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# An investigation of the effects of procalcitonin testing on antimicrobial prescribing in respiratory tract infections in an Irish university hospital setting: a feasibility study

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**Background:** Diagnostic uncertainty and a high prevalence of viral infections present unique challenges for antimicrobial prescribing for respiratory tract infections (RTIs). Procalcitonin (PCT) has been shown to support prescribing decisions and reduce antimicrobial use safely in patients with RTIs, but recent study results have been variable.

**Methods:** We conducted a feasibility study of the introduction of PCT testing in patients admitted to hospital with a lower RTI to determine if PCT testing is an effective and worthwhile intervention to introduce to support the existing antimicrobial stewardship (AMS) programme and safely decrease antimicrobial prescribing in patients admitted with RTIs.

**Results:** A total of 79 patients were randomized to the intervention PCT-guided treatment group and 40 patients to the standard care respiratory control group. The addition of PCT testing led to a significant decrease in duration of antimicrobial prescriptions (mean 6.8 versus 8.9 days, $P=0.012$) and decreased length of hospital stay (median 7 versus 8 days, $P=0.009$) between the PCT and respiratory control group. PCT did not demonstrate a significant reduction in antimicrobial consumption when measured as DDDs and days of therapy.

**Conclusions:** PCT testing had a positive effect on antimicrobial prescribing during this feasibility study. The successful implementation of PCT testing in a randomized controlled trial requires an ongoing comprehensive education programme, greater integration into the AMS programme and delivery of PCT results in a timely manner. This feasibility study has shown that a larger randomized controlled trial would be beneficial to further explore the positive aspects of these findings.

## Introduction

Antimicrobial resistance (AMR) is a major risk to public health globally that leads to increasing healthcare costs, treatment failure and increased morbidity and mortality.[1–3] There is a strong association between suboptimal antimicrobial prescribing and AMR.[4] To optimize prescribing, hospital antimicrobial stewardship (AMS) programmes should target areas of high antimicrobial prescribing. One such area is respiratory tract infections (RTIs). Shorter antimicrobial courses offer one potential solution to the overuse of antimicrobials for RTIs[5] and there is evidence to support such strategies,[6,7] even in severe hospital infections.[8]

Diagnostic uncertainty and a high prevalence of viral infections present unique challenges for antimicrobial prescribing for RTIs.[9–12] This contributes to overuse and/or suboptimal use of antimicrobials[13,14] for RTIs such as community-acquired pneumonia (CAP), including prolonged treatment courses of up to 11 days,[15] without a correlation between duration of treatment and infection severity.[15,16] Physicians are often reluctant to shorten antimicrobial course durations due to the fear of incomplete pathogen eradication, which could potentially lead to relapse and associated morbidity and mortality.[6] There is also a high rate of antimicrobial continuation where viral infections,[17] including influenza,[18] are identified due to overriding concerns about secondary bacterial

infections. However, a recent study has shown a bacterial co-infection rate of only 40%.[11]

To address these issues, there is a growing interest in the use of novel diagnostic techniques and biomarkers as an AMS tool.[19] It is important that AMS programmes investigate the opportunity afforded by these new techniques and the potential they offer to optimize antimicrobial treatment more promptly[20] and change prescribing behaviour.[21] Procalcitonin (PCT) testing is one such diagnostic technique. PCT is a peptide precursor to the hormone calcitonin. It is usually undetected but is upregulated in response to a bacterial infection following stimulation of bacteria-induced cytokines.[22] Upregulation of PCT is blocked in viral infections due to the release of the cytokine IFNγ, resulting in a higher specificity of PCT to distinguish between bacterial and viral infections when compared with other inflammatory markers such as C-reactive protein (CRP).[23] PCT levels decrease rapidly when patients are recovering from infection.[24] Hence it offers the potential to support clinical decision-making for the initiation and discontinuation of antimicrobials in patients with a clinical suspicion of a bacterial infection when considered along with the clinical assessment of the patients. PCT has been shown to support prescribing decisions and reduce antimicrobial use safely in patients with RTIs,[25–28] but findings from recent studies have been variable,[29,30] so it is unclear if it is an effective intervention as part of an AMS programme.

The purpose of this study was to conduct a feasibility study to determine if PCT testing is an effective and worthwhile intervention to introduce in a university teaching hospital to support the existing AMS programme and safely decrease antimicrobial prescribing in patients admitted with RTIs.

## Methods

We conducted a single-centre, randomized, open-label feasibility study of the introduction of PCT testing in patients admitted to hospital with a lower RTI (LRTI) under the care of the respiratory medicine team during on-call acute unselected general medical take to determine if PCT testing had an impact on antimicrobial consumption and patient's length of stay (LOS) in hospital. The study was conducted in a single 321 bed inner city, voluntary acute university teaching hospital, which is part of the South/South West Hospital Group[31] in the Republic of Ireland. It is a Model 3 (smaller general)[32] hospital with a 24 h emergency department and ICU, and admits undifferentiated acute medical and surgical patients. The hospital has an established AMS programme, and no significant changes were made to the AMS policies or programme during this study.

