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Original article

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ABSTRACT

Objectives: We aimed at assessing the efficacy and safety on antibiotic exposure of a strategy combining a respiratory multiplex PCR (mPCR) with enlarged panel and daily procalcitonin (PCT) measurements, as compared with a conventional strategy, in adult patients who were critically ill with laboratory-confirmed SARS-CoV-2 pneumonia.

Methods: This multicentre, parallel-group, open-label, randomized controlled trial enrolled patients admitted to 13 intensive care units (ICUs) in France. Patients were assigned (1:1) to the control strategy, in which antibiotic streamlining remained at the discretion of the physicians, or interventional strategy, consisting of using mPCR and daily PCT measurements within the first 7 days of randomization to streamline initial antibiotic therapy, with antibiotic continuation encouraged when PCT was >1 ng/mL and discouraged if < 1 ng/mL or decreased by 80% from baseline. All patients underwent conventional microbiological tests and cultures. The primary end point was antibiotic-free days at day 28.

Results: Between April 20th and November 23rd 2020, 194 patients were randomized, of whom 191 were retained in the intention-to-treat analysis. Respiratory bacterial co-infection was detected in 48.4% (45/93) and 21.4% (21/98) in the interventional and control group, respectively. The number of antibiotic-free days was 12.0 (0.0; 25.0) and 14.0 (0.0; 24.0) days, respectively (difference, −2.0, (95% CI, −10.6 to 6.6), p=0.89). Superinfection rates were high (51.6% and 48.5%, respectively). Mortality rates and ICU lengths of stay did not differ between groups.

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Discussion: In severe SARS-CoV-2 pneumonia, the mPCR/PCT algorithm strategy did not affect 28-day antibiotics exposure nor the major clinical outcomes, as compared with routine practice.
Muriel Fartoukh, Clin Microbiol Infect 2023;29:734

Introduction

Antibiotics have been largely prescribed in the early management of patients with severe SARS-CoV-2 pneumonia [1–5], as the clinical diagnosis of bacterial co-infection is challenging, as well as because of the reported high rates of bacterial co-infection in other acute viral pneumonias, mainly influenza [6]. However, data on the prevalence of early bacterial co-infection in severe SARS-CoV-2 pneumonia remain limited and controversial, ranging from 8% to 30% [7–10], although most series suggest a low prevalence averaging 10% [11]. Guidelines recommend using empiric antimicrobial therapy in mechanically ventilated patients and respiratory failure, with daily assessment for de-escalation and re-evaluation of the duration of therapy based on the microbiological results and the patients' clinical status [12,13]. However, even in the context of a confirmed viral pneumonia, physicians may be reluctant to withdraw antibiotics in patients who are critically ill, unless accurate microbiological diagnostic tests are available. Biomarkers, such as procalcitonin (PCT), have been suggested to better indicate the disease severity than bacterial co-infection during viral respiratory infection [14], although follow-up measurements may help streamline therapy. To avoid unnecessary and prolonged antimicrobial therapy, accurate and rapid molecular diagnostic testing, such as respiratory multiplex PCR (mPCR) with enlarged panels, together with daily PCT measurements, could be combined in a personalized antibiotic strategy for a more rational use of antibiotics [15–17]. We thus planned the MULTICOV (use of a respiratory MULTIplex PCR and procalcitonin to reduce antibiotic exposure in patients with severe confirmed COVID-19 pneumonia) study to test the hypothesis that an algorithm combining mPCR and daily PCT measurements might reduce antibiotics exposure in patients with severe confirmed SARS-CoV-2 pneumonia, with higher clinical efficacy and safety than routine practice.

Methods

Study design

The MULTICOV trial was a multicentre, parallel-group, open-label, randomized controlled trial, conducted in 13 French intensive care units (ICUs) of university-teaching hospitals. Patients were assigned to the intervention group (mPCR/PCT algorithm strategy) or the control group (conventional strategy).

Participants

Eligible patients were critically ill adult patients (aged ≥18 years) admitted to the ICU with a confirmed SARS-Cov2 pneumonia. Please see supplemental material for the eligibility and non-eligibility criteria. The study protocol was approved by the French ethical committee (Comité de Protection des Personnes Sud-Méditerranée V; April 9, 2020) and health authorities (Agence Nationale de Sécurité du Médicament et des Produits de Santé), and written informed consent was obtained from patients or next of kin. This trial is registered with ClinicalTrials.gov, NCT04334850 and EUDRACT, 2020-001324-33.

Randomization and masking

Patients were randomly assigned in a 1:1 ratio to the mPCR/PCT algorithm strategy or to the conventional strategy as soon as possible after the ICU admission, using a secure web-based response system available in each study centre (CleanWEB, Telemedicine Technologies, S.A.S). Randomization was stratified on centre. The block randomization list was established by an independent statistician. Investigators had no access to the randomization list and were blinded to the size of blocks.

Interventions

At inclusion, routine laboratory tests (including PCT blood concentration) as well as microbiological investigations (performed within 24 hours before or after inclusion), including blood cultures, *Streptococcus pneumoniae* and *Legionella pneumophila* urinary antigen assays, and a respiratory tract secretions sample for Gram stain examination and cultures, were recommended in all patients. In the conventional strategy, antibiotics tailoring and discontinuation remained at the discretion of the physicians, according to the microbiological documentation obtained with conventional tests.

