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Evaluation of procalcitonin as an antimicrobial stewardship tool in SARS-CoV-2 infection: a retrospective cohort study.

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ABSTRACT

It can be a diagnostic challenge to identify COVID-19 patients in whom antibiotics can be safely withheld. We evaluate the effectiveness of a guideline implemented at Sheffield Teaching Hospitals NHS Foundation Trust that recommends withholding antibiotics in patients with a “negative” serum procalcitonin (PCT), defined as ≤0.25ng/ml. Results showed reduced antibiotic consumption in this patient group, without increase in mortality, alongside a reduction in subsequent carbapenem prescriptions during admission for those with a negative PCT. Our results suggest effectiveness of this guideline, and recommend further research to identify the optimal cut-off value for procalcitonin in this setting.

INTRODUCTION

In patients with COVID-19, the presentation of fever, tachypnoea and hypoxia, together with lung infiltrates on chest imaging and a frequent rise in biomarkers such as C-reactive protein (CRP) [1], presents a challenge to rational use of antimicrobials as it is difficult to confidently exclude bacterial co-infection. Rates of true bacterial co-infection are estimated to be only 7 to 14% [2-4]. Despite this, early in the pandemic 80% of patients with COVID-19 received antibiotic treatment [5]. Strategies to accurately identify patients with COVID-19 who do not have bacterial co-infection are needed to reduce

antimicrobial prescriptions and promote antimicrobial stewardship. [10] National Institute for Health and Care Excellence (NICE) guidance on pneumonia in the context of COVID-19 has recommended further research into the use of procalcitonin (PCT) for this purpose.

We set out to evaluate whether inclusion of measurement of PCT in a hospital guideline for antibiotic prescription in COVID-19 had an impact on i) antibiotic usage and ii) outcomes in patients with confirmed COVID-19 at a large NHS Foundation Trust Hospital in the United Kingdom (UK).

METHODS

Study Design, Study Site and Population

This retrospective observational study was undertaken at two sites of Sheffield Teaching Hospitals NHS Foundation Trust (STHNHFT).

Eligible patients were ≥18 years old and diagnosed with COVID-19 between 5 March and 15 April 2020 with a positive SARS-CoV-2 reverse-transcriptase polymerase chain reaction (RT-PCR) result on nose and/or throat swabs and/or deep respiratory samples, and had a PCT assay undertaken within 48 hours of collection of the first positive SARS-CoV-2 sample. Patients with both community and nosocomial acquisition of COVID-19 were included. STHNFT guidelines recommended that antibiotics could be withheld in COVID-19 patients with a

PCT value of ≤0.25ng/ml unless felt necessary by a senior clinician, as concomitant bacterial infection is considered unlikely below this level [18].

Patients diagnosed before 5th March 2020 were excluded as at this point COVID-19 was managed as a high consequence infectious disease and patients were admitted regardless of symptom severity. The enrolment end date of 15th April was before mandatory SARS-CoV-2 screening of all patients admitted to hospital was introduced.

The study was granted approval by the STHNFT Clinical Effectiveness Unit. (Ref: 9863)

Data Collection and Outcomes

Demographic and clinical characteristics of patients were drawn from existing laboratory, pharmacy and clinical databases and from examination of physical and electronic patient notes. Data was entered into an electronic case report form (Access 2010, Microsoft, Redmond, WA, USA).

Primary outcome was antibiotic consumption in WHO defined daily doses (DDD) per day alive over 28 days after COVID-19 diagnosis and days of treatment (DOT). 28-day outcome was recorded as discharged, still in hospital or died.

Data on antibiotic-associated adverse events were collected including hospital-acquired pneumonia/ventilator-associated pneumonia (HAP/VAP), *Clostridioides difficile* infection, Meticillin-resistant *Staphylococcus aureus* (MRSA) acquisition

and isolation of an extended-spectrum beta-lactamase (ESBL) or AmpC beta-lactamase-producing organism from a clinical sample.

Case definitions for DDD, DOT and HAP/VAP can be read in supplementary materials.

