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1	Evaluation of procalcitonin
2	as an antimicrobial
3	stewardship tool in SARS-
4	CoV-2 infection: a
5	retrospective cohort study.
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37 38 20	Keywords. Antimicrobial stewardship, COVID-19, Procalcitonin, SARS-CoV-2, bacterial co-infection,

39 superadded infection

41 ABSTRACT

42

43 It can be a diagnostic challenge to identify COVID-19 patients 44 in whom antibiotics can be safely withheld. We evaluate the 45 effectiveness of a guideline implemented at Sheffield Teaching 46 Hospitals NHS Foundation Trust that recommends withholding 47 antibiotics in patients with a "negative" serum procalcitonin 48 (PCT), defined as ≤0.25ng/ml. Results showed reduced 49 antibiotic consumption in this patient group, without increase in 50 mortality, alongside a reduction in subsequent carbapenem 51 prescriptions during admission for those with a negative PCT. 52 Our results suggest effectiveness of this guideline, and 53 recommend further research to identify the optimal cut-off 54 value for procalcitonin in this setting. 55

56 INTRODUCTION

57 In patients with COVID-19, the presentation of fever, 58 tachypnoea and hypoxia, together with lung infiltrates on chest 59 imaging and a frequent rise in biomarkers such as C-reactive 60 protein (CRP) [1], presents a challenge to rational use of 61 antimicrobials as it is difficult to confidently exclude bacterial 62 co-infection. Rates of true bacterial co-infection are estimated 63 to be only 7 to 14% [2-4]. Despite this, early in the pandemic 64 80% of patients with COVID-19 received antibiotic treatment 65 [5]. Strategies to accurately identify patients with COVID-19 66 who do not have bacterial co-infection are needed to reduce

- 67 antimicrobial prescriptions and promote antimicrobial
- 68 stewardship. [10] National Institute for Health and Care
- 69 Excellence (NICE) guidance on pneumonia in the context of
- 70 COVID-19 has recommended further research into the use of
- 71 procalcitonin (PCT) for this purpose.
- 72 We set out to evaluate whether inclusion of measurement of
- 73 PCT in a hospital guideline for antibiotic prescription in COVID-
- 19 had an impact on i) antibiotic usage and ii) outcomes in
- 75 patients with confirmed COVID-19 at a large NHS Foundation
- 76 Trust Hospital in the United Kingdom (UK).
- 77

78 METHODS

79 Study Design, Study Site and Population

- 80 This retrospective observational study was undertaken at two
 81 sites of Sheffield Teaching Hospitals NHS Foundation Trust
- 82 (STHNHFT).
- Eligible patients were ≥ 18 years old and diagnosed with

84 COVID-19 between 5 March and 15 April 2020 with a positive

- 85 SARS-CoV-2 reverse-transcriptase polymerase chain reaction
- 86 (RT-PCR) result on nose and/or throat swabs and/or deep
- 87 respiratory samples, and had a PCT assay undertaken within
- 48 hours of collection of the first positive SARS-CoV-2 sample.
- 89 Patients with both community and nosocomial acquisition of
- 90 COVID-19 were included. STHNFT guidelines recommended
- 91 that antibiotics could be withheld in COVID-19 patients with a

- 92 PCT value of ≤0.25ng/ml unless felt necessary by a senior
- 93 clinician, as concomitant bacterial infection is considered
- 94 unlikely below this level [18].
- 95 Patients diagnosed before 5th March 2020 were excluded as at
- 96 this point COVID-19 was managed as a high consequence
- 97 infectious disease and patients were admitted regardless of
- 98 symptom severity. The enrolment end date of 15th April was
- 99 before mandatory SARS-CoV-2 screening of all patients
- 100 admitted to hospital was introduced.
- 101 The study was granted approval by the STHNFT Clinical
- 102 Effectiveness Unit. (Ref: 9863)