In the interventional strategy, an additional broad panel respiratory PCR (Supplementary material) was performed on tracheal aspirate, broncho-alveolar lavage or sputum, using the BioFire FilmArray Pneumonia/Pneumonia plus (PNplus) Panels (BioFire Diagnostics, LLC) [18]. An algorithm of early antibiotics adaptation and discontinuation, adapted from the study of Bouadma et al. [19], was used, according to the PCT value and kinetics, for a recommended maximum duration of 7 days. This algorithm was applied as soon as possible after randomization, and repeated daily until day 7 (D7) (Fig. S1).

In both arms, antimicrobial stewardship was encouraged, with a recommended maximal duration of 7 days for antibiotic therapy, unless otherwise microbiologically indicated (Table S1).

Given the expected recruitment, the study was initially planned for a 6-month duration, including a 3-month follow-up period. Due to the resolution of the first wave of the pandemic in France by the end of May 2020, the study was extended for 3 additional months to allow enrolling the planned number of patients.

Outcomes

The primary end point was the number of antibiotic-free days for all reasons at D28 after randomization (D0). The secondary end points included cumulative antibiotics duration and number of days of antibiotics exposure for all reasons at D28 or death, incidence rates of bacterial superinfections (defined as episodes of infection occurring after at least 48 hours of hospitalization in the ICU, separating clinically suspected and microbiologically documented episodes) at D28, incidence rates of colonization/infection with multidrug resistant bacteria and *Clostridioides difficile*

infections at D28, lengths of ICU and hospital stay, mortality rates at D28 and D90, and quality of life at D90, using a quality-of-life questionnaire (EQ5D5L) [20].

Statistical analysis

Based on the preliminary data from Italy available at the time of study planning, we estimated the number of patients to include, with 97 patients in each group, i.e. 194 patients in total (Supplementary material).

The primary outcome was compared in the intent-to-treat population (ITT), defined as all randomized patients with written informed consent (Wilcoxon rank-sum test). For patients with missing outcome data at D28 or who died before D28, simple imputation was performed, considering the number of antibiotic-free days as zero in both groups. Sensitivity analyses were performed on the per-protocol population (PP), which comprised randomized patients without major protocol violations/deviations: missing eligibility criteria, non-adherence to the randomized strategy or to the defined algorithm, or missing data for the primary end point (Supplementary material for additional details on these measurements). Outcome adjudicators were blinded to the treatment arm.

Results

From 20 April 2020 to 23 November 2020, 194 patients with a severe confirmed SARS-CoV-2 pneumonia were included and randomized in the 13 participating centres. Three of them had no written consent available (all in the intervention group). Among the 191 patients eligible for analyses, 93 patients were allocated to the interventional strategy and 98 patients to the conventional strategy (Fig. 1).

Characteristics of patients at enrolment

The patients were enrolled after a median interquartile range of 2.0 (0.5; 5.0) days from diagnosis of SARS-CoV2 infection, and 1.0 (0.0; 2.0) day of hospitalization in wards. Patients' characteristics at baseline did not differ between groups (Table 1). Prior or ongoing

