Efficacy and safety of antimicrobial stewardship prospective audit and feedback in patients hospitalised with COVID-19 (COVASP): a pragmatic, cluster-randomised, non-inferiority trial

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Summary

Background The COVID-19 pandemic has been associated with increased antimicrobial use despite low rates of bacterial co-infection. Prospective audit and feedback is recommended to optimise antibiotic prescribing, but high-quality evidence supporting its use for COVID-19 is absent. We aimed to study the efficacy and safety of prospective audit and feedback in patients admitted to hospital for the treatment of COVID-19.

Methods COVASP was a prospective, pragmatic, non-inferiority, small-unit, cluster-randomised trial comparing prospective audit and feedback plus standard of care with standard of care alone in adults admitted to three hospitals in Edmonton, AB, Canada, with COVID-19 pneumonia. All patients aged at least 18 years who were admitted from the community to a designated study bed with microbiologically confirmed SARS-CoV-2 infection in the preceding 14 days were included if they had an oxygen saturation of 94% or lower on room air, required supplemental oxygen, or had chest-imaging findings compatible with COVID-19 pneumonia. Patients were excluded if they were transferred in from another acute care centre, enrolled in another clinical trial that involved antibiotic therapy, expected to progress to palliative care or death within 48 h of hospital admission, or managed by any member of the research team within 30 days of enrolment. COVID-19 unit and critical care unit beds were stratified and randomly assigned (1:1) to the prospective audit and feedback plus standard of care group or the standard of care group. Patients were masked to their bed assignment but the attending physician and study team were not. The primary outcome was clinical status on postadmission day 15, measured using a seven-point ordinal scale. We used a non-inferiority margin of 0·5. Analysis was by intention to treat. The trial is registered with ClinicalTrials.gov, NCT04896866, and is now closed.

Findings Between March 1 and Oct 29, 2021, 1411 patients were screened and 886 were enrolled: 457 into the prospective audit and feedback plus standard of care group, of whom 429 completed the study, and 429 into the standard of care group, of whom 404 completed the study. Baseline characteristics were similar for both groups, with an overall mean age of 56·7 years (SD 17·3) and a median baseline ordinal scale of 4·0 (IQR 4·0–5·0). 301 audit and feedback events were recorded in the intervention group and 215 recommendations were made, of which 181 (84%) were accepted. Despite lower antibiotic use in the intervention group than in the control group (length of therapy 364·9 *vs* 384·2 days per 1000 patient days), clinical status at postadmission day 15 was non-inferior (median ordinal score 2·0 [IQR 2·0–3·0] *vs* 2·0 [IQR 2·0–4·0]; p=0·37, Mann-Whitney *U* test). Neutropenia was uncommon in both the intervention group (13 [3%] of 420 patients) and the control group (20 [5%] of 396 patients), and acute kidney injury occurred at a similar rate in both groups (74 [18%] of 421 patients in the intervention group and 76 [19%] of 399 patients in the control group). No intervention-related deaths were recorded.

Interpretation This cluster-randomised clinical trial shows that prospective audit and feedback is safe and effective in optimising and reducing antibiotic use in adults admitted to hospital with COVID-19. Despite many competing priorities during the COVID-19 pandemic, antimicrobial stewardship should remain a priority to mitigate the overuse of antibiotics in this population.

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Introduction

The COVID-19 pandemic, caused by the SARS-CoV-2 virus, continues to be a substantial contributor to unnecessary antibiotic use and has accelerated the antimicrobial resistance crisis.[1] COVID-19 management guidelines recommend the judicious use of antibiotics and to initiate antibiotic therapy only if concurrent bacterial infection is strongly suspected or confirmed.[2] Despite these recommendations, studies involving mainly patients admitted to hospital with COVID-19 suggest that 74·6% of such patients are prescribed antibiotics.[3] This figure is in contrast to the low incidence

Research in context

Evidence before this study

Despite low rates of bacterial co-infections in patients with COVID-19, antibiotics are prescribed at a disproportionately high rate according to a 2020 meta-analysis. Prospective audit and feedback is a core strategy within an antimicrobial stewardship programme that could be used to address antibiotic overuse in these patients. However, the evidence supporting the use of this strategy and addressing its safety for inpatients is currently of low quality, relying on cohort or quasi-experimental designs. Furthermore, no evidence has been published to support the use of prospective audit and feedback in rationalising antibiotics for patients admitted to hospital with COVID-19 pneumonia. We searched PubMed for clinical trials evaluating the effect of prospective audit and feedback on rationalising antibiotic use in inpatients with COVID-19 from 2019 to 2021 using the search terms "COVID-19" and "prospective audit and feedback", "antimicrobial stewardship", or "antibiotic rationalisation" and filtered for "clinical trial". We placed no limitations on language. Three studies were identified: our published protocol, one clinical trial evaluating the use of azithromycin for COVID-19 management in the community, and one trial evaluating rapid molecular testing for the treatment of community-acquired pneumonia.

Added value of this study

To our knowledge, this is the first clinical trial evaluating prospective audit and feedback plus standard of care compared with standard of care alone in patients admitted to hospital with COVID-19. This trial has a small-unit, cluster-randomisation design and provides high-quality evidence supporting the use of prospective audit and feedback within an antimicrobial stewardship programme to rationalise antibiotic use in patients who are admitted to hospital with COVID-19. Unlike previous studies of antimicrobial stewardship programmes, this study also prioritises clinical status as the primary outcome and shows that prospective audit and feedback is non-inferior to standard of care alone and does not result in clinically meaningful harm. We showed that antibiotic use was high in patients with COVID-19 despite low rates of bacterial co-infection, resulting in a high rate of guideline-discordant antibiotic prescribing. Most audit and feedback interventions in this study involved discontinuing antibiotics when no bacterial entity was suspected or confirmed, or shortening the duration of therapy in alignment with guidelines. Overall antibiotic use was lower in the prospective audit and feedback plus standard of care group than in the group receiving standard care alone, with no difference in the clinical status of patients at postadmission day 15, indicating that prospective audit and feedback within an antimicrobial stewardship programme is effective at reducing antibiotic use in patients who are admitted to hospital with COVID-19 without negatively affecting their clinical status.