103 Data Collection and Outcomes

- 104 Demographic and clinical characteristics of patients were
- 105 drawn from existing laboratory, pharmacy and clinical
- 106 databases and from examination of physical and electronic
- 107 patient notes. Data was entered into an electronic case report
- 108 form (Access 2010, Microsoft, Redmond, WA, USA).
- 109 Primary outcome was antibiotic consumption in WHO defined
- 110 daily doses (DDD) per day alive over 28 days after COVID-19
- 111 diagnosis and days of treatment (DOT). 28-day outcome was
- 112 recorded as discharged, still in hospital or died.
- 113 Data on antibiotic-associated adverse events were collected
- 114 including hospital-acquired pneumonia/ventilator-associated
- 115 pneumonia (HAP/VAP), *Clostridioides difficile* infection,
- 116 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.
- 120 Case definitions for DDD, DOT and HAP/VAP can be read in
- 121 supplementary materials.

122 Statistical Analysis:

- 123 All values from patients meeting eligibility criteria were
- 124 summarised using the most appropriate form, either using
- 125 frequency/percentages, or medians with IQR (Inter-Quartile
- 126 Range). Differences between demographics were analysed
- 127 with the suitable significance test, depending on whether
- 128 parametric assumptions were met as is detailed each table. To
- 129 investigate the relationship between PCT positivity and total
- 130 DDD and between antibiotic receipt at 48 hours post-diagnosis
- 131 and meropenem prescription, linear and logistic regression
- 132 models were explored adjusting for demographic confounders
- 133 (age, sex, ethnicity and comorbidities.) All statistical analyses
- 134 were performed in Stata version 16.1 (StataCorp 2019. Stata
- 135 Statistical Software: Release 16. College Station, TX:
- 136 StataCorp LLC.)
- 137

138 **RESULTS**

139 Study Population

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

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

151 Compliance with Guideline

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

156 Antibiotic Usage

157 Data on total DDD of antibiotics received in the 28-day follow-158 up period and DDD per alive day are presented in Figure 1A 159 and Supplementary Table 1. Patients with a negative PCT 160 received significantly fewer DDDs of antibiotics (both total and 161 per alive day) than those with positive PCT with a median DDD 162 of 3.0 vs 6.8 (p<0.001). A log-linear model was computed in 163 order to explore the relationship with PCT positivity after 164 adjusting for demographic confounders (comorbidities, age, 165 sex, ethnicity) to ensure regression assumptions were met. A 166 statistically significant relationship between PCT and total DDD 167 remained after accounting for these confounders; on average a

- 168 person with PCT>0.25 had almost three times as many DDDs
- 169 of antibiotics compared to those ≤ 0.25 (coefficient 2.72,
- 170 95%CI: 2.03, 3.62, p<0.001) (Supplementary Table 2).

171 Patient 28-Day Outcomes

- 172 Over the 28-day follow-up period, 116 (32%) of the included
- 173 patients died, 229 (62%) were discharged and 23 (6%) were
- 174 still in hospital. Median length of stay was 8.35 days. 47 (13%)
- 175 were admitted to intensive care, and of these, 32 (68%) were
- 176 intubated and ventilated. The PCT, age and 28-day mortality
- 177 distribution of the patients are illustrated graphically in Figure
- 178 2. In the negative PCT group, 62 (28%) patients died
- 179 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
- 181 the positive PCT group (p=0.007).
- 182 Meropenem was the only carbapenem used in the study
- 183 population. With specific reference to meropenem
- 184 consumption, positive PCT was associated with a 3-fold
- 185 increase in the odds of receiving any meropenem during the
- 186 course of the admission (OR= 3.16, 95% CI: 1.50, 6.65,
- 187 p=0.002) after adjusting for demographic confounders (Figure
- 188 1B and Supplementary Table 3).
- 189 There was no significant difference in rates of infective
- 190 complications between positive and negative PCT groups as
- 191 illustrated in Supplementary Table 2.