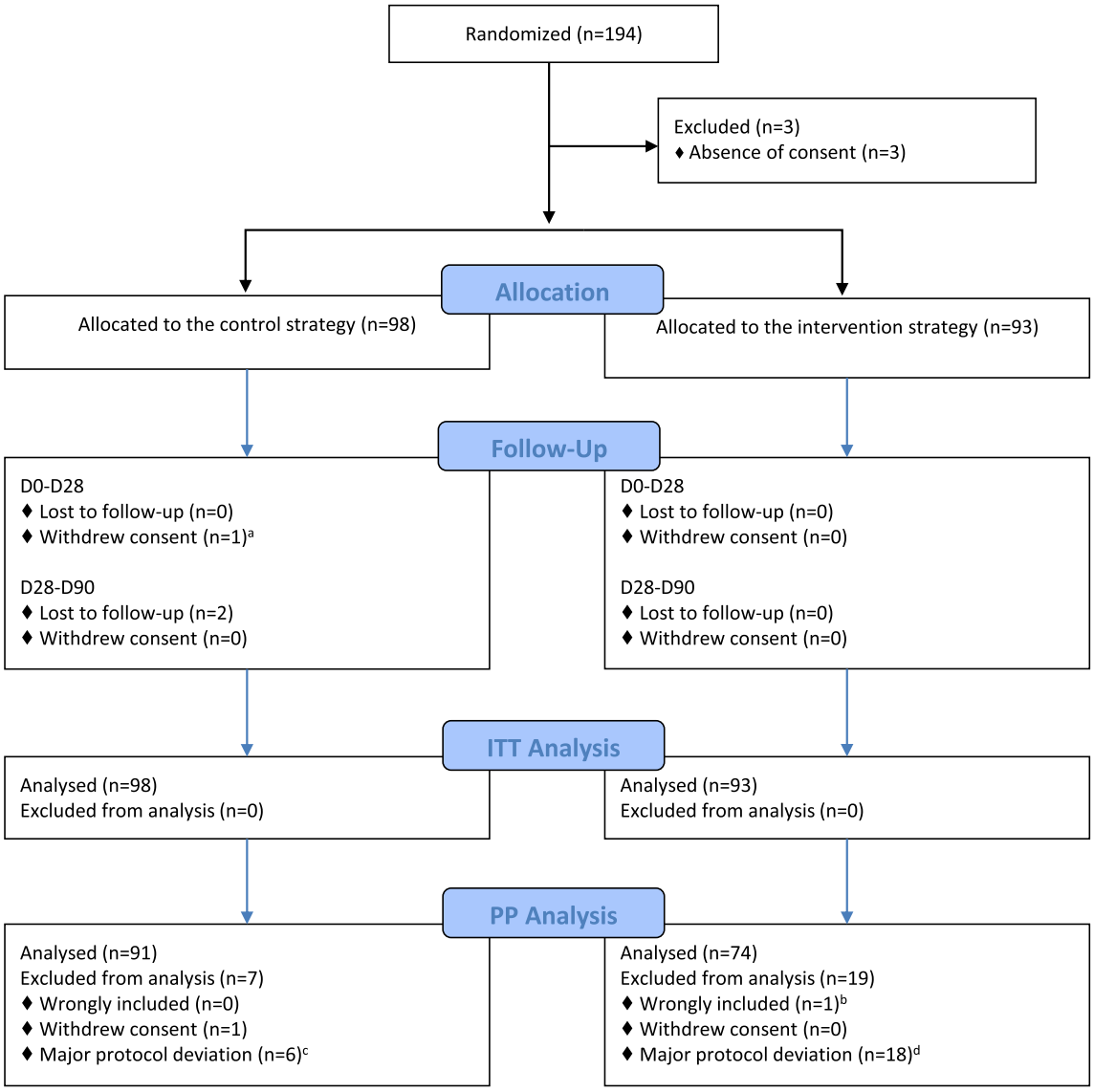

Fig. 1. Flow diagram of the study population in the MULTICOV trial. [a]Consent withdrawal at day 6 after randomization. [b]Non–confirmed SARS-CoV-2 pneumonia. [c]mPCR performed within 24 hours after randomization ($n = 1$) or before randomization ($n = 5$). [d]mPCR not performed ($n = 3$) or not valid ($n = 1$), or non-adherence to the mPCR/PCT algorithm ($n = 14$). mPCR, multiplex PCR; PCT, procalcitonin.

Table 1
Baseline characteristics of the patients enrolled in the MultiCov trial, according to the allocated strategy

	Overall population, ($N = 191$)	Interventional strategy, ($n = 93$)	Conventional strategy, ($n = 98$)
Demographics and comorbid conditions			
Age, (y)	64.4 (13.0)	65.0 (12.1)	63.8 (13.8)
Gender, male	135 (70.7)	64 (68.8)	71 (72.4)
Body mass index, (kg/m^2)[a]	30.3 (6.2)	31.0 (6.5)	29.6 (5.9)
At least one comorbid conditions	139 (72.8)	62 (66.7)	77 (78.6)
Arterial hypertension	96 (50.3)	45 (48.4)	51 (52.0)
Diabetes mellitus	62 (32.5)	29 (31.2)	33 (33.7)
Cardiovascular disease	108 (56.5)	51 (54.8)	57 (58.2)
Cerebro-vascular disease	7 (3.7)	2 (2.2)	5 (5.1)
Chronic respiratory disease	43 (22.5)	19 (20.4)	24 (24.5)
Chronic renal failure	20 (10.5)	10 (10.8)	10 (10.2)
Immunocompromised status[b]	6 (3.2)	2 (2.2)	5 (5.2)
Before ICU admission			
Time from diagnosis of SARS-CoV-2 infection to ICU admission (d)[c]	2.0 (0.0; 5.0)	2.0 (0.0; 5.0)	2.0 (0.0; 6.0)
Time from hospitalization to ICU admission (d)	1.0 (0.0; 2.0)	1.0 (0.0; 2.0)	1.0 (0.0; 2.0)
Hospitalization in the wards (≥48h)	68 (35.6)	37 (39.8)	31 (31.6)
Antibiotics received	158 (82.7)	80 (86.0)	78 (79.6)
Third-generation cephalosporin	123 (64.4)	64 (68.8)	59 (60.2)
Macrolide	101 (52.9)	54 (58.1)	47 (48.0)
Others	51 (26.7)	22 (23.7)	29 (29.6)
Specific medications[d]	119 (62.3)	62 (66.7)	57 (58.2)
NSAIDs	6 (3.1)	4 (4.3)	2 (2.0)
Steroids	117 (61.3)	62 (66.7)	55 (56.1)
Antiviral agents	5 (2.6)	2 (2.2)	3 (3.1)
Immune-based agents	2 (1.0)	1 (1.1)	1 (1.0)
On ICU admission			
Reason(s) for ICU admission			
Acute respiratory failure	190 (99.5)	93 (100)	97 (99.0)
Sepsis/shock	0	0	0
Acute renal failure	0	0	0
Acute neurological failure	0	0	0
Other[e]	1 (0.5)	0	1 (1.0)
Severity scores			
Baseline SOFA score[f]	4.0 (3.0; 7.0)	4.0 (3.0; 9.0)	4.0 (3.0; 7.0)
Baseline SAPS II	39.7 (16.3)	40.9 (16.7)	38.6 (15.9)
Vital organ support			
Non-invasive mechanical ventilation[b]	17 (8.9)	9 (9.8)	8 (8.2)
High flow nasal oxygen[b]	87 (45.8)	38 (41.3)	49 (50.0)
Invasive mechanical ventilation[b]	52 (27.4)	29 (31.5)	23 (23.5)
Vasopressor support[g]	32 (17.1)	19 (21.1)	13 (13.4)
Initial laboratory examinations			
PaO2/FiO2, (mmHg)[n]	121.7 (81.0; 178.0)	120.0 (80.0; 186.3)	124.5 (82.8; 178.0)
Lactates, mmol/L [i]	1.5 (0.6)	1.5 (0.5)	1.5 (0.6)
White blood cell count, (×109/L) [j]	9.2 (4.6)	9.1 (4.4)	9.3 (4.9)
Absolute lymphocyte count, (×109/L)[k]	0.7 (0.5; 1.0)	0.6 (0.5; 1.0)	0.7 (0.5; 1.0)
Platelets count, (×109/L) [l]	246.4 (95.7)	244.4 (99.8)	248.3 (92.2)
C-reactive protein, (mg/L)[m]	0.3 (0.1; 120.9)	0.4 (0.1; 114.0)	0.3 (0.1; 123.0)
Procalcitonin, (µg/L) [n]	0.3 (0.1; 0.8)	0.3 (0.1; 1.1)	0.3 (0.1; 0.6)
Fibrinogen, (g/L)[o]	6.7 (1.5)	6.8 (1.4)	6.6 (1.6)

