# Combined use of a broad-panel respiratory multiplex PCR and procalcitonin to reduce duration of antibiotics exposure in patients with severe community-acquired pneumonia (MULTI-CAP): a multicentre, parallel-group, open-label, individual randomised trial conducted in French intensive care units

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## ABSTRACT

**Introduction** At the time of the worrying emergence and spread of bacterial resistance, reducing the selection pressure by reducing the exposure to antibiotics in patients with community-acquired pneumonia (CAP) is a public health issue. In this context, the combined use of molecular tests and biomarkers for guiding antibiotics discontinuation is attractive. Therefore, we have designed a trial comparing an integrated approach of diagnosis and treatment of severe CAP to usual care.

**Methods and analysis** The multiplex PCR and procalcitonin to reduce duration of antibiotics exposure in patients with severe-CAP (MULTI-CAP) trial is a multicentre (n=20), parallel-group, superiority, open-label, randomised trial. Patients are included if adult admitted to intensive care unit for a CAP. Diagnosis of pneumonia is based on clinical criteria and a newly appeared parenchymal infiltrate. Immunocompromised patients are excluded. Subjects are randomised (1:1 ratio) to either the intervention arm (experimental strategy) or the control arm (usual strategy). In the intervention arm, the microbiological diagnosis combines a respiratory multiplex PCR (mPCR) and conventional microbiological investigations. An algorithm of early antibiotic de-escalation or discontinuation is recommended, based on mPCR results and the procalcitonin value. In the control arm, only conventional microbiological investigations are performed and antibiotics de-escalation remains at the clinician's discretion. The primary endpoint is the number of days alive without any antibiotic from the randomisation to day 28. Based on our hypothesis of 2 days gain in the intervention arm, we aim to enrol a total of 450 patients over a 30-month period.

## Strengths and limitations of this study

- The multiplex PCR and procalcitonin to reduce duration of antibiotics exposure in patients with severe community-acquired pneumonia trial is a multicentre, parallel-group, open-label, superiority randomised trial comparing the efficacy and safety of an original management strategy to usual care in patients with community-acquired pneumonia admitted to the intensive care unit.
- The original management strategy combines a broad-panel respiratory multiplex PCR (mPCR) and procalcitonin to an algorithm of early antibiotic de-escalation or discontinuation, based on early microbiological results, including the mPCR results, and the procalcitonin value.
- The primary endpoint is the number of antibiotic-free days at day 28 following randomisation, defined as the number of days alive without any antibiotic, neither intravenous nor oral, from the randomisation to day 28.
- Strengths of the study are its randomised, multicentre design, and its innovative approach combining molecular tests and biomarkers to reduce duration of antibiotics exposure.
- The main limitation is the open-label design; loss of follow-up and access to data regarding antibiotics exposure after hospital discharge may prove challenging.

**Ethics and dissemination** The MULTI-CAP trial is conducted according to the principles of the Declaration of Helsinki, is registered in Clinical Trials and has been approved by the Committee for Protection of Persons and the National French Drug Safety Agency. Written informed consents are obtained from all the patients (or representatives). The results will be disseminated through educational institutions, submitted to peer-reviewed journals for publication and presented at medical congresses.
**Trial registration number** NCT03452826; Pre-results.

## INTRODUCTION

Community-acquired pneumonia (CAP) is a frequent and life-threatening disease. Its annual incidence is estimated about 1.6–9 cases per 1000 habitants in Europe.[1] The admission to the intensive care units (ICUs) concerns 10%–20% of inpatients with CAP, with a median duration of ICU stay of 7 days and a mortality reaching up to 50%.[2–6] Bacterial microorganisms constitute the main group of pathogens, S*treptococcus pneumoniae* being the predominant bacterium. However, the role of respiratory viruses has been highlighted in the last decade, with the routine availability of nucleic acid amplification tests. Therefore, at least four series have reported results from a wide use of multiplex PCR (mPCR) tests in ICU patients with CAP,[7–10] with a rate of viral documentation ranging from 23% to 49% of cases.

