

Algorithm for rational use of Film Array Pneumonia Panel in bacterial coinfections of critically ill ventilated COVID-19 patients

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- 1 Title: Algorithm for rational use of FilmArray Pneumonia Panel in bacterial coinfections of
- 2 critically ill ventilated COVID-19 patients
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29 Abstract

The FilmArray® Pneumonia Panel has proven to be an effective tool for rapid detection of main respiratory pathogens. However, its rational use needs appropriate knowledge and formation regarding its indication and interpretation. Herein, we provide some advices to help with success of its daily routine use, particularly in critically ill ventilated COVID-19 patients. Clinical Trial registration number: NCT04453540. Keywords: Covid-19 / bacterial coinfection / antimicrobial stewardship / pneumonia / critically ill / molecular diagnosis

Since the start of the pandemic Covid-19 outbreak, molecular respiratory panel such as 43 FilmArray® Pneumonia Panel (FAPP; bioMérieux, France) has been widely used in critically 44 45 ill patients for bacterial coinfections management. Regarding its performance for pathogens and antimicrobial resistance detection (Suppl. Table 1), all authors highlighted FAPP interest 46 47 for antimicrobial stewardship, especially antibiotic sparing [1-6]. However, FAPP interpretation could be challenging [4,5]. Indeed, as evoked by Maataoui et al., one of the 48 reasons of a non-optimal use of FAPP was the "lack of knowledge and confidence in the test" 49 50 [4]. The present study reports the lessons from the implementation of FAPP during the first COVID-19 outbreak, when a training on "how to use FAPP" could not be performed due to 51 52 the work overload.

53 This is a multicenter retrospective analysis (clinicalTrial.gov NCT04453540) of all critically ill patients who were admitted to the Nancy and Reims University Hospitals (six ICUs) from 54 March to May 2020, with COVID-19 and respiratory failure requiring invasive mechanical 55 ventilation (IMV). The local institutional ethics committee approved this study (Comité 56 d'éthique du CHRU de Nancy, N°CO-20). Informed consent was obtained from all 57 participants and/or their legal guardians. Presence of SARS-CoV-2 was diagnosed using RT-58 PCR. All patients with suspicion of bacterial pneumonia were eligible. The decision to 59 prescribe FAPP was at the discretion of the clinician. Only patients with concomitant FAPP, 60 conventional culture (CC) and Gram stain were included. Samples were endotracheal 61 62 aspirates (ETA) and bronchoalveolar lavages (BAL). Results of the FAPP and Gram stain were available for the intensivists within four hours. A first result of the CC was available 63 64 after one day with a definitive result within five days. For quantitative culture, only the bacteria above the following threshold were considered: 10⁴ CFU/mL for BAL and 10⁵ 65 CFU/mL for ETA. Phenotypic drug susceptibility testing was performed according to the 66

recommendations of the antibiogram committee of the French Society for Microbiology (CA-67 SFM)/European Committee for Antibiotic Susceptibility Testing (EU-CAST). A 68 69 multidisciplinary expert committee (MEC) composed of intensivists, infectious disease specialists and microbiologists from both centers analyzed retrospectively the contribution of 70 71 FAPP compared to CC in the treatment decision of pneumonia according to criteria from Weiss et al. [7]. Antibiotics used to treat any concomitant infection were not considered by 72 the MEC. Early bacterial coinfections, represented by community-acquired pneumonia 73 (CAP), were defined as infections occurring during the first 48h of ICU admission. The 74 75 ventilator-associated pneumonia (VAP) were defined as infections occurring after 48h of 76 IMV. Multiple tests from the same patient were considered independent when performed 77 during distinct infectious episodes. Categorical data were analyzed using chi-square test or Fisher's exact test. Statistical analyses were performed by an independent statistician using 78 SAS 9.4 software (SAS Institute, Inc, Cary, N.C.). 79

Overall, 344 patients with a positive SARS-CoV-2 RT-PCR were admitted in the 80 participating ICUs of whom 90 fulfilled eligibility criteria. Samples were 74 ETA and 45 81 BAL. Characteristics and ICU data are presented in Table 1. Bacteriological results were 82 presented in Tables 2 and 3. The rate of clinically confirmed CAP and VAP were 5.0% and 83 40.3%, respectively. Bacterial pathogens were detected by FAPP (45.4%) and/or by CC 84 (38.7%) in 41 and 34 ETA and in 13 and 12 BAL, respectively. The adequacy between FAPP 85 and CC in pathogen detection was better (p=0.017) for BAL (95.6%) than for ETA (79.7%). 86 Staphylococcus aureus and Pseudomonas aeruginosa were the most prevalent pathogens. 87 Two cases of negative FAPP (no detection of Morganella morganii) have led to inappropriate 88 discontinuation of empirical antibiotic therapy. Two Extended-Spectrum β -lactamase ESBL 89 (not-CTX-M)-producing Enterobacter cloacae and one 3GC-resistant P. aeruginosa were 90

