Use of procalcitonin for antibiotic stewardship in patients with COVID-19: A quality improvement project in a district general hospital

Authors: Christina Peters,[A] Kelly Williams,[A] Elena A Un,[A] Louisa Little,[B] Abeer Saad,[C] Katherine Lendrum,[D] Naomi Thompson,[E] Nicholas D Weatherley[F] and Amanda Pegden[G]

ABSTRACT

Antibiotic stewardship during the COVID-19 pandemic is an important part of a comprehensive strategy to improve patient outcomes and reduce long-term adverse effects secondary to rising antibiotic resistance. This report describes a quality improvement project which incorporates the use of procalcitonin (PCT) testing to rationalise antibiotic prescribing in patients with suspected or confirmed COVID-19 at Chesterfield Royal Hospital. Data were collected from 118 patients with a total of 127 PCT levels checked over a period of 20 days. Each PCT level was correlated with the subsequent antibiotic outcome as well as the result of the COVID-19 PCR swab. Results indicate that antibiotics were either never started or were stopped within 48 hours in 72% of COVID-confirmed cases with a PCT less than 0.25 µg/L. Our findings suggest that procalcitonin testing, when used in combination with thorough clinical assessment, is a safe, simple and sustainable way of reducing antibiotic use in COVID-19.

Introduction

The rapid rise of antimicrobial resistance is a major public health concern. Extensive antibiotic use in global healthcare settings is associated with greater morbidity and mortality secondary to complex drug-resistant infections and severe diarrhoeal illnesses such as *Clostridium difficile* colitis.[1] The resulting cost of prolonged hospital stays and expensive treatment courses puts additional unnecessary strain on an already overburdened healthcare system. Antimicrobial stewardship is an important component of the multifaceted approach needed to reduce rising resistance rates and improve long-term health outcomes.

Emergence of the COVID-19 pandemic has served to exacerbate pre-existing pressures in healthcare provision. A major concern raised by the World Health Organization has been the prolific use of antibiotics in patients with suspected COVID-19.[2] Guidelines released by WHO in May 2020[3] have subsequently advised limiting the use of empiric antibiotics to only those patients with severe symptoms thought to be caused by COVID-19. Translation of guidelines into practice has been understandably challenging as clinicians struggle to contend with the effects of the virus in a setting clouded by anxiety, urgency and ambiguity of viral presentation. With few treatment options available and considerable overlap of symptoms between COVID-19 and bacterial pneumonia, the reflex prescription of antibiotics has become routine.[4]

The basis of antibiotic use in a viral setting hinges on the possibility of bacterial co-infection. Retrospective studies from both the UK[5] and China[6] have shown that the incidence of secondary infection in COVID-19 is lower than that of influenza, accounting for only 10–15% of hospitalised patients in comparison with more than 30% in influenza.[7,8] Nonetheless, the early days of the pandemic in the UK saw the majority of suspected COVID-19 cases being treated with antibiotics in an effort to reduce the impact of possible bacterial co-infection. An important principle of antibiotic stewardship is the avoidance of unnecessary antibiotics and avoidance of needlessly prolonged treatment courses. Prompt identification of patients to whom this applies may help reduce antibiotic prescribing rates and consequently antibiotic resistance.

Many hospitals, nationally and internationally, have begun to use procalcitonin (PCT) as an aid to rationalise antibiotic therapy.[9] PCT is a protein biomarker for the presence and severity of bacterial infection. Levels rise within 12 hours of bacterial involvement and decrease as the host immune system begins to control the infection. Unlike other inflammatory biomarkers (CRP and ESR), PCT levels remain low in the context of non-bacterial causes

