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par

Florian GUILLOTIN

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POTENTIAL IMPACT ON ANTIMICROBIAL THERAPY OF RAPID MULTIPLEX PCR FOR MICROBIOLOGICAL DIAGNOSIS OF HEALTH CARE ASSOCIATED PNEUMONIA IN CRITICALLY ILL PATIENTS, A PROSPECTIVE OBSERVATIONAL CLINICAL AND ECONOMIC STUDY

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Président : Monsieur le Professeur David BOUTOILLE

Directeur de thèse : Monsieur le Professeur Antoine ROQUILLY

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Abréviations

BAL Bronchoalveolar Lavage

CEA Cost-Effectiveness Analysis

C3G Third Generation Cephalosporin

DRG Diagnostic Related Group

FAPP FilmArray® Pneumonia *plus* Panel

HAP Hospital-Acquired Pneumonia

ICU Intensive Care Units

LOS Length Of Stay

MDR Multidrug-Resistant

MRSA Methicillin-resistant Staphylococcus aureus

PCR Polymerase Chain Reaction

VHAP Mechanically Ventilated Hospital-Acquired Pneumonia

VAP Ventilation Associated Pneumonia

Introduction

Ventilator-Associated Pneumonia (VAP) are a frequent complication and one of the main cause of antibiotics use in intensive care units (ICU)[1]. VAP are associated with prolonged duration of mechanical ventilation and hospital stay, and generate elevated healthcare costs [2][3][4]. Moreover, VAP caused by difficult-to-treat multidrug-resistant (MDR) bacteria are increasingly prevalent [5] and result in significant morbidity and mortality [6].

Early and adequate antimicrobial treatment could alleviate VAP-related mortality, but is medically challenging [7][8]. To decrease the risk of treatment failure, a broad-spectrum empirical antimicrobial therapy is recommended to treat VAP at risk of MDR bacteria. Validated risk factors for MDR bacteria are a prior infection/colonization with MDR bacteria, an antimicrobial therapy in the preceding 90 days, and a late-onset VAP, i.e. within or after the 5th day of hospitalization [9][10]. However, the use of these criteria leads to frequent un-necessary broad-spectrum antimicrobial therapy [11], which substantially increases the risk of selection of resistant Gram-negative bacilli (collective risk) [12] without providing any individual benefit.

Hence, there is a medical need to reduce the turnaround time for bacterial identification and antimicrobial susceptibility testing. Rapid multiplex molecular tests offer this opportunity and are now routinely used in the form of syndromic panels in different clinical situations, such as bloodstream, respiratory, gastrointestinal, or central nervous system infections[13][14]. The FilmArray® Pneumonia *plus* Panel (FAPP) allows the detection of 18 bacteria, 5 resistance genes, and 9 viruses involved in VAP. This molecular test demonstrated a combined 96.2% positive percent agreement (PPA) and 98.1% negative percent agreement (NPA) for the qualitative identification of 15 bacterial targets, when compared to routine bacterial culture

[15]. In a prospective cohort of 100 patients with HAP, we compared the diagnosis performance of FAPP with conventional testing and found that FAPP enhanced the positivity rate of conventional diagnostic testing, with increased recognition of coinfections and reduced time-to-results (4 h 15 min on average vs. 64–70 h with culture) [16]. In this study, using the clinical data of the same cohort, we simulated the theoretical impact of FAPP results on antibiotics use at mechanically ventilated heath care associated pneumonia (VHAP) diagnosis. Our second objective was to assess the cost-effectiveness of this new molecular test.

Methods

Ethics

This study was approved by a local ethic committee (GNEDS, Nantes, France). Patients and next-of-kin were informed of their participation to this study, and the possibility to be opposed to their data collection.

Study design

This was a prospective study, conducted in 3 ICUs of a tertiary hospital in France between October 2018 and January 2020. One bacteriological laboratory performed centralized analysis for the three ICUs, located in two sites separated by ten kilometers.

End points

The primary endpoint was the number of days of broad-spectrum antimicrobial therapy.