193 **DISCUSSION**

194 This observational study reveals success of a local guideline

195 advising against antibiotic use for patients with confirmed

- 196 COVID-19 and PCT level ≤0.25ng/ml, leading to reduced
- 197 antibiotic consumption compared to national statistics [5],
- 198 without negative impact on patient 28-day outcome.
- 199 Clinicians were encouraged to request a PCT for any patient
- 200 requiring admission to hospital with COVID. The guideline was
- 201 discussed with relevant admitting specialities, particularly
- 202 those in the accident and emergency and acute medicine
- 203 departments. The use of procalcitonin in an electronic 'COVID
- 204 order set' also promoted its use.
- 205 28-day mortality figures in this study (28% PCT \leq 0.25ng/ml,
- 206 36% PCT > 0.25ng/ml) are similar to data published by the
- 207 ISARIC consortium, the largest COVID-19 patient registry in
- 208 the UK, suggesting implementation of the guideline did not
- 209 cause harm. [5]
- 210 The adopted PCT threshold of 0.25ng/ml was intentionally
- 211 conservative and it may be that a higher threshold can be
- adopted safely. Further research to evaluate the optimal cut-off
- 213 value for PCT in which antibiotics can be safely withheld is
- 214 recommended.
- 215 Though the guideline was well received and implemented
- there were still a proportion of patients with negative PCT who
- 217 received antibiotics. Local investigations of rationale for

- 218 antibiotic prescription in these patients needs to be
- 219 undertaken.
- 220 This higher mortality seen in the PCT >0.25ng/ml group
- 221 supports those of other authors, demonstrating an association
- between higher PCT values and severe disease or death [27,
- 223 28]. It is likely that higher PCT in these patients reflects
- 224 bacterial superinfection and consequent impairment in
- 225 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
- 228 antimicrobial stewardship through use of a higher PCT
- threshold or other parameters.
- 230 Reducing the unnecessary use of antibiotics through this
- 231 guideline is a key component to mitigating the risk of
- antimicrobial resistance. The risk of severe COVID-19 disease
- 233 increases with age and the elderly are also at greatest risk of
- the adverse consequences of excessive antibiotic use [29].
- 235 We demonstrated a 3-fold increase in the odds of carbapenem
- 236 prescription in those with a positive PCT. This is important in
- 237 the context of the increasing global incidence of
- 238 carbapenemase-producing Enterobacteriales. Our study
- shows impact of early rationalised antimicrobial therapy on
- 240 later prescription of broad spectrum agents.
- 241 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

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

248 CONCLUSIONS

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

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- 417 Figure 1: A) Antibiotic consumption as demonstrated by
- 418 average DDD & average meropenem DDD between



419 positive and negative PCT groups, stratified by age

420

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



Table 1. Baseline demographics of patients stratified by PCT level

Procalcitonin level (ng/ml)		≤0.2 5	>0.2 5	Total	p-value
T + 1 N - (0/)		210	150	260	
Total No (%)		(59)	(41)	368	
)	
Age at admission		76	77.4	76	0.417
Median (IQR)		/5	/4	/5	p=0.417
		(01- 84)	(60- 82)	(60- 83)	Ψ
Δαο	18-30	12	9(6)	22	n = 0.84.9
nge	10-39	(6)	5 (0)	22	#
	40-49	13	6(4)	19	
		(6)			
	50-59	26	22	48	
		(12)	(15)		
	60-69	32	27	59	
		(15)	(18)		
	70-79	51	33	84	
		(23)	(22)		
	80+	83	53	136	
		(38)	(35)		
Sex	Male	123	98	221	n=0.086
JCA	Maie	(56)	(65)	221	p=0.000 *
	Female	95	52	147	
	1 01110	(44)	(35)		
BMI (n=330)	<20	16 (8)	9 (7)	25	p=0.885 *
	20-25	51	40	91	
		(26)	(30)		
	25-30	66	44	110	
		(34)	(33)		
	30+	62	42	104	
		(32)	(31)		
Ethnicity	White	172	112	284	p=0.428
		(79)	(75)		#
	Black	13	13	26	
		(6)	(9)		
	Asian	11	5 (3)	16	
		(5)			
	Mixed	1(0)	1(1)	2	
	Other	3 (1)	3 (2)	6	
	Not	11	14	25	
	stated	(5)	(9)		