Implications of all the available evidence

The finding that prospective audit and feedback within an antimicrobial stewardship programme is a successful strategy to optimise antibiotic therapy in patients who are admitted to hospital with COVID-19 is of great relevance given that this study, together with the available evidence, shows that antibiotic use is high among these patients, with many prescriptions being guideline discordant. Despite many competing priorities during the COVID-19 pandemic, antimicrobial stewardship should remain a priority to mitigate the pervasive overuse of antibiotics in patients with the disease. Further studies are required to show generalisability to other infectious entities; however, this study outlines that carefully designed clinical trials are possible in antimicrobial stewardship.

of bacterial co-infections, estimated at 3·5%, and secondary bacterial infections, estimated at 14·3%, as reported by a 2020 meta-analysis.[4] The large number of patients admitted to hospital with COVID-19 during the pandemic, combined with high rates of antibiotic prescribing, has resulted in alarming increases in antibiotic use, with one study showing a quadrupling of ceftriaxone use and a doubling of azithromycin use during the initial stages of the pandemic.[5] Experts agree that antimicrobial stewardship programme interventions are needed.[6–8] With the recognised strain on hospital resources and personnel during the COVID-19 pandemic, diversion from antimicrobial stewardship activities has reportedly been common, raising the need for high-quality studies showing the essential role of antimicrobial stewardship programmes in facilitating the optimal use of antimicrobials in patients with COVID-19.[6,9]

Prospective audit and feedback is recommended as a core strategy within an antimicrobial stewardship programme. In general, evidence supporting key antimicrobial stewardship interventions in the inpatient setting tends to be of low quality and heterogeneous, dominated by single-centre observational or quasi-experimental study designs.[10–12] Few randomised clinical trials have evaluated the efficacy and safety of antimicrobial stewardship interventions and, to our knowledge, no evidence has been published to support an organised antimicrobial stewardship intervention to minimise antibiotic use in patients admitted to hospital with COVID-19 pneumonia. This low-quality evidence is, in part, due to inherent difficulties with randomisation at the individual-participant level. When studying the effect of a prospective audit and feedback intervention on physician-level antibiotic prescribing, it is not possible to randomise at the programme, hospital, or unit level, or at the physician level without creating bias related to imbalances in patient medical complexity or baseline prescribing behaviours of the physician.[13] A

cluster-randomisation study design, at the level of individual hospital beds, could overcome this challenge by effectively minimising baseline imbalances. We report the results of a multicentre, pragmatic, cluster-randomised trial that evaluated the safety and efficacy of rationalising antibiotic therapy with an antimicrobial stewardship prospective audit and feedback intervention plus standard of care versus standard of care alone in patients who were admitted to hospital for the treatment of COVID-19.

Methods

Study design

We did a prospective, multicentre, pragmatic, non-inferiority, small-unit, cluster-randomised clinical trial of prospective audit and feedback plus standard of care versus standard of care alone in patients with SARS-CoV-2 infection who were admitted to hospital for the treatment of COVID-19 pneumonia. The study was conducted in three acute care hospitals in Edmonton, AB, Canada, with a combined total of 1487 beds. Enrolment for the trial began on March 1, 2021, and ended on Oct 29, 2021. The University of Alberta Research Ethics Board and the Covenant Health Research Centre granted approval (Pro00105598). The details of the study protocol are published elsewhere,[13] with protocol amendments stated in appendix 1 (p 5).

Participants

All patients aged at least 18 years admitted from the community to a designated study bed with microbiologically confirmed SARS-CoV-2 infection in the 14 days before hospital admission were included if they had an oxygen saturation of 94% or lower on room air, required supplemental oxygen, or had chest-imaging findings compatible with COVID-19 pneumonia. Patients were excluded if they were transferred in from another acute care centre, enrolled in another clinical trial that involved antibiotic therapy, expected to become palliative or progress to death within 48 h of hospital admission, or managed by any member of the research team within 30 days of enrolment. A waiver of consent was granted by the University of Alberta Research Ethics Board.

Randomisation and masking

The prospective audit and feedback intervention was applied to attending physicians to establish the effect of optimisation of antibiotic prescribing, guided by antimicrobial stewardship strategies, on patient outcomes. However, owing to physician localisation, cluster randomisation at the physician level was not possible without creating bias, as it would have inadvertently resulted in unit-level randomisation and the associated imbalances in treatment groups given the differences in acuity between units. For this reason, we randomised at the level of patient beds to effectively minimise imbalances, resulting in the lowest-level cluster-randomisation for an antimicrobial stewardship study.

Each hospital generated a line list of all beds in adult COVID-19 units and critical care units for randomisation at study onset, including theoretical surge beds in the event of overcapacity. Randomisation was stratified by COVID-19 unit beds and critical care unit beds and was done by computer, with beds allocated in a 1:1 ratio to prospective audit and feedback plus standard of care or standard of care alone. Randomisation was block balanced, and permuted blocks were stratified by intensive care unit or ward type. Block sizes were randomly varied between two and four. Members of the antimicrobial stewardship team were aware of bed allocation and were responsible for enrolment. Although masked to the level of randomisation and bed allocation at the time of randomisation, attending staff became aware that their antibiotic prescriptions were subject to audit and feedback after receiving a recommendation. Patients were masked to bed randomisation. The allocation sequence was generated by the study statistician (MY), who was not masked to bed randomisation.