### Ethics

The study was approved by the Clinical Research Ethics Committee of the Cork Teaching Hospitals [approval code ECM 4 (w) and ECM 3 (III)]. Written informed consent was obtained from all participants prior to study enrolment.

### Education and training

The microbiology laboratory scientists received technical advice and training on the operation of the PCT assay from the manufacturer prior to study commencement. They also received a presentation on the introduction of PCT testing in the hospital.

The respiratory medicine team received three presentations at the respiratory journal club meetings and provision of written materials electronically. Presentations consisted of evidence supporting PCT use in practice, limitations of PCT testing, PCT measurement, and interpretation using a PCT-based antimicrobial prescribing algorithm (Appendix S1, available as Supplementary data at *JAC* Online). Presentations were given prior to the study commencement and following medical staff rotation changes. The study protocol (Appendix S2), study flow chart and the PCT-based antimicrobial prescribing algorithm were provided to all physicians electronically.

### Recruitment and consent

#### Inclusion criteria

Adult patients ≥18 years of age, admitted to hospital under the care of the respiratory teams with an initial diagnosis of an acute LRTI (i.e. CAP[33] with severity defined by CURB-65 score[34], LRTIs[35], exacerbation of asthma[36], COPD[37], bronchiectasis[38], interstitial lung disease[39] and influenza[35]) and commenced on antimicrobial therapy were identified from the daily admission census or by the respiratory medicine teams.

The randomization process stratified patients according to presence or absence of severe COPD GOLD Stage D criteria 2017[37] to ensure balanced treatment allocation. Patients were then randomly allocated in a 2:1 ratio to either the PCT-guided treatment group or the standard care respiratory control group. Randomization was carried out using sequentially numbered opaque sealed envelopes. A second general control group of patients admitted under general medicine teams with a diagnosed acute LRTI and who received standard care (no PCT measurement) was recruited to provide a comparison of antimicrobial prescribing in RTIs by non-respiratory specialist physicians in the hospital.

#### Exclusion criteria

Exclusion criteria were: unable to give written informed consent due to language restrictions; cognitive impairment or severe dementia; readmission to hospital within 30 days of previous admission; immunosuppression (neutropenic, chemotherapy, radiation therapy or immunosuppressive therapy) other than corticosteroid use; life-threatening medical comorbidities leading to possible imminent death; do not resuscitate (DNR) status; concurrent chronic infections necessitating prolonged antimicrobial treatment (cystic fibrosis, TB, infective endocarditis, osteo-articular infections, hepatic or cerebral abscesses, chronic prostatitis); >24 h of appropriate antimicrobial therapy prior to initial PCT level; active IVDUs; and pregnant women.

### Intervention

PCT testing was commenced in the microbiology department following completion of staff training and instrument validation. It was available during routine working hours (Monday to Friday, 9 am–5 pm). PCT serum concentrations were measured using the VIDAS BRAHMS PCT (assay range 0.05–200 μg/L) (bioMérieux, France).

PCT serum concentrations were interpreted using an evidence-based algorithm (Appendix S1),[40] which has been validated in previous studies[28,29] recommending antimicrobials strongly discouraged for PCT levels <0.1 μg/L, discouraged for levels 0.1–0.25 μg/L, encouraged for levels >0.25–0.5 μg/L and strongly encouraged for levels >0.5 μg/L. The algorithm also included specific overruling criteria where antimicrobials could be considered in the case of respiratory or haemodynamic instability; life-threatening comorbidity; need for ICU admission; PCT <0.1 μg/mL: and CAP with CURB-65 >3 or COPD stage IV; PCT <0.25 μg/mL: CAP with CURB-65 >2; localized infection (abscess, empyema); immunocompromised (other than corticosteroids); or concomitant infection in need of antimicrobials.

The antimicrobial prescribing advice generated from the PCT algorithm was verbally communicated to the respiratory medicine team, and this advice was non-binding. The respiratory medicine team retained prescribing autonomy regarding clinical decisions irrespective of the PCT level or algorithm-generated antimicrobial prescribing advice. The algorithm adherence for antimicrobial prescribing recommendations was recorded

at 24 h following the PCT test for all patients along with the rationale for prescribing decisions. Algorithm adherence was defined as antimicrobial therapy that was continued or discontinued in accordance with the PCT cut-off ranges. Non-adherence was defined as antimicrobial therapy that was not discontinued despite low PCT levels. Overriding criteria were not considered when measuring adherence but were recorded as reasons for non-adherence.

Patients were followed until their discharge. A further follow-up of medical records took place at 30 days after admission to identify readmitted patients and readmitted patients with infection relapse.

Patient recruitment ran from 1 June 2017 to 31 May 2018. Figure 1 represents the patient hospital journey with an RTI.