g -		Missin	7 (3)	2(1)	9	
Any comorbidity No 38 31 69 $p=0.435$ Yes 180 119 299 * Hypertension No 140 96 236 $p=0.965$ Hypertension No 140 96 236 $r Diabetes (1 or 2) No 154 110 264 r Yes 64 40 104 r r r Gardiovascular disease No 134 101 235 r<$		g				
Any comorbidity No 38 31 69 p=0.435 IT7 (21) - * Yes 180 119 299 Hypertension No 140 96 236 Yes 78 54 132 * Tes 78 54 132 * Diabetes (1 or 2) No 154 110 226 p=0.973 (21) (27) (27) * * * Ves 64 40 104 (29) (27) * Cardiovascular disease No 134 101 235 p=0.972 Yes 84 49 133 (39) (33) * Asthma No 195 134 329 p=0.972 Malignancy No 183 140 323 * * Malignancy No 198 144 33 * * *	A 1 · 1·.	NT	20	21	(0	0.425
Image: 177 121 299 Yes 180 119 299 Hypertension No 140 96 236 Yes 78 54 132 (64) (64) Yes 78 54 132 (71) (73) (71) $(72$	Any comorbidity	NO	38	$\frac{31}{(21)}$	69	p=0.435 *
Tes 100 119 2.99 Hypertension No 140 96 236 p=0.965 Yes 78 54 132 * Diabetes (1 or 2) No 154 110 264 p=0.965 Ves 64 40 104 * * Cardiovascular disease No 134 101 235 p=0.250 Kes 64 49 133 * * Asthma No 134 101 235 p=0.250 Malignancy Yes 84 49 133 * Yes 23 16 39 * * Malignancy No 183 140 323 * Yes 35 10 45 * * Immunosuppresse No 199 136 335 * (9) (9) (9) 9 * * Yes <		Voc	100	(21)	200	-
Image: constraint of the sector of		res	(83)	(79)	299	
Hypertension No 140 96 236 p=0.965 Yes 78 54 132 ************************************			(03)	(75)		
No 164 (64) (64) (61) (71) (73) (71) (73) (71) (73) (71) (73) (71) (73) (71) (73) (71) (73) (71) (73) (71) (73)	Hypertension	No	140	96	236	p=0.965
Yes 78 (36) 54 (36) 132 (36) Diabetes (1 or 2) No 154 (71) 110 (73) Pelo.573 ** Yes 64 (29) 40 (27) 104 (29) Pelo.573 ** Cardiovascular disease No 134 (61) 101 (67) 235 (61) pelo.250 (67) Yes 84 (39) 49 (33) 133 pelo.250 ** Asthma No 195 (89) 134 (89) 329 (89) pelo.972 ** Malignancy No 195 (11) 134 (11) 323 (16) pelo.077 ** Malignancy No 183 (16) 140 (7) 323 (16) pelo.077 ** Immunosuppresse d No 183 (16) 140 (7) 335 pelo.972 ** Ves 199 (19) 136 (13) 335 (16) pelo.972 * * Malignancy No 183 (16) 140 (19) 335 pelo.973 ** Malignancy No 177 (12) 299 (9) 136 (9) 335 pelo.973 ** Malignancy No 177 (12) <td>ny per conoron</td> <td></td> <td>(64)</td> <td>(64)</td> <td>200</td> <td>*</td>	ny per conoron		(64)	(64)	200	*
Image: state of the s		Yes	78	54	132	-
Diabetes (1 or 2) No 154 (71) 110 (73) 264 (73) p=0.573 * Yes 64 40 104 * Yes 64 40 104 * Cardiovascular disease No 134 101 235 p=0.250 Yes 84 49 133 * * Cardiovascular disease No 195 134 329 p=0.972 (89) (89) (89) * * * Asthma No 195 134 329 p=0.972 (89) (89) (89) * * * Malignancy No 183 140 323 p=0.007 Wes 35 10 45 * * Immunosuppresse No 199 136 335 p=0.839 (91) (91) (91) * * * Greener 199 14 33 *			(36)	(36)		