Procedures

The intervention was antibiotic audit and feedback for attending physicians caring for patients with COVID-19 who were admitted to an intervention-group bed and given antibiotics from enrolment to postadmission day 15. Audit and feedback was done prospectively, on weekdays (with the exception of statutory holidays), by physician and pharmacist members of each site-based antimicrobial stewardship team. Real-time verbal and written feedback were provided to the attending team if antimicrobial stewardship recommendations were made.

See Online for appendix 1

The initial audit and feedback was done on the day that an eligible patient was enrolled in the study, if and when they were prescribed an antibiotic. Follow-up audits were conducted weekly thereafter (within 3 days to account for weekends or statutory holidays), and on an ad-hoc basis if a new antibiotic was prescribed, until the primary endpoint at postadmission day 15. Appropriateness of antimicrobial prescribing was assessed against local clinical practice guidelines.[14] In clinical scenarios lacking clear guidelines, appropriateness was defined by the opinion of the antimicrobial stewardship team members who did the the audit. The focus of antimicrobial stewardship recommendations was to rationalise and optimise antibiotic use—defined as discontinuing therapy for patients for whom bacterial co-infection was not suspected or confirmed, and optimising the duration, dose, and spectrum of antimicrobial therapy for patients for whom antibiotics were warranted. The antimicrobial stewardship team did not physically interact with the patient. The attending physician ultimately decided whether to accept any recommendations suggested during audit and feedback.

	All (N=833)	PAF + SOC (N=429)	SOC (N=404)
Mean age (SD), years	57 (17)	56 (17)	57 (17)
Sex			
Male	469 (56%)	249 (58%)	220 (54%)
Female	364 (44%)	180 (42%)	184 (46%)
Charlson comorbiditiy index >4	145 (17%)	64 (15%)	81 (20%)
Mean weight (SD), kg	90 (26)	91 (27)	89 (26)
Baseline ordinal scale at enrolment			
Not on supplemental oxygen (3)	138 (17%)	72 (17%)	66 (16%)
On supplemental oxygen (4)	428 (51%)	223 (52%)	205 (51%)
On high-flow oxygen therapy or non-invasive mechanical ventilation (5)	205 (25%)	101 (24%)	104 (26%)
On invasive mechanical ventilation (6)	62 (7%)	33 (8%)	29 (7%)
Admitting service			
COVID-19 ward	709 (85%)	357 (83%)	352 (87%)
Intensive care unit	124 (15%)	72 (17%)	52 (13%)
Attending physician specialty			
General internal medicine	595 (71%)	293 (68%)	302 (75%)
Pulmonary	26 (3%)	17 (4%)	9 (2%)
Family medicine	77 (9%)	43 (10%)	34 (8%)
Intensive care	124 (15%)	72 (17%)	52 (13%)
Other	11 (1%)	4 (1%)	7 (2%)
Infectious diseases consultation	10 (1%)	7 (2%)	3 (1%)
Mean peripheral leukocyte count (SD), ×10⁹/L	7·61 (4·7)	7·49 (3·67)	7·75 (5·54)
Mean neutrophil count (SD), ×10⁹/L	5·97 (3·43)	5·88 (3·13)	6·06 (3·72)
Mean serum creatinine concentration (SD), µmol/L	99 (119)	97 (121)	100 (117)
Mean C-reactive protein concentration (SD), mg/L	110·8 (77·6)	109·1 (79·4)	112·7 (75·8)
Sputum culture			
Not done	752 (90%)	388 (90%)	364 (90%)
Positive growth	15 (2%)	9 (2%)	6 (1%)
Respiratory pathogen panel			
Not done	719 (86%)	365 (85%)	354 (88%)
Positive	2 (<1%)	1 (<1%)	1 (<1%)
Negative	112 (13%)	63 (15%)	49 (12%)
Bacterial growth in blood culture			
Not done	250 (30%)	137 (32%)	113 (28%)
Positive growth	15 (2%)	8 (2%)	7 (2%)
Chest x-ray			
Not done	2 (<1%)	0	2 (1%)
Clear	50 (6%)	27 (6%)	23 (6%)
Patchy infiltrates	613 (74%)	311 (73%)	302 (75%)
Consolidation	72 (9%)	41 (10%)	31 (8%)
Other	96 (12%)	50 (12%)	46 (11%)
Therapy			
Dexamethasone	768 (92%)	394 (92%)	374 (93%)
Tocilizumab	304/832 (37%)	157 (37%)	147/403 (37%)
Casirivimab–imdevimab	94/651 (14%)	47/361 (13%)	47/290 (16%)
Remdesivir	40/653 (6%)	17/361 (5%)	23/292 (8%)

Data are n (%) unless otherwise specified. PAF=prospective audit and feedback. SOC=standard of care.

Table 1: **Baseline characteristics**

Only antibiotics were included and audited. Prescriptions were excluded from audit and feedback if they were single doses or were discontinued before audit, and were excluded from audit and final analysis if used for surgical or medical prophylaxis. All pre-existing antimicrobial stewardship initiatives continued throughout the study period, including prospective audit and feedback for specific antibiotics of interest (carbapenems, daptomycin, linezolid, tigecycline, and site-dependent fluoroquinolones); however, pre-existing initiatives were not used for any patients enrolled in this trial.