Data are *n* (%), mean (SD) or median (IQR, 25; 75%).
ICU, intensive care unit; NSAIDs, non-steroidal anti-inflammatory drugs; PaO2/FiO2, ratio of partial pressure of arterial oxygen (PaO2) to the fraction of inspired oxygen (FiO2); SAPSII, Simplified Acute Physiology Score; SOFA, Sequential Organ Failure Assessment.

[a] Missing value in intervention/control group: 2/5.
[b] Missing value in intervention/control group: 0/1.
[c] Missing value in intervention/control group: 1/0.
[d] See Table 2 for details.
[e] Malaise.
[f] Missing value in intervention/control group: 3/6.
[g] Missing value in intervention/control group: 3/1.
[h] Missing value in intervention/control group: 8/6.
[i] Missing value in intervention/control group: 11/8.
[j] Missing value in intervention/control group: 4/3.
[k] Missing value in intervention/control group: 21/18.
[l] Missing value in intervention/control group: 6/6.
[m] Missing value in intervention/control group: 15/26.
[n] First sample obtained within 24 hours of inclusion. Number of missing value in intervention/control group: 2/7. All but two patients had PCT measurement obtained within 24 hours of inclusion in the intervention group. These two patients had positive microbiological results, and the algorithm was applied at D2.
[o] Missing value in intervention/control group: 12/20.

Table 2
Main co-interventions

Co-intervention	Overall population, ($N = 191$)	Interventional strategy, ($n = 93$)	Conventional strategy, ($n = 98$)
Before inclusion (within the wk preceding ICU referral)			
At least one antiviral agent	5 (2.6)	2 (2.2)	3 (3.1)
Remdesivir	3 (1.6)	1 (1.1)	2 (2.0)
Other antiviral agents	2 (1.0)	1 (1.1)	1 (1.0)
Immune-based agent			
Steroids	117 (61.3)	62 (66.7)	55 (56.1)
Interleukin 6 inhibitors	1 (0.5)	1 (1.1)	0 (0)
Other immune-based agents	1 (0.5)	0 (0)	1 (1.0)
During ICU stay (between D1 and D14)			
At least one antiviral agent[a]	19 (10.2)	11 (12.4)	8 (8.2)
Chloroquine/hydrocholoroquine[a]	1 (0.5)	0 (0)	1 (1.0)
Remdesivir[a]	10 (5.4)	7 (7.9)	3 (3.1)
Other antiviral agents[a]	8 (4.3)	4 (4.5)	4 (4.1)
Immune-based agent			
Steroids[b]	178 (94.2)	87 (94.6)	91 (93.8)
Other immune-based agents[a]	3 (1.6)	1 (1.1)	2 (2.1)
Therapeutic anticoagulation[c]	80 (44.2)	34 (39.5)	46 (48.4)

Data are *n* (%). No Covid-directed drug other than those listed were administered before inclusion or during the ICU stay.
D1, day 1; D14, day 14.
[a] Missing values in intervention/control group: 4/1.
[b] Missing values in intervention/control group: 1/1.
[c] Missing values in intervention/control group: 7/3.

antibiotics were administered to most patients (158/191; 83%), combining mainly third-generation cephalosporins and macrolides. Steroids and/or antiviral agents had been administered during the week preceding ICU referral in 117/191 (61%) patients and 5/191 (2.6%) patients, respectively (Table 2).

Initial microbiological workup, early bacterial co-infection and empirical antibiotics

Empirical antibiotics were administered in the ICU to 180/191 (94%) patients, including 89 and 91 patients in the intervention and control groups, respectively. Details of initial microbiological workup and documentation are reported Table 3. All isolates identified (except *Staphylococcus non aureus* in blood culture) were considered and treated with antibiotics. Overall, early bacterial co-infection was detected in 45/93 (48.4%) patients (intervention group) and 21/98 (21.4) patients (control group). At least one bacterial microorganism was identified using all conventional tests in 40/179 (22%) patients (22/89 [21.3] in the intervention group and 21/90 [23%] in the control group); most patients (33/40) had a monomicrobial infection. *Streptococcus spp.*, *S. aureus*, Enterobacterales. and *Pseudomonas aeruginosa* accounted for 75% (38/51) of the bacterial species identified.

In the interventional strategy, an adequate mPCR was obtained in 89/93 (96%) patients. Microorganisms were detected in 36/89 (40%) of these patients. Positive results were mainly monomicrobial (22/36). Genetic markers of antibiotic resistance were detected in 7/89 (8%), either in association with bacterial detection ($n = 6$), or isolated ($n = 1$). Altogether, *S. aureus*, *Haemophilus influenzae*, *Streptococcus species*, and *Enterobacterales* were the main potentially pathogenic bacteria detected (51/59; 86%). Respiratory viruses were detected twice in addition to SARS-Cov-2, with no bacteria–virus co-infection.

