Procalcitonin to Guide Antibacterial Prescribing in Patients Hospitalised with COVID-19

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Abstract

Background: Antibacterial prescribing in patients presenting with COVID-19 remains discordant to rates of bacterial co-infection. Implementing diagnostic tests to exclude bacterial infection may aid reduction in antibacterial prescribing.

Method: A retrospective observational analysis was undertaken of all hospitalised patients with COVID-19 across a single-site NHS acute Trust (London, UK) from 01/12/20-28/2/21. Electronic patient records were used to identify patients, clinical data, and outcomes. Procalcitonin (PCT) serum assays, where available on admission, were analysed against electronic prescribing records for antibacterial prescribing to determine relationships with a negative PCT result (<0.25mg/L) and antibacterial course length.

Results: Antibacterial agents were initiated on admission in 310/624 (49.7%) of patients presenting with COVID-19. 33/74 (44.5%) patients with a negative PCT on admission had their treatment stopped within 24 hours. 6/49 (12.2%) patients who had antibacterials started but a positive PCT had their treatment stopped. Microbiologically confirmed bacterial infection was low (19/594; 3.2%); no correlation was seen with PCT and culture positivity (p=1). Lower mortality (15.6% vs 31.4%;p=0.049), length of hospital stay (7.9days vs 10.1days;p=0.044), and intensive care unit (ICU) admission (13.9% vs 40.8%;p=0.001) were seen among patients with low PCT.

Conclusion: This retrospective analysis of community acquired COVID-19 patients demonstrates the potential role of PCT in excluding bacterial co-infection. A negative PCT on admission correlates with shorter antimicrobial courses, early cessation of therapy and predicts lower frequency of ICU admission. Low PCT may support decision making in cessation of antibacterials at the 48-72 hour review.

Background:

Early analysis of COVID-19 cohorts demonstrated a low incidence of microbiologically confirmed bacterial co-infection in patients presenting with community onset viral infection (3–5% in community onset infection, increasing among patients requiring more intensive healthcare interventions throughout their admission)[1,2, 3]. Despite the data on low incidence of bacterial co-infection, high antibacterial prescribing is still evident in COVID-19 patient management[4].

Even with low rates of positive bacterial coinfection, without a method to distinguish at-risk patient groups, cautious over-prescribing of antibacterials will continue[5, 6]. Work to date has highlighted the potential for traditional biomarkers (e.g. CRP and neutrophils) to exclude bacterial co-infection but most of this work was completed before the introduction of dexamethasone as standard of care[7]. The use of procalcitonin (PCT) has been suggested as a more sensitive analysis of bacterial co-infection but real-life data on PCT in COVID-19 is limited[8, 9]. PCT may be elevated by non-bacterial causes including ARDS in COVID-19 therefore the positive predictive value of PCT may be limited. However, a negative PCT result in COVID-19 patients may offer antimicrobial stewardship (AMS) teams some utility in identifying patients with low probability of bacterial infection. To analyse the impact of PCR as an AMS tool among patients
with COVID-19, we undertook a retrospective analysis of community onset COVID-19 managed in an acute hospital setting.

**Patients And Methods:**

A retrospective observational analysis was undertaken of all hospitalised patients with COVID-19 across a single-site NHS acute Trust; Chelsea and Westminster Foundation Trust (London, UK). All patients with confirmed SARS-CoV-2 between 01/12/2021-28/02/2021 were included. Electronic patient records (Millenium®, Cerner Corp., USA, and ICNet®, Baxter, UK[10]) and microbiology laboratory data (Sunquest® v8.3) were used to identify patients, clinical data, and outcomes. Procalcitonin serum assays (Alinity i B·R·A·H·M·S, Abbott, VA, USA); values of 0.25pg/ml at 6-24hours post-COVID diagnosis were defined as low risk of bacterial co-infection in community-onset COVID-19. Electronic prescribing records were analysed to identify antibacterial prescribing on admission and at 48–72 hour review. The utility of a diagnostic test on AMS interventions in patients with early death (72hours from admission or SARS-CoV-2 detection) is unclear, therefore we have excluded this cohort from analysis on PCT usage.