91 isolated by CC without detection of resistance gene by FAPP. Regarding the six samples with 92 methicillin-resistance of *S. aureus* (MRSA) detected in FAPP, only three have a *S. aureus*-93 positive culture and all where methicillin-susceptible (MSSA). According to MEC analysis, 94 FAPP-based therapeutic decision was concordant with CC-based therapeutic decision in 91% 95 for BAL compared with 69% for ETA (p=0.009). The most contribution of FAPP regarding 96 antibiotic prescription was antibiotic spare (**Table 2**). However, we observed that intensivists 97 considered FAPP for treatment only in 42.0% (50/119) of cases.

98 These results confirmed the usefulness of FAPP to rapidly diagnose bacterial coinfection.
99 However, there is a room for improvement of its use and interpretation. Herein, we suggest
100 four tips for a tailored use of FAPP in critically ill ventilated patients:

Training for mastering FAPP by the intensivists is required for successful utilization
 in the daily routine practice. We believe that an appropriate knowledge about FAPP
 performance and results interpretation should led to a better antibiotic use. Therefore, a
 collaboration between microbiologists and intensivists is mandatory.

FAPP should be performed on BAL to avoid over-diagnosis of bacterial coinfection.
 Lower relevance of FAPP results from ETA compared to BAL for treatment could be
 explained by detection of not significant bacteria from the tracheobronchial colonization.
 However, if BAL could not be performed, ETA could be used with cautious interpretation
 of FAPP results.

3. Conventional culture should be systematically performed in parallel. To detect bacteria not included in the FAPP [5] and to confirm resistance gene detection. For Gramnegative bacilli, FAPP detects only CTX-M ESBL. Moreover, as previously described [8], FAPP led to over-detection of MRSA that could lead to an overuse of anti-MRSA antibiotics, especially in case of local ecology with low prevalence of MRSA. Indeed,

among the 6 samples with MRSA detected in FAPP (5 ETA and 1 BAL), only three (2 ETA and 1 BAL) had a *S. aureus*-positive culture and all where MSSA. Such discordance could be explained either by the co-occurrence of a *S. aureus* with an empty *SCCmec* cassette and methicillin-resistant negative coagulase staphylococci, or by a mixed specimen of MSSA and MRSA, respectively above and below the threshold of culture detection.

Therapeutic decision must be re-evaluated with the result of 2-days conventional 121 4. culture. The delay of 2 days for definitive CC interpretation should cover slowing 122 growing bacteria (low bacterial load or prior antimicrobial treatment) as well as drug 123 124 susceptibility testing results. Moreover, of 65 negative-FAPP, 62 (95.4%) showed 5-days 125 negative culture and 3 (4.6%) were positive (for outside-panel bacteria) but within 2 days of culture. Consequently, in absence of i) severity criteria, namely septic shock or severe 126 ARDS (according to Berlin criteria), and of ii) Gram-negative bacilli at Gram stain, 127 empirical antibiotic therapy could be stopped based on a negative-FAPP result. 128

In the present study, a FAPP use based on these tips would allow 65.6% of antibiotic spare in bacterial coinfection and a better adequacy of empirical antibiotic treatment. Regarding VAP, FAPP should consider local ecology for optimal interpretation, especially for resistance detection (i.e. *P. aeruginosa* with non-enzymatic resistance). Based on our results, we propose an algorithm to improve the use of FAPP for antibiotic stewardship at the bedside (**Figure 1**). Further studies are now warranted to demonstrate that rational use of FAPP will also improve patient outcome.

137 Disclosure of interest: The authors declare that they have no conflict of interest pertaining to138 this study.

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Fig. 1. Clinical algorithm for initiating antibiotics using FAPP in bacterial coinfection of
critically ill COVID-19 patients. IMV, invasive mechanical ventilation; BAL,
bronchoalveolar lavage; FAPP, FilmArray® Pneumonia Panel; ATB, antibiotics; GNB,
Gram-negative bacilli.