Authors: [A]internal medicine trainee, Chesterfield Royal Hospital, Chesterfield, UK; [B]foundation year 2 doctor, Chesterfield Royal Hospital, Chesterfield, UK; [C]respiratory medicine and general internal medicine specialty registrar, Chesterfield Royal Hospital, Chesterfield, UK; [D]consultant in emergency medicine and emergency department clinical lead, Chesterfield Royal Hospital, Chesterfield, UK; [E]microbiology consultant, Chesterfield Royal Hospital, Chesterfield, UK; [F]NIHR academic clinical lecturer in respiratory medicine, University of Sheffield, Sheffield, UK, UK; [G]sepsis lead and consultant in acute medicine, Chesterfield Royal Hospital, Chesterfield, UK
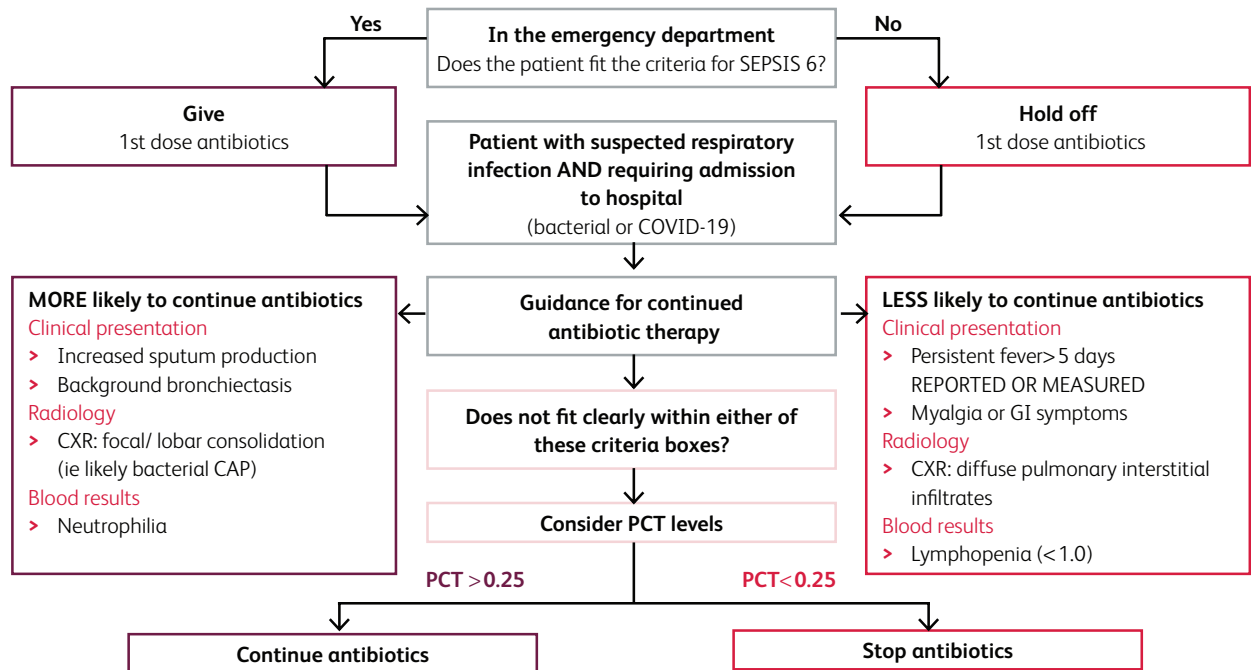
Fig 1. Guideline for rationalising antibiotics in patients with suspected or confirmed COVID-19.

of infection and inflammation.[10] A large-scale meta-analysis has previously demonstrated the use of PCT as a helpful guide for the safe reduction of antibiotic prescription rates in COPD patients.[11] As such, it seems likely that PCT can be used to reduce unnecessary antibiotic prescriptions in patients with symptoms of COVID-19.

National guidelines from NICE do not currently advise routine use of PCT for antibiotic stewardship in COVID-19.[12] Centres that are already using PCT have been encouraged to participate in research to improve current evidence on the value of PCT for antibiotic stewardship in COVID-19. This report describes a quality improvement project (QIP) which incorporates the use of PCT as part of a comprehensive strategy comprising routine radiological, bedside and biochemical features to help rationalise antibiotic prescribing in patients with suspected or confirmed COVID-19 at Chesterfield Royal Hospital. The aim of this project was to determine the extent to which PCT testing influenced antibiotic prescribing. Although the true impact of antibiotic overuse during the pandemic remains to be seen, rapid, real-time adaptation is critical to mitigate associated harm.

Methods

In order to promote antibiotic stewardship in patients with suspected or confirmed COVID-19, a new hospital guideline (Fig 1) was developed with input from a multidisciplinary team comprising consultants in respiratory, microbiology, emergency medicine, acute medicine and the sepsis lead. The quality improvement team consisted of three consultants, two registrars, three internal medicine trainees and one F2 doctor.