Outcomes

Safety of the antimicrobial stewardship intervention was defined as a non-different outcome on the seven-point ordinal scale between the two study groups. The primary outcome was the clinical status of the patient on postadmission day 15 measured with a seven-point ordinal scale, defined as 1 point: not hospitalised and able to resume normal daily activities; 2 points: not hospitalised and unable to resume normal daily activities; 3 points: hospitalised and not on supplemental oxygen; 4 points: hospitalised and on supplemental oxygen; 5 points: hospitalised and on high-flow oxygen therapy or non-invasive mechanical ventilation; 6 points: hospitalised and on extracorporeal membrane oxygenation or invasive mechanical ventilation; 7 points: death.

Prespecified exploratory analyses of secondary outcomes were an assessment of clinical outcomes (length of stay in hospital, in-hospital mortality, 30-day mortality, mortality associated with *Clostridioides difficile*, and 30-day re-admission rate), antimicrobial stewardship outcomes (antimicrobial use measured in length of therapy and days of therapy normalised by patient-days for the duration of hospital stay [capped at 30 days], number of audits, types of recommendation, and acceptance rate), microbiological outcomes (incidence of multidrug-resistant organism isolation and *C difficile* infection at 30 days), and adverse events (incidence of neutropenia and acute kidney injury, according to Kidney Disease Improving Global Outcomes definitions) at 30 days. Multidrug resistance was defined as non-susceptibility to one or more agents in three or more antimicrobial categories active against the isolated bacteria. Resistance to methicillin in the case of *Staphylococcus aureus* and vancomycin in the case of *Enterococcus* species defined the strain as multidrug-resistant, regardless of resistance to other antimicrobials.[15]

Patients were followed and analysed in the group to which they were assigned regardless of patient movement within or between study sites.

Statistical analysis

We calculated the sample size estimation to show that an antimicrobial stewardship intervention was non-inferior to standard of care regarding COVID-19 outcomes measured using the seven-point ordinal scale. On the basis of previous studies that used the same scale,[16] we defined the non-inferiority margin at 0·5 of the predicted mean score of the seven-point ordinal scale, which

corresponds to a 20% change in the scale. 530 patients (265 per group) were needed to show a significant non-inferiority of the intervention group, with 80% power and 2·5% one-sided alpha assuming standard deviation of 2 and the non-inferiority margin of 0·5. When 260 patients were recruited in the control group, we did a non-comparative sample size recalculation that did not result in a change from the previous sample size estimate. We used Power Analysis and Sample Size 2019 (Pass; NCSS, Kaysville, UT, USA) for power calculations.

The primary analysis was a two-sample comparison of the clinical ordinal scale scores between the intervention and control groups. We used the Mann-Whitney *U* test to assess non-inferiority of the intervention group, using a one-sided level of 0·025 to declare significance. Data are reported as median and IQR.

Categorical secondary and exploratory outcomes were analysed between groups by χ^2 tests. Continuous secondary and exploratory outcomes were tested with a Student's *t* test or a Mann-Whitney *U* test if assumptions for the *t* test were not satisfied. Categorical data are presented as absolute and relative frequencies. Continuous variables are presented as mean, SD, median, quartiles, and minimum and maximum. All statistical analyses were done using SAS version 9.4. All secondary, exploratory, and subgroup analyses were prespecified and are considered exploratory. The study is registered at ClinicalTrials.gov, NCT04896866.

Role of the funding source

There was no funding source for this study.

Results

Between March 1 and Oct 29, 2021, 1411 patients were screened for eligibility, of whom 886 met the inclusion criteria for enrolment. 457 patients were allocated to the prospective audit and feedback plus standard of care group and 429 to the standard of care group. Of these, 53 patients were subsequently excluded on the basis of predetermined exclusion criteria: two became enrolled in another clinical trial involving antibiotic therapy, seven were switched to palliative care within 48 h of enrolment, and 44 received care from a physician (n=16) or pharmacist (n=28) in the research team. The remaining 833 patients completed the study and were included in the analysis: 429 in the prospective audit and feedback plus standard of care group and 404 in the standard of care group (figure 1).

Patients in the intervention and control groups were balanced in terms of demographics and baseline clinical characteristics (table 1). Overall, the mean age was 56·7 years (SD 17·3). 364 (44%) of 833 patients were female and 469 (56%) were male (according to sex assigned at birth). The Charlson Comorbidity Index was greater than 4 in 145 (17%) patients and the median baseline ordinal scale was 4·0 (IQR 4·0–5·0). 124 (15%) of 833 patients were directly admitted to an intensive care unit and the remaining 709 (85%) were hospitalised