Statistical Analysis:

All values from patients meeting eligibility criteria were summarised using the most appropriate form, either using frequency/percentages, or medians with IQR (Inter-Quartile Range). Differences between demographics were analysed with the suitable significance test, depending on whether parametric assumptions were met as is detailed each table. To investigate the relationship between PCT positivity and total DDD and between antibiotic receipt at 48 hours post-diagnosis and meropenem prescription, linear and logistic regression models were explored adjusting for demographic confounders (age, sex, ethnicity and comorbidities.) All statistical analyses were performed in Stata version 16.1 (StataCorp 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC.)

RESULTS

Study Population

A total of 368 patients met the eligibility criteria and were included in the analysis; overall 60% were male, with a median

age of 75. Of these, 218 (59%) had a PCT level ≤0.25ng/ml (negative) and 150 (41%) had a level >0.25ng/ml (positive). Patient demographics and comorbidities stratified by PCT results are seen in Table 1. There was no significant difference in demographics between the two groups in terms of age, sex, BMI or ethnicity. Comorbidities between the two groups were also similarly distributed with the exception of malignancy, which was more common in the negative PCT group. There were no pregnant women in the cohort.

Compliance with Guideline

Of those patients with a negative PCT, 73 (33%) were on antibiotics 48 hours after their COVID-19 diagnosis compared to 126 (84%) with a positive PCT ($p<0.001$) suggesting good compliance with the guideline.

Antibiotic Usage

Data on total DDD of antibiotics received in the 28-day follow-up period and DDD per alive day are presented in Figure 1A and Supplementary Table 1. Patients with a negative PCT received significantly fewer DDDs of antibiotics (both total and per alive day) than those with positive PCT with a median DDD of 3.0 vs 6.8 ($p<0.001$). A log-linear model was computed in order to explore the relationship with PCT positivity after adjusting for demographic confounders (comorbidities, age, sex, ethnicity) to ensure regression assumptions were met. A statistically significant relationship between PCT and total DDD remained after accounting for these confounders; on average a

person with PCT>0.25 had almost three times as many DDDs of antibiotics compared to those ≤0.25 (coefficient 2.72, 95%CI: 2.03, 3.62, p<0.001) (Supplementary Table 2).

Patient 28-Day Outcomes

Over the 28-day follow-up period, 116 (32%) of the included patients died, 229 (62%) were discharged and 23 (6%) were still in hospital. Median length of stay was 8.35 days. 47 (13%) were admitted to intensive care, and of these, 32 (68%) were intubated and ventilated. The PCT, age and 28-day mortality distribution of the patients are illustrated graphically in Figure 2. In the negative PCT group, 62 (28%) patients died compared to 54 (36%) of those with a positive PCT (p=0.021), and 19 (9%) were admitted to ITU, compared with 28 (19%) of the positive PCT group (p=0.007).

Meropenem was the only carbapenem used in the study population. With specific reference to meropenem consumption, positive PCT was associated with a 3-fold increase in the odds of receiving any meropenem during the course of the admission (OR= 3.16, 95% CI: 1.50, 6.65, p=0.002) after adjusting for demographic confounders (Figure 1B and Supplementary Table 3).

There was no significant difference in rates of infective complications between positive and negative PCT groups as illustrated in Supplementary Table 2.

DISCUSSION

This observational study reveals success of a local guideline advising against antibiotic use for patients with confirmed COVID-19 and PCT level ≤0.25ng/ml, leading to reduced antibiotic consumption compared to national statistics [5], without negative impact on patient 28-day outcome.

Clinicians were encouraged to request a PCT for any patient requiring admission to hospital with COVID. The guideline was discussed with relevant admitting specialities, particularly those in the accident and emergency and acute medicine departments. The use of procalcitonin in an electronic 'COVID order set' also promoted its use.

28-day mortality figures in this study (28% PCT ≤ 0.25ng/ml, 36% PCT > 0.25ng/ml) are similar to data published by the ISARIC consortium, the largest COVID-19 patient registry in the UK, suggesting implementation of the guideline did not cause harm. [5]

The adopted PCT threshold of 0.25ng/ml was intentionally conservative and it may be that a higher threshold can be adopted safely. Further research to evaluate the optimal cut-off value for PCT in which antibiotics can be safely withheld is recommended.

Though the guideline was well received and implemented there were still a proportion of patients with negative PCT who received antibiotics. Local investigations of rationale for

antibiotic prescription in these patients needs to be undertaken.