Protocol observance and strategy adherence

The observance of the interventional strategy, including adherence to the mPCR/PCT algorithm ($n = 75/93$; 81%) was fairly good (Fig. 1). However, follow-up PCT measurements were often obtained in the control group, although not recommended nor required in this group. Please see supplementary material for additional details and Fig. S2.

Primary outcome

At D28 after randomization, the median number of days free of antibiotics (whether administered for initial bacterial co-infection, other concomitant infection or bacterial superinfection) was 12.0 (0.0; 25.0) days in the interventional strategy ($n = 93$), and 14.0 (0.0; 24.0) days ($n = 91$) in the conventional strategy (difference, −2.0 (95% CI, −10.6 to 6.6); p = 0.89) (Table 4) (Figs. 2 and 3). These results were consistent in the sensitivity analyses restricted to the PP population (14.0 [0.0; 25.0] days ($n = 74$) vs. 15.0 [2.0; 24.0] days ($n = 91$); difference, −1.0 (95% CI, −10.7 to 8.7); p = 0.93), and using binomial-negative models with random effect on the centre on the ITT population (p = 0.82) and on the PP population (p = 0.93) (Table S2). However, the number of antibiotic-free days was 2-day higher at D7 in the intervention group when the algorithm was adhered to (per-protocol analysis) compared with the control group (Supplementary material for all post-hoc analyses as well as Tables S3–S6 and Figs. S3 and S4).

Secondary outcomes

At D28 or D90, there was no difference between the two strategies in the secondary outcomes (Table 4 and Fig. S5). There was no difference either in the incidence of administration of new antibiotics for a first clinical suspicion of bacterial superinfection at D28, considering the competing event of death (subdistribution hazard ratio (sHR) 1.22 [95% CI, 0.83–1.79]; p = 0.31; $n = 190$) (Fig. S6).

Exploratory analyses

No difference was found between the two groups regarding episodes of bacterial superinfection (Table S7), use of broad- and narrow-spectrum antibiotics (Table S8 and S9), and ventilator support at D28 (Table S10).

Discussion

This randomized controlled trial, testing the efficacy and safety of a strategy combining a respiratory mPCR with enlarged panel performed on lower respiratory tract secretions specimens and PCT blood measurements in patients who are critically ill with SARS-CoV-2 pneumonia, failed to show a decrease of the overall antibiotic exposure or to improve clinical outcomes at D28, as compared with routine management. However, when the algorithm was adhered to (per-protocol analysis), the number of antibiotic-free days after randomization was 2-day higher at D7 in the intervention group than in the control group.

Previous reports have suggested low rates of bacterial co-infection in hospitalized patients with SARS-CoV-2 pneumonia, although somewhat higher in patients who were critically ill [1,2,5]. In a retrospective study [11], the prevalence of bacterial co-infection identified within 48 hours after intubation, using standard culture-dependent methods, was three times lower in SARS-CoV2 (9.7%) than in influenza (33.6%) pneumonia, suggesting that most patients may not require antimicrobial treatment. In the context of severe SARS-CoV-2 viral pneumonia, antibiotics may thus have been used in excess, at least in the early stage [1,3,21]. However, small series using mPCR have reported much higher rates of bacterial co-infection of up to 40% [8,10,16], involving similar

Table 3
Initial microbiological workup and documentation

	Overall population	Interventional strategy	Conventional strategy
Conventional tests			
Patients level	*N* = 191	*N* = 93	*N* = 98
Conventional tests positive/performed and analysed,[a] number positive / total samples analysed (*n*/*Ntot*) (%)	40/179 (22.3)	19/89 (21.3)	21/90 (23.3)
Blood cultures	3/158 (1.9)	1/80 (1.3)	2/78 (2.6)
Legionella pneumophila urinary antigen test	1/124 (0.8)	0/61 (0)	1/63 (1.6)
Streptococcus pneumoniae urinary antigen test	3/93 (3.2)	1/49 (2.0)	2/44 (4.5)
At least one respiratory tract secretions sample	37/156 (23.7)	18/81 (22.2)	19/75 (25.3)
Sputum	19/101 (18.8)	11/55 (20.0)	8/46 (17.4)
Tracheal aspirate	11/62 (17.7)	4/31 (12.9)	7/31 (22.6)
Broncho-alveolar lavage	7/32 (21.9)	3/19 (15.8)	4/13 (30.8)
Tests level			
Among all conventional tests			
Total number of conventional tests performed	*n* = 580	*n* = 300	*n* = 280
Total number of conventional tests positive/performed and analysed, *n*/*Ntot* (%)	44/576 (7.6)	20/299 (6.7)	24/277 (8.7)
Time between conventional tests and inclusion, d			
mean (SD)	−0.4 (1.0)	−0.5 (1.0)	−0.3 (1.0)
median (interquartile range)	0.0 (−1.0; 0.0)	0.0 (−1.0; 0.0)	0.0 (−1.0; 0.0)
Among all respiratory tests performed			
Total number of respiratory tract samplings performed	*n* = 199	*n* = 106	*n* = 93
Total number of respiratory tract samplings positive/performed and analysed, *n*/*Ntot* (%)[a]	37/195 (19.0)	18/105 (17.1)	19/90 (21.1)
Time between respiratory tract samplings and inclusion, (d)	*n* = 199	*n* = 106	*n* = 93
mean (SD)	−0.1 (1.0)	−0.2 (0.9)	0.0 (1.0)
median (IQR)	0.0 (−1.0; 0.0)	0.0 (−1.0; 0.0)	0.0 (0.0; 0.0)
Among all non-respiratory tests performed			
Total number of non-respiratory tract samplings performed	*n* = 381	*n* = 194	*n* = 187
Total number of non-respiratory tract samplings positive/performed and analysed, *n*/*Ntot* (%)	7/381 (1.8)	2/194 (1.0)	5/187 (2.7)
Time between non-respiratory tract samplings and inclusion, (d)			
Mean (SD)	−0.5 (1.0)	−0.7 (1.0)	−0.4 (0.9)
median (IQR)	−1.0 (−1.0; 0.0)	−1.0 (−1.0; 0.0)	0.0 (−1.0; 0.0)
Bacterial microorganisms identified (all conventional tests), *n* (%)	*n* = 51	*n* = 24	*n* = 27
Streptococcus spp.	12 (23.5)	3 (12.5)	9 (33.3)
Staphylococcus aureus	7 (13.7)	3 (12.5)	4 (14.8)
Enterobacterales	13 (25.5)	9 (37.5)	4 (14.8)
Pseudomonas aeruginosa	6 (11.8)	3 (12.5)	3 (11.1)
Others[b]	13 (25.5)	6 (25.0)	7 (25.9)
mPCR			
mPCR positive/performed, n/Ntot (%)[c]		36/89 (40.4)	
Sputum		26/54 (48.1)	
Tracheal aspirate		7/21 (33.3)	
Broncho-alveolar lavage		3/13 (23.1)	
Bacterial microorganism detected, *n* (%)		*n* = 59	
Staphylococcus aureus		19 (32.2)	
Haemophilus influenzae		14 (23.7)	
Streptococcus spp.		6 (10.2)	
Enterobacterales		12 (20.3)	
Others[d]		8 (13.6)	
Viruses, *n* (%)[e]		*n* = 2	
Human Rhinovirus–Enterovirus		2 (100)	
Others		0	