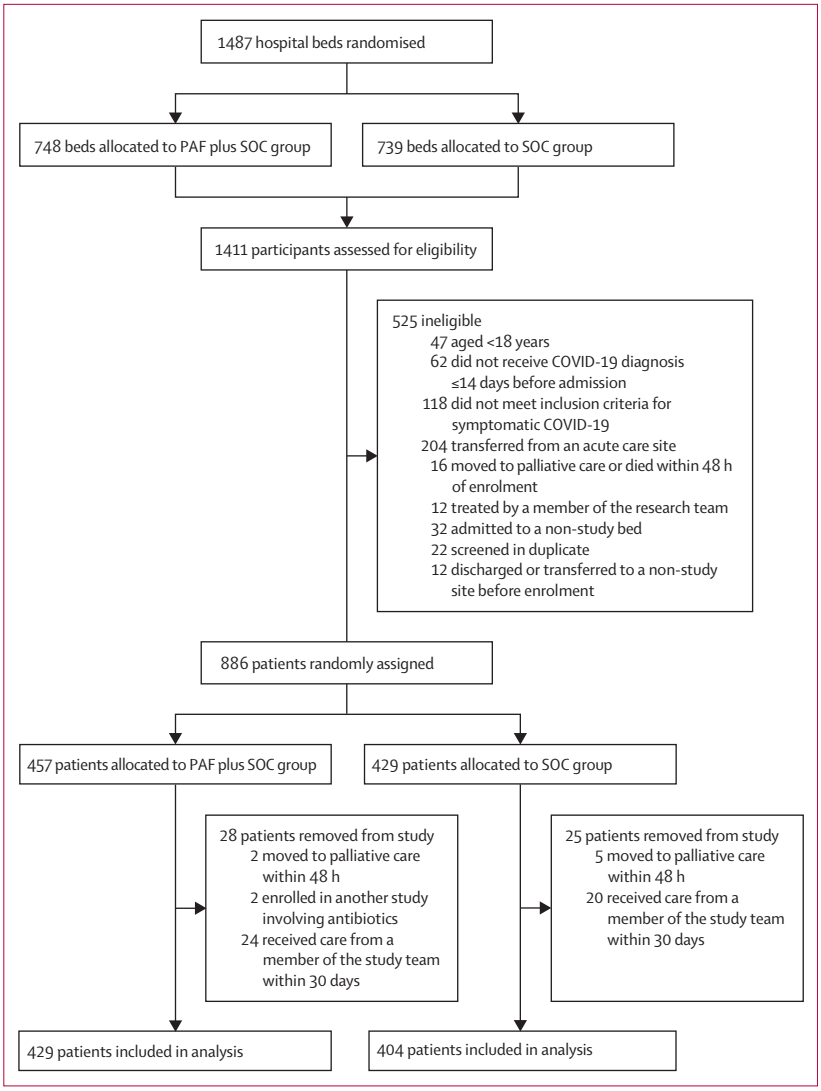

Figure 1: **Trial profile**
PAF=prospective audit and feedback. SOC=standard of care.

on a conventional ward, with 595 (71%) of 833 patients attended by a general internal medicine specialist. Blood cultures yielded bacterial growth in 15 (2%) of 833 patients, and respiratory cultures grew an organism of clinical significance in 15 (2%) patients. Respiratory cultures were classified as not clinically significant if the patient had no symptoms related to the positive respiratory culture and the attending physician found no need for treatment. Of the 114 (17%) patients for whom a respiratory pathogen panel was recorded (NxTAG Respiratory Pathogen Panel, Luminex (Toronto, ON, Canada), enterovirus or rhinovirus was identified in one patient in each group. The most common COVID-19 therapies received were dexamethasone (768 [92%] patients) and tocilizumab (304 [37%] patients).

The clinical status of patients on postadmission day 15 was assessed as the primary outcome. The ordinal scale

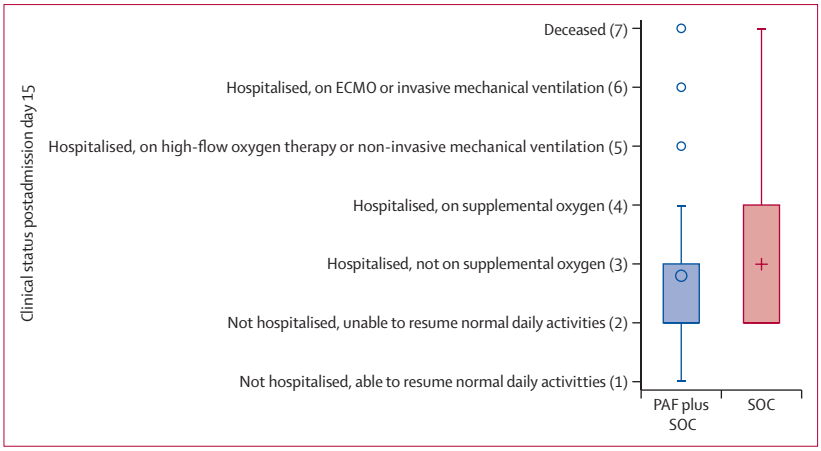

Figure 2: **Clinical status measured on a seven-point ordinal scale at postadmission day 15**
Median is 2·0 (IQR 2·0–3·0) for the PAF + SOC group and 2·0 (2·0–4·0) for the SOC group (Mann-Whitney *U* test, p=0·37). The box boundaries represent IQR, the bottom of the box is the median, symbols inside the box represent the mean, whiskers show the maximum and minimum observations, and circles outside the box represent outliers. ECMO=extracorporeal membrane oxygenation. PAF=prospective audit and feedback. SOC=standard of care.

	PAF + SOC (N=429)	SOC (N=404)
Mean acute length of hospital stay (SD, 95% CI), days*	9·59 (8·84, 8·75–10·43)	11·03 (14·69, 9·59–12·47)
In-hospital mortality (%, 95% CI)	46 (11%, 8%–14%)	51 (13%, 9%–16%)
30-day mortality (%, 95% CI)	46 (11%, 8%–14%)	50 (12%, 9%–16%)
30-day re-admission (%, 95% CI)	19 (4%, 3%–6%)	21 (5%, 3%–7%)
Clostridioides difficile infection (%)	1 (<1%)	0
Clostridioides difficile-associated mortality	0	0

Data are n (%) except where specified. PAF=prospective audit and feedback. SOC=standard of care. *Acute length of stay is not normally distributed; median is 7·0 (IQR 4·0–12·0) for the PAF + SOC group and 7·0 (4·0–12·0) for the SOC group.

Table 2: **Secondary clinical outcomes**

	PAF + SOC	SOC
Mild neutropenia	11/420 (3%)	20/396 (5%)
Severe neutropenia	2/420 (<1%)	0
Acute kidney injury		
All	74/421 (18%)	76/399 (19%)
Stage 1	47/421 (64%)	57/399 (75%)
Stage 2	15/421 (20%)	10/399 (13%)
Stage 3	12/421 (16%)	9/399 (12%)

Data are n/N (%). PAF=prospective audit and feedback. SOC=standard of care.

