Impact of rapid multiplex PCR on management of antibiotic therapy in COVID-19-positive patients hospitalized in intensive care unit

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Abstract
Because the diagnosis of co/superinfection in COVID-19 patients is challenging, empirical antibiotic therapy is frequently initiated until microbiological analysis results. We evaluated the performance and the impact of the BioFire® FilmArray® Pneumonia plus Panel on 112 respiratory samples from 67 COVID-19 ICU patients suspected of co/superinfections. Globally, the sensitivity and specificity of the test were 89.3% and 99.1%, respectively. Positive tests led to antibiotic initiation or adaptation in 15% of episodes and de-escalation in 4%. When negative, 28% of episodes remained antibiotic-free (14% no initiation, 14% withdrawal). Rapid multiplex PCRs can help to improve antibiotic stewardship by administering appropriate antibiotics earlier and avoiding unnecessary prescriptions.

Keywords Superinfection · Coinfection · COVID-19 · Multiplex PCR · Antibiotic stewardship

Background
During the first wave of the SARS-CoV-2 pandemic, about 30% of hospitalized COVID-19 patients were admitted to intensive care units (ICU) for acute respiratory failure and most of them were ventilated [1]. Hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) are the most common healthcare-associated infections in ICU patients and leading causes of death [2]. COVID-19 ICU patients typically experience long stays and are widely exposed to corticosteroids and other immunosuppressive drugs resulting in an increased risk of VAP and HAP [3]. Persistent fever, high C-reactive protein and procalcitonin levels, and highly disturbed X-ray images, all associated with COVID-19, complicate the diagnosis of co/superinfections [4]. Thus, empirical treatment, which may include broad-spectrum antibiotics, is frequently introduced for 48-72 h before obtaining the results of the microbiological analyses [5]. Rapid characterization of bacteria causing infections is thus pivotal in the management of severe COVID-19 patients, and thus the appropriate use of antibiotics [6]. BioFire® FilmArray® Pneumonia plus Panel (bioMérieux, France) is a rapid multiplex PCR (mPCR), directly performed on respiratory samples, allowing detection of 18 bacteria, 9 viruses, and 7 antibiotic resistance genes within 1.5 h.

Here, we assessed the performance of the mPCR and its impact on antibiotic therapy during the COVID-19 outbreak in a single center with two ICUs.

Methods
Study design
This observational and retrospective study was performed between January 29 and April 30, 2020, in the two ICUs (medical and surgical) of Bichat-Claude Bernard University Teaching Hospital (Paris, France).
Patient selection

The mPCR was performed at physician request in the bacteriology laboratory on respiratory samples of COVID-19 patients suspected of bacterial co/superinfections. Results were transmitted immediately upon completion of the test.

Microbiological performance

Respiratory samples were analyzed using conventional microbiological methods (gold standard). Upon arrival of the sample, a direct smear examination was performed. The sample and serial dilutions (10^{-2} and 10^{-4}) were plated on Colombia agar + 5% horse blood, Chocolate agar PolyViteX, Drigalski agar, and Columbia ANC agar + 5% horse blood (bioMerieux, Marcy l’Etoile, France), and incubated at 35 ± 2 °C in aerobic, anaerobic, and 5% CO2 conditions. The number of bacteria in the original specimen was estimated by colony counts and was expressed as CFU/mL. Bacterial identification was performed using mass spectrometry (Biotyper, Bruker Daltonics, Germany). Antibiotic susceptibility testing (AST) was performed using the disc diffusion method on Mueller–Hinton media (Bio-Rad, Marnes-la-Coquette, France) from colonies isolated after primary culture, according to the recommendations of the EUCAST (www.eucast.com). ESBL in Enterobacteriales and methicillin resistance in staphylococci were determined phenotypically on AST. The carbapenemase genes were confirmed by Xpert® Carba-R (Cepheid, Sunnyvale, USA). We evaluated the performance of the mPCR compared to conventional method considering (i) all microorganisms identified in culture and (ii) microorganisms that reached microbiological thresholds (10^7 colony-forming unit/mL for sputum, 10^5 for endotracheal aspiration (ETA), 10^4 for bronchoalveolar lavages (BAL), and 10^3 for mini-BAL). When a discrepancy was observed, no further tests were performed.