[a] The results of conventional tests performed were unavailable in the interventional strategy and in the conventional strategy in four and eight patients, respectively (regarding all conventional tests), and in one and three patients (regarding sputa). Normal respiratory flora, identified in 44 (49%) patients in the interventional strategy and in 35 (39%) patients in the conventional strategy, was not considered as pathogenic.

[b] Others ($n = 13$) included coagulase-negative *Staphylococci* ($n = 6$), *L. pneumophila* ($n = 1$), *H. influenzae* ($n = 1$), *Achromobacter xylodoxidans* ($n = 1$), *Acinetobacter* sp. ($n = 1$), *Bacillus cereus* ($n = 1$), *Moraxella catarrhalis* ($n = 1$), and *Stenotrophomonas maltophilia* ($n = 1$).

[c] Three mPCR were missing and one inadequate in the interventional group. The panel included bacteria (*Streptococcus pneumoniae*, *S. aureus*, *Streptococcus agalactiae*, *Streptococcus pyogenes*, *H. influenzae*, *Escherichia coli*, *Klebsiella oxytoca*, *K. pneumonia*, *Proteus* spp, *Enterobacter cloacae–aerogenes*, *Serratia marcescens*, *P. aeruginosa*, *Acinetobacter baumannii*, *Mycoplasma pneumoniae*, *Chlamydophyla pneumoniae*, *L. pneumophila*, and *Moraxella catarrhalis*), respiratory viruses (Adenovirus, Coronavirus, Human Rhinovirus–Enterovirus, Human Metapneumovirus, Influenza A, Influenza B, Parainfluenza Virus, and Respiratory Syncitial Virus), and seven antibiotic resistance markers.

[d] Others ($n = 8$) included *P. aeruginosa* ($n = 4$), *Acinetobacter baumannii* ($n = 3$), and *L. pneumophila* ($n = 1$).

[e] No virus other than SARS-Cov2 was associated with bacteria detected.

microorganisms as those in community-acquired pneumonia (CAP). Therefore, accurate diagnostic methods appear warranted to help identify patients needing antibiotic therapy as well as avoid or withdraw unnecessary therapy in those who do not need such therapy [11,16,21].

In our study, most patients had been exposed to antibiotics before ICU referral, and received new empirical antibiotics on ICU admission, as per current guidelines [12,13]. Although a respiratory tract secretions sample was obtained within 24 hours of ICU admission in most patients, the rate of bacterial identification was twice higher using molecular than conventional testing. Similarly to previous studies [8,10,11], the main microorganisms identified in our trial were Gram-positive cocci, Enterobacterales, *P. aeruginosa*, and *H. influenzae*, with either testing.

