	0.0335	-0.0163	0.0833	0.1853
Sex (male *vs.* female)	0.4423	-0.7302	0.0833	0.4571
Category of pneumonia (NHCAP *vs.* CAP)	0 8781	-1.9331	0.6754	0.4571
Aspiration pneumonia	0.8978	-0.7077	2.5033	0.2708
ADROP score	0.2597	-0.5103	1.0297	0.5060
PSI class	-0.0941	-1.1288	0.9406	0.8576
BMI (kg/mm^2)	0.0461	-0.0907	0.1828	0.5064
Albumin on admission (g/dL)	-0.7515	-1.9236	0.4205	0.2070
PCT on admission (ng/mL)	8.6265	-3.298	20.5510	0 1549
CRP on admission (mg/dL)	-0.0192	-0.1194	0.0810	0.7055
WBC on admission (/mm^3)	0.0000.	-0.0001	0.0002	0.6278
Number of involved segments	-0.1228	-0.3587	0.1130	0.3050
Extent of pneumonia shadow	1.1343	-0.2017	2.4702	0.0955
Malignancy	1.0863	-1.7521	3.9246	0.4506
Diabetes mellitus	0.36	-1.0154	1.7355	0.6056
Dementia	-0.8873	-2.4742	0.6996	0.2709
Chronic heart failure	-0.2658	-2.1617	1.6302	0.7821
Chronic lung disease	0.4476	-0.8753	1.7704	0.5047
Cerebrovascular disease	-0.174	-2.1611	1.8130	0.8626
Kidney disease	-0.4185	-3.6886	2.8517	0.8007
Liver disease	1.4675	.-3.6700	6.6050	0.5732
Antibiotics before admission (Yes *vs.* No)	-0.6289	-1.9331	0.6754	0.3421
PCT-guide (Yes *vs.* No)	-1.563	-2.6681	-0.4580	0.0059**

Definition of extent of pneumonia shadow is described in the Patients and methods sections of the main text.
** p<0.01

Table 8: Multivariable linear regression analysis of factors related to duration of antibiotic use H patients with procalcitonin-guided and control 2 groups with low procalcitonin levels.

systolic blood pressure> 90 mmHg, arterial oxygen saturation> 90% or PO2> 60 mmHg (room air), ability of oral intake, and normal mental status [1]. There have been reports that the use of antibiotics has been shortened by PCT-guided antibiotic management without increasing mortality in patients with pneumonia [3-6]. We prospectively examined the usefulness of discontinuing antibiotics using PCT guides for CAP or NHCAP with increased PCT on admission, and using the antibiotic for 3 days (median) without increasing the recurrence of pneumonia

or the 30-day mortality rate was shortened [12]. However, it is unclear whether it is useful for hospitalized pneumonia patients to discontinue antibiotics with a PCT guide in daily clinical practice. Not only patients without PCT elevation, but patients with aspiration pneumonia and dementia are excluded from the study design. In the present study, we found the usefulness of PCT-guided antibiotic discontinuation in all hospitalized CAP and NHCAP patients irrespective of PCT levels on admission and comorbidities in daily clinical practice.

Patients with low PCT on admission were not enrolled in previous studies. In addition, many studies on antimicrobial use by PCT guides do not recommend starting antibiotics for patients with low PCT on admission. In a clinical trial of PCT-guided antimicrobial therapy in CAP, 15% of patients with low initial PCT did not use antibiotics [6]. However, in actual clinical practice, it is difficult for doctors in charge to judge that patients with pneumonia, particularly moderate and severe pneumonia, will not be given antibiotics.

In this study, 40-50% of pneumonia patients with low PCT on admission had moderate or severe pneumonia. In this study, antibiotics were administered to all patients diagnosed with pneumonia. In previous studies, antibiotics were withheld in only 1% of patients with pneumonia in the control group [6]. To our knowledge, this is the first study to discontinue antibiotics with a PCT guide in patients with low PCT on admission.