The algorithm, which was introduced on 8 April 2020, advised using PCT in cases where bacterial co-infection could not be ruled out. Although this was not an evidence-based approach, the

MDT felt it would be the best means to minimise potential harm from early antibiotic withdrawal. Once a PCT level was checked, results were made available electronically with recommendations as shown in Table 1. PCT cut-off levels have been adapted from the ProHOSP randomised controlled trial (RCT) investigating the effect of PCT-guided antibiotic prescribing in lower respiratory tract infections.[13] PCT cut-offs in the majority of RCTs have been consistent at 0.25 μg/L and 0.5 μg/L in ward and ITU patients respectively.[14] A lower cut-off level of 0.25 μg/L was chosen for this study as ITU patients were excluded from analysis. Furthermore, this helped reduce the risk of under-treating bacterial co-infection.

164 PCT levels were carried out between 8 April 2020 and 27 April 2020 on a total of 143 patients with suspected or confirmed COVID-19. The date of each PCT result was correlated with the start and end dates of any antibiotic courses. The COVID-19 status was also checked for each patient. As the number of PCT results does not equate to the number of patients (due to repeat PCT levels in some patients), each 'case' refers to the number of times bacterial co-infection has been suspected (ie more than once in some patients).

To analyse the data, cases were grouped into categories based on PCT level (<0.25 μg/L, 0.25–0.49 μg/L, ≥0.5 μg/L). Each PCT

Table 1. Recommendation of antibiotic use based on procalcitonin result

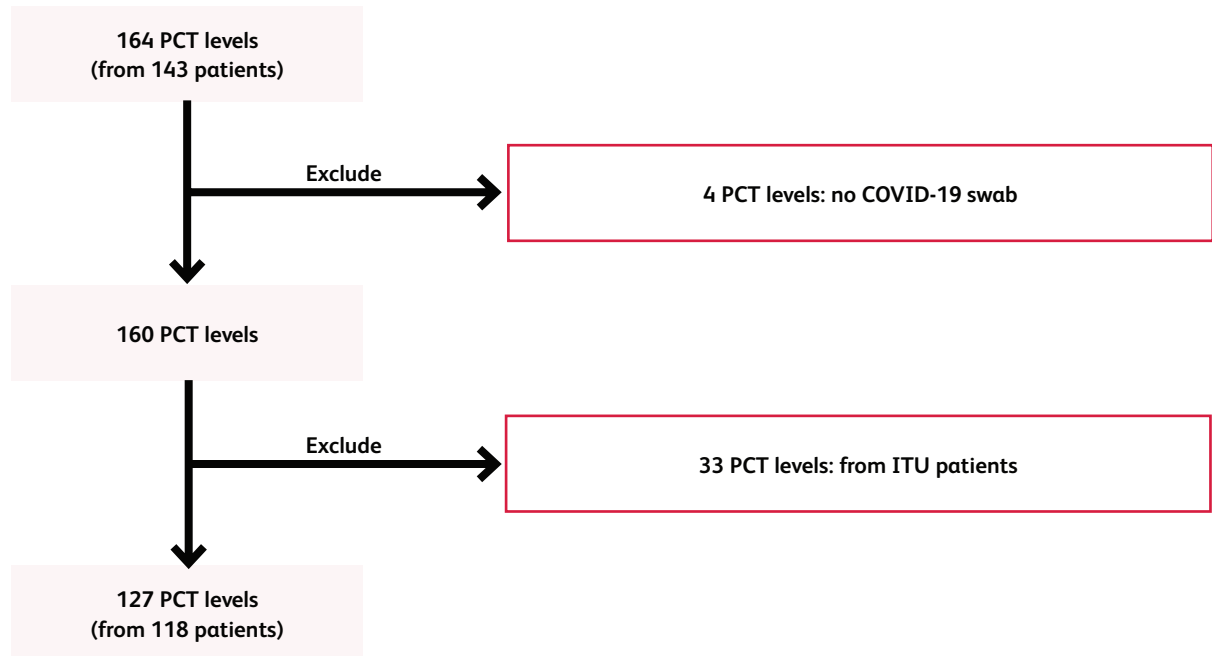|	
Procalcitonin <0.1 μg/L	Antibiotics strongly discouraged
Procalcitonin 0.1–0.24 μg/L	Antibiotics discouraged
Procalcitonin 0.25–0.49 μg/L	Antibiotics encouraged
Procalcitonin ≥0.5 μg/L	Antibiotics strongly encouraged