In patients with severe CAP, the recommended empirical antibiotic therapy is a combination of broad-spectrum intravenous therapies, targeting *S. pneumoniae, Staphylococcus aureus,* Enterobacterales, *Legionella* sp and other atypical micro-organisms.[11–13] Antibiotic therapy has to be reassessed after 48–72 hours of therapy.[11 13 14] In case of microbiological documentation, spectrum should be narrowed. This targeting is promoted by scientific societies[11 15] and is justified by ecological and economic considerations.[13 16 17] However, antibiotic de-escalation is only occasionally performed by clinicians in hospitalised patients with CAP.[18–22] Reasons are many, inherent to beliefs and convictions of clinicians, and to logistical and organisational constraints.[23] Moreover, a beneficial impact of antibiotic de-escalation has not been clearly established in severe CAP.[18 24 25] In terms of treatment duration, antibiotic therapy in CAP inpatients should not be administered for more than 8 days,[11] and even less,[15 26] except for cases with documented difficult-to-eradicate bacteria such as *Pseudomonas aeruginosa* and *S. aureus* and complicated, that is, with excavation or pleural empyema. This duration might be safely shortened to 5 days when clinical response to the treatment is favourable.[15 26] However, series of inpatients with CAP have reported a median duration of antibiotic treatment of more than 10 days.[27 28]

At the time of the worrying emergence and spread of bacterial resistance, reducing the selection pressure in patients with CAP should be a major public health issue. One attractive area of improvement would be to reduce exposure to antibiotics. In this context, the use of molecular tests that may improve aetiological diagnosis and guide treatment is attractive. Recently, broad-panel respiratory mPCRs have been developed, which test a large panel of CAP pathogens including bacteria and viruses. This molecular approach of the overall microbiological diagnosis has been explored in addition to the conventional investigations in patients with lower respiratory tract infections, with promising results in terms of antibiotic saving.[29–32]

Another way for reducing antibiotic exposure is to use procalcitonin, an interesting biomarker for the aetiological diagnosis of CAP. Procalcitonin has been used to guide antibiotics initiation and/or discontinuation in lower respiratory tract infections,[33 34] in addition to microbiological investigations and clinical judgement.[35 36] Specifically, its performance to discriminate patients with and without bacterial coinfection during viral pneumonia such as Influenza is attractive.[37–41] To date, only one trial has assessed the therapeutic impact of a proactive diagnostic strategy combining a respiratory mPCR (17 viruses and three intracellular bacteria) and the procalcitonin measurement. This single-centre randomised controlled trial included 300 inpatients with non-pneumonic lower respiratory tract infections. In the intervention arm, procalcitonin measurement and mPCR were performed, and an usual procalcitonin-guided algorithm of antibiotics discontinuation was proposed to clinicians. The primary endpoint (total duration of antibiotic therapy) did not differ between the two groups.[42]

Combining a respiratory broad-panel mPCR and procalcitonin could be an innovative approach for lower the overall antibiotics exposure. Indeed, with increasing the sensitivity of the microbial diagnosis, antibiotic de-escalation should be facilitated; with better identifying patients without bacterial pneumonia, antibiotics discontinuation should be also accelerated. Antibiotic saving may reduce the selection pressure, the incidence of colonisation with multidrug-resistant or highly resistant bacteria and the incidence of ICU-acquired superinfections. It may result in a lower use of broad-spectrum antibiotics, a lower morbidity and a subsequent lower overall cost of hospital care.

We, thus, designed a trial to compare two diagnostic and therapeutic management strategies of severe CAP. In the experimental strategy arm, the microbiological diagnosis combines a broad-panel respiratory mPCR (FilmArray *Pneumonia Panel Plus (FA-PPP),* BioFire Biomérieux) with conventional microbiological investigations. An algorithm of early antibiotic de-escalation or discontinuation is recommended, based on early microbiological results, including the mPCR results, and the procalcitonin value. In the usual strategy arm, only conventional microbiological investigations are performed and antibiotics de-escalation remains at the clinician's discretion.