Diabetes (1 or 2) No 154 110 264 p=0.573 Yes 64 40 104 * Yes 64 40 104 * Cardiovascular disease No 134 101 235 p=0.250 Yes 84 49 133 * * Cardiovascular disease No 195 134 329 p=0.250 Kes 84 49 133 * * * Asthma No 195 134 329 p=0.972 * Malignancy Yes 23 16 39 * * Malignancy No 183 140 323 p=0.007 * Malignancy No 183 140 323 p=0.33 * Malignancy No 199 136 335 p=0.973 * Malignancy No 199 14 33 * * <td></td> <td></td> <td></td> <td></td> <td></td> <td></td>						
$ \begin{array}{ c c c c c c c } \hline (71) & (73) & & & & & & & & & & & & & & & & & & &$	Diabetes (1 or 2)	No	154	110	264	p=0.573
Yes 64 40 104 (29) (27) (27) (27) Cardiovascular disease No 134 101 235 $p=0.250$ Yes 84 49 133 (39) (33) (39) (33) (39) (33) (40) ((71)	(73)		*
(29) (27) (27) Cardiovascular disease No 134 101 235 $p=0.250$ Yes 84 49 133 $p=0.250$ $*$ Yes 84 49 133 $p=0.250$ $*$ Asthma No 195 134 329 $p=0.972$ Malignancy No 195 134 329 $p=0.972$ Malignancy No 183 140 323 $p=0.007$ Malignancy No 193 14 33 $p=0.973$ Malignancy No 199 136 335 $p=0.973$ Malignancy No 177		Yes	64	40	104	
Cardiovascular disease No 134 (61) 101 (67) 235 (67) $p=0.250$ * Yes 84 49 133 * Yes 84 49 133 * Asthma No 195 134 329 $p=0.972$ Asthma No 195 134 329 $p=0.972$ Malignancy No 183 140 323 $p=0.072$ Malignancy No 183 140 323 $p=0.072$ Malignancy No 183 140 323 $p=0.007$ Malignancy No 183 140 323 $p=0.007$ Malignancy No 199 136 335 $p=0.839$ Malignancy No 199 136 335 $p=0.839$ Malignancy No 199 14 33 $p=0.973$ Malignancy No 177 122 299 $p=0.973$ Malignane Yes			(29)	(27)		
No 134 101 235 $p=0.250$ disease Yes 84 49 133 * Yes 84 49 133 * * Asthma No 195 134 329 $p=0.972$ Malignancy No 183 140 323 $p=0.972$ Malignancy No 183 140 323 $p=0.007$ Malignancy No 199 136 335 $p=0.007$ Maisease Yes 199 136 335 $p=0.973$ Maisease No 177 122 299 $p=0.973$ (B1) (B1) (B1) $e=0$ $e=0.973$ $e=0.973$ Maisease Yes 26 25 51 $e=0.173$ $e=0.173$ $e=0.173$ $e=0.173$	Cardiana la	Na	124	101	225	
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Tes 34° 47° 133° (39)(33)(33)AsthmaNo195134329Yes231639(11)(11)(11)(11)(11)(11)MalignancyNo183140323Yes351045(16)(7)*MalignancyNo19314323Yes351045(16)(7)*Yes191433(9)(9)(9)*Yes191433(19)(19)(19)*Yes412869(19)(19)(19)Yes262551(12)(17)122175Yes262551(12)(17)122175PregnancyNo218150368No218150368N/AYes0000	uisease	Voc	(01) Q4	(07)	122	
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Asthma No 195 (89) 134 (89) 329 (89) $p=0.972$ * Yes 23 16 39 (11) 314 323 * Yes 23 16 39 * * * Malignancy No 183 140 323 $p=0.007$ * Malignancy No 199 136 335 $p=0.0973$ * Immunosuppresse No 177 122 299 $p=0.973$ * Gisease Yes 41 28 69 * * (19) (19) (19) 195 317 * *				(33)		