Fig 2. Flow chart of exclusion criteria for data analysis. PCT levels were excluded from ITU patients because in this setting PCT levels are checked repeatedly to assess for ventilator-associated pneumonia and/or infection severity rather than as a guide for antibiotic prescribing, and because the complexity and severity of illness risks confounding PCT levels to an extent where PCT might no longer be fit for purpose in the context of antibiotic stewardship.

result was correlated with the outcome of the COVID-19 PCR swab in order to determine the proportion of cases in each group that tested positive and negative for COVID-19. In all cases where a PCT level was correlated with a positive COVID-19 PCR swab, the antibiotic outcome was identified and divided into cases where antibiotics had not been started (pending PCT result), or where antibiotics were started but then stopped within 48 hours of PCT result, or continued, escalated or de-escalated. The results were also analysed by stratification into COVID-19 PCR swab result (see supplementary material, S1).

Results

Of the 164 PCT levels that were carried out in the 20-day period between 8 April 2020 and 27 April 2020, a few were excluded from data analysis. Fig 2 outlines the number of excluded PCT levels and the reasons why they were not analysed.

Data from the remaining 127 PCT levels were analysed. It is important to note that nine ward-based patients had two PCT levels checked on different days during their admission. In most cases the second PCT was checked due to recurrent temperature spikes or a failure to recover despite initial treatment. As each PCT level represents discrete clinical scenarios, these have been included in the data analysis but have been treated as separate 'cases'.

Demographics of all included cases are outlined in Table 2.

The antibiotic outcome following PCT result in patients with confirmed COVID-19 is summarised in Fig 3.

Among patients who were confirmed to have COVID-19, the pie-charts in Fig 3 show increasing antibiotic use with increasing PCT level. Shades of green have been used to represent cases

| Table 2. Demographics of included cases		
	Procalcitonin (PCT) levels (N=127)	**COVID-PCR status**
Sex		
Men	70	Positive: 43 (61.4%) Negative: 27 (38.6%)
Women	57	Positive: 29 (50.9%) Negative: 28 (49.1%)
Clinical setting		
Emergency department	73	
Ward	54	
Procalcitonin (PCT) groups		
PCT <0.25 µg/L	77	Positive: 40 (51.9%) Negative: 37 (48.1%)
0.1; 0.07–0.16 (median; interquartile range)		
PCT 0.25–0.49 µg/L	18	Positive: 13 (72.2%) Negative: 5 (27.8%)
0.355; 0.30–0.385 (median; interquartile range)		
PCT ≥0.5 µg/L	32	Positive: 19 (59.4%) Negative: 13 (40.6)
1.26; 0.785–3.27 (median; interquartile range)		
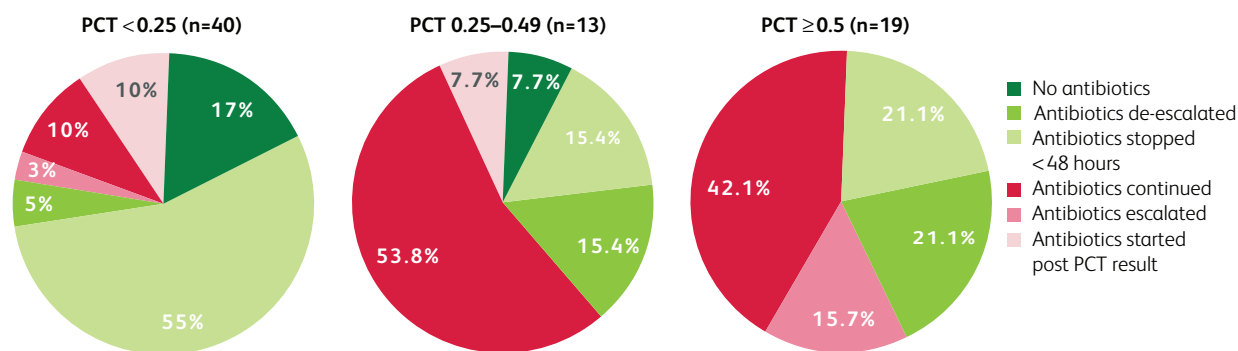
Fig 3. Pie charts showing antibiotic outcomes for all confirmed COVID-19 cases in each procalcitonin category. In all cases where antibiotics were prescribed, the outcome following procalcitonin result (ie started, stopped, continued, escalated or de-escalated) is also shown.