### Objective

To assess the effectiveness and safety of an original management strategy combining a broad-panel respiratory mPCR and an algorithm of early antibiotic

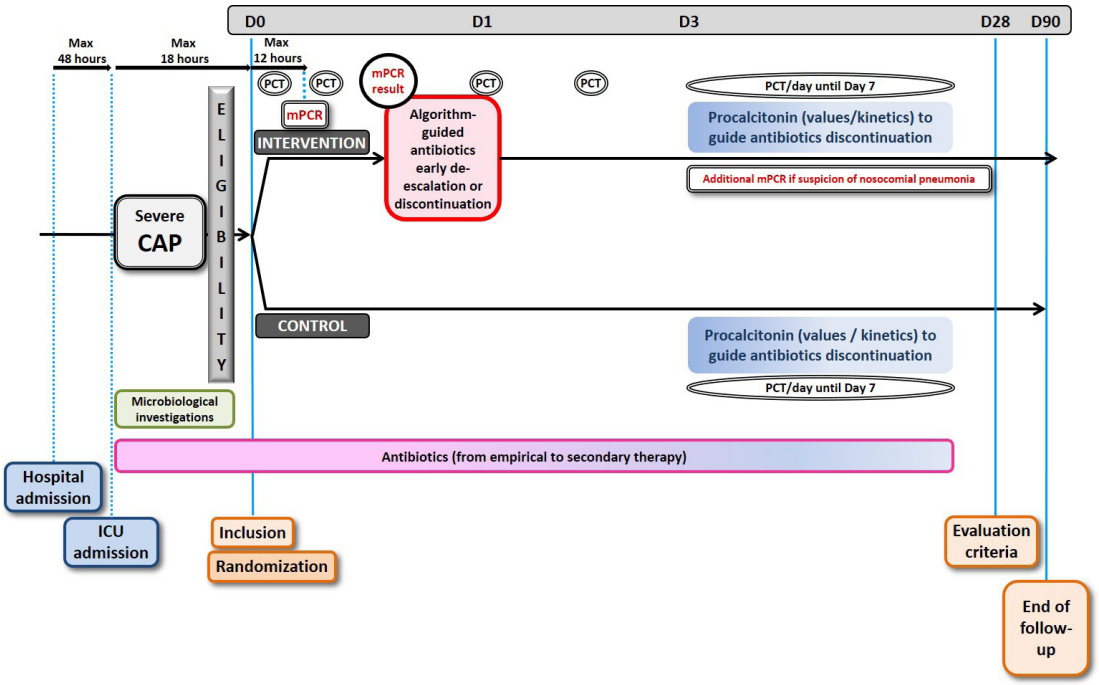


**Figure 1** Trial design. In the intervention arm, before the end of day 1, clinicians have to consider all the early microbiological results (mPCR FA-PPP, urine antigen assays, blood cultures and Gram stain examination of respiratory tract sample) and procalcitonin before the end of day 1, and subsequently to apply an algorithm of early antibiotics discontinuation or de-escalation (red square). This algorithm is described in figure 2. In both arms, at day 3 and day after day until day 7, clinicians are encouraged to consider antibiotic discontinuation, based on procalcitonin values and kinetics. CAP, community-acquired pneumonia; FA-PPP, FilmArray Pneumonia Panel Plus; ICU, intensive care unit; mPCR, multiplex PCR.

de-escalation or discontinuation, compared with usual care, in ICU patients with CAP.

## METHODS AND ANALYSIS

### Trial design

The multiplex PCR and procalcitonin to reduce duration of antibiotics exposure in patients with severe CAP (MULTI-CAP) trial is a national multicentre (N=20), parallel-group, open-label, superiority randomised controlled trial comparing in ICU patients with CAP the efficacy and safety of a management strategy combining a broad-panel respiratory mPCR and an algorithm of early antibiotic de-escalation or discontinuation to usual care. The trial design is depicted in figure 1. The total study duration is 33 months, with 450 patients to be included over 30 months.