Table 3: **Adverse events**

score for patients in the prospective audit and feedback plus standard of care group was similar to that of patients in the standard of care group (median score 2·0 [IQR 2·0–3·0] *vs* 2·0 [2·0–4·0]; p=0·37, Mann-Whitney *U* test; figure 2). Given the reportedly higher incidence of bacterial co-infection or secondary infection and associated poorer prognosis of patients in critical care, a predefined subgroup analysis was conducted for the intensive care cohort, in which the clinical status at postadmission day 15 was also similar for patients in the prospective audit and feedback plus standard of care group compared with those in the standard of care group (median score 4·0 [IQR 2·0–6·0] *vs* 5·0 [2·0–6·0]; p=0·28, Mann-Whitney *U* test).

The secondary outcomes of in-hospital mortality, 30-day mortality, acute length of hospital stay, and 30-day re-admission rates were similar for both groups (table 2). One patient (in the intervention group) was identified as having a *C difficile* infection, and no *C difficile*-associated deaths were recorded. Multidrug-resistant organisms were isolated from patients at similar rates in both groups (11 [3%] of 429 patients in the prospective audit and feedback plus standard of care group and 11 [3%] of 404 patients in the standard of care group), most commonly from the urinary tract (11 [50%] of 22 patients) or respiratory tract (9 [40%] of 22 patients; appendix 1 p 2). *Escherichia coli* (n=10) and methicillin-resistant *S aureus* (n=7) were the most common such organisms isolated (appendix 1 p 2). In terms of adverse events, neutropenia was uncommon in both the intervention group (13 [3%] of 420 patients for whom data were available) and the control group (20 [5%] of 396 patients for whom data were available). Acute kidney injury occurred at a similar rate in the intervention group (74 [18%] of 421 patients for whom data were available) and the control group (76 [19%] of 399 patients for whom data were available; table 3).

Antibiotics were prescribed for 438 (53%) of 833 patients at enrolment. Of the 429 patients allocated to the intervention group, 203 (47%) were prescribed at least one antibiotic at enrolment, and another 32 (7%) had antibiotics prescribed at a later point. 301 prospective audit and feedback events (235 initial audits and 66 follow-up audits) were conducted. The two most common antibiotics audited were ceftriaxone (216 prescriptions) and azithromycin (167 prescriptions), in keeping with the recommended regimen for a hospitalised, community-acquired case of pneumonia according to local guidelines. The next most common antibiotic prescription was for piperacillin–tazobactam (31 prescriptions). A pulmonary infection was the most cited indication, recorded in 271 (89%) of 304 cases. When assessed against local prescribing guidelines, 111 (37%) of 301 antibiotic regimens were deemed guideline concordant. The remaining 190 (63%) regimens were considered guideline discordant, predominantly because of unnecessary antibiotic use (122, 57%). 215 distinct recommendations were made to optimise care, with an acceptance rate of 84% (181 of 215). These recommendations were discontinuation of antibiotic therapy as bacterial infection was not suspected or confirmed in 122 (57%) instances, a change in duration of therapy in 45 (21%) instances (a shorter duration was recommended in 25 cases), a change in antibiotic agent in 18 (8%) instances (a less broad-spectrum agent was recommended in nine cases), a change in dose in 16 (7%) instances, and a route change in six (3%) instances. A further eight antimicrobial stewardship recommendations were made, suggesting

additional investigations in six (2%) instances and infectious diseases consultation in two (1%) instances (appendix 1 p 3).

The mean length of antibiotic therapy from enrolment to postadmission day 15 was shorter in the intervention group (2·0 days [SD 3·0]) than in the control group (2·4 days [3·0]; p<0·0020, Mann-Whitney *U* test). Overall antibiotic use during the index hospital stay (capped at 30 days) was lower in the group receiving prospective audit and feedback plus standard of care than in the group receiving standard of care alone (length of therapy 364·9 *vs* 384·2 days per 1000 patient days, p=0·0006; 544·5 *vs* 561·2 days of therapy per 1000 patient days, p=0·0060, Mann-Whitney *U* test).

Discussion

In this pragmatic, cluster-randomised clinical trial, antibiotic prospective audit and feedback in patients admitted to hospital for the treatment of COVID-19 was a successful strategy to optimise antibiotic therapy and reduce its duration, without negatively affecting clinical status of patients at postadmission day 15. We found high rates of antibiotic use (53%) despite low rates of culture-positive bacterial co-infection (4%), contributing to a high rate of guideline-discordant antibiotic use among the 63% of patients whose antibiotics were reviewed. Prospective audit and feedback was an effective means of ensuring judicious use of antibiotics in this population, with lower antibiotic use in the intervention group than in the control group (364·9 *vs* 384·2 days per 1000 patient days), showing that this strategy is safe and effective to ensure rationalised antibiotic use in patients treated in hospital for COVID-19.

Several organisations, including WHO and the UK National Institute for Health and Care Excellence, recommend prospective audit and feedback as a key antimicrobial stewardship strategy.[17,18] This recommendation is supported by cohort and quasi-experimental studies that, owing to inherent limitations in study design, make it challenging to draw rigorous conclusions. To our knowledge, this is the first trial to evaluate antimicrobial stewardship in the form of prospective audit and feedback that uses a small-unit, cluster-randomisation method to effectively achieve randomisation down to the participant level, thereby producing robust trial data supporting the use of this strategy in rationalising antibiotic therapy, using COVID-19 pneumonia as the model disease. Because the principle of assessing antibiotic appropriateness against guidelines is applicable to other infections, the benefits of prospective audit and feedback we have shown can potentially be extrapolated to other infectious entities.