All data were anonymised and collated on Excel 2017. Descriptive statistics were derived, using GraphPad® (v8, 2018). Chi squared/Fisher's exact tests was used for analysis of categorical data and Mann-Whitney U test for non-parametric continuous variables.

This project was registered as a service evaluation with the Chelsea & Westminster NHS Foundation Trust Antimicrobial Stewardship Committee (02/02/2021).

**Results:**

730 patients with confirmed SARS-CoV-2 were identified during the study period; see Table 1.
Table 1
COVID-19 patient and infection-related characteristics, London, Dec 2020-Feb 2021 (UK wave 2).

|                                | Antibacterials initiated on admission (n = 280) | Nil antibacterials initiated on admission (n = 314) | Comment |
|--------------------------------|-------------------------------------------------|--------------------------------------------------|---------|
| Age (IQR)                      | 67.5yo (54.5–79.5)                               | 62.2yp (40.2–78.5)                                | p = 0.00228 |
| Adult                          | 276                                              | 298                                              | p = 0.0204 |
| Sex (male/total)               | 151/280                                          | 153/314                                          | p = 0.2180 |
| Ethnicity                      | 106                                              | 124                                              |         |
| White (any)                    | 22                                               | 28                                               |         |
| Asian (any)                    | 21                                               | 22                                               |         |
| Black (any)                    | 5                                                | 13                                               |         |
| Mixed (any)                    | 126                                              | 127                                              |         |
| Blood culture sent             | 200/280 (71%)                                    | 175/314 (56%)                                    | p = < 0.0001 |
| - +ve culture within 5 days of admission (of clinical importance) | 1*                                                | 0                                                |         |
|                                | 13#                                              | 3$                                               |         |
| - +ve culture after 5 days admission (of clinical importance)       |                                                   |                                                  |         |
| Respiratory MC&S sent         | 70/280 (25%)                                     | 41/314 (13%)                                     | p = 0.0002 |
| - +ve culture within 5 days of admission (of clinical importance) | 12 patients ##                                  | 5 patients $$                                   |         |
|                                | 22 patients **                                   | 7 patients ~                                     |         |

* = K. pneumoniae, # = E. faecalis (x4), E. faecium (x2), C. albican, C. glabrata, E.coli, H. alive, K. pneumonia, MRSA (x2) & Pseudomonas aeruginosa; $ = B. ovatus, E. faecium X2, Candida spp. X3 & S. marcesens; ** = (P. aeruginosa x 8, K. pneumonia x3, C. koseri, K. aerogenes, H. alvei, E. faecium, M. morganii (x2), MRSA x4, S. maltophilia (x5), S. marescens; ## = (K. pneumonia (x3), MSSA (x2), S. pneumonia, P. aeruginosa (x2), P. mirabilis, M. morganii, E. cloacae, H. influenzae); $$ = (E.coli, MRSA, MSSA x3, H. influenzae (mixed with MSSA); ~ (Pseudomonas spp. (x5), K. aerogenes and mixed (MRSA, Raoltella spp., S. marcesens, S. maltophilia)

Chi squared/Fisher's exact tests was used for analysis of categorical data and Mann-Whitney U test for non-parametric continuous variables.
| Antibacterials initiated on admission (n = 280) | Nil antibacterials initiated on admission (n = 314) | Comment |
|-----------------------------------------------|-------------------------------------------------|---------|
| Legionella urinary antigen                     | 59/280                                          | p = 0.004 |
| All negative                                  | 32/314                                          |         |
| Pneumococcal urinary antigen                  | 52/280                                          | p = 0.0046 |
| One positive result                           | 32/314                                          |         |
| Viral Resp Screen                             | 59/280                                          | p = < 0.0001 |
| All negative                                  | 28/314                                          |         |
| Peak CRP in 72hr of admission                 | 83 (41–143)                                     | p = 0.0000268228 |
| WCC on admission                              | 6.7 (5–9.6)                                     | p = 0.985431 |
| Treatment received during admission           |                                                 |         |
| Steroids                                      | 225/280                                         | p = < 0.0001 |
| Remdesivir                                    | 99/280                                          | p = < 0.0001 |
| Favipirivir                                   | 33/280                                          | p = < 0.0001 |
| Tocilizumab                                   | 1/280                                           | p = 1    |