### Patients

Patients are included if adult (≥18 years) admitted to ICU for a CAP. Patients can be included only once. Diagnosis of pneumonia is based on the following criteria: (1) two clinical criteria among temperature >37.8°C, respiratory rate >25/min, chest pain, cough, expectoration, localised crackles with or without signs of pleural effusion, pulse oximetry less than 92% while breathing room air and (2) a newly appeared parenchymal infiltrate, assessed by clinicians on chest X-ray and/or CT scan. Pneumonia is considered as community-acquired if the time between hospital admission and ICU referral is below or equal to 48 hours. No minimal score of severity (ie, Pneumonia Severity Index or CURB (Confusion, Urea, Respiratory rate, Blood pressure) score) is required; pneumonia is considered severe per se, since the patient requires intensive care. Exclusion criteria included pregnancy, congenital immunodeficiency, HIV infection with CD4 lymphocyte count below 200/µL or unknown in the last year, haematologic malignancy, neutropenia (<1000 leucocytes/µL or <500 neutrophils/µL) within the previous 30 days, immunosuppressive drugs within the previous 30 days (including anticancer chemotherapy and post-transplantation therapies), corticosteroids above or equal to 20 mg/d of prednisone for more than 14 days, COPD with previous history of colonisation/infection with *P. aeruginosa*, tracheostomy and cystic fibrosis.

### Randomisation

Eligible ICU patients (or their next of kin depending of the patient's situation) are informed about the trial by clinician. Once written informed consent has been given, eligible patients are randomised using a Web-based system (Cleanweb, Telemedecine Technologies, S.A.S.) and assigned either to control or to intervention arm in 1:1 ratio. Randomisation has to be performed before the 18th hour following ICU admission. Balanced-block randomisation is computer generated and stratified on participating site. Different widths of random permutation blocks were used and were not communicated to the sites.

### Standard of care

The usual strategy (control arm) is based on the standard of care for CAP, in accordance with international guidelines.[11 14 15] Conventional microbiological investigations are performed as soon as possible after ICU admission, including blood cultures, *S. pneumoniae* and *L. pneumophila* urine antigen assays, and a respiratory tract sample for Gram stain examination and 2-day quantitative culture.[11 14 15] The respiratory tract sample may be non-invasive (sputum) or invasive (bronchoalveolar lavage, protected distal sample or tracheal aspirate, under fiberoptic guidance or blindly), at the clinician's discretion. *L. pneumophila* urine antigen assay may be repeated after 24 hours in case of high clinical suspicion. Additional microbiological samples may be collected, that is, pleural fluid or cerebrospinal fluid, at the clinician's discretion. During the epidemic Influenza season, a respiratory tract sample (either proximal, nasopharyngeal swab, or distal) for influenza PCR (simplex PCR) is recommended. In case of a clinical suspicion of *Chlamydia pneumoniae* and/or *Mycoplasma pneumoniae*, antibody blood testing combined with PCR (simplex PCR) on a distal respiratory tract sample is encouraged.[11 14 15] All these microbiological samples will be analysed in the routine microbiology laboratory of each centre, and their results communicated to the clinicians as soon as possible, as per usual care.

All the biological investigations are performed at the clinician's discretion, except the dosage of plasma concentration of procalcitonin at inclusion, 12 hours after inclusion, then daily from day 3 to day 7. ICU physicians are encouraged to perform a chest X-ray at inclusion. Chest CT scan may be performed at the clinician's discretion, as per usual care.