### Outcomes

The primary outcomes were to quantify the individual inpatient antimicrobial consumption, prescription duration and the inpatient LOS. Following a recent systematic review which recommended that antimicrobial use should be expressed in at least two metrics simultaneously,[41] antimicrobial consumption was measured using DDDs, days of therapy (DOT) and prescription duration. DDDs were calculated using the Anatomical Therapeutic Chemical/Defined Daily Dose (ATC/DDD) index of the WHO Collaborating Centre for Drug Statistics Methodology,[42] but were not adjusted for hospital activity. DOT[43] calculates individual patient-days of antimicrobial exposure and accounts for dosing and frequency of each drug. Antimicrobial prescription duration was measured in days (defined as the number of days between the commencement and discontinuation of antimicrobials). The LOS was defined as the date of discharge minus the date of admission.

Secondary outcomes were number of infection- and antimicrobial-related adverse events during inpatient LOS including mortality, hospital readmission within 30 days and infection relapse requiring readmission within 30 days. Algorithm adherence for antimicrobial prescribing recommendations was measured.

A qualitative process evaluation of the study was conducted in parallel with this feasibility study and will be reported in a subsequent paper.

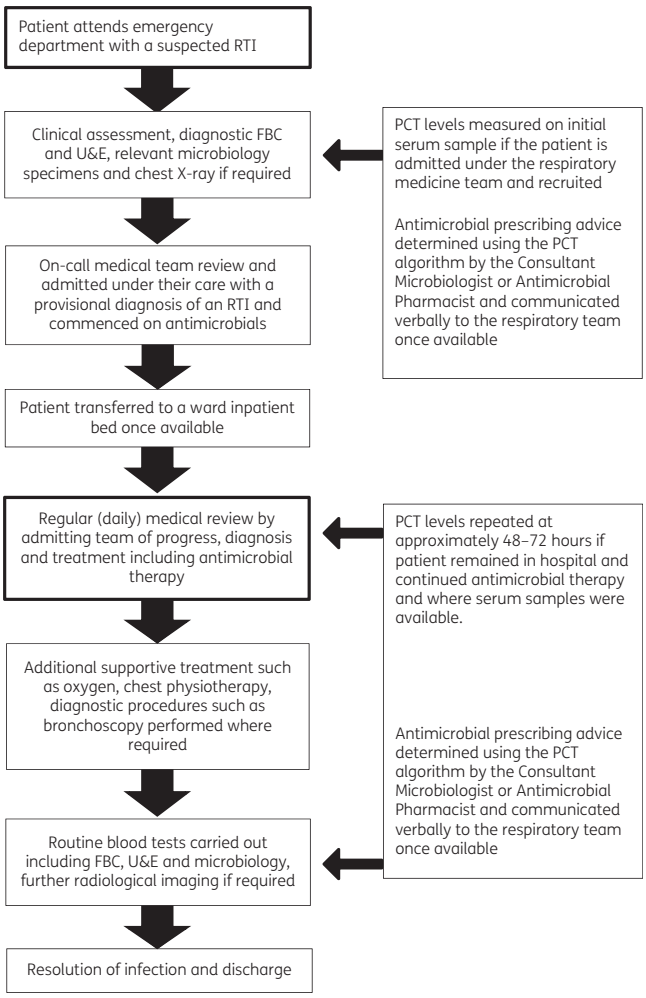


**Figure 1.** Patient hospital journey with an RTI. FBC, full blood count; U&E, urea and electrolytes.

### Statistical methods

A Microsoft Access database (version 1903) was developed to record the study data. Statistical analysis was conducted using R (version 3.4.0) and was carried out on an ITT basis.

The primary outcome of antimicrobial consumption between the PCT and respiratory control arms was evaluated using the non-parametric Wilcoxon Rank Sum test. A Kaplan–Meier curve was used to analyse the median time to discharge between the PCT and respiratory control groups.

$\chi^2$ Tests were used to evaluate differences between the PCT and respiratory control arms for all secondary outcomes, i.e. the number of adverse events and readmissions and infection relapses requiring readmission both within 30 days.

## Results

The respiratory medical teams admitted 823 general medical patients of whom 313 patients were classified as having a respiratory infection or respiratory disorder during the recruitment period of 1 June 2017 to 31 May 2018. A CONSORT flow diagram of recruitment can be seen in Figure 2.

A further 48 patients were recruited to the general control group.

Demographic data and study overview are presented in Table 1. Clinical findings of patients on admission to hospital are given in Table 2.

There were several differences between the baseline characteristics of the PCT group and the respiratory control group. The PCT group contained more male patients (60% versus 42%) and active smokers (25% versus 12.5%).

There were several differences in final diagnosis between the PCT group and the respiratory control group with asthma (3.8% versus 15%), CAP (10% versus 7.5%) and LRTI (30.4% versus 17.5%). CAP severity in the PCT group had CURB-65 scores ranging from 0 to 3 with a mean of 1.87, while the CAP severity in the respiratory control group had CURB-65 scores ranging from 0 to 1 with a mean of 0.66.

The clinical findings on admission were similar between the PCT and respiratory control groups, with two exceptions where the PCT group had a higher percentage of patients who were productive of sputum on admission (49% versus 37%) and patients prescribed antibiotics prior to admission (35% versus 25%).