Evaluation of impact on antibiotic treatment

Antibiotics were recorded at D−1, D0, D+1, and D+2 following mPCR. Antibiotic changes after mPCR results were categorized into “continuation,” “no initiation,” and “withdrawal” for negative mPCR, and into “continuation,” “initiation,” “adaptation,” “de-escalation,” and “inadequacy” for positive mPCR. We defined “adaptation” as the introduction of an effective antibiotic (based on AST) on causative bacteria that were not correctly treated before the results of the mPCR. We defined “de-escalation” as the appropriate use of a narrower-spectrum antibiotic for beta-lactam antibiotics [7]. “Inadequacy” was considered when mPCR results led to an ineffective antibiotic on causative bacteria.

Ethics

The Committee for Research Ethics in Anesthesia and Critical Care (CERAR) authorized the study (No. IRB 00010254-2020-171).

Results

Demographical characteristics

During the study period, 191 COVID-19 patients were hospitalized in both ICUs (126 in medical and 65 in surgical ICU) among whom 67 had at least one mPCR. Median age was 57 years (IQR 46-65), and 82% were males. At admission, the median SAPS II score was 34 (IQR 25-52), 52 (76%) patients had at least one comorbidity, and 58 (87%) were overweight. Sixty-four patients (96%) were under invasive mechanical ventilation. Antibiotics were administered before admission to ICU in 53 (79%) patients. The mortality rate in ICU was 57% (Table 1).

Microbiological outcomes

A total of 112 clinical samples (77 mini-BAL, 28 BAL, 4 sputa, and 3 ETA) from 67 patients were analyzed (38 patients had one mPCR, 19 had 2, and 10 had ≥3). The mPCR was performed on 8 suspected cases of community-acquired pneumonia (CAP), 16 HAP (non-ventilated patients), and 88 VAP. Median hospital and ICU stay before mPCR for suspected HAP were 6 (IQR 3-11) and 2 (2-5) days respectively, and for suspected VAP, 9 (5-12) and 7 (4-12) days.

Overall, 33% (37/112) of mPCR detected at least one bacteria resulting in a positivity rate of 1/8 (13%) in suspicion of CAP, 2/16 (13%) in HAP, and 34/88 (39%) in VAP episodes.

Isolated bacteria numbered 62 in total: 1 Haemophilus influenzae in the CAP and 12 Pseudomonas aeruginosa, 10 Staphylococcus aureus, 9 Escherichia coli, 14 Klebsiella spp., 4 Acinetobacter baumannii, and 12 others in HAP/VAP.

Only one sample was found positive for virus (adenovirus).

Globally, 43/62 bacteria were identified both by culture and by mPCR, 5 by mPCR only, and 14 (including 5 not spanned by the panel) by culture only. The 5 bacteria not included in the panel were Stenotrophomonas maltophilia (n
Morganella morganii (n = 1), and Burkholderia gladioli (n = 1). We observed a global sensitivity of 89.3% (95% CI 80.0-98.5) and a specificity of 99.1% (95% CI 98.7-99.5), a positive predictive value (PPV) of 52.1% (95% CI 38.0-66.2), and a negative predictive value (NPV) of 99.9% (95% CI 99.7-100.0) (Table S1).

When considering microorganisms included in the panel and isolated at clinical threshold, 25/48 bacteria were identified by both methods and 23/48 by mPCR only, which yielded a sensitivity of 100% (95% CI 100.0–100.0), a specificity of 98.8% (95% CI 98.4-99.3), a PPV of 52.1% (95% CI 38.0–66.2), and an NPV of 100% (95% CI 100.0–100.0) (Table 2).

No significant difference in performance was observed between the first tests and those conducted later.

The quantification of bacteria detected by culture and mPCR was concordant in only 21% (9/43) of cases, and in 72% (31/43), the mPCR resulted in higher quantification.

