BRIEF REPORT

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.

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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% CO_2 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*

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

= 3), *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 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 bla_{CTX-M}, 1 bla_{NDM}, 2 bla_{VIM}, and 1 $mecA/C$+MRJE in agreement with the AST results. Three mPCR results were false positive: 2 bla_{VIM} and 1 bla_{CTX-M} which were never detected by conventional methods, despite subsequent cultures on selective media.

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]
A									
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
	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
	Serratia marcescens	0	2	0	110		98.2	0.0	100.0
	Acinetobacter calcoaceticus-baumannii complex	1	2	0	109	100.0	98.2	33.3	100.0
	Pseudomonas aeruginosa	6	5	0	101	100.0	95.3	54.5	100.0
	Haemophilus influenzae	1	1	0	110	100.0	99.1	50.0	100.0
	Moraxella catarrhalis	0	0	0	112		100.0		100.0
Total		20	19	0	1193	100.0	98.4	51.3	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
	Streptococcus agalactiae	0	0	0	112		100.0		100.0
	Streptococcus pyogenes	0	0	0	112		100.0		100.0
Total		5	4	0	439	100.0	99.1	55.6	100.0
Atypical	Chlamydia pneumoniae	0	0	0	112		100.0		100.0
	Legionella pneumophila	0	0	0	112		100.0		100.0
	Mycoplasma pneumoniae	0	0	0	112		100.0		100.0
Total		0	0	0	336		100.0		100.0
Total		25	23	0	1968	100.0 [100.0-100.0]	98.8 [98.4-99.3]	52.1 [38.0-66.2]	100.0 [100.0-100.0]
B									
Gram −	Escherichia coli	7	0	2	103	77.8	100.0	100.0	98.1
	Enterobacter cloacae complex	2	0	0	110	100.0	100.0	100.0	100.0
	Klebsiella aerogenes	5	1	1	105	83.3	99.1	83.3	99.1
	Klebsiella oxytoca	0	0	0	112		100.0		100.0
	Klebsiella pneumoniae group	4	2	1	105	80.0	98.1	66.7	99.1
	Proteus spp.	0	0	2	110	0.0	100.0		98.2
	Serratia marcescens	2	0	0	110	100.0	100.0	100.0	100.0
	Acinetobacter calcoaceticus-baumannii complex	3	0	1	108	75.0	100.0	100.0	99.1
	Pseudomonas aeruginosa	11	0	1	100	91.7	100.0	100.0	99.0
	Haemophilus influenzae	1	1	0	110	100.0	99.1	50.0	100.0
	Moraxella catarrhalis	0	0	0	112		100.0		100.0
Total		35	4	8	1185	81.4	99.7	89.7	99.3
Gram +	Staphylococcus aureus	8	1	1	102	88.9	99.0	88.9	99.0
	Streptococcus pneumoniae	0	0	0	112		100.0		100.0
	Streptococcus agalactiae	0	0	0	112		100.0		100.0
	Streptococcus pyogenes	0	0	0	112		100.0		100.0

Table 2 (continued)

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]
Total		8	1	1	438	88.9	99.8	88.9	99.8
Atypical	*Chlamydia pneumoniae*	0	0	0	112	-	100.0	-	100.0
	Legionella pneumophila	0	0	0	112	-	100.0	-	100.0
	Mycoplasma pneumoniae	0	0	0	112	-	100.0	-	100.0
Total		0	0	0	336	-	100.0	-	100.0
Total		43	5	9	1959	82.7 [71.4-94.0]	99.7 [99.5-100.0]	89.6 [80.9-98.2]	99.5 [99.2-99.8]

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

Table 3 Impact of BioFire® FilmArray® Pneumonia Panel plus (mPCR) on antibiotic therapy

Initial antibiotic therapy before mPCR	Positive mPCR							Negative mPCR			
	Total	n	Continuation	Initiation	Adaptation	De-escalation	Inadequacy	n	Continuation	No initiation	Withdrawal
Suspicion of CAP											
3rd generation cephalosporin	5	0	0	0	0	0	0	5	3	0	2
Piperacillin tazobactam	3	1	0	0	0	1	0	2	1	0	1
Total CAP (%)	8	1	0	0	0	1 (100)	0	7	4 (57)	0	3 (43)
Suspicion of HAP/VAP											
No antibiotic	29	13	0	13	0	0	0	0	0	16	0
Penicillins	1	1	1	0	0	0	0	0	0	0	0
Amoxicillin clavulanate	4	2	0	0	1	1	0	2	2	0	0
3rd generation cephalosporin	28	7	3	0	1	2	0	21	12	0	9
4th generation cephalosporin	7	3	2	0	2	0	1	4	3	0	1
Piperacillin tazobactam	10	1	0	0	0	1	0	9	6	0	3
Carbapenems	22	9	9	0	0	0	0	13	13	0	0
Others	3	0	0	0	0	0	0	3	3	0	0
Total HAP/VAP (%)	104	36	15 (42)	13 (36)	3 (8)	4 (11)	1 (3)	68	39 (57)	16 (24)	13 (19)
Overall total (%)	112		15 (14)	13 (12)	3 (3)	5 (4)	1 (1)		43 (38)	16 (14)	16 (14)

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 bla_{VIM}, 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

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.

Declarations

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