Although prescribers often recognise that bacterial co-infections are uncommon and antibiotics are overused in patients with COVID-19, no high-quality evidence is available to reassure prescribers that stopping antibiotics in this population is safe. Previous studies suggest that antibiotics make a minimal contribution to care, with one study[19] reporting no difference in antibiotic use between patients who survived COVID-19 and those who did not. A retrospective analysis[20] of an intensive care cohort showed a similar mortality rate between patients who did and did not receive antibiotic therapy before treatment in the intensive care unit.[20] Similarly, another ward-based study[21] conducted a multivariate regression analysis and showed no association between antibiotic therapy and the combined outcome of death or transfer to intensive care. However, these studies did not account for prescriber bias (ie, withholding antibiotics only in mild infections). Given that many (57%) of the prospective audit and feedback recommendations in our study consisted of stopping antibiotics in cases in which a bacterial co-infection was not suspected, our study shows that antimicrobial-stewardship-mediated discontinuation of antibiotics that have already been ordered by the attending team (presumably due to concerns for a bacterial infection) is safe. The acceptance rate for discontinuing antibiotics was high, which reflects the ability of the antimicrobial stewardship team to skilfully identify non-bacterial infections and provide clinical rationale to reassure prescribers that antibiotics are not warranted, therefore acting as a valuable resource when the need for antibiotics is debatable.

COVID-19 management guidelines are more liberal regarding antibiotic use for patients in critical care owing to the higher rate of bacterial secondary infection in this population, cited at 8·1% according to one meta-analysis,[4] and with a reported range of 0–31·6% in various retrospective studies.[22] We therefore conducted a predetermined subgroup analysis and found that the safety of prospective audit and feedback was maintained in the critical care population, with a similar ordinal scale score at postadmission day 15 for patients treated in intensive care from both the control group and the intervention group. In patients with COVID-19 who are admitted to the intensive care unit, empirical antibiotics for potential bacterial causes of clinical deterioration are common, and 89% of patients in our intensive care subgroup were taking antibiotics at enrolment. However, guidelines maintain that a reassessment at 48–72 h is prudent to ensure antibiotic cessation if a bacterial cause is not apparent, or optimisation if such a cause is confirmed. Prospective audit and feedback as part of an antimicrobial stewardship strategy can ensure that this reassessment occurs within a busy pandemic setting, in which the workload in an intensive care unit can be demanding and unpredictable.

Antibiotic prescribing on admission to hospital was common, with approximately half of the patients in our cohort on antibiotic therapy at the time of enrolment. Although still disproportionately higher than the rate of culture-confirmed bacterial co-infection in our patients (4%), studies suggest that antibiotics are typically prescribed for approximately 75% of patients who are

treated in hospital for COVID-19,[3] suggesting that our rate of prescribing is lower than average. One potential explanation is the learned effect derived from the feedback component of the prospective audit and feedback intervention, given that the percentage of patients who were prescribed antibiotic therapy at enrolment decreased over time in both groups and with each pandemic surge. However, this explanation is challenging to confirm, as there have been reports of reduced antibiotic prescribing for patients with COVID-19 over time as prescribers feel more comfortable with managing the disease strictly as a viral infection.[5]

The main objective of this study was to compare the clinical status of patients at postadmission day 15 to ensure that there was no difference between the prospective audit and feedback plus standard of care group and the standard of care group. The study was therefore underpowered for the secondary clinical outcomes; however, a trend towards a reduction in in-hospital mortality, 30-day mortality, length of hospital stay, and re-admissions was seen in the intervention group. Although further study is required, an improvement in these patient outcomes as a result of prospective audit and feedback would be anticipated given that the negative outcomes associated with unnecessary antibiotic use have been documented for patients with COVID-19. The use of penicillin or meropenem in patients with COVID-19 without suspected bacterial pneumonia was shown to be associated with an increased risk of death in a retrospective cohort study[23] and combination antibiotics have been shown to be a significant predictor of subsequent nosocomial infection in patients who were hospitalised with COVID-19.[24] Although we attempted to compare antibiotic-related adverse events and *C difficile* infection between the two groups, the number of events was small, limiting any conclusions regarding the effect of prospective audit and feedback on these parameters.

An increase in antimicrobial resistance has been described during the COVID-19 pandemic resulting from the overuse of antibiotics.[25] Several cohort studies have found varying rates of multidrug-resistant co-infections; however, when focusing on studies with larger sample sizes (n>1000), the estimated rate of resistant co-infections ranges from 0·2% to 9%.[25] We identified a multidrug-resistant organism from 3% of our patients. The multidrug-resistant infection rate in our study could be underestimated given the short follow-up period of 30 days, as the relationship between antimicrobial exposure and resistance can be temporally distant and confounded by infection prevention and control practices.

Our clinical trial has several strengths related to the study design, which aligns with the consensus recommendations of an expert panel convened to evaluate antimicrobial stewardship interventions.[12] First, this multicentre study enrolled patients with a large range of illness severity, from both community and academic centres, resulting in a diverse patient population. Second, our study used a small-unit cluster randomisation that is, to our knowledge, the first of its kind within antimicrobial stewardship literature. Owing to a lack of feasibility, randomised clinical trials are challenging to conduct in antimicrobial stewardship, resulting in a tendency to conduct quasi-experimental studies or large-unit cluster randomisation by hospital or unit. Our method of cluster randomisation at the bed level effectively mitigates biases related to patient and prescriber localisation, thereby ensuring a homogeneous sample of patients with COVID-19 per prescriber. Third, we preselected the ordinal scale, a standardised and effective metric to assess clinical status, as our primary outcome in order to confirm the non-inferiority of the prospective audit and feedback intervention. Previously, clinical outcomes have rarely been investigated in hospital-based antimicrobial stewardship studies, resulting in insufficient power to exclude clinically meaningful harm. Fourth, our predetermined exploratory analysis of secondary outcomes was more comprehensive than that in previous studies, permitting a greater understanding of the effect of prospective audit and feedback on clinical as well as microbiological outcomes in patients with COVID-19, recognising that little data exists on *C difficile* and multidrug-resistant infection rates in these patients. Finally, previous studies showed the overuse of antibiotics in patients with COVID-19 by comparing overall antibiotic use with the rate of culture positivity. We additionally included data on the appropriateness of antibiotic use measured against guidelines and correlated this with prospective audit and feedback recommendations, thereby providing more granular data on the degree and nature of antibiotic overuse and where prospective audit and feedback can have the greatest effect.