* = K. pneumoniae, # = E. faecalis (x4), E. faecium (x2), C. albican, C. glabrata, E.coli, H. alive, K pneumonia, MRSA (x2) & Pseudomonas aeruginosa; $ = B. ovatus, E. faecium X2, Candida spp. X3 & S. marcesens; ** = (P. aeruginosa x 8, K. pneumonia x3, C. koseri, K. aerogenes, H. alvei, E. faecium, M. morganii (x2), MRSA x4, S. maltophilia (x5), S. marescens; ### = (K. pneumonia (x3), MSSA (x2), S. pneumonia, P. aeruginosa (x2), P. mirabilis, M. morganii, E. cloacae, H. influenzae); $$$ = (E.coli, MRSA, MSSA x3, H. influenzae (mixed with MSSA); ~ (Pseudomonas spp. (x5), K. aerogenes and mixed (MRSA, Raoltella spp., S. marcesens, S. maltophilia)

Chi squared/Fisher's exact tests was used for analysis of categorical data and Mann-Whitney U test for non-parametric continuous variables
Antibacterials were initiated within 48 hours of admission in 310/624 (49.7%) patients presenting with COVID-19 (Figure S1). On admission, 33/74 (44.5%) patients with a negative PCT on day 0/1 had their treatment stopped within 24 hours. 6/49 (12.2%) patients who had antibacterials started but a positive PCT had their treatment stopped. In those patients continued on antibacterials beyond 72hours, a further 58/128 had PCT assays taken to guide empiric antibacterial therapy. Of these, 40/58 had PCT < 0.25 and 23/40 (57.5%) had their antimicrobials stopped within the subsequent 24 hours.

| Initial ABX therapy            | Antibacterials initiated on admission (n = 280) | Nil antibacterials initiated on admission (n = 314) | Comment |
|--------------------------------|-----------------------------------------------|-----------------------------------------------|---------|
| Amoxicillin/Doxycycline        | 199                                           | 3                                             | -       |
| Amoxicillin/Macrolide          | 3                                             | 2                                             | -       |
| Amoxicillin monoRx             | 10                                            |                                               | -       |
| Co-amoxiclav +/- atypicals     | 27                                            |                                               | -       |
| Ceftriaxone +/- atypicals      | 4                                             |                                               | -       |
| Doxycycline monoRx             | 6                                             |                                               | -       |
| Levofloxacin                   | 3 (azithromycin monoRx and ciprofloxacin x2)   |                                               | -       |
| Tazocin +/- atypical           |                                               |                                               | -       |
| Other                          |                                               |                                               |         |
| Systemic antifungals (any time during admission) | 21                                            | 1                                             |         |
|                                 | 2 x Voriconazole (Aspergillus), 9 x Ambisome (VAP empiric), 4xAnidulafunign (invasive Candida infection), 6xFluconazole (invasive/local Candida infection) | 1 x Ambisome (VAP empiric) |         |
| In-hospital mortality at 30 days | 54/280                                        | 63/314                                       | p = 0.1792 |

*= K. pneumoniae; # = E. faecalis (x4), E. faecium (x2), C. albican, C. glabrata, E.coli, H. alive, K. pneumonia, MRSA (x2) & Pseudomonas aeruginosa; § = B. ovatus, E. faecium X2, Candida spp. X3 & S. marcesens; ** = (P. aeruginosa x 8, K. pneumonia x3, C. koseri, K. aerogenes, H. alvei, E. faecium, M. morganii (x2), MRSA x4, S. maltophilia (x5), S. marescens; ## = (K. pneumonia (x3), MSSA (x2), S. pneumonia, P. aeruginosa (x2), P. mirabilis, M. morganii, E. cloacae, H. influenzae); $$ = (E.coli, MRSA, MSSA x3, H. influenzae (mixed with MSSA); ~ (Pseudomonas spp. (x5), K. aerogenes and mixed (MRSA, Raoltella spp., S. marcesens, S. maltophilia)