where PCT helped reduce antibiotic use, while shades of pink/red represent cases where antibiotics have been started, continued or escalated post PCT level. The first pie chart shows a low rate of initial prescription or early stoppage of antibiotics in 77.5% of all COVID-confirmed cases with PCT <0.25. Cases with PCT in the mid (0.25–0.49) or high (≥0.5) ranges were continued on antibiotics (61.5% and 57.9% respectively).

For the nine patients that had two PCT levels checked on different days, Table 3 shows the first and second PCT results along with the days they were taken and the associated COVID-19 status and antibiotic outcomes. Patients 4 and 6 were both started on antibiotics in the time between their first and second PCT result. The outcome of this newly started course of antibiotics following repeat PCT level is given in the table below.

Discussion

Of the 127 cases in whom bacterial co-infection was queried in patients with suspected or confirmed COVID-19, just above 60% of cases (n=77) had a PCT result that was not suggestive of bacterial involvement (ie PCT<0.25). Regardless of COVID-19 status, 72.7% of these cases (n=56) were either never started on antibiotics, or had antibiotics stopped within 48 hours of PCT result. Similar figures are seen for patients with confirmed COVID-19, with 72.5% of cases (n=29) with a PCT<0.25 either never starting antibiotics or having antibiotics stopped within 48 hours. Given that hospital guidelines only advised PCT use in clinically ambiguous cases, it can be expected that a full antibiotic course would have been completed in all 127 cases in the absence

Table 3. Antibiotic outcomes for patients with repeat procalcitonin levels				
	First PCT, μg/L	**Second PCT, μg/L**	**COVID-19 swab**	**Antibiotic outcome following PCT**
Patient 1	0.11 (15 April 2020)*	0.15 (22 April 2020)*	POS POS	1st PCT: Stopped <24hrs 2nd PCT: Continued
Patient 2	0.05 (17 April 2020)*	0.17 (20 April 2020)*	POS POS	1st PCT: Stopped <24hrs 2nd PCT: No antibiotics
Patient 3	0.02 (12 April 2020)*	0.11 (26 April 2020)*	NEG POS	1st PCT: Stopped <24hrs 2nd PCT: De-escalated
Patient 4	0.08 (12 April 2020)*	0.08 (27 April 2020)*	NEG NEG	1st PCT: No antibiotics 2nd PCT: Started + escalated
Patient 5	0.1 (16 April 2020)*	0.1 (17 April 2020)*	NEG NEG	1st PCT: No antibiotics 2nd PCT: No antibiotics
Patient 6	0.2 (23 April 2020)*	0.25 (26 April 2020)†	POS POS	1st PCT: No antibiotics 2nd PCT: Started + continued
Patient 7	0.11 (25 April 2020)*	0.8 (26 April 2020)‡	POS POS	1st PCT: De-escalated 2nd PCT: Continued
Patient 8	0.26 (17 April 2020)†	0.21 (20 April 2020)*	POS POS	1st PCT: Continued 2nd PCT: Stopped <24hrs
Patient 9	0.65 (18 April 2020)‡	0.37 (22 April 2020)†	POS POS	1st PCT: Continued 2nd PCT: De-escalated

*Low procalcitonin group; †mid-range procalcitonin group; ‡high procalcitonin group. NEG = negative, POS = positive.

of PCT testing. Based on this data, we showed that PCT use has helped reduce antibiotic prescriptions in all COVID-suspected or confirmed cases by 44%, with levels being used to guide antibiotic therapy in just under three quarters of cases.