Patients may have been treated with antibiotics before ICU referral, for example, in the emergency room, given the severity of pneumonia. Otherwise, antibiotics have to be started as soon as possible after ICU admission. The recommended empirical antibiotic therapy is an intravenous combination of a third-generation cephalosporin (ceftriaxone or cefotaxime) with a macrolide or an antipneumococcal fluoroquinolone, except for patients with risk factors for *P. aeruginosa* and/or methicillin-resistant *S. aureus*, in accordance with guidelines.[11 14 15] Oseltamivir is considered during the Influenza epidemic season. Anyhow, the final decision for the choice of antimicrobials (drugs and dose regimen) is at the discretion of the ICU physicians. The initial antibiotic regimen is maintained during the first 72 hours after inclusion/randomisation, unless other microbiological indication or if a microbiological documentation is early obtained. At day 3, and day after day until day 7, clinicians are encouraged to consider antibiotic discontinuation, based on procalcitonin values and kinetics as previously described[27] (discontinuation strongly encouraged if procalcitonin <0.25 µg/L; discontinuation encouraged if procalcitonin ≥0.25 µg/L and <0.5 or decrease by ≥80% from peak concentration; continuation encouraged if procalcitonin ≥0.5 µg/L and decrease by <80% from peak concentration; continuation strongly encouraged if procalcitonin ≥1 µg/L). Regardless of the procalcitonin values and kinetics, the recommended maximal duration of antibiotics is 7 days, unless otherwise indicated (10–14 days for *S. aureus*, 14 days for *P. aeruginosa*, *Legionella* sp and atypical bacteria). When pneumonia is documented, clinicians are encouraged to narrow the spectrum of antibiotics, based on antibiotic sensitivity test, as followed: amoxicillin for *S. pneumoniae*, antistaphylococcal penicillin for *S. aureus*, antipseudomonal β-lactam plus either antipseudomonal fluoroquinolone or amikacin for *P. aeruginosa*, levofloxacin plus rifampicin for *L. pneumophila*, macrolide for other atypical bacteria, β-lactam plus β-lactamase inhibitor for enterobacterales, β-lactam±β-lactamase inhibitor for *Haemophilus influenzae*. Oral therapy switch is encouraged when treatment response is favourable, according to Halm *et al*.[43] The final decision for the management of antimicrobials (drugs, dose regimen, way of administration, duration) remains at the discretion of the clinicians.

### Intervention

In the intervention arm (experimental strategy), in addition to conventional microbiological investigations, a respiratory tract sample (either invasive (bronchoalveolar lavage fluid or tracheal aspirate) or non-invasive (sputum)) is collected as soon as possible (in maximum 12 hours after randomisation). The sample is transported to the routine microbiology laboratory of each centre and the respiratory broad-panel mPCR *FA-PPP* is performed.

Before the end of day 1, clinicians have to consider all the early microbiological results (mPCR *FA-PPP*, urine antigen assays, blood cultures and Gram stain examination of respiratory tract sample) and procalcitonin, and subsequently to apply an algorithm of early antibiotics discontinuation or de-escalation (figure 2). Briefly, discontinuation is encouraged in case of no bacterial documentation and a procalcitonin <1 ng/mL; discontinuation is even strongly encouraged if a viral documentation is concurrently obtained. Otherwise, antibiotic continuation is encouraged, but with narrowing the spectrum as much as possible (de-escalation). Specifically, if no atypical bacteria (*Chlamydophila pneumoniae, M. pneumoniae, Legionella* sp) is identified, the discontinuation of macrolide (or fluoroquinolone) is strongly encouraged; if *S. pneumoniae* is identified (without another bacteria), amoxicillin should be the preferred β-lactam. Finally, in patients still receiving antibiotics, the procalcitonin (values and kinetics) is used day after day, until day 7 to guide discontinuation (see above). The adherence to the algorithm is collected prospectively from investigators as well as the reasons for overruling it.

Additionally, in case of a suspicion of nosocomial pneumonia during the first 28 days following randomisation, clinicians are encouraged to perform an additional mPCR *FA-PPP* and to consider the results of both the mPCR and the conventional bacteriological investigations to manage antibiotics. The suspicion of nosocomial pneumonia, either ventilator-associated or non-ventilator-associated, is based on usual clinical, radiological and biological data. If several episodes of suspicion of nosocomial pneumonia