Our trial has several limitations. First, antibiotic prescribing could have been lower than usual in both groups owing to the Hawthorne effect. The modification of physicians' prescribing habits when they are aware of antimicrobial stewardship monitoring has been well documented.[26] Although the waiver of consent precluded physician awareness of specific audit events, they were aware that audit and feedback was occurring in a general sense, which probably resulted in a tendency to be more self-critical of their prescribing. Second, physician learnings derived from the prospective audit and feedback plus standard of care group could have been applied to other patients, including those in beds randomised to receive standard of care, thereby resulting in some degree of contamination. This effect was potentially minimised by rapid physician turnover, characterised by weekly handover and many transient care providers. Regardless, this intervention spillover reflects real-world settings, in which the effect of prospective audit and feedback often extends beyond the individual encounter and begins to permeate a

physician's regular prescribing, highlighting the pragmatic nature of our study.

Physicians who specialise in the treatment of infectious diseases are well positioned to facilitate optimal treatment and reinforce antimicrobial stewardship principles; however, their role in the COVID-19 pandemic varies between centres and is often dependent on their availability. The rate of consultation with infectious disease specialists was low in our study, and would need to be considered before extrapolating the results to centres with greater involvement of such physicians.

Although co-infections were accounted for in our study design, the short (15-day) duration of the prospective audit and feedback intervention risks missing antibiotic rationalisation for secondary bacterial infections, which often occur more than 14 days after diagnosis with COVID-19.[27] As secondary infections are estimated to be more common (14·3%) than co-infections (3·5%),[4] they represent a high-yield target for antimicrobial stewardship programmes that could be addressed in future studies.

53 patients were removed from the study protocol after allocation (28 in the intervention group and 25 in the control group), the predominant reason (n=44) being that the patient received care directly from a member of the antimicrobial stewardship programme team or study team after enrolment, either in their capacity as a team pharmacist or during an infectious disease consultation. As per the original study protocol, these patients were excluded owing to inherent biases derived from the direct interaction of a patient with an unmasked study member who could then influence the patient's treatment course, including decisions regarding antibiotic treatment.

Unlike most non-pandemic respiratory viral infections, COVID-19 has the benefit of effective therapeutics and vaccines, with higher-than-average vaccine uptake. Our study did not contain data on vaccination. Although randomisation, in addition to stratification by admission to the intensive care unit, would theoretically distribute patients with different vaccination statuses similarly between groups, the potential protective effect of vaccination towards disease progression, combined with the use of prognosis-altering therapeutic agents, could result in a theoretical bias towards non-inferiority. Moreover, this bias could reduce the generalisability to future pandemic and other non-pandemic viruses.

We acknowledge that no gold standard exists to diagnose or refute a bacterial pneumonia among patients with COVID-19. Compelling data on biochemical markers, such as procalcitonin, to stratify patients with COVID-19 by risk is scarce,[28] and has not been previously recommended when deciding to start or withhold antibiotics for community-acquired or hospital-acquired pneumonia.[29] Although various COVID-19 co-infection prediction models have been studied, many rely on findings from CT scans, which are not routinely conducted in this population, and none of these models have been externally validated.[28] Our approach to assessing the likelihood of a bacterial co-infection through combining clinical symptoms, biochemistry (excluding procalcitonin, which is not available for routine clinical use at the study sites), and microbiology results in a comprehensive assessment in accordance with that recommended by multiple guidelines.[2,30]

Among patients hospitalised with COVID-19 pneumonia, rationalising antibiotic therapy with antimicrobial stewardship prospective audit and feedback interventions did not negatively affect patient outcomes despite an overall reduction in antibiotic use. Despite many competing priorities during the COVID-19 pandemic, antimicrobial stewardship should remain a priority to mitigate the pervasive overuse of antibiotics in patients with the disease. Further studies are required to show generalisability to other infectious entities, such as with other viral pneumonias; however, this study outlines that carefully designed clinical trials are possible in antimicrobial stewardship.

Contributors

JZC, HLH, and CC were responsible for conceptualisation. JZC, HLH, CL, JS, SR, KZ, MS, and HK-M curated the data. MY conducted the data analysis. JZC, HLH, DK, KED, SWS, CL, JS, SR, KZ, MS, HK-M, and CC contributed to the methodology and investigations. JZC and HLH provided project administration. JZC and HLH wrote the original draft and JZC, HLH, DK, KED, SWS, CL, JS, SR, KZ, MS, HK-M, and CC reviewed and edited the manuscript. JZC, HLH, and MY accessed and verified the data. JZC, HLH, and CC had final responsibility for the decision to submit for publication. CC supervised the study.

Declaration of interests

DK declares a clinical trial and research grant from Pulmocide and AVIR Pharma, and payment for education lectures from GSK and AVIR Pharma, both unrelated to this manuscript. All other authors declare no competing interests.

Data sharing

Data collected for the study are internal to Alberta Health Services and Covenant Health and will not be made available to others. The study protocol, statistical analysis plan, and supporting documentation are available in appendices 1–5.

See **Online** for appendices 2–5

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