- ^a Endotracheal aspirate samples could be used but need cautious interpretation regarding the
- 197 risk of over-diagnosis due to tracheobronchial colonization
- ^b Septic shock (according to SEPSIS-3) or severe ARDS (according to Berlin criteria)

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200 Ethics consideration

The institutional ethics committee approved this study (Comité d'éthique du CHRU de Nancy, N°CO-20). All experiments were performed in accordance with guidelines and regulations. Informed consent was obtained from all participants and/or their legal guardians.

Authors' contributions: EN and CA participated equally in this work. EN, CA and TG contributed substantially to the study design and the writing of the manuscript. EN, CA, TG, CT, AG contributed to the acquisition, analysis and interpretation of data. CT and AG made critical revision of the manuscript.

characteristics of patients
(

Variables	Patients N=90
Male Sex	72 (80.0)
Age (years)	65 [58.3-70.0]
Obesity (BMI >40 kg/m ²)	6 (6.6)
Comorbidities:	
Hypertension	50 (55.5)
Diabetes	27 (30.0)
Immune deficiency	18 (20)
Chronic respiratory failure	10 (11.0)
Chronic hemodialysis	1 (1.0)
Cirrhosis	1 (1.0)
ICU data:	
SAPS 2 score	44 [36-61]
ICU LOS (days)	23 [14-37]
IMV duration (days)	17 [11-27]
ECMO	10 (11)
ICU mortality	25 (28)

211 Data are presented as: n (%) – median [IQR]

212 Immune deficiency: diabetes, neoplasia, transplant, neutropenia/aplasia, immunosuppressive

therapy / SAPS 2 score: Simplified Acute Physiology Score II / LOS: Length of stay / IMV:

214 invasive mechanical ventilation.

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Table 2. Bacteriological results according to the type of pneumonia and contribution of the

218 panel FAPP on antibiotic prescription

	Samples N=119	
	CAP	VAP
Type of suspected pneumonia	27 (22.7)	92 (77.3)
Confirmed diagnostic of pneumonia	6	48
(% among suspected / % among total)	(22.2 / 5.0)	(52.2 / 40.3)
Type of samples:		
ETA	15	59
BAL	12	33
Antibiotics 48h prior to samples	15 (55.6)	40 (43.5)
Bacterial copathogens:	FAPP / CC	FAPP / CC
Staphylococcus aureus	0 / 0	17/12
Pseudomonas aeruginosa	0 / 0	11/11
Haemophilus influenzae	4 / 0	6/3
Escherichia coli	0 / 0	9/5
Klebsiella pneumoniae	1/1	6/6
Enterobacter cloacae	0 / 0	5/5
Klebsiella aerogenes	0 / 0	4/2
Proteus spp.	0 / 0	4/3
Serratia marcescens	0 / 0	3/3
Streptococcus agalactiae	0 / 0	3/1
Moraxella catarrhalis	1/0	1/1
Mycoplasma pneumoniae	1 / NA	0 / NA

Morganella morganii	NA / 0	NA / 2
Hafnia alvei	NA / 0	NA / 1 ^a
Providencia stuartii	NA / 0	NA / 1 ^a
Resistance detection:	FAPP / AST	FAPP / AST
MRSA	0 / 0	6/0
3GC-R Gram-negative bacilli	0 / 0	5 / 6 ^b
Type of pneumonia	CAP	VAP
Contribution of FAPP at first intensivist		
decision ^c		
No modification of empirical antibiotics	0	3 (7.5)
Speeded-up adequate antibiotic	2 (20.0)	9 (22.5)
Antibiotic spare ^d	8 (80.0)	20 (50.0)
Inappropriate antibiotic treatment	0	7 (17.5)
Inappropriate stopped antibiotic	0	1 (2.5)
Contribution of FAPP based on MEC		
analysis ^e		
No modification of empirical antibiotics	1 (3.7)	11 (12.0)
Speeded-up adequate antibiotic	4 (14.8)	13 (14.1)
Antibiotic spare ^d	22 (81.5)	56 (60.9)
Inappropriate antibiotic treatment	0	10 (10.9)
Inappropriate stopped antibiotic	0	2 (2.2)

219 Data are presented as: n (%)

ETA: endotracheal aspirate / BAL: bronchoalveolar lavage / CAP: community-acquired pneumonia (defined as infections occurring during the first 48h of ICU admission) / VAP: ventilator-associated pneumonia / FAPP: FilmArray® Pneumonia Panel / CC: conventional culture / AST: antimicrobial susceptibility testing / MRSA: methicillino-resistant *Staphylococcus aureus* / 3GC-R: third generation cephalosporins resistance / NA: not applicable (species not detected either by the FAPP or by the CC) / MEC: multidisciplinary expert committee.