Instantia Instantia <thinstantia< th=""> <thinstantia< th=""> <thinstantia< th=""></thinstantia<></thinstantia<></thinstantia<>	Asthma	No	195	134	329	p=0.972
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Image: system of text in tex text in tex text in tex text in tex text in text in text in tex		Yes	23	16	39	
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$\begin{array}{ c c c c c c c } & (84) & (93) & & & & & & & & & & & & & & & & & & &$	Malignancy	No	183	140	323	p=0.007
Yes351045Immunosuppresse dNo199136335 $p=0.839$ Mo199136335 $p=0.839$ *Yes191433(9)(9)*Yes191433(9)(9)*Chronic lung diseaseNo177122299 $p=0.973$ Kes412869**Yes412869**ImpairmentNo192125317 $p=0.196$ Yes262551**Yes262551**PregnancyNo218150368N/AYes0.(0)0.(0)0010			(84)	(93)		*
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$		Yes	35	10	45	
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Inimultiosuppresse dNo199136533 $p=0.839$ d(91)(91)**Yes191433*(9)(9)(9)(9)*Chronic lung diseaseNo177122299 $p=0.973$ (81)(81)(81)(81)*Yes412869*(19)(19)(19)**Chronic renal impairmentNo192125317 $p=0.196$ Yes262551*Yes262551*PregnancyNo218150368N/AYes0.(0)0.(0)00	Immunoquannaqqq	No	100	126	225	n-0.020
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	d	NO	(91)	(91)	222	p=0.839 *
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	u	Yes	19	14	33	-
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$\begin{array}{c ccccccccccccccccccccccccccccccccccc$			(-)	(*)		
disease(81)(81) 1 Yes412869(19)(19)(19)(19)(19)(19)Chronic renal impairmentNo192125317Yes262551(12)(17)(17)PregnancyNo218150368No218150368N/AYes0.(0)0.(0)0	Chronic lung	No	177	122	299	p=0.973
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	disease		(81)	(81)		*
(19) (19) (19) (19) (19) (19) (19) (19) (19) (19) (19) (19) (19) (19) (19) (19) (19) (19) (10) (10) (100) (100) (100) (100) (100) (100) (100) (100)		Yes	41	28	69	
Chronic renal impairment No 192 125 317 p=0.196 Yes 26 25 51 * Yes 26 25 51 * Pregnancy No 218 150 368 N/A Yes 0.00 0.00 0 0			(19)	(19)		
Chronic renal impairment No 192 125 317 p=0.196 Yes 26 25 51 * Yes 26 25 51 * Pregnancy No 218 150 368 N/A (100 (100))) 0						
Impairment (88) (83) * Yes 26 25 51 (12) (17) * Pregnancy No 218 150 368 N/A (100 (100))	Chronic renal	No	192	125	317	p=0.196
Yes 26 25 51 (12) (17) - Pregnancy No 218 150 368 N/A (100 (100 - - - - Yes 0.00 0.00 0 0 -	impairment	X	(88)	(83)	-1	*
(12) (17) Pregnancy No 218 150 368 N/A (100 (100))) Yes 0.00 0.00 0		res	26 (12)	$\frac{25}{(17)}$	51	
Pregnancy No 218 150 368 N/A (100 (100)))) Yes 0.00 0.00 0 0			(12)	(1/)		
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	Pregnancy	No	218	150	368	N/A
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	i regnancy	110	(100	(100	500	11/11
		Yes	0 (0)	0 (0)	0	1