In this study, the period of antibiotic use was shortened even in patients with PCT-guided antibiotic withdrawal and low PCT on admission. It may be explained by peak levels of PCT after several days of hospitalization in some patients. Regardless of the PCT at the time of hospitalization, it was considered important to be able to apply antibiotic discontinuation with a PCT guide to pneumonia patients in hospital.

Our previous PCT-guided study of antimicrobial treatment did not include patients with aspiration pneumonia or dementia, but these pneumonia patients tend to increase in daily practice in an aging society. This study included patients with these comorbidities, and PCT-guided discontinuation of antibacterials has shortened the period of antibiotic use without increasing the recurrence of pneumonia. To our knowledge, this is the first study to investigate the usefulness of discontinuing antibiotics on PCT guides in patients with aspiration pneumonia or dementia.

Antibiotic withdrawal due to PCT has been reduced by 1-2 days in median duration of antibiotic compared to the control group in this study, but the median of 8 days in the PCT guide group is longer than at least 5 days recommended by IDSA / ATS guidelines on antimicrobial use in CAP patients [1]. The duration of antibiotic use increases as the PSI class increases [10], and NHCAP requires longer antibiotic treatment than CAP [14]. The study included many elderly people, moderate and severe pneumonia, and NHCAP with high PCT. In this study, the possibility of extending the period of use for antibacterial drugs was considered. In addition, patients with aspiration pneumonia were included, and multiple regression analysis revealed that aspiration pneumonia was significantly associated with antimicrobial use duration. In this study, 134 of 272 PCT guide groups had no PCT measurements on day 5. In addition, about two-thirds of patients were discontinued from antibiotics at PCT <0.1 ng / mL. If antibiotics were discontinued on the day when PCT was measured on day 5 and the PCT level was below 0.2 ng / mL in the PCT guide group, the median (interquartile range) duration of antibiotic treatment was 7.0 (5.0, 10.0) In this study, the first quartile of the antibiotic treatment period was 5 days, consistent with a minimum of 5 days recommended by IDSA / ATS.

In Western countries, it is recommended to discontinue antibiotics at PCT 0.25 ng / mL or less. We obtained a value of 0.22 ng / mL for the PCT cutoff value that distinguishes bacterial pneumonia from non-bacterial pneumonia (mainly mycoplasma pneumonia and Chlamydophila pneumonia). For safety reasons, antimicrobials were discontinued using a PCT value of 0.20 ng / mL.

In this study, men sex only or men sex and NHCAP were independent of pneumonia recurrence, but PCT antibiotic withdrawal was not associated with pneumonia recurrence. This was thought to mean that discontinuation of antibiotics by PCT did not increase the recurrence of pneumonia. Toledo et al. reported that those who lived with a child under 15 years of age, had more than 3 visits in the past 90 days, chronic respiratory failure, heart failure, chronic liver disease, and admission to a nursing home were associated with 30-day readmissions. [19].

This is the limit of this research. First, it was done backwards. Second, there were few patients with low PCT and patients with relapsed pneumonia. Third, it was done in a single hospital. Fourth, the follow-up period is short. Because of these limitations, care should be taken when interpreting the results, especially when discontinuing antibiotics with PCT-guided . Finally, in this study, the duration of antibiotic use was longer than that recommended by the guidelines. Confirming the results requires randomized and multi-hospital research.

Conclusion

PCT-guided antibiotic discontinuation might be useful for shortening the duration of antibiotic treatment without increasing pneumonia recurrence within 30 days after antibiotic discontinuation for hospitalized pneumonia patients in daily clinical practice irrespective of PCT levels on admission.

Declarations

Ethics approval and consent to participate

This human study was performed in accordance with the Declaration of Helsinki and was approved by the Fukuoka University Medical Ethics Review Board. The review board exempted the acquisition of informed consent from patients.

Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

S.T. and N.N. conceived of the presented idea, and developed the theory and performed the computations. S.T, N.N., T.A., T.H., H.M., S.U., T.A., Y.Y., H.Y., K.W., N.I.,Y.U., and I.H. provided the study materials and patients. M.F. and K.W. supervised the findings of this work. All authors discussed the results and contributed the final manuscript.

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