Regarding antibiotic resistance, the mPCR test detected 8 blaCTX-M, 1 blaNDM, 2 blaVIM, and 1 mecA/C+MRJE in agreement with the AST results. Three mPCR results were false positive: 2 blaVIM and 1 blaCTX-M which were never detected by conventional methods, despite subsequent cultures on selective media.

| Table 1 Patient characteristics | Number (%) (n = 67) | Median (IQR) |
|--------------------------------|--------------------|--------------|
| Patients                       |                    |              |
| Age (years)                    | 57 (46-65)         |              |
| Male                           | 55 (82)            |              |
| Comorbid conditions            |                    |              |
| BMI                            | 29.5 (25.7-33.2)   |              |
| Diabetes                       | 19 (28)            |              |
| Renal failure                  | 14 (21)            |              |
| Respiratory failure            | 18 (27)            |              |
| Heart failure                  | 23 (34)            |              |
| Smoking                        | 4 (6)              |              |
| Alcoholism                     | 3 (4)              |              |
| Hypertension                   | 32 (48)            |              |
| Transplants                    | 9 (13)             |              |
| Cancer                         | 2 (3)              |              |
| Ventilation                    |                    |              |
| Mechanic ventilation           | 64 (96)            |              |
| Suspicion of VAP               | 36 (54)            |              |
| Suspicion of HAP               | 24 (36)            |              |
| Severity of disease            |                    |              |
| Days of intensive care         | 19 (12-36)         |              |
| SAPS II score                  | 34 (25-52)         |              |
| Days of mechanic ventilation   | 14 (7-44)          |              |
| Deaths                         | 38 (56)            |              |
| Antibiotics before admission   | 53 (79)            |              |
| Samplings*                     |                    |              |
| BAL                            | 24 (35)            |              |
| Mini-BAL                       | 47 (69)            |              |
| Sputum                         | 4 (6)              |              |
| Tracheal aspiration            | 3 (4)              |              |
| First FilmArray                |                    |              |
| Days after hospital admission  | 7 (4-12)           |              |
| Days after admission to ICU    | 5 (2-8)            |              |
| Days after mechanical ventilation| 4 (0-8)        |              |

*Total > 100% because 34 patients have more than 1 sample
Table 2  Analytical performance of BioFire® FilmArray® Pneumonia plus Panel compared to culture, taking into account microbiological thresholds (A) and irrespective of thresholds (B). Se, sensitivity; Sp, specificity; PPV, positive predictive value; NPV, negative predictive value

| Organisms | True positive (culture = mPCR) | False positive (mPCR +/culture −) | False negative (culture +/mPCR −) | True negative (culture +/mPCR −) | Se (%) [95% CI] | Sp (%) [95% CI] | PPV (%) [95% CI] | NPV (%) [95% CI] |
|-----------|-------------------------------|-----------------------------------|-----------------------------------|---------------------------------|----------------|----------------|----------------|----------------|
| Gram −   |                               |                                   |                                   |                                 |                |                |                |                |
| Escherichia coli | 4                             | 3                                 | 0                                 | 105                             | 100.0          | 97.2           | 57.1           | 100.0          |
| Enterobacter cloacae complex | 2                             | 0                                 | 0                                 | 110                             | 100.0          | 100.0          | 100.0          | 100.0          |
| Klebsiella aerogenes | 4                             | 2                                 | 0                                 | 106                             | 100.0          | 98.1           | 66.7           | 100.0          |
| Klebsiella oxytoca | 0                             | 0                                 | 0                                 | 112                             | 100.0          | 100.0          | 100.0          | 100.0          |
| Klebsiella pneumoniae group | 2                             | 4                                 | 0                                 | 106                             | 100.0          | 96.4           | 33.3           | 100.0          |
| Proteus spp. | 0                             | 0                                 | 0                                 | 112                             | 100.0          | 100.0          | 100.0          | 100.0          |
| Serratia marcescens | 0                             | 2                                 | 0                                 | 110                             | 100.0          | 98.2           | 0.0            | 100.0          |
| Actinobacteria  | 1                             | 2                                 | 0                                 | 109                             | 100.0          | 98.2           | 33.3           | 100.0          |
|  |  |  |  |  |  |  |  |  |
| Gram +   |                               |                                   |                                   |                                 |                |                |                |                |
| Staphylococcus aureus | 5                             | 4                                 | 0                                 | 103                             | 100.0          | 96.3           | 55.6           | 100.0          |
| Streptococcus pneumoniae | 0                             | 0                                 | 0                                 | 112                             | 100.0          | 100.0          | 100.0          | 100.0          |
| Streptococcus agalactiae | 0                             | 0                                 | 0                                 | 112                             | 100.0          | 100.0          | 100.0          | 100.0          |
| Streptococcus pyogenes | 0                             | 0                                 | 0                                 | 112                             | 100.0          | 100.0          | 100.0          | 100.0          |
|  |  |  |  |  |  |  |  |  |
| Atypical  |                               |                                   |                                   |                                 |                |                |                |                |
| Chlamydia pneumoniae | 0                             | 0                                 | 0                                 | 112                             | 100.0          | 100.0          | 100.0          | 100.0          |
| Legionella pneumophila | 0                             | 0                                 | 0                                 | 112                             | 100.0          | 100.0          | 100.0          | 100.0          |
| Mycoplasma pneumoniae | 0                             | 0                                 | 0                                 | 112                             | 100.0          | 100.0          | 100.0          | 100.0          |
|  |  |  |  |  |  |  |  |  |
| Total     | 25                            | 23                                | 0                                 | 1968                            | 100.0          | 98.8           | 52.1           | 100.0          |