### PCT testing and results

The 79 patients randomized to the PCT group had a total of 163 PCT levels taken [median of 2 tests per patient (range 1–6)]. Overall the PCT levels had a median value of 0.075 μg/L (IQR

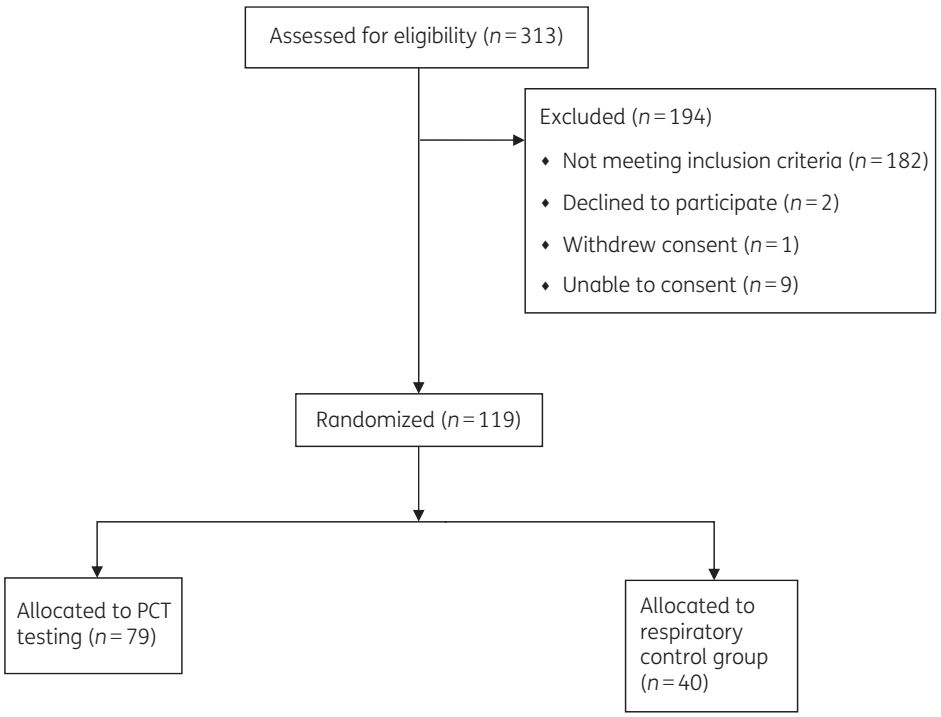


**Figure 2.** CONSORT 2010 flow diagram.

**Table 1.** Demographic data and study overview

| | Study group | | | |
|---|---|---|---|---|
| Variable | overall | PCT | respiratory control | general control |
| Participants, *n* (%) | 167 (100) | 79 (47.3) | 40 (24.0) | 48 (28.7) |
| Gender, *n* (%) | | | | |
| female | 79 (47.3) | 31 (39.2) | 23 (57.5) | 25 (52.1) |
| male | 88 (52.7) | 48 (60.8) | 17 (42.5) | 23 (47.9) |
| Age, years (mean ± SD) | 68.7 ± 14 | 68.6 ± 13.6 | 68.4 ± 15.3 | 69.1 ± 13.9 |
| Co-existing conditions and risk factors, *n* (%) | | | | |
| smoking status | | | | |
| non-smoker | 50 (30) | 26 (32.9) | 13 (32.5) | 11 (23) |
| smoker | 33 (20) | 20 (25.3) | 5 (12.5) | 8 (16.6) |
| ex-smoker | 84 (50) | 33 (41.8) | 22 (55) | 29 (60.4) |
| asthma | 28 (16.8) | 13 (16.5) | 10 (25) | 5 (10.4) |
| COPD A–C | 58 (34.7) | 23 (29.1) | 10 (25) | 25 (52) |
| COPD D | 24 (14.4) | 10 (12.7) | 5 (12.5) | 9 (18.8) |
| bronchiectasis | 16 (9.6) | 9 (11.4) | 3 (7.5) | 4 (8.3) |
| interstitial lung disease | 7 (4.2) | 4 (5) | 2 (5) | 1 (2.1) |
| Final diagnosis, *n* (%) | | | | |
| asthma | 11 (6.6) | 3 (3.8) | 6 (15) | 2 (4.2) |
| CAP | 18 (10.8) | 8 (10) | 3 (7.5) | 7 (14.6) |
| COPD | 62 (37.1) | 24 (30.4) | 13 (32.5) | 25 (52) |
| LRTI | 45 (27) | 28 (35.4) | 7 (17.5) | 10 (20.8) |
| other LRTIs | 20 (12) | 10 (12.6) | 7 (17.5) | 3 (6.2) |
| non-respiratory related | 11 (6.6) | 6 (7.6) | 4 (10) | 1 (2.1) |