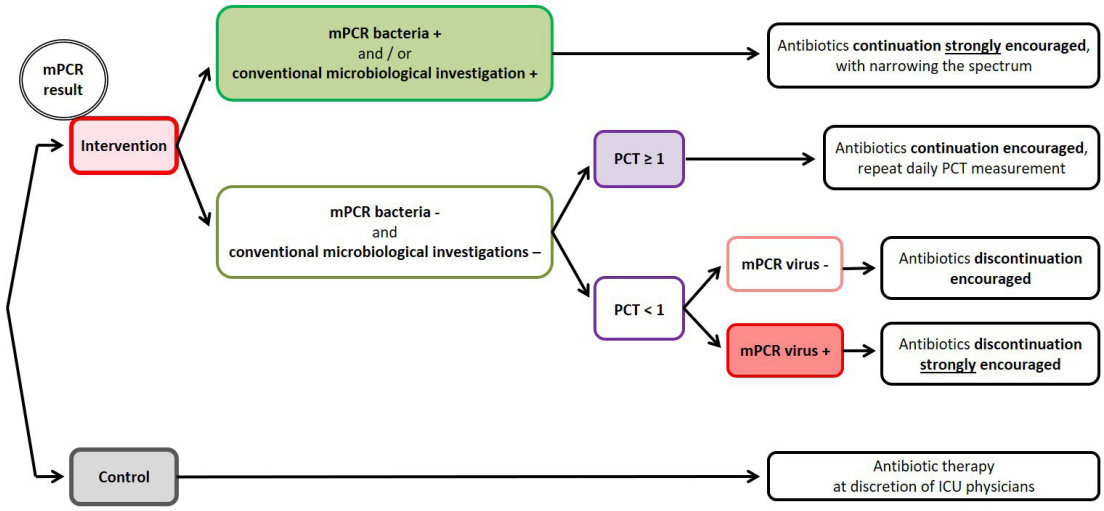


**Figure 2** Algorithm of early antibiotics de-escalation or discontinuation. The algorithm is applied in the intervention arm only (see red square, figure 1). mPCR, multiplex PCR; ICU, intensive care unit; PCT, procalcitonin.

occur, clinicians can perform several mPCR *FA-PPP* (as much as the number of episodes).

## Follow-up

Patients are followed for 90 days, with daily visits during 7 days, at discharge (or day 28 whatever comes first) and at day 90. Visits are performed by investigators. In case of hospital discharge prior to day 28, patient's vital status and antibiotic exposure after hospital discharge are collected by phone calls to patient or his/her next-of-kin or general practitioner. Similarly, information regarding hospital readmission is collected by phone at day-90.

## Endpoints

The primary endpoint is the number of antibiotic-free days at day 28, defined as the number of days alive without any antibiotic, neither parenteral nor enteral, from the randomisation to day 28. Patients who die before day 28 have a 0 value. Drugs of the therapeutic subgroup J01 of the Anatomical Therapeutic Chemical classification system are considered as antibiotics. Conversely, neither selective digestive/oropharyngeal decontamination nor topical antibiotics (eg, inhaled delivery) are considered as antibiotic therapies. Secondary endpoints, related to the effectiveness, cost-effectiveness and safety of the experimental strategy, are listed in table 1.

## Sample size

Based on the PRORATA (use of PROcalcitonin to Reduce patients' exposure to AnTibiotics in intensive cAre units) study,[27] a previous trial that explored the use of procalcitonin to reduce duration of antibiotic treatment in ICU patients with sepsis, a number of days alive without antibiotics of 11±7 days (mean±SD) is expected. A sample size of 450 patients would provide 80% power to detect a 2-day gain in the experimental strategy group considering a two-sided alpha of 5% and a non-parametric test and a 10% loss to follow-up.

## Recruitment

In the participating ICUs, the number of patients with CAP admitted to each ICU ranges from 20 to 25 per year. With respect to these numbers, we can reasonably think that the targeted sample size can be reached over the chosen study period (450 patients over 30 months in 20 centres, meaning 0.75 patient/month/centre).

## Main statistical analysis

Statistical analysis will be performed at the end of the trial after blinded review and database lock. The statistician will be blinded from the treatment allocation. Principal analysis will be performed on the intention-to-treat population defined as all patients as randomised. Baseline characteristics of patients will be described in each group. Qualitative data will be reported as frequencies and percentages; quantitative as mean and SE or as median and interquartile interval, depending on the variable distribution.