This higher mortality seen in the PCT >0.25ng/ml group supports those of other authors, demonstrating an association between higher PCT values and severe disease or death [27, 28]. It is likely that higher PCT in these patients reflects bacterial superinfection and consequent impairment in outcome in many cases. It is also possible that PCT is raised in severe COVID-19 disease independent of bacterial infection, which would open the possibility of further improvements in antimicrobial stewardship through use of a higher PCT threshold or other parameters.

Reducing the unnecessary use of antibiotics through this guideline is a key component to mitigating the risk of antimicrobial resistance. The risk of severe COVID-19 disease increases with age and the elderly are also at greatest risk of the adverse consequences of excessive antibiotic use [29].

We demonstrated a 3-fold increase in the odds of carbapenem prescription in those with a positive PCT. This is important in the context of the increasing global incidence of carbapenemase-producing Enterobacteriales. Our study shows impact of early rationalised antimicrobial therapy on later prescription of broad spectrum agents.

The limitations of our study include the fact that it is from a single centre and retrospective in design. Further research with a prospective design to evaluate the utility of procalcitonin

(with varying cut-off values) as a diagnostic marker to improve antimicrobial stewardship in COVID-19 is needed.

CONCLUSIONS

This study shows that a procalcitonin-based guideline can be a useful tool in rationalising antibiotic use in COVID-19 patients.

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Figure 1: A) Antibiotic consumption as demonstrated by average DDD & average meropenem DDD between positive and negative PCT groups, stratified by age

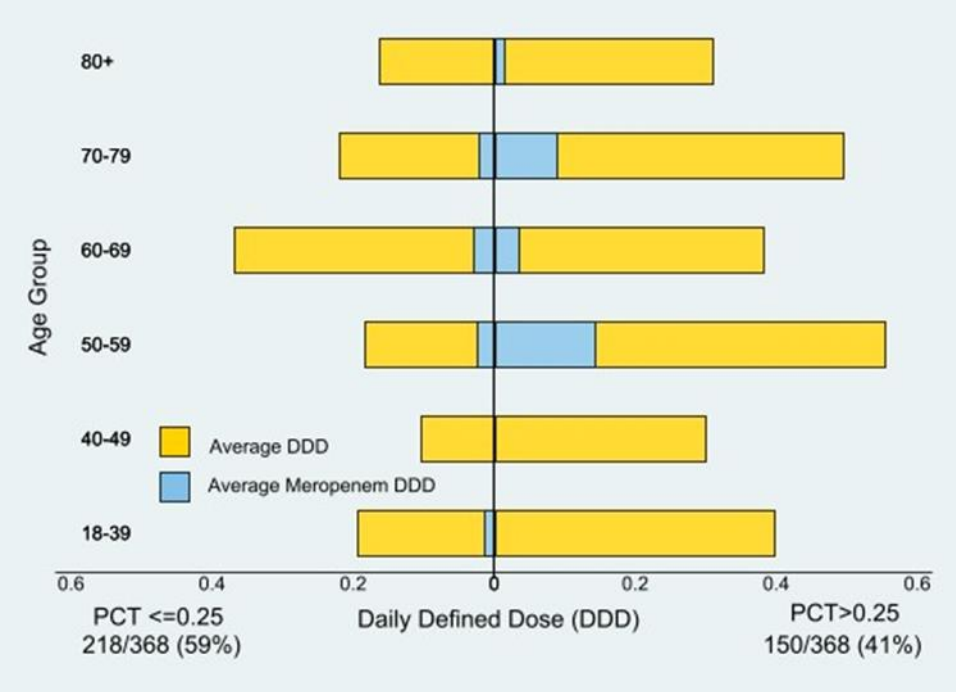

Figure 1B: Mortality outcomes for positive and negative PCT groups stratified by age