**Table 2.** Clinical findings on admission to hospital

| | Total (*n*=167) | PCT (*n*=79) | Respiratory control (*n*=40) | General control (*n*=48) |
|---|---|---|---|---|
| Respiratory rate, breaths/min | 22.1 ± 5 | 22.1 ± 5.4 | 21.1 ± 3.7 | 22.7 ± 5.2 |
| Systolic blood pressure, mmHg | 133 ± 23.1 | 130.9 ± 22.9 | 136 ± 20.9 | 134 ± 25 |
| Diastolic blood pressure, mmHg | 75 ± 14.1 | 74.8 ± 12 | 78.6 ± 14.8 | 72.3 ± 16.1 |
| Heart rate, beats/min | 91.8 ± 20.1 | 93.4 ± 23.3 | 91.2 ± 16.7 | 89.8 ± 16.7 |
| Temperature, °C | 36.8 ± 0.8 | 36.8 ± 0.8 | 36.9 ± 0.8 | 36.8 ± 0.9 |
| Rigors, *n* (%) | 24 (14.4) | 11 (13.9) | 6 (15) | 7 (14.6) |
| Fever, *n* (%) | 18 (10.8) | 8 (10.1) | 5 (12.5) | 5 (10.4) |
| Chills, *n* (%) | 15 (9) | 10 (12.7) | 1 (2.5) | 4 (8.3) |
| Number of clinical signs of infection | 1.8 ± 1.3 | 1.9 ± 1.3 | 1.7 ± 1.2 | 1.8 ± 1.3 |
| Documented signs of respiratory illness | | | | |
| cough, *n* (%) | 132 (79) | 64 (81) | 31 (77.5) | 37 (77) |
| shortness of breath, *n* (%) | 101 (60.5) | 45 (57) | 23 (57.5) | 33 (68.7) |
| productive of sputum, *n* (%) | 81 (48.5) | 39 (49.4) | 15 (37.5) | 27 (56.2) |
| dyspnoea, *n* (%) | 49 (29.3) | 22 (27.8) | 10 (25) | 17 (35.4) |
| pleuritic pain, *n* (%) | 26 (15.6) | 10 (12.7) | 9 (22.5) | 7 (14.6) |
| respiratory failure, *n* (%) | 19 (11.4) | 8 (10.1) | 5 (12.5) | 6 (12.5) |
| abnormal chest exam, *n* (%) | 144 (86.2) | 70 (88.6) | 31 (77.5) | 43 (89.6) |
| abnormal radiological findings, *n* (%) | 94 (56.3) | 42 (53.2) | 21 (52.5) | 28 (58.3) |
| CURB-65 score (CAP patients) | 1.56 ± 1.05 | 1.87 ± 1.05 | 0.66 ± 0.47 | 1.57 ± 1.05 |
| number of signs of acute respiratory illness | 3.9 ± 1.4 | 3.8 ± 1.4 | 3.8 ± 1.4 | 4 ± 1.3 |
| Antimicrobials prescribed pre-admission, *n* (%) | 59 (35.3) | 28 (35.4) | 10 (25) | 21 (43.7) |
| Corticosteroids prescribed pre-admission, *n* (%) | 34 (20.4) | 14 (17.7) | 7 (17.5) | 13 (27) |
| Infection source | | | | |
| community, *n* (%) | 149 (89.2) | 70 (88.6) | 32 (80) | 47 (98) |
| healthcare, *n* (%) | 13 (7.8) | 6 (7.6) | 6 (15) | 1 (2) |
| hospital, *n* (%) | 5 (3) | 3 (3.8) | 2 (5) | 0 (0) |

Values are shown as mean ± SD unless otherwise stated.

0.05–0.26). The initial PCT level was ≤0.24 μg/L for 58 patients (including 38 patients with an initial PCT level of ≤0.05 μg/L). The study outcomes can be seen in Table 3 and Figure 3. Statistical analysis was conducted on the PCT and respiratory control group only, and does not include comparison with the general control group.

There was no significant difference in antimicrobial consumption when measured as DDDs (11.1±7.5 versus 13.1±10.7, *P*=0.218) (mean ± SD) or DOT (8.9±6.3 versus 11±7.6, *P*=0.077) of patients between the PCT and respiratory control group. Median values of both metrics, DDD (8.66 versus 9.57) and DOT (7.5 versus 8.25), showed a decrease of 9% in antimicrobial consumption per patient.

There was a significant difference in the antimicrobial duration in days between the PCT and respiratory control groups (median 7 versus 8 days, *P*=0.0125). There was also a significant difference between the PCT and respiratory control groups in the median LOS (*P*=0.009), and this can also be seen in the Kaplan–Meier curves in Figure 4.

In the analysis of secondary outcomes, there was no significant difference between the PCT and respiratory control group in the incidence of adverse events during inpatient hospital stay (*P*=0.9852), the rate of hospital readmission (*P*=0.1507) and the rate of infection relapse requiring readmission both within 30 days (*P*=0.0924).

Algorithm compliance is displayed in Table 4. Overall PCT algorithm compliance per patient was 35% within 24 h of the PCT level being taken. Twenty-five patients had high PCT levels (≥0.25 μg/L) where the algorithm recommendation was to continue antimicrobial treatment and algorithm compliance was 100%. Sixty-seven patients had low PCT levels (<0.25 μg/L) where the algorithm recommendation was to discontinue antimicrobial treatment and algorithm compliance was low (10%). In these instances, the reasons for non-adherence were based on a clinical decision in 55/112 (49%) PCT levels, with the remaining 57/112 (51%) PCT levels based on meeting various algorithm overriding criteria [respiratory or haemodynamic instability; life-threatening comorbidity; need for ICU admission; or localized infection (abscess, empyema)].