Although mPCRs have been shown to increase the rate of microbiological diagnosis in CAP [22,23], and have been suggested to improve antibiotic stewardship [24], robust data on the therapeutic management and impact on outcomes of patients of a pathogen-guided strategy are lacking. The usefulness of a PCT-guided strategy to guide antibiotics discontinuation has also been

Table 4
Primary and secondary outcomes of patients

End points	Interventional strategy ($n = 93$)	Conventional strategy ($n = 98$)	Difference, % (95% CI)	*P*
Primary outcome at d 28[a]				
Antibiotic-free days in the ITT population, $n = 191$, median (IQR)	12.0 (0.0; 25.0), $n = 93$	14.0 (0.0; 24.0), $n = 98$	−2.0 (−10.6 to 6.6)	0.89
Antibiotic-free days in the PP population, $n = 165$, median (IQR)	14.0 (0.0; 25.0), $n = 74$	15.0 (2.0; 24.0), $n = 91$	−1.0 (−10.7 to 8.7)	0.93
Secondary outcomes at d 28				
Number of days of antibiotics exposure, median (IQR)	9.0 (4.0; 21.0), $n = 93$	8.0 (4.0; 17.0), $n = 97$	1.0 (−2.6 to 4.6)	
Cumulative antibiotics duration, median (IQR)	11.0 (5.0; 27.0), $n = 93$	10.0 (5.0; 22.0), $n = 97$	1.0 (−4.3 to 6.3)	
Patients treated with broad-spectrum antibiotics, *n* (%)	91/93 (97.8)	92/97 (94.8)	3.0 (−3.2 to 9.7)	
Patients treated with narrow-spectrum antibiotics, *n* (%)	59/93 (63.4)	52/97 (53.6)	9.8 (−4.4 to 24.0)	
Patients with clinically suspected bacterial superinfection, *n* (%)	48/93 (51.6)	47/97 (48.5)	3.2 (−11.2 to 17.5)	
Patients with microbiologically documented bacterial superinfection, *n* (%)	43/48 (89.6)	38/47 (80.9)	8.7 (−6.2 to 24.0)	
Colonization/infection with multidrug resistant bacteria or *Clostridioides difficile*, *n* (%)	9/79 (11.4)	11/79 (13.9)	−2.5 (−13.6 to 8.6)	
Patients receiving ventilatory support, *n* (%)	22/71 (31.0)	13/72 (18.1)	12.9 (−1.5 to 27.1)	
Serious adverse events, *n* (%)[b]	33/93 (35.5)	38/98 (38.8)		
Mortality rate, %	20/93 (21.5)	25/97 (25.8)	−4.3 (−16.7 to 8.1)	0.49
Secondary outcomes at d 90[c]				
Mortality rate, %	33/93 (35.5)	30/95 (31.6)	3.9 (−9.7 to 17.6)	0.57
Quality of life (EQ5D5L score), median (IQR)	0.76 (0.66; 0.89), $n = 24$	0.85 (0.50; 0.91), $n = 24$	−0.08 (−0.23 to 0.06)	
Health status (VAS 0-100)[d], median (IQR)	85 (70; 90), $n = 17$	85 (65; 100), $n = 14$	0.0 (−15.0 to 10.0)	

Abbreviations: EQ5D5L, EuroQuol 5 dimensions questionnaire; IQR, interquartile range; ITT, intention-to-treat; PP, per-protocol population; VAS, visual analogic scale.
Data are *n* (%) or median (interquartile range, 25; 75%).
[a] In the ITT population, the number of antibiotic-free days for all causes at D28 was 0 for the 45 patients who died and for one patient on premature discontinuation (see Table S2 for sensitivity analyses).
[b] Serious adverse events occurred in 71 patients, 63 of whom died (33 and 30 in the interventional and the conventional strategy groups, respectively).
[c] In the conventional strategy, 2 patients were lost to follow-up between D28 and D90. Quality of life at day 90 was assessed using a quality-of-life questionnaire (EQ5D5L).
[d] Health status (VAS 0-100) is a component of EQ5D5L.

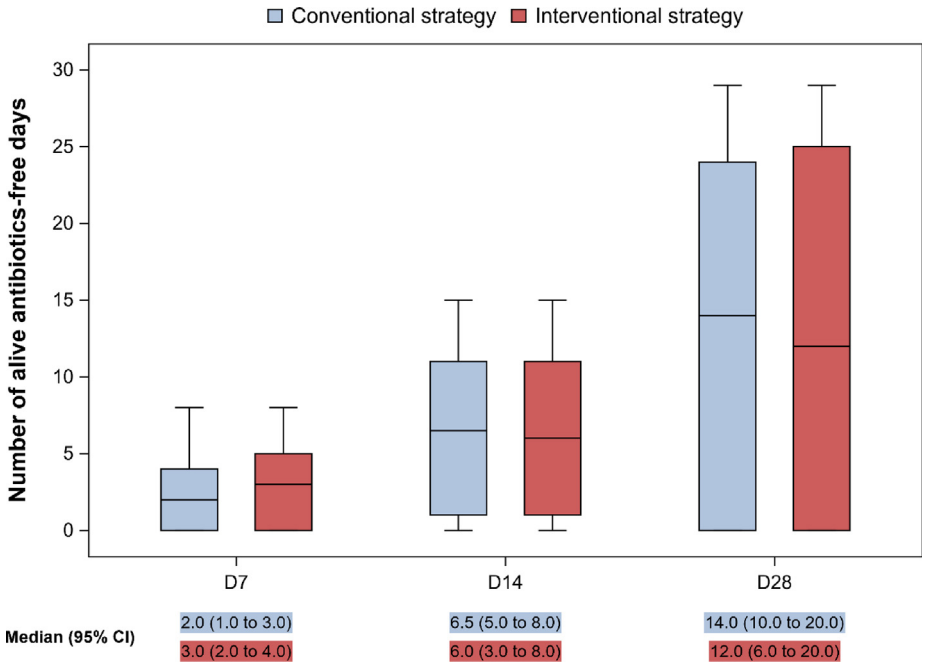

Fig. 2. Number of antibiotics-free days at D7, D14, and D28 according to the strategy. The length of the box represents the interquartile range (25th–75th percentiles); the horizontal line inside the box represents the median; and the vertical lines issuing from the box extend to the minimum and maximum values.

suggested in severe CAP [19,25,26]. In a recent randomized controlled trial conducted at two tertiary care centres in Switzerland, mPCR examination of broncho-alveolar lavage decreased the duration of inappropriate antibiotic therapy in patients admitted to the hospital with suspected Gram-negative pneumonia, as compared with conventional culture [27]. In our study, we observed a fairly good adherence to the interventional algorithm. Although antibiotics were administered at a high rate for the initial episode after randomization in the two strategies, they were discontinued earlier in the interventional strategy, despite a high rate of bacterial detection in the former.