The third pie chart in Fig 3 shows an unexpectedly high number of COVID-19 cases with a high PCT who have had their antibiotics either stopped within 48 hours (n=4) or had them de-escalated (n=4). The reasoning for this was further investigated. In the four patients whose antibiotics were stopped within 48 hours, three had antibiotics withdrawn after being started on end of life care. The last patient had their PCT level checked 11 days after their COVID-19 swab, by which time a 10-day course of broad-spectrum IV antibiotics had already been completed. All four of the patients in the 'de-escalated' category were stepped down from IV to oral antibiotics, likely based on a broader clinical picture rather than PCT alone.

For the nine patients with repeat PCT levels, data in Table 3 help categorise PCT fluctuations and the resulting response in antibiotic prescribing. In most cases, the second PCT level was checked due to a clinical deterioration or poor response to treatment. In the five patients in whom PCT levels remained stable on repeat measurement, the response to the second PCT level is less likely to be compliant with the guideline compared to the first. Clinicians appear to have taken extra precautions in the context of a persistently unwell patient. Conversely, in patients with consecutive PCT levels spanning two different ranges, clinicians seem to be reassured in either de-escalating or continuing antibiotics, depending on the trend. Further analysis is required to determine the management of patients with a low PCT result and a negative COVID-19 PCR swab.

Evidence from this QIP suggests that PCT is a safe and effective guide for antibiotic stewardship within the sample population. Few studies have specifically investigated the practical use of PCT for antibiotic stewardship in ward-based COVID-19 patients in the UK. Data from this QIP will address this area. However, multicentre trials will be necessary in order to validate this approach or suggest alternate means of antibiotic rationalisation in COVID-19. Such a trial would involve randomisation of suspected COVID-19 patients to either an intervention group with PCT-directed antibiotic therapy or a control group with Gestalt physician guided therapy. Primary endpoint would be exposure to antibiotics, with secondary endpoint being length of stay. Relevant safety endpoints include mortality and need for ventilator assistance and antibiotics within 14 days of admission. An alternative approach would be a direct comparative study assessing the frequency of antibiotic prescribing in hospitals that utilise PCT-guidance versus those that use a stand-alone respiratory panel (comprising inflammatory markers, chest imaging, sputum cultures and COVID-19 PCR swab). Findings from such a study would facilitate a review of national guidance regarding the use of PCT as a guide for antibiotic prescribing in COVID-19.

Limitations

As this report describes a single-centre, retrospective study on PCT-guided antibiotic prescribing at a district general hospital, results are not necessarily reflective of prescribing behaviours at other institutions. Furthermore, PCT testing during the pandemic was facilitated at Chesterfield Royal Hospital by pre-existing use of PCT for guiding antibiotic prescribing in COPD patients. If PCT testing is restricted or unavailable at other hospitals, generalisability of this project would be limited. In turn, this would impact the success of this work on a larger scale.

Since ITU patients were excluded from this study, the use of PCT in severely unwell COVID-19 patients remains unclear. While this could have resulted in possible bias with regards to the overall benefit of PCT, exclusion of ITU patients was necessary as higher PCT cut-off levels have typically been used in this setting.[14] Additionally, ITU patients in the initial data set had up to four PCT levels measured during their admission, which is suggestive of PCT being used as a prognostic tool rather than as a guide for antibiotic prescribing. It is therefore likely that excluding ITU patients has reduced overall bias. Multicentre prospective trials are necessary in order to determine accurate PCT cut off values and facilitate future studies that examine the use of PCT both in a ward-based setting as well as exclusively within the context of ITU.

Data analysis in this study assumes that all PCT levels checked, including repeat PCTs for ward-based patients, were used as a guide for antibiotic prescribing. Although this was likely the case for the majority of patients, repeat PCT levels were sometimes checked days after completing an antibiotic course as a measure of improving infection. The small proportion of cases in which PCT was used as a prognostic marker might have skewed the final outcome of data analysis.

In addition to the use of PCT, it is likely that several other factors influenced antibiotic prescribing. These include radiological, biochemical and bedside features of bacterial infection as well as patient risk factors (such as being immunocompromised) and severity of illness at presentation. This study aimed to promote PCT as part of a pragmatic strategy to limit antibiotic use when clinical presentation and standard respiratory panel were not able to rule out bacterial co-infection. The prospective guideline in Fig 1 was intended to improve standardisation; however, given the multitude of factors involved in treatment choice, there is a need for further research into standardising this approach.