Secondary endpoints were 1) the clinical efficiency of the current antimicrobial therapy strategy based on bacterial culture results compared to a simulated antimicrobial therapy strategy using the FilmArray® Pneumonia assay results, 2) the number of days of narrow-spectrum antimicrobial therapy and of carbapenems with each strategy, 3) the difference of rate of non-optimal empiric antimicrobial therapy.

Study population

Mechanically-ventilated adult patients where included at the time of VHAP diagnosis. Ventilator-associated pneumonia was defined on European guidelines as follow: a new or persistent radiological pulmonary infiltrate without another obvious cause combined with two clinical signs among fever, purulent endotracheal secretions, hyperleukocytosis or leukopenia, and increasing oxygen requirements[17]. Respiratory specimens were obtained before any modification or introduction of new antimicrobial therapy by bronchoalveolar lavage (BAL) and/or by endotracheal aspiration.

Bacteriological Analysis

Each respiratory specimen was analyzed by standard culture and using the FAPP panel as soon as possible, and time-to-results was collected. Culture was realized and interpreted independently of the multiplex PCR, as previously described [16]. Physicians in charge of the patients were blinded of the multiplex PCR results. The resistance genes and all bacteria detected with FAPP, whatever their bin level (DNA copies/mL), were taken into account for the FAPP-based antibiotic simulation.

Definitions

Broad-spectrum antimicrobial therapy was defined as molecules with activity against *P. aeruginosa* including piperacillin-tazobactam, cefepime, ceftazidime, ciprofloxacin and carbapenems,. Narrow-spectrum antimicrobial therapy had no activity against *P. aeruginosa* such as cefotaxime, ceftriaxone, amoxicillin–clavulanate, and ofloxacin.

Antimicrobial therapy was considered optimal when all the pathogens found in culture were susceptible to empiric antimicrobial therapy and no alternative with a narrower spectrum was available. Un-necessary broad-spectrum treatment was considered if all pathogens were susceptible to narrow-spectrum antimicrobial agents.

Microbial treatment failure corresponded to the isolation in culture of one or more pathogen resistant to the empiric antimicrobial therapy.

Antimicrobial therapy groups

Three antimicrobial therapies were compared: one was the real-life treatment, and two were simulated by two medical experts in critically ill patients who reviewed the medical records: one was proposed on the basis of international ERS/ESICM/ESCMID/ALAT recommendations[7], and the other on the basis of FAPP results. In order to limit the risk of bias, the experts were kept blinded of the real-life treatment. In case of disagreement between the two experts, a college of six clinicians blindly reviewed the case to determine the simulated treatment.

- Real-life treatment. Amoxicillin – clavulanate was recommended up to 10 days of ICU length of stay (LOS) if the patient was admitted for trauma or brain-injury and had no prior antimicrobial treatment of more than 48h [17]. For non-traumatic patients, narrow spectrum antimicrobial treatment was recommended up to 5 days of ICU LOS.

- Recommendations-based treatment. The antimicrobial spectrum of the empirical therapy was adapted to risk factors for MDR bacteria (late-onset VAP after day 5, recent history of antimicrobial therapy or prior infection/colonization with MDR bacteria). This therapy was narrowed according to the results of standard culture to be effective against all pathogens identified.
- FAPP-based treatment. An antimicrobial stewardship based on the pathogens and resistance genes identified with the rapid multiplex PCR was developed by intensivists, infectiologists and microbiologists of our hospital, and followed for the treatment simulation (Supplemental Table 1). This treatment was secondarily adjusted to the results of standard culture, if needed.

Data collection

Clinical data were prospectively collected and anonymized : age, LOS, admission's motif, IGSII, vasopressors therapy, PaO2/FiO2 ratio, risk factors for MDR pathogen infection, MRSA risk factors, in-ICU and in-hospital mortality, antimicrobial treatment, second episode of pneumonia.