Chi squared/Fisher’s exact tests was used for analysis of categorical data and Mann-Whitney U test for non-parametric continuous variables.
Patients with PCT repeated on days 0 and 1 were analysed to assess the reliability of a single PCT assay result. A total of 5/16 patients with a reported negative PCT (<0.25pg/ml) on admission had contradictory results (>0.25pg/ml) in the proceeding 24 hours (Figure S2).

A low burden of community onset bacterial infection was evident (19/594; 3.2%) with significant bacterial isolates). High PCT values did not correlated with likelihood of subsequent culture positive pyogenic infections, with 2/51 (3.9%) patients with a high PCT having a significant culture from blood/chest/urine, and 3/77 (3.9%) with a low PCT having a significant culture (p = 1; Table 2).
Table 2
Antibacterial usage on admission for patients presenting with community acquired pneumonia, London, Dec 2020-Feb 2021 (UK wave 2).

|                              | PCT < 0.25 in 1st 48hr | PCT ≥ 0.25 in 1st 48hr | Significance |
|------------------------------|------------------------|------------------------|--------------|
| Initiated ABX on admission   | 77/127 (60.6%)         | 51/69 (73.9%)          | P = 0.0835   |
| ABX continued for > 72hours  | 41/77 (53.2%)          | 44/51 (86.3%)          | P = < 0.0001 |
| Duration of ABX median (IQR) days | 4 (1.5–7)            | 6 (4–9)                | P = 0.00222  |
| Peak CRP in first 72hr       | 78 (46–119)            | 170 (117–246)          | P = < 0.0001 |
| Median (IQR)                 |                        |                        |              |
| WCC on admission             | 6.1 (4.5–9.2)          | 7(4.65–10.35)          | P = 0.34722  |
| In-hospital mortality at 30 days | 12/77 (15.6%)        | 16/51 (31.4%)          | P = 0.0487   |
| ITU admission (any time)     | 11/79 (13.9%)          | 20/49 (40.8%)          | P = 0.0012   |
| Length of admission          | 7.9 (4.85–14.9) days   | 10.1 (6.1–30.1) days   | P = 0.04444  |
| Median (IQR)                 |                        |                        |              |
| Any carbapenem usage during admission | 6/127 (4.7%)       | 15/69 (21.7%)          | P = 0.0005   |
| Any systemic antifungal treatment during admission | 5/127 (3.9%)       | 13/69 (18.8%)          | P = 0.0012   |
| CA-Bacteraemia               | 0                      | 1 (K. pneumoniae)      | -            |
| Pneumococcal antigen positive| 0                      | 0                      | -            |
| CA-culture positive bacteria in sputum | 3 (E. cloacae, M. morganii, P. mirabilis) | 1 (P. aeruginosa) | - |
| Follow up +ve PCT (AFTER 5 DAYS ADM)* | 4/25                  | 14/33                  | P = 0.0452   |

*A follow up PCT was defined as a PCT after 5 days admission that was greater than the admission PCT or represented a new PCT > 0.25 when admission testing was not completed. CA = community acquired

Chi squared/Fisher’s exact tests was used for analysis of categorical data and Mann-Whitney U test for non-parametric continuous variables.

CRP correlates with procalcitonin in our cohort, with a 78 (46–119 IQR) and 170 (117–246) seen with patients with admission negative and positive PCT, respectively (p = < 0.0001). In 45 patients with admission (first 72 hours) CRP < 50 and a follow-up admission PCT level, a negative PCT was identified in 37/45 (82.2%) of patients.
Discussion:

This retrospective analysis of community acquired COVID-19 patients admitted to a London hospital demonstrates the potential role of PCT in excluding concurrent bacterial co-infection. A negative PCT on admission correlates with shorter antimicrobial courses, early cessation of therapy and predicts lower ITU admission during the admission. Confirming true bacterial infection is challenging in this cohort; the presence of a bacterial pathogen from many sample types (including sputum) may indicate true invasive infection or colonisation. Positive sterile samples (e.g. blood culture) are uncommon in even invasive respiratory bacterial infections therefore the presence or exclusion of bacteraemia cannot be reliably used to exclude respiratory tract infections.