High rates of health care and ventilator-associated pneumonia have been reported in patients who were critically ill with COVID-19 and are associated with longer duration of mechanical ventilation and length of ICU stay, as well as increased 28-day mortality [21]. In our study, episodes of bacterial superinfection were clinically suspected (and most often [85%] microbiologically documented) resulting in the administration of new antibiotics in half of

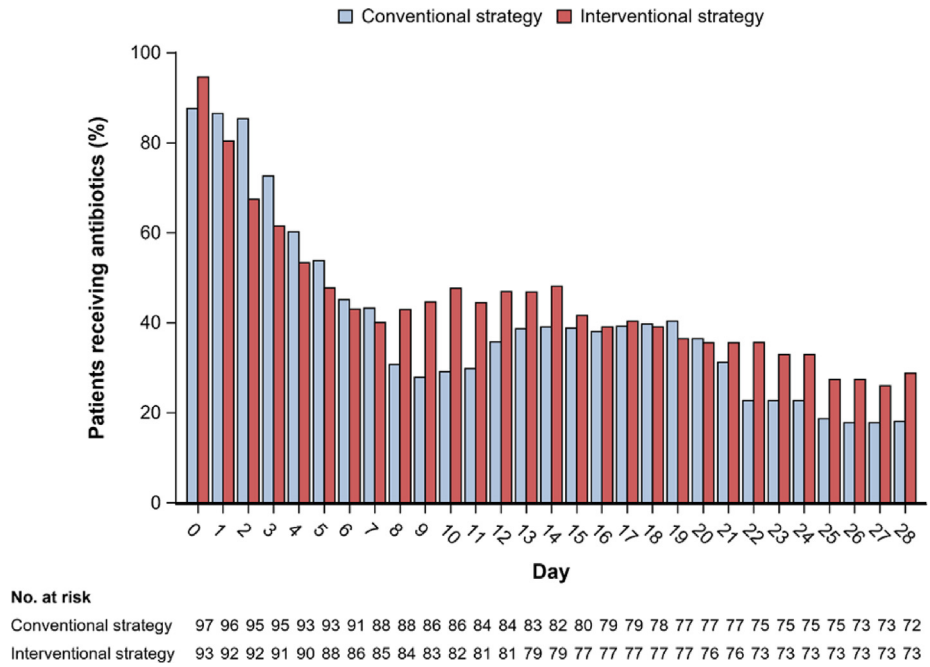

Fig. 3. Daily overall antibiotics exposure rate up to day 28 among the patients at risk, according to the strategy.

the patients in both groups, and a similar number of antibiotic-free days for all reasons at D28, questioning the overall impact of a pathogen-targeted and PCT-guided strategy on overall antibiotics exposure, as compared with routine practice [27]. Antimicrobial stewardship teams were not involved in the intervention delivery, and their involvement might have improved the intervention impact [28,29].

Limitations of this study

First, the primary end point at D28 may have been too ambitious relative to the duration of the intervention (7 days), and considering the high burden of health care-associated infections and related antimicrobial treatments in patients who are critically ill with COVID-19, which may have been underestimated at the time of the study design. Future directions should assess the therapeutic impact of rapid diagnostic testing and antimicrobial stewardship bundle at shorter time point and in selected populations of patients, such as those with severe viral pneumonia and negative testing for bacterial co-infection. Second, most patients had received antibiotics when respiratory tract samples were collected, which may have decreased the diagnostic yield of conventional tests, as compared with molecular tests, and possibly induce physicians to limit antibiotic use in the control group as compared with the intervention group where antibiotics were encouraged if mPCR was positive for bacteria. It should be noted, however, that although the molecular test includes a quantitative assessment of the pathogens detected, identification of bacterial species may not be synonymous of infection. This is particularly the case when testing sputum samples in non-intubated patients [18], which were the majority of samples obtained in our trial. Third, an unexpected high proportion of patients had repeated PCT measurements obtained in the conventional group, which may have contributed to minimize differences between groups in terms of antibiotics streamlining.

To summarize, the strategy using a mPCR- and PCT-guided strategy in patients who are critically ill with SARS-CoV-2 pneumonia failed in decreasing antibiotics exposure and clinical outcomes at D28, as compared with a conventional strategy. Despite negative results on overall antibiotics exposure and outcomes at D28, the intervention may be associated with early antibiotics savings. Further studies are needed to delineate the optimal populations and acute respiratory infections, which may benefit of such a combined strategy.

Author contributions

M.F., G.V., A.R., and T.S. conceived and designed the study. M.F., G.V., S.T., A.R., and T.S. analysed and interpreted the data. M.F., G.V., S.T., A.R., and T.S. drafted the article. All authors participated in the critical revision of the manuscript and provided final approval to submit the current version of this manuscript.

Transparency declaration

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Access to data

Consultation by the editorial board or interested researchers may be considered, subject to prior determination of the terms and conditions of such consultation and in respect for compliance with the applicable regulations.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2023.01.009.

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