Medico-economic evaluation

We conduct a cost-effectiveness analysis (CEA) comparing the real life antimicrobial therapy strategy based on bacterial culture results to the simulated antimicrobial therapy strategy using the FAPP results, to evaluate efficiency of FAPP. CEA was carried out during a time horizon that includes the resolution of the infectious episode and from the hospital perspective, indeed, health care consumption related to an infection and its management are included in the diagnostic related group (DRG). Effectiveness was evaluated on the optimization of antibiotic

prescription: number of days of ineffective empirical antibiotic or with unnecessary broad spectrum. Considered costs are those related to antimicrobial therapy, and those associated with FAPP use. We did not considered costs related to culture tests because they are made in all cases. Costs are expressed in euros 2021. Data were obtained using the patient medical files. A sensitivity analysis was conducted on the FAPP price. We also conducted a budget impact analysis to estimate the financial impact of the FAPP use in our hospital.

Statistical analysis

No information was available to estimate the reduction of broad spectrum antimicrobial therapy with FAPP. We thus could not calculate a priori the number of patients to be included to guarantee a statistical power of 80%. We decided to include 100 patients for feasibility. We performed a statistical analysis following a hierarchical and sequential strategy to test the primary and secondary hypotheses. The hypotheses involved two hypotheses ranked according to their clinical relevance: first the comparison between in the recommendations-based simulation and FAPP-based treatment. Then, the comparison between real-life and FAPP-based treatment. The effect of such a procedure is that no confirmatory claims can be based on variables that have a rank lower than or equal to that variable whose null hypothesis was the first that could not be rejected [18, 19]. The type I error rate remained controlled at 5% for each test. The secondary endpoints were tested using the same procedure.

For continuous variable, the statistical test was a paired Student test or a Wilcoxon paired test if the normality conditions was not satisfied. For binary variables, the McNemar test was used for paired comparisons.

Results

Characteristics of the population

One hundred patients were included in this study. Demographic characteristics are presented in Table 1. The most frequent causes of admission were severe trauma (42%) and medical conditions (32%). The median time of ICU LOS before VHAP was 5 days, [IQR: 3-9]. The median PaO2 on FiO2 rapport at the time of VHAP was 135 [IQR : 102-195], and 21% patients received vasopressors at the time of VHAP diagnosis. The ICU mortality rate was of 21% among participants. Results of the conventional cultures are shown in Figure S1 of the supplemental.

As described in Figure 1, a broad-spectrum empirical therapy was prescribed in 37% of patients in the FAPP-based simulated treatment, 47% in real life and 88% in the recommendations-based simulated treatment ($p<0.01$ versus real life and FAPP). A carbapenem was used in 6% of patients in the PCR guided group, 12% in the real group and 13% in the guidelines guided group. The β-lactams used in the different groups are described in figure S2.