Seven patients had their antimicrobial treatment discontinued in compliance with the algorithm when PCT levels were low (<0.25 μg/L). This resulted in shorter course lengths in five patients (<7 days), one course length completion as planned at 7 days and early antimicrobial discontinuation (day 2) in a patient with influenza. There were no hospital readmissions among these patients.

In a further nine patients where there was initial non-compliance with the algorithm recommendations when measured at 24 h, their antimicrobial treatment was subsequently modified, resulting in a shorter course length in seven patients (<7 days), and two further patients discontinued antimicrobials

**Table 3.** Primary and secondary outcome data

| | PCT ($n$=79) | Respiratory control ($n$=40) | General control ($n$=48) | $P$ value |
|---|---|---|---|---|
| Primary outcomes, mean ± SD (median) | | | | |
| DDDs per patient | 11.1 ± 7.5 (8.66) | 13.1 ± 10.7 (9.57) | 18.5 ± 11 (16.5) | 0.218 |
| DOT per patient | 8.9 ± 6.3 (7.5) | 11 ± 7.6 (8.25) | 13.7 ± 11.1 (11.63) | 0.077 |
| total duration of inpatient antimicrobials (days) | 6.8 ± 2.8 (7) | 8.9 ± 4 (8) | 8.4 ± 3.6 (8) | 0.0125* |
| LOS (days) | 7.4 ± 4.3 (7) | 10.5 ± 6.1 (8) | 8.9 ± 3.8 (8) | 0.009* |
| Secondary outcomes, $n$ (%) | | | | |
| hospital readmission within 30 days | 7 (8.9) | 8 (20) | 7 (14.6) | 0.1507 |
| relapse of infection within 30 days | 6 (7.6) | 8 (20) | 6 (12.5) | 0.0924 |
| adverse events | 6 (7.6) | 3 (7.5) | 4 (8.3) | 0.9852 |

*Statistical significance was set as $P<0.05$, and $P$ values relate to the comparison between the PCT and respiratory control groups.

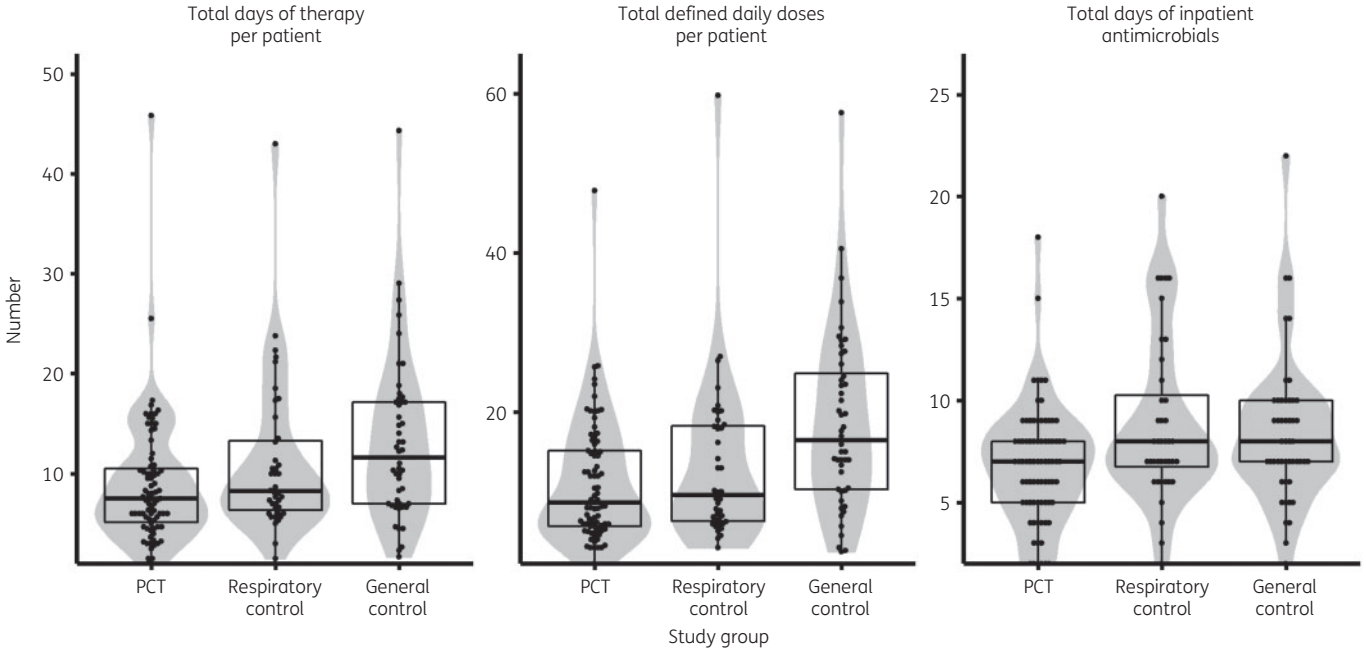


**Figure 3.** Main antimicrobial consumption outcomes.

prior to discharge. There was one patient readmitted to hospital with infection among these patients.