A/B: 20/20 [95% CI: 100.0-100.0] 98.8 [95% CI: 98.4-99.3] 52.1 [95% CI: 38.0-66.2] 100.0 [95% CI: 100.0-100.0]

B: 22/22 [95% CI: 100.0-100.0] 99.0 [95% CI: 98.4-99.3] 99.3 [95% CI: 89.7-99.3] 100.0 [95% CI: 100.0-100.0]
Impact on antibiotic therapy

In all, mPCR led to antibiotic changes in 38/112 (34%) episodes (16 withdrawals, 13 initiations, 3 adaptations, 5 de-escalations, and one change resulting in inadequacy).

Among the 8 suspicions of CAP, for which all patients were treated, the positive mPCR result led to a de-escalation and the 7 negatives to 3 antibiotic withdrawals and 4 continuations (Table 3).

Among the 104 suspicions of HAP/VAP, 36 mPCR results were positive and 68 were negative.

Of positives, 36% (13/36) had antibiotic initiation, 8% (3/36) led to antibiotic therapy adaptation, and 4 (11%) to de-escalation. In one episode, neither the pre- nor the post-mPCR antibiotic therapy was adequate because of the presence of an unexpected *Stenotrophomonas maltophilia* not spanned by the mPCR panel.

Of negatives, 24% (16/68) remained antibiotic-free and 13 (19%) led to antibiotic withdrawal. However, in 57% (39/68) episodes, antibiotics were maintained due to severe sepsis (n = 20), infection from another site (n = 9), continuation of previous treatment (n = 7), or severely immunocompromised patients (n = 3) (Table 3).

Discussion

Here, we showed that the mPCR could help in improving antibiotic therapy in COVID-19 ICU patients suspected of pneumonia superinfection, by administrating an earlier adequate antibiotic therapy and by sparing unnecessary antibiotics.

We observed that the main species identified by mPCR, in our population composed exclusively by ICU patients, were Gram-negative bacilli, especially *P. aeruginosa*, *E. coli*, and *Klebsiella* spp. which is consistent with other studies that have evaluated the same kit in ICU patients [8–10].

In our study, the mPCR provided good overall performance for bacteria, with a PPV of 85.6% which is above what has been found in previous studies (between 46.9 and 79.6%) and an NPV of 99.5% which is consistent with previous studies [10–13]. Other studies showed positive and negative percentage agreement of mPCR compared to culture between 90 and 98.4% and 96 and 97% respectively [9, 12, 14].

However, bacterial panel is not exhaustive and can miss some species causing HAP or VAP such as *M. morganii* or *S. maltophilia*. We also observed that in some cases, bacteria were detected by culture and not by mPCR, which was already described previously, since the manufacturer threshold is $10^{3.5}$ genomic copies/mL [12, 15]. On the other hand, we observed that, when the bacteria were only detected by mPCR, the patients had received antibiotics active on these germs in the
previous days, which could explain why they were not found in culture.

As in other studies, we observed good concordance for the detection of resistance genes; however, three resistances detected by the mPCR were not found phenotypically, among which two blavIM, which remain unexplained due to the very low number of Gram-negative bacilli carrying this gene, were isolated in the laboratory.

Our study is one of the first to analyze the impact of mPCR on the management of antibiotic therapy in COVID-19 patients suspected of bacterial pneumonia [16]. Only 33% of mPCR were positive, lower than in other studies, in which it ranged between 58.5 and 74.6%, confirming the difficulty of diagnosing bacterial superinfection in COVID-19 ICU patients [9, 10, 12, 14].