Difficulties identifying the small numbers of patients who may benefit from antibacterial results early in their presentation in among the wider excess antibacterial usage remains a challenge. Procalcitonin has conflicting supporting evidence for its role in COVID-19[8, 11]. Concerns about raised PCT results in response to ARDs have been suggested to limit its utility. Separate to that potential for false positives, our data suggests a negative PCT is associated with better prognosis for the patient but moreover we find a temporal relationship with low PCT value and subsequent early cessation of antibacterials.

The reproducibility of PCT on admission was concerning. Early PCT sampling (< 6 hours of admission) may result in false negative results with contradictory results seen at 24 hour follow up in a subset of our group. It is possible that some of patients without follow-up PCT values may reflect falsely low results and detract from our projections. We continue to advise avoiding PCT assays on day 0 and advocate PCT sampling the day after admission where the negative predictive value is expected to be more robust.

Our analysis contains numerous limitations. The lack of a definitive test to confirm or exclude bacterial co-infection does not allow us to calculate specificity and sensitivity for this test in cohort. The reliance on direct culture for confirming and excluding infection for respiratory based bacterial infections is known to be limited and may underestimate the true incidence. Not all patients had a PCT value due to a) limited reagent in early December 2020 and b) guidelines only advised PCT testing when bacterial infection was suspected. Not all bacterial infections originate from the respiratory tract therefore patients on antibacterials for non-respiratory tract infection on admission has been excluded from initial analysis. Follow up treatments of healthcare-associated infections are not discussed in detail due the heterogeneity of presentation; most hospital related bacterial infections are iatrogenic and related to ventilation or central line use.

The ambition to reduce unnecessary antibacterials in patients presenting with COVID-19 infection continues. Identifying the patient groups that may benefit from antibacterial therapy is more challenging but a PCT assay in the first 48 hours may provide utility in excluding possible bacterial infection. Low PCT (< 0.25pg/ml) correlates with low probability of bacterial infection and supports decision making to aid cessation of antibacterials at the 48–72 hour review. The utility may be further increased as we see increasing usage of IL-6 inhibitors for COVID19 management where CRP monitoring becomes obsolete.
Abbreviations

AMS – antimicrobial stewardship

ARDS – acute respiratory distress syndrome

COVID-19 – coronavirus disease 2019

CRP – C reactive protein

PCT – procalcitonin

IL-6 – interleukin-6

ITU – intensive treatment unit

IQR – interquartile range

Declarations

Ethics approval and consent to participate

The project was registered and approved by the Chelsea and Westminster NHS Foundation Trust clinical governance department. The need for informed patient consent was waived for this study. All data collected are stored in concordance with the Data Protection Act and the General Data Protection Regulation.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study is available at https://doi.org/10.6084/m9.figshare.14838312.v1

Competing interests

LSPM has consulted for/received speak fees from bioMerieux (2013–2021), DNAelectronics (2015), Dairy Crest (2017–2018), Pfizer (2018–2021), Eumedica (2016–2021), Profile Pharma (2018), Shionogi (2021), and Umovis Labs (2020-2021), and received research grants from the UK National Institute for
Health Research (NIHR; 2013–2019), and CW+ Charity (2018–2021). SH has consulted for/received speak fees for Pfizer (2020-21), Eumedica (2020), Bowmed (2021) and Shionogi (2020-21).

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This study was carried out as part of our routine work.

Authors' contributions

S.H. designed the study methodology. S.H. collated the data. All authors reviewed the themes during data analysis and contributed comments. S.H. drafted the initial manuscript with all authors contributing significantly to revising this for submission. All authors agreed on the final version for submission to the journal.

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**Supplementary Files**

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