Algorithm compliance by indication was as follows; CAP (80%), asthma (50%), LRTI (30%), COPD (12.5%) and influenza virus (42%). PCT levels and algorithm compliance were found to be low in patients with COPD stage D and structural lung conditions such as bronchiectasis and interstitial lung disease. In these cases, the clinical judgement of physicians was to override the algorithm recommendations and continue antimicrobials.

### *Microbiology-positive specimens*

Thirty-eight patients (23%) had positive microbiology results. Relevant respiratory results included: 13 influenza virus, 10 bacterial isolates from respiratory specimens and 7 yeast isolates from respiratory specimens.

### *Adverse events*

Infection- and antimicrobial-related adverse events included gastrointestinal (antimicrobial-related diarrhoea, one patient) renal function (acute kidney injury secondary to antimicrobials, one patient), liver function (increased liver function tests secondary to antimicrobials, one patient), respiratory disorders (hospital-acquired pneumonia, hospital-acquired influenza and respiratory deterioration, three patients) and other events (two patients).

### *Mortality during the study*

Five patients included in the study died during their hospital stay: four from the PCT group and one from the respiratory control group (age range 75–94 years). All had multiple comorbidities including cardiac (congestive cardiac failure, atrial fibrillation), renal and

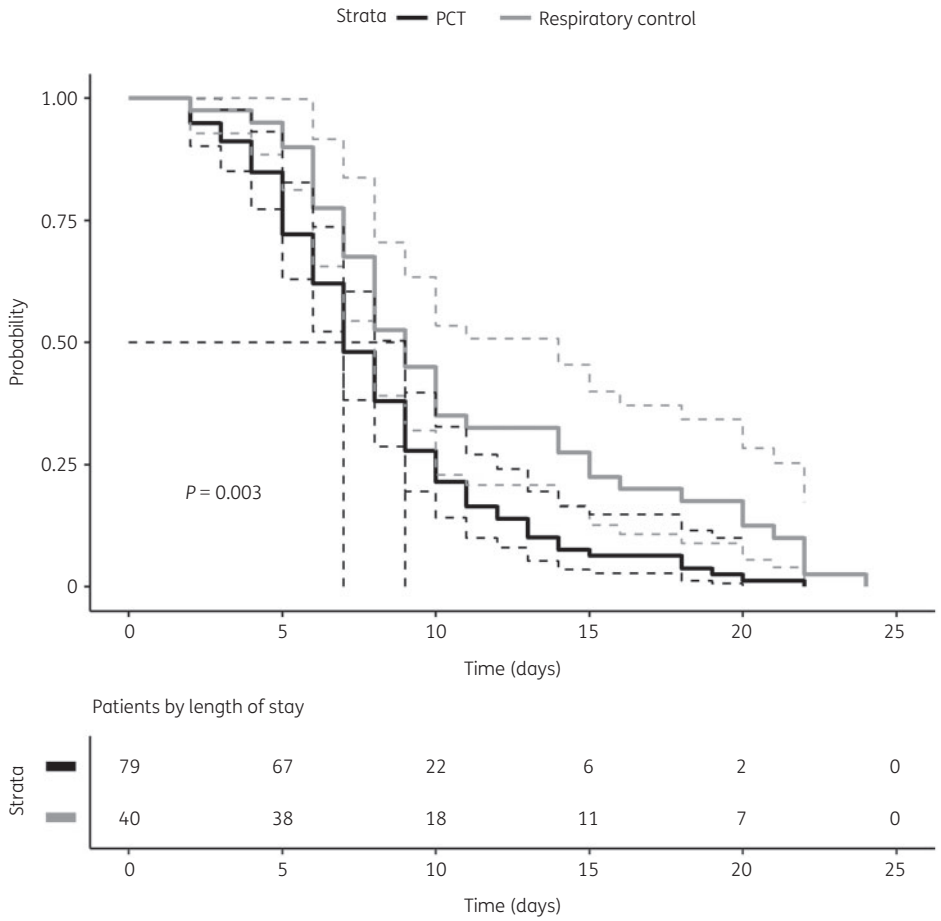


**Figure 4.** Comparison of time to discharge probability for PCT versus respiratory control arms: Kaplan–Meier curves. Median probability of discharge is given by the horizontal dashed line. The grey and black dashed lines show the 95% CIs.

**Table 4.** PCT algorithm compliance

| PCT level (μg/L) | Algorithm recommendation | No. of patients | No. of PCT test results | No. of patients compliant with algorithm | No. of patients non-compliant with algorithm | % of patients compliant with algorithm |
|---|---|---|---|---|---|---|
| ≤0.05 to <0.25 | antimicrobial therapy discouraged | 67 | 119 | 7 | 60 | 10% |
| ≥0.25 | antimicrobial therapy encouraged | 25 | 44 | 25 | 0 | 100% |

new or existing cancer diagnosis. Antimicrobial treatment decisions for these patients were based on clinical decisions.