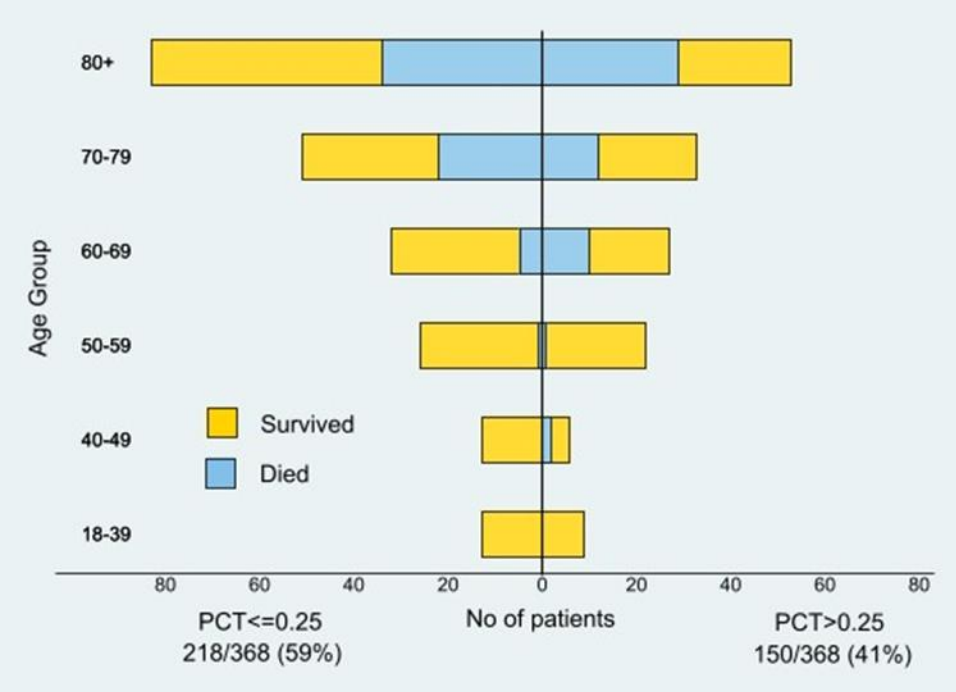

Table 1. Baseline demographics of patients stratified by PCT level

Procalcitonin level (ng/ml)		≤0.25	>0.25	Total	p-value
Total No (%)		218 (59)	150 (41)	368 (100)	
Age at admission					
Median (IQR)		75 (61-84)	74 (60-82)	75 (60-83)	p=0.417 $
Age	18-39	13 (6)	9 (6)	22	p=0.849 #
	40-49	13 (6)	6 (4)	19	
	50-59	26 (12)	22 (15)	48	
	60-69	32 (15)	27 (18)	59	
	70-79	51 (23)	33 (22)	84	
	80+	83 (38)	53 (35)	136	
Sex	Male	123 (56)	98 (65)	221	p=0.086 *
	Female	95 (44)	52 (35)	147	
BMI (n=330)	<20	16 (8)	9 (7)	25	p=0.885 *
	20-25	51 (26)	40 (30)	91	
	25-30	66 (34)	44 (33)	110	
	30+	62 (32)	42 (31)	104	
Ethnicity	White	172 (79)	112 (75)	284	p=0.428 #
	Black	13 (6)	13 (9)	26	
	Asian	11 (5)	5 (3)	16	
	Mixed	1 (0)	1 (1)	2	
	Other	3 (1)	3 (2)	6	
	Not stated	11 (5)	14 (9)	25	

	Missing	7 (3)	2 (1)	9	
Any comorbidity	No	38 (17)	31 (21)	69	p=0.435 *
	Yes	180 (83)	119 (79)	299	
Hypertension	No	140 (64)	96 (64)	236	p=0.965 *
	Yes	78 (36)	54 (36)	132	
Diabetes (1 or 2)	No	154 (71)	110 (73)	264	p=0.573 *
	Yes	64 (29)	40 (27)	104	
Cardiovascular disease	No	134 (61)	101 (67)	235	p=0.250 *
	Yes	84 (39)	49 (33)	133	
Asthma	No	195 (89)	134 (89)	329	p=0.972 *
	Yes	23 (11)	16 (11)	39	
Malignancy	No	183 (84)	140 (93)	323	p=0.007 *
	Yes	35 (16)	10 (7)	45	
Immunosuppressed	No	199 (91)	136 (91)	335	p=0.839 *
	Yes	19 (9)	14 (9)	33	
Chronic lung disease	No	177 (81)	122 (81)	299	p=0.973 *
	Yes	41 (19)	28 (19)	69	
Chronic renal impairment	No	192 (88)	125 (83)	317	p=0.196 *
	Yes	26 (12)	25 (17)	51	
Pregnancy	No	218 (100)	150 (100)	368	N/A
	Yes	0 (0)	0 (0)	0	