According to the guidelines, an antibiotic therapy should be started as soon as possible in severe patients suspected of VAP or HAP. Thus, a treatment is frequently introduced while awaiting the results of microbiological cultures and the use of mPCR could allow earlier decisions. Here, we observed that, when the mPCR was positive, an antibiotic initiation or an adaptation of the treatment was achieved in 44% of HAP/VAP. In fact, most patients were antibiotic-free before the results of mPCR. Indeed, since mPCR results were available 1.5 h after reception of the sample and immediately transmitted, intensivists could wait to introduce antibiotics in less severe patients. For the same reason, we observed only 11% de-escalation, which is lower than the 40% expected in studies simulating the impact of mPCR [8, 17]. Waiting for the results before initiating or modifying an antibiotic treatment could not have been observed in the previously published studies, as all of them were conducted by simulating an availability of the results and estimating a potential impact on an antibiotic treatment already introduced.

Many studies report overuse of antibiotics in COVID-19 patients and physicians worry about an increase in antibiotic resistance in this context [5, 18, 19]. Here, we observed that in 43% of suspected CAP with negative mPCR, the antibiotic therapy was stopped. Similarly, in suspected HAP/VAP with negative mPCR, 19% were antibiotic discontinued and 24% stayed antibiotic-free. However, despite the high NPV of the test, in half the cases, the previous antibiotic therapy, mainly carbapenems, was maintained at least for 48h. The main reason was the severe status of the patients, possibly due to lack of knowledge and confidence in the test.

As limits, our study was conducted in a single center with a limited number of patients and may be difficult to extrapolate to other centers with different local epidemiology. Second, no supplementary analyses were undergone when discordances were observed since our study was performed retrospectively to describe the impact of such test in the management of pneumonia and antibiotic prescription due to the increase of antibiotic use during the first wave of COVID-19. In addition, the

| Table 3 | Impact of BioFire® FilmArray® Pneumonia Panel plus (mPCR) on antibiotic therapy before mPCR |
|---------|--------------------------------------------------------------------------------------------------------------------------------|
| Initial antibiotic therapy before mPCR | Continuation | Initiation | Adaptation | De-escalation | Inadequacy |
| Total n | Total CAP (%) | No antibiotic | 3rd generation cephalosporin | Penicillins | Piperacillin tazobactam | Carbapenems | Others |
| Total n | Total HAP/VAP (%) | No antibiotic | 4th generation cephalosporin | Piperacillin tazobactam | Carbapenems | Others |
| 5 | 29 | 3 | 104 | 5 | 1.5 (43) |

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respiratory samples were not frozen to allow additional molecular analysis. Thus, false positive and false negative results should be taken with caution especially considering that conventional culture is an imperfect gold standard.

Conclusion

Rapid mPCR is a useful and accurate tool in COVID-19 patients in whom bacterial co/superinfection diagnosis is difficult. It could lead to early adaptation or de-escalation of treatment when positive, and decrease antibiotic prescription when negative, thus contributing to the fight against antibiotic resistance.

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Author contribution  Conception and design of the work: NM, JFT, and LAL. Acquisition of data: NM, LC, JP, ATD, LL, BLJ, and MM. Analysis and interpretation of data: NM and LAL. Draft of the manuscript: NM and LAL. Revision of the manuscript: NM, LC, JP, ATD, LL, BLJ, MM, CD, ERo, ERu, PM, JFT, and LAL. All authors have approved the manuscript and support submission to European Journal of Clinical Microbiology & Infectious Diseases.

Data availability  The datasets used and/or analyzed during the current study are available from the corresponding author.

Code availability  Not applicable.

Declarations

Ethics approval and consent to participate  Data were collected prospectively, anonymously during the study period, in compliance with the GDPR. The study complied with the Standards for the Reporting of Diagnostic Accuracy Studies recommendations. All study participants provided informed consent.

Consent for publication  Not applicable.

Competing interests  ERu received funds from bioMérieux and speaking fees from Mobidiag. JFT received lecture fees from bioMérieux and participates, outside of the submitted work, on the advisory boards of MSD, Pfizer, Bayer, Nabriva, Gilead, BD, 3M, Paratek. LA received speaking fees from bioMérieux.

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