## Discussion

This feasibility study of the introduction of PCT testing has shown a positive effect on antimicrobial prescribing resulting in a decrease in the duration of antimicrobial courses in patients with RTIs and a decrease in LOS without an increase in adverse events or readmission to hospital. The median duration of antimicrobial treatment was reduced from 8 to 7 days, and antimicrobial consumption fell by 9% when measured as DDD and DOT. This study confirms the findings of previous PCT trials[28,44] that it is an effective and worthwhile intervention to safely reduce antimicrobial exposure in patients with RTIs and supports the AMS programme. However, there were several findings that may have influenced the outcomes and these need to be considered when viewing the overall results and considering progression to, and design of, a full randomized controlled trial (RCT).

Overall PCT algorithm compliance was 35%, and compliance with stopping recommendations was 10% when PCT levels were low (<0.25 μg/L). The reasons for non-compliance were clinical judgement (49%) and meeting pre-determined overriding criteria (51%). PCT was a new diagnostic test in the hospital, and physicians can require time to become familiar with and develop confidence in the use of PCT testing.[45] Other studies have found

that algorithm compliance can be variable, ranging from 35% to 80%.[44] An international, multicentre study found that centres with experience of using PCT and ongoing reinforcement of PCT-guided AMS had higher algorithm compliance than PCT-naive centres.[44] Protocol-driven studies[28,46] have also shown higher algorithm compliance and greater impact on antimicrobial prescriptions than studies taking a quality improvement implementation approach.[29]

Algorithm compliance must improve significantly in a future trial to maximize the potential impact of PCT testing on antimicrobial prescribing decisions but also acknowledging the limitations of PCT and that physicians cannot rely on PCT alone to guide antibiotic therapy.[23] In a future trial, this should be addressed by a more comprehensive educational programme and more effective incorporation into the AMS programme to reinforce PCT recommendations. Such an approach has been shown to be effective[30,46,47] and is required for interventions such as PCT to realize their full benefit.[19] The educational element of this study may not have been sufficient. A future trial should consider the inclusion of more frequent educational presentations prior to and during the intervention, and include case reviews of PCT patients. Consideration should be given to the development of pocket cards, incorporation into local electronic antimicrobial prescribing guidelines and availability of results on the hospital electronic laboratory reporting system.[46]

Delays in availability of PCT results may have also decreased the impact of the intervention and contributed to poor algorithm compliance, with 38% of PCT serum results not available until the next day (24 h after the serum sample was taken). This included results which were delayed or unavailable for 12 patients until after they were discharged. In a future trial, prompt availability of PCT levels is important. This would allow physicians to consider PCT along with routine biochemistry and blood analysis and the patients' clinical parameters at the point of care when making antimicrobial prescribing decisions. Consideration should be given to measurement of algorithm adherence at 48 h to account for unforeseen delays in PCT result availability or delayed physician review of PCT results.

There were several factors involved in patient recruitment which may have influenced the primary outcomes of the study and should be addressed in a future trial design. These were the variation in infection severity between the PCT and respiratory control groups and the inclusion of patients who were already prescribed antimicrobials prior to hospital admission. These factors can be addressed in a suitably powered future RCT with the inclusion of illness severity scores and the use of multivariate and subgroup analysis.

A future RCT would include a broader range of physicians rather than respiratory specialists alone. Antimicrobial consumption in the general control group of patients in this study was higher than in either of the respiratory groups. The addition of PCT testing to the existing AMS programme may have the potential to have a greater impact on this patient group.

### *Strengths and limitations*

The study was conducted in a setting where PCT was a newly available test to physicians. A broad range of RTIs were recruited. The study took place over a calendar year and included seasonal variation in illness and prescribing. Patients were randomized to intervention or control, thus reducing selection bias. Serial PCT measurements were available to guide antimicrobial prescribing.

The study had some limitations. The study population had a clinical need for antimicrobial treatment, so the study was designed to examine the duration of therapy and LOS, rather than investigating the potential to withhold antimicrobial therapy. The study results may have been influenced by a study effect. Both the PCT and respiratory control groups were treated by the same group of physicians who all received education and, as they were aware that their behaviour was being monitored, this may have resulted in a Hawthorne effect.[48] The intervention was confined to one medical speciality which may limit its generalizability to other medical specialties and settings. Further limitations included the need for patient consent, and PCT results which were not available at the point of clinical decision-making in a small number of cases.

## Conclusions

PCT testing had a positive effect on antimicrobial prescribing during this feasibility study. Several factors were identified which may have influenced the outcomes and the intervention implementation. The successful implementation of PCT testing requires an ongoing comprehensive education programme, greater integration into the AMS programme and delivery of PCT results in a timely manner. This feasibility study has shown that a larger RCT would be beneficial to further explore the positive aspects of these findings.

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## Transparency declarations

None to declare.

## Supplementary data

Supplementary Appendices S1 and S2 are available as Supplementary data at *JAC* Online.

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