Finally, the familiarity of the assessing clinician with PCT testing as well as treatment of COVID-19 and the presence of hospital guidelines would have all impacted antibiotic prescribing. These confounding factors emphasise the need for larger scale studies and/or meta-analyses in order to make definitive conclusions on the effects of PCT on antibiotic use in COVID-19 patients.

Conclusion

PCT testing in patients with suspected or confirmed COVID-19 at Chesterfield Royal Hospital has helped clinicians rationalise antibiotic prescribing and ultimately led to a reduction in unnecessary antibiotic use. PCT, when used in combination with thorough clinical assessment, is a safe, simple and sustainable way of reducing antibiotic use in COVID-19. With the likelihood of a second peak of cases in the future, continued use of PCT testing will be a valuable guide for antibiotic therapy. Further studies are needed to investigate the benefit of PCT on a broader scale and aid development of a standardised guideline. ∎

Supplementary material

Additional supplementary material may be found in the online version of this article at www.rcpjournals.org/clinmedicine:
S1 – Results stratified by COVID-19 PCR swab result.

Acknowledgements

Conflicts of interest

References

1 Llor C, Bjerrum L. Antimicrobial resistance: risk associated with anti-biotic overuse and initiatives to reduce the problem. *Ther Adv Drug Saf* 2014;5:229–41.

2 Getahun H, Smith I, Trivedi K *et al. Tackling antimicrobial resist-ance in the COVID-19 pandemic.* World Health Organization, 2020. Available from www.who.int/bulletin/volumes/98/7/20-268573/en/ [Accessed 10 July 2020].

3 World Health Organization. *Clinical management of COVID-19: Interim guidance.* WHO, 2020. Available from www.who.int/publications-detail-redirect/clinical-management-of-covid-19 [Accessed 10 July 2020].

4 Hsu J. How COVID-19 is accelerating the threat of antimicrobial resistance. *BMJ* 2020;18:369.

5 Hughes S, Troise O, Donaldson H *et al.* Bacterial and fungal coinfec-tion among hospitalised patients with COVID-19: A retrospective cohort study in a UK secondary care setting. *Clin Microbiol Infect* 2020;26:1395–9.

6 Zhou F, Yu T, Du R *et al.* Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospec-tive cohort study. *Lancet* 2020;395:1054–62.

7 Lansbury L, Lim B, Baskaran V, Lim WS. Co-infections in people with COVID-19: a systematic review and meta-analysis. *J Infect* 2020;81:266–75.

8 Chertow DS, Memoli MJ. Bacterial coinfection in influenza: a grand rounds review. *JAMA* 2013;309:275–82.

9 Huttner BD, Catho G, Pano-Pardo JR *et al.* COVID-19: don't neglect antimicrobial stewardship principles! *Clin Microbiol Infect* 2020;26:808–10.

10 Wacker C, Prkno A, Brunkhorst FM, Schlattmann P. Procalcitonin as a diagnostic marker for sepsis: a systematic review and meta-analysis. *Lancet Infect Dis* 2013;13:426–35.

11 Mathioudakis AG, Chatzimavridou-Grigoriadou V, Corlateanu A, Vestbo J. Procalcitonin to guide antibiotic administration in COPD exacerbations: a meta-analysis. *Eur Respir Rev* 2017;26:160073.

12 National Institute for Health and Care Excellence. Tests to guide decisions about using antibiotics. In: *COVID-19 rapid guideline: antibiotics for pneumonia in adults in hospital (NICE guideline [NG173]).* NICE, 2020. Available from www.nice.org.uk/guidance/ng173/chapter/2-Tests-to-guide-decisions-about-using-antibiotics.

13 Schuetz P, Christ-Crain M, Thomann R *et al.* Effect of procalcitonin-based guidelines vs standard guidelines on antibiotic use in lower respiratory tract infections: the ProHOSP randomized controlled trial. *JAMA* 2009;302:1059–66.

14 Rhee C. Using procalcitonin to guide antibiotic therapy. *Open Forum Infect Dis* 2017;4:ofw249.

Address for correspondence: Dr Amanda Pegden, Chesterfield Royal Hospital, Chesterfield Road, Calow, Chesterfield S44 5BL, UK.
Email: amanda.pegden1@nhs.net