Fishers Exact test; $ Mann-Whitney U test; * Chi-square test; IQR= Inter-Quartile Range; BMI= Body Mass Index

Supplementary Table 1. Antibiotic use and 28-day outcomes in patients stratified by PCT level

Procalcitonin level (ng/ml)		≤0.25	>0.25	Total	p-value
Total (%)		218 (59)	150 (41)	368 (100)	
Clinical Outcomes					
28 day outcome	Died	62 (28)	54 (36)	116 (32)	p=0.021#
	Discharged	147 (67)	82 (55)	229 (62)	
	Still in hospital	9 (4)	14 (9)	23 (6)	
Intubated	No	207 (95)	129 (86)	336 (91)	p=0.004#
	Yes	11 (5)	21 (14)	32 (9)	
Admitted to ITU	No	199 (91)	122 (81)	321 (87)	p=0.007#
	Yes	19 (9)	28 (19)	47 (13)	
Length of stay					
Median (IQR)		8.7 (4.9-15.3)	9.0 (5.9-18.8)	8.9 (5.3-16.1)	p=0.054$
Antibiotic outcomes					
Total DDD received					
Median (IQR)		3.0 (0.3-6.3)	6.8 (3.6-10.4)	4.2 (1.3-8.3)	p<0.001$
Total Antibiotic DOT					
Median (IQR)		2 (0-5)	5 (4-9)	5 (1-7)	p<0.001$
DDD received/alive day					
Median (IQR)		0.14 (0.02 - 0.31)	0.37 (0.19 - 0.76)	0.23 (0.08 - 0.48)	p<0.001$

Days of treatment per alive day to day 28					
Median (IQR)		0.11 (0.00 - 0.25)	0.32 (0.18 - 0.60)	0.18 (0.04 - 0.39)	p<0.001$
Infective complications					
HAP/VAP	No	190 (87)	127 (85)	317	p=0.497 *
	Yes	28 (13)	23 (15)	51	
Significant respiratory tract isolate		12	11		
ESBL/AmpC isolation	No	213 (98)	148 (99)	361	p=0.705#
	Yes	5 (2)	2 (1)	7	
MRSA	No	218 (100)	149 (99)	367	p=0.408#
	Yes	0 (0)	1 (1)	1	
CDAD	Yes	0(0)	0(0)	0(0)	
Significant blood culture isolate		2	7		

Fishers Exact test; $ Mann-Whitney U test; * Chi-Square test; DDD= Defined Daily Dose; DOT=Days Of Treatment; IQR= Inter-Quartile Range; ITU= Intensive Treatment Unit; HAP= Hospital-Acquired Pneumonia; VAP= Ventilator-Associated Pneumonia; ESBL= Extended Spectrum Beta Lactamase; MRSA= Methicillin-Resistant *Staphylococcus aureus*. CDAD= *Clostridioides difficile* associated disease. Significant respiratory tract isolates excluded normal oral flora and significant blood culture isolates excluded common skin contaminants.

Supplementary Table 2: Log-linear regression model of total DDDs of antibiotics received vs. PCT result

		Coefficient	95% CI
PCT	≤0.25	*Ref*	-
	>0.25	2.72	2.03, 3.62
Sex	Female	*Ref*	-
	Male	1.06	0.76, 1.45
Age	18-39	1.08	0.49, 2.17
	40-49	0.35	0.09, 0.86
	50-59	1.25	0.71, 2.13
	60-69	1.29	0.78, 2.06
	70-79	1.16	0.75, 1.74
	80+	*Ref*	-
Ethnicity	White	*Ref*	-
	Black	0.88	0.44, 1.64
	Asian	1.59	0.71, 3.33
	Mixed	1.52	0.11, 10.07
	Other	0.67	0.12, 2.21
	Not stated	0.80	0.40, 1.48
	Missing	0.03	-0.09, 0.32
Comorbidities	Hypertension	0.88	0.62, 1.23
	Diabetes Mellitus	1.04	0.72, 1.48
	Cardiovascular disease	0.76	0.51, 1.09
	Asthma	0.95	0.56, 1.56
	Malignancy	0.81	0.48, 1.30
	Immunosuppressed	0.81	0.45, 1.39
	Chronic lung disease	1.14	0.76, 1.68
	Chronic renal impairment	0.83	0.51, 1.32
Constant		1.01	0.52, 1.84