427 # 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

Procalcitoni		≤0.25	>0.25	Total	p-value
n level					
(ng/ml)					
Total (%)		218	150	368	
		(59)	(41)	(100)	
<u>Clinical Outra</u>					
Clinical Outco	Diad	()	F 4	11(0.021#
28 day	Died	62	54	(22)	p=0.021*
outcome	Diachargo	(20)	(30)	(32)	
	Discharge	(67)	02 (55)	(62)	
	u Still in	$\left(07\right)$	(55)	22	
	Suii III bocnital	9(4)	(0)	23 (6)	
	nospitai		(9)	(0)	
Intubated	No	207	120	326	n=0.004#
mubateu	INO	(95)	(86)	(01)	p=0.004"
	Voc	11	21	22	
	165	(5)	(14)	(0)	
		(3)	(14)	(9)	
Admitted to	No	199	122	321	n=0.007#
ITH	NO	(91)	(81)	(87)	p=0.007
110	Ves	19	28	47	
	103	(9)	(19)	(13)	
			(1)	(15)	
Length of stay					
Median (IOR)	8.7	9.0	8.9	p=0.054 ^{\$}
	,	(4.9-	(5.9-	(5.3-	r · · · ·
		15.3)	18.8)	16.1)	
			Í	Í	
Antibiotic ou					
Total DDD rec	eived				
Median (IQR))	3.0	6.8	4.2	p<0.001\$
		(0.3-	(3.6-	(1.3-	
	•	6.3)	10.4)	8.3)	
Total Antibiot					
Median (IQR)	2 (0-	5 (4-	5 (1-	p<0.001\$
	1	5)	9)	7)	
DDD received					
Median (IQR)		0.14	0.37	0.23	p<0.001\$
		(0.02	(0.19	(0.08	
		-	-	-	
		0.31)	0.76)	0.48)	

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

432 # Fishers Exact test; \$ Mann-Whitney U test; * Chi-Square test; DDD=

433 Defined Daily Dose; DOT=Days Of Treatment; IQR= Inter-Quartile Range;

434 ITU= Intensive Treatment Unit; HAP= Hospital-Acquired Pneumonia; VAP=

435 Ventilator-Associated Pneumonia; ESBL= Extended Spectrum Beta

436 Lactamase; MRSA= Methicillin-Resistant *Staphylococcus aureus*. CDAD=

437 *Clostridioides difficile* associated disease. Significant respiratory tract

438 isolates excluded normal oral flora and significant blood culture isolates

- 439 excluded common skin contaminants.
- 440
- 441
- 442

443

445 Supplementary Table 2: Log-linear regression model of total

446 DDDs of antibiotics received vs. PCT result

		Coefficient	95% CI
РСТ	≤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	0.76	0.51, 1.09
	disease		
	Asthma	0.95	0.56, 1.56
	Malignancy	0.81	0.48, 1.30
	Immunosuppressed	0.81	0.45, 1.39
	Chronic lung	1.14	0.76, 1.68
	disease		
	Chronic renal	0.83	0.51, 1.32
	impairment		
Constant		1.01	0.52, 1.84

447 Note: Due to the log-normal distribution of total DDD received, the

448 outcome was log-transformed (after adding the smallest non-zero

449 constant to ensure those that received zero antibiotics were included

450 in the analysis). This step ensured that linear model assumptions,

451 specifically normality of residuals, were met.

452

453

454 Supplementary Table 3: Logistic regression model of

455 meropenem use vs. PCT result

		Odds	95% CI
		Ratio	
РСТ	≤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

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

		Odds	95% CI
		Ratio	
РСТ	≤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	0.52	1.19, 1.42
	disease		
	Chronic renal	1.26	0.46, 3.48
	impairment		
Constant		0.02	0.00, 0.13

467 Supplementary Case Definitions

468 **Defined Daily Doses (DDD):** As per WHO description. Where

different DDDs are defined for oral and parenteral preparations, the

- 470 parenteral figure was used for calculations to avoid inappropriate
- 471 weighting by route of administration for some commonly used agents

- 472 (e.g. clarithromycin) which would not be relevant from a stewardship
- 473 perspective [20].
- 474 **Days of treatment (DOT):** Defined as the number of days in the 28-
- 475 day period for which any antibiotics were prescribed.

476 Hospital Acquired Pneumonia/ ventilator associated pneumonia:

- 477 HAP/VAP was defined as commencement of a new antibacterial
- 478 agent for a presumed chest source at least 48 hours after COVID-19
- 479 diagnosis, alongside either new elevation of white blood cell count or
- 480 neutrophils or positive sputum culture for a likely pathogen. This
- 481 pragmatic definition was used as other definitions of HAP/VAP are
- 482 challenging to apply the context of COVID-19 due to the clinical and
- 483 radiological features of the disease.
- 484
- 485