The primary endpoint will be compared using Wilcoxon-Mann-Whitney non-parametric test. Effect size and its 95% CI will be given. The period of interest will begin at the randomisation date. Principal analysis will be performed considering the worst-case scenario hypothesis in case of missing data. Sensitivity analyses will be performed considering the best-case scenario and the per-protocol population (all patients as randomised and treated without major protocol violation identified before database lock). Secondary analyses will be performed, by using generalised linear model with Poisson distribution for the number of antibiotic-free days at day 28, considering the worst-case scenario and multiple imputation for missing data as sensitivity analysis. In case of data overdispersion, generalised linear model with negative binomial distribution could be preferred. Furthermore, cumulative event curves will be assessed with the Kaplan-Meier method, and HR estimate will be calculated using stratified Cox proportional hazard model. Secondary endpoints will be analysed on available data. Analysis of secondary endpoints will be extensively detailed in the statistical plan. All tests will

**Table 1** Primary and secondary outcomes

| Outcome | Definition |
|---|---|
| Primary outcome | |
| Antibiotic-free days | The number of days alive without any antibiotic (ATC class J01) from inclusion to day 28; when the patient deceases during the first 28 days, the number is defined as zero |
| Secondary outcomes | |
| Overall mortality rate | At day 28 and day 90 |
| Antibiotics exposure | Number of defined daily dose per 100 patient-days of narrow-spectrum antibiotics (amoxicillin, oxacillin/cloxacillin, cephalosporin I and II, macrolides, anti-pneumococcal fluoroquinolones, rifampicin, clindamycin, trimethoprim-sulfamethoxazole) and broad-spectrum (others) |
| Antibiotics duration | Number of days with antibiotics from inclusion to day 28 |
| Respiratory superinfections | Incidence rates of microbiologically documented bacterial respiratory superinfections form inclusion to day 28 |
| Resistant pathogens | Incidence rates of colonisation/infection with multidrug-resistant bacteria and *Clostridioides difficile* infections form inclusion to day 28 |
| Relapse of pneumonia | Incidence rate of relapse (same pathogen) from inclusion to day 28 |
| Stay duration | Duration of ICU and hospital stay |
| Quality of life | Quality of life at day 90, using the EQ5D questionnaire |
| Performance of mPCR | Sensitivity, specificity and likelihood ratios of the broad-panel mPCR Film Array for the diagnosis of pneumonia, taking the conventional microbiological tests as reference |

ATC class J01 refers to subgroup J01 of the ATC classification system.
According to the Center for Disease Control and Prevention, a multidrug-resistant bacterium is an isolate that is resistant to at least one antibiotic in three or more drug classes.
Relapse of pneumonia is defined as a new episode of pneumonia, after an initial clinically significant improvement, documented to the same pathogen, from inclusion to day 28.
The performance of the mPCR will be assessed only for the bacterial targets of the panel.
EQ-5D refers to the standardized non-disease specific instrument developped by EuroQol organization. This instrument allows to describe and value health-related quality of life.
ATC, Anatomical Therapeutic Chemical; ICU, intensive care unit; mPCR, multiplex PCR.

be two sided and a p value <0.05 will indicate statistical significance. Statistical analysis will be performed using SAS V.9.4 software (SAS Institute).

## Cost-effectiveness analysis

The economic evaluation is combined with the clinical trial and explores possible combinations of costs and effectiveness results of the experimental strategy (intervention arm), as compared with the usual strategy (control arm). We follow the recommendations of the CHEERS (Consolidated Health Economic Evaluation Reporting Standards) statement for single trial-based economic evaluations.[44] The endpoint is the incremental cost-effectiveness ratio (ICER) using the composite clinical endpoint (day 90 composite of all-cause death and infection recurrence) as an effectiveness criterion. The choice of a cost-effectiveness study for the primary analysis was prompted by low expected impact of antibiotic de-escalation on the quality of life. The analysis will be conducted from the perspective of the French healthcare system (limited to the hospital and based on the entire population of patients included in the trial). Resources will be collected prospectively at the patient level. The study is planned, undertaken and will be analysed according to the intention-to-treat principle. The cost of the panel, procalcitonin and antibiotics will be estimated for each patient in both arms.