Tableau 1: Characteristics of clinicals data at inclusion and survival

Demographics and baseline characteristics of the patients

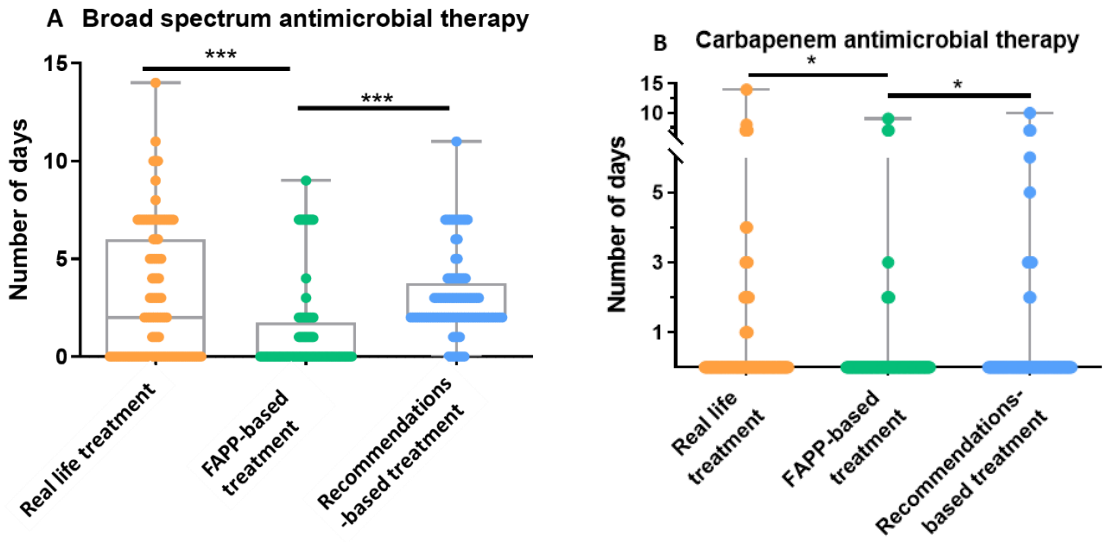
Patients	Numbers (n=100)	Median [IQR]
Age, years		57 [38.25-64.25]
Hospital length of stay before inclusion, days		6 [3.75-10]
ICU length of stay before inclusion, days		5 [3-9]
Medical history of ESBL colonization or infection	2 (2%)	
Risk factors for MRSA colonization	6 (6%)	
Antibiotics exposure in the 90 days before inclusion	40 (40%)	
Severity of disease		
IGS II		43.64 [32-54.25]
PaO2/FiO2 at the time of VHAP		135 [102-195]
Septic shock	21(21%)	
Reason for ICU admission		
Trauma	42 (42%)	
Burn	7 (7%)	
Emergency surgery	5 (5%)	
Scheduled surgery	13 (13%)	
Medical	32 (32%)	
Other	1 (1%)	
Mortality in ICU	21 (21%)	
28 days mortality	17 (17%)	

Primary outcome

The median duration of broad-spectrum antibiotics was 0 [0-1.25] day in the FAPP-based treatment simulation as compared to 2 [0-6] days in real life and 2 [2-3.25] days in the recommendations-based treatment simulation ($p < 0.0001$ versus two others) (Figure 1 A).

*Figure 1: A Median and IQR of days under broad spectrum antibiotics in the real life and in the FAPP-based treatment and Recommendations-based treatment. ***: p<0.001*

B Median and IQR of days under carbapenem antibiotics in the real life and in the FAPP based treatment and recommendations-based treatment.: p<0.01*



Secondary outcomes

In FAPP-based treatment, carbapenems were administrated for 0.32 (SD: 1,38) day *versus* 0.54 (SD: 1.69) days for the recommendations-based treatment (p=0.03) and 0.74 (SD: 2.11) days for real life treatment (p=0.01). Narrow-spectrum antibiotics were used for 6 [1-7] days in the FAPP-based treatment simulation, versus 4 [0-5] days in the recommendations-based treatment simulation and 4 [0-7] days in real-life (p<0.01 for comparison with real life) (Table 2).