^a The isolation of *H. alvei* and *P. stuartii* in CC had no impact on antibiotic therapy as they
were covered by the antibiotics administered following the detection of other pathogens
detected by FAPP.

^b Among 3GC-resistant Gram-negative bacilli, 3 CTX-M were detected by both FAPP and

231 CC, 2 CTX-M were detected only by FAPP, 2 ESBL not belonging to CTX-M as well as one

232 3GC-resistant *P. aeruginosa* were detected only by CC.

^c A contribution of FAPP at first intensivist decision was noted in 50 samples (42.0%).

^d Decrease unnecessary antibiotic use (interruption or de-escalation).

- ^e Theoretical contribution of FAPP after MEC analysis of the 119 samples (100.0%).
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Table 3. Bacteriological results according to the type of respiratory samples

	Samples N=119	
	ETA (n=74)	BAL (n=45)
Type of pneumonia		
CAP : suspected/confirmed	15/5	12/1
VAP : suspected/confirmed	59 / 34	33 / 14
Antibiotics 48h prior to samples (n=55)	32 (58)	23 (42)
Positive direct examination	39 (53)	14 (33)
Presence of Gram +	6 (15)	3 (21)
Presence of Gram –	9 (23)	1 (7)
Polymicrobial	24 (62)	10 (72)
Infection polymicrobial		
FAPP $(n=18)$	14 (77)	4 (23)
Mean number of bacteria detected	2.2	2.25
CC (n=8)	5 (62)	3 (38)
Mean number of bacteria detected	2.2	2
Bacterial copathogens:	FAPP / CC	FAPP / CC
Staphylococcus aureus	12/6	5/6
Pseudomonas aeruginosa	10/ 10	1 / 1
Haemophilus influenzae	7/2	3/1
Escherichia coli	7/4	2/1
Klebsiella pneumoniae	6/6	1/1
Enterobacter cloacae	3/3	2/2
Klebsiella aerogenes	3/1	1/1
Proteus spp.	4/3	0 / 0
Serratia marcescens	2/2	1/1
Streptococcus agalactiae	2/1	1/0
Moraxella catarrhalis	2/1	0/0
Mycoplasma pneumoniae	1 / NA	0 / NA
Morganella morganii	NA / 1	NA / 1
Hafnia alvei	NA / 1 ^a	NA / 0
Providencia stuartii	NA / 1 ^a	NA / 0
Resistance detection:	FAPP / AST	FAPP / AST
MRSA	5/0	1/0
<u>3GC-R Gram-negative bacillib</u>	4/3	1/3

239 Data are presented as: n (%)

ETA: endotracheal aspirate / BAL: bronchoalveolar lavage / CAP: community-acquired
pneumonia (defined as infections occurring during the first 48h of ICU admission) / VAP:
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251 3GC-resistant *P. aeruginosa* were detected only by CC.

Figure 1. Clinical algorithm for initiating antibiotics using FAPP in bacterial coinfection ofcritically ill COVID-19 patients.



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IMV, invasive mechanical ventilation; BAL, bronchoalveolar lavage; FAPP, FilmArray®
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 risk of over-diagnosis due to tracheobronchial colonization

- ^b Septic shock (according to SEPSIS-3) or severe ARDS (according to Berlin criteria)
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Supplementary Table 1. Targets identified by the FAPP assay

Category	Result type	Targets
Viruses	qualitative	Adenovirus, coronavirus, human metapneumovirus, human rhinovirus/enterovirus, influenza A virus, influenza B virus, parainfluenza virus, respiratory syncytial virus
Atypical bacteria	qualitative	Chlamydophila pneumoniae, Legionella pneumophila, Mycoplasma pneumoniae
Bacteria	semi- quantitative*	Acinetobacter calcoaceticus-Acinetobacter baumannii complex, Enterobacter cloacae complex, Escherichia coli, Haemophilus influenzae, Klebsiella aerogenes, Klebsiella oxytoca, Klebsiella pneumoniae, Moraxella catarrhalis, Proteus spp., Pseudomonas aeruginosa, Serratia marcescens, Staphylococcus aureus, Streptococcus agalactiae, Streptococcus pneumoniae, Streptococcus pyogenes
Antimicrobial resistance markers	qualitative	CTX-M, KPC, NDM, IMP, VIM, OXA-48 like <i>mecA/mecC</i> and MREJ

266 * Reported as 10^4 , 10^5 , 10^6 , or $\ge 10^7$ copies/mL.

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