Medical care costs for the index hospitalisation and in-trial follow-up period are assessed using a combination of resource-based and event-based methods. The total costs of the initial hospital admission will be estimated from the time of admission (it is not possible to estimate the stay from the time of randomisation only) using the total length of stay and ICU length of stay and use of life support systems combined with the specific DRG (Diagnostic-Related Group) costs (not charges) extracted from the hospitals' claims database. Readmissions (up to day 90) will be included in the cost calculations, using the specific DRG costs. The ICER (difference in total day 90 costs/difference in day-90 all-cause death and infection recurrence) will be calculated in the intervention and control arms. Resource use data will be presented as means with SE of the mean despite non-normal distribution because they better represent per patient data than median values and compared using non-parametric test. Costs, day-90 death and recurrence will be presented as means with 2.5% to 97.5% bootstrapped intervals. Between-group comparisons of costs will be performed using the bootstrap t-test. A joint comparison of costs and effects will be performed by non-parametric bootstrapping with 1000 resamples. The result of the bootstrap replications will be presented on the cost-effectiveness plane to estimate the probability that the intervention is incrementally or decrementally cost-effective.

## Patients and public involvement

Patients and/or the public were not involved in the design, or conduct, or analysis or reporting plans of the MULTI-CAP trial.

## ETHICS AND DISSEMINATION

### Ethical approval and consent to participate

The MULTI-CAP trial is conducted according to the principles of the Declaration of Helsinki. The present trial is registered in Clinical Trials and has been approved by the Committee for protection of persons (CPP Ile de France V) and the National French Drug Safety Agency.

Before inclusion, written informed consent is obtained from the patient (or next-of-kin) by the study investigator. In case of a patient unable to receive information and/or to express his will, and a next-of-kin unidentified or unreachable, an emergency procedure is applied, meaning that the patient is included and the consent of the patient (or next-of-kin) is sought as soon as possible.

### Dissemination

The results of this trial will be disseminated to the participating hospitals and through educational institutions (French Society for Intensive Care, European Society for Critical care Medicine), submitted to peer-reviewed journals for publication and presented at medical meetings and congresses.

### Expected outcomes

To the best of our knowledge, the MULTI-CAP trial is the first to investigate the impact of a diagnosis and therapeutic management strategy, combining a broad-panel respiratory mPCR and the procalcitonin in patients with severe CAP. The algorithm of early antibiotics de-escalation or discontinuation should enable to use antibiotics lesser and better in patients randomised in the intervention arm. If our hypothesis is demonstrated, in terms of efficacy (diagnosis, treatment and prognosis) and cost-effectiveness, this may change practice and make this proactive diagnostic and therapeutic approach a future standard or care. The costs savings from antibiotic de-escalation may not be important compared with the total ICU costs, however, by illustrating the direct benefit to the patient in terms of antibiotic saving and morbidity/mortality such as ICU-acquired superinfections in one hand, and benefits in hospital and across the community, on the other hand, we will encourage the use of these tests through the medical community. Therefore, their use in patients with CAP might increase, with expected ecological and economic benefits for the whole community.

### Data availability statement

Deidentified individual-participant data underlying the findings described in the manuscript of the study will be available and shared on reasonable request through an approving committee. Consultation by an editorial board may be considered, subjected to prior determination of the terms and conditions of such consultation and with respect to compliance with the applicable regulations.

### Trial status

The trial protocol V.1.2 was approved on 9 July 2018; the latest protocol version is V.4.0, approved after minor changes on 7 August 2020. The first centre was opened on 27 September 2018, and the first patient was included on 4 October 2018. The end of recruitment is expected during the last semester of 2021, and patients will be followed up thereafter.

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**Collaborators** The MULTI-CAP study group includes the following collaborators: Keyvan Razazi, Jean Dellamonica, Jean-Christophe Navellou, Pierre-Francois Dequin, Pierre-Edouard Bollaert, Marc Gainnier, Julien Bohe, Eric Maury, Saad Nseir.

**Contributors** GV, MF, TS and J-FT conceived and designed the MULTI-CAP trial. LB and AR calculated the sample size and developed the statistical plan. ID-Z conceived the cost-effectiveness analysis. J-FT is the principal investigator and supervised the planning of the trial. GV drafted the manuscript. LA-L, CV, LA, KK, BM, JP, J-CR, JR, CS, BS and YT-L contributed to draft the design of the MULTI-CAP trial. All authors revised the manuscript for important intellectual content and read and approved the final version of the manuscript.

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