Note: Due to the log-normal distribution of total DDD received, the outcome was log-transformed (after adding the smallest non-zero constant to ensure those that received zero antibiotics were included in the analysis). This step ensured that linear model assumptions, specifically normality of residuals, were met.

Supplementary Table 3: Logistic regression model of meropenem use vs. PCT result

		Odds Ratio	95% CI
PCT	≤0.25	*Ref*	-
	>0.25	3.16	1.50, 6.65
Sex	Female	*Ref*	-
	Male	1.63	0.72, 3.69
Age	18-39	0.68	0.07, 6.59
	40-49	N/A	N/A
	50-59	4.72	1.42, 15.63
	60-69	1.64	0.46, 5.86
	70-79	4.73	1.72, 13.06
	80+	*Ref*	-
Ethnicity	White	*Ref*	-
	Black	1.29	0.35, 4.74
	Asian	0.57	0.06, 5.43
	Mixed	N/A	-
	Other	1.00	0.08, 12.98
	Not stated	0.42	0.08, 2.08
	Missing	N/A	-
Comorbidities	Hypertension	0.93	0.44, 1.97
	Diabetes Mellitus	0.85	0.37, 1.96
	Cardiovascular disease	0.85	0.37, 1.98
	Asthma	0.97	0.30, 3.15
	Malignancy	0.17	0.02, 1.34
	Immunosuppressed	0.76	0.22, 2.64
	Chronic lung disease	0.52	0.19, 1.41
	Chronic renal impairment	1.01	0.39, 3.09
Constant		0.02	0.00, 0.12

Supplementary Table 4: Logistic regression model of meropenem use vs. ongoing prescription of antibiotics 48 hours after COVID-19 diagnosis

		Odds Ratio	95% CI
PCT	≤0.25	*Ref*	-
	>0.25	3.64	1.52, 8.63
Sex	Female	*Ref*	-
	Male	1.41	0.62, 3.24
Age	18-39	0.58	0.06, 5.52
	40-49	N/A	-
	50-59	4.21	1.27, 13.90
	60-69	1.52	0.43, 5.41
	70-79	4.34	1.57, 12.01
	80+	*Ref*	-
Ethnicity	White	*Ref*	-
	Black	1.37	0.38, 4.90
	Asian	0.36	0.04, 3.37
	Mixed	N/A	-
	Other	0.98	0.08, 12.21
	Not stated	0.41	0.08, 2.01
	Missing	N/A	-
Comorbidities	Hypertension	0.97	0.46, 2.05
	Diabetes Mellitus	0.73	0.32, 1.67
	Cardiovascular disease	0.81	0.35, 1.87
	Asthma	1.06	0.33, 3.42
	Malignancy	0.14	0.02, 1.09
	Immunosuppressed	0.72	0.21, 2.46
	Chronic lung disease	0.52	1.19, 1.42
	Chronic renal impairment	1.26	0.46, 3.48
Constant		0.02	0.00, 0.13

Supplementary Case Definitions

Defined Daily Doses (DDD): As per WHO description. Where different DDDs are defined for oral and parenteral preparations, the parenteral figure was used for calculations to avoid inappropriate weighting by route of administration for some commonly used agents

(e.g. clarithromycin) which would not be relevant from a stewardship perspective [20].

Days of treatment (DOT): Defined as the number of days in the 28-day period for which any antibiotics were prescribed.

Hospital Acquired Pneumonia/ ventilator associated pneumonia:

HAP/VAP was defined as commencement of a new antibacterial agent for a presumed chest source at least 48 hours after COVID-19 diagnosis, alongside either new elevation of white blood cell count or neutrophils or positive sputum culture for a likely pathogen. This pragmatic definition was used as other definitions of HAP/VAP are challenging to apply the context of COVID-19 due to the clinical and radiological features of the disease.