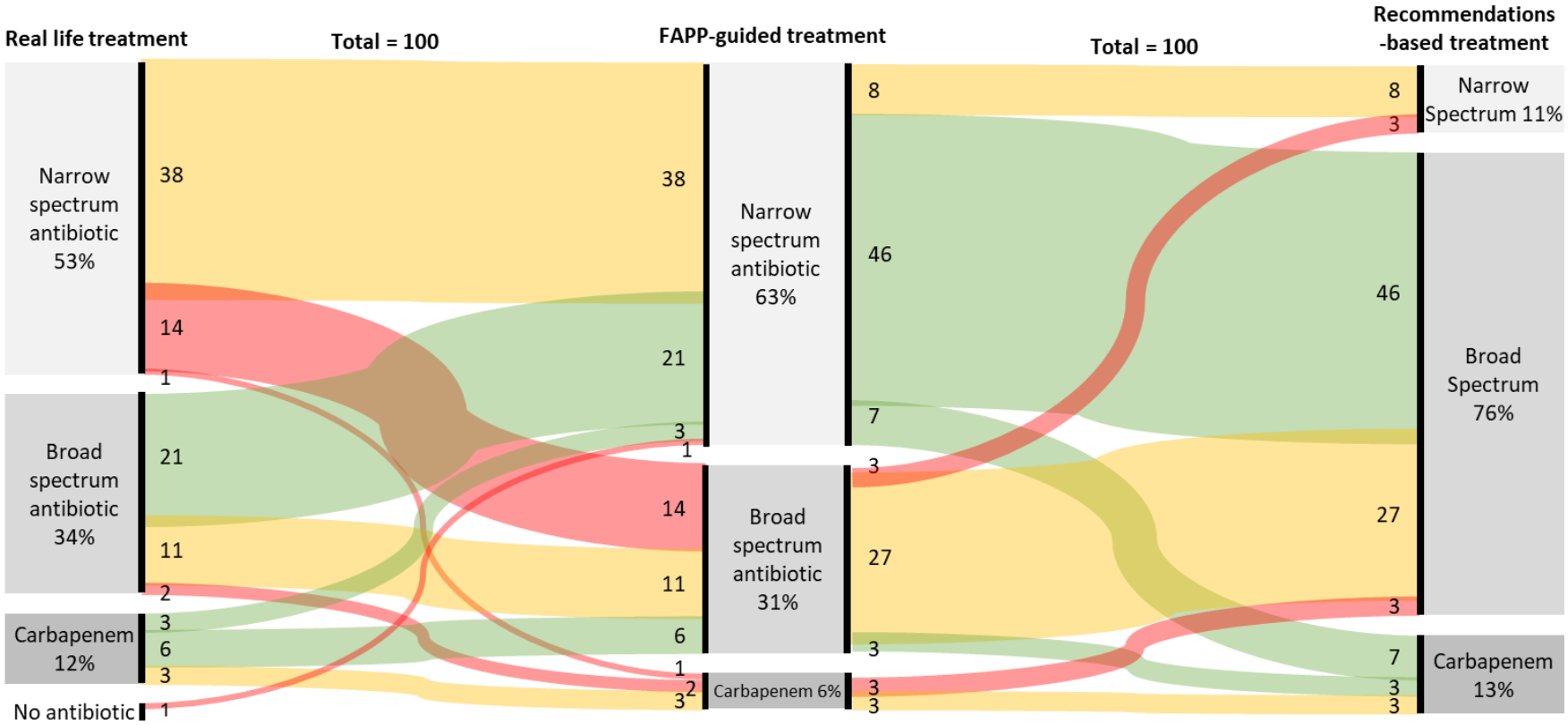
Use of multiplex PCR would have led to modification of the empirical antimicrobial therapy in 48% of patients compared to real life (Figure 2). This modification was a de–escalation for 30 (30%) patients and an escalation for 18 (18%) patients.

Table2: Primary and secondary outcomes.

		FAPP based treatment	Recommendations-based treatment			Real life treatment		
		days	days	difference with PCR	p Value	days	difference with PCR	p Value
Broad Spectrum Antibiotics	Mean (SD)	1.26 ± 2.34	2.97 ± 2.02	1.71 ± 1.55	< 0.0001	2.99 ± 3.37	1.73 ± 2.88	< 0.0001
	Median (IQR)	0[0-1.25]	2[2-3.25]	2[0-2]		2[0-6]	0[0-4]	
Carbapenem	Mean (SD)	0.32 ± 1.38	0.54 ± 1.69	0.22 ± 1.03	0.03	0.74 +/- 2.11	0.41 ± 1.56	0.01
	Median (IQR)	0[0-0]	0[0-0]	0[0-0]		0[0-0]	0[0-0]	
Narrow spectrum antibiotics	Mean (SD)	4.49 ± 2.94	3.01 ± 2.48	-1.48 ± 1.50	< 0.0001	3.61 ± 3.01	-0.88 ± 2.95	0.002
	Median (IQR)	6[1-7]	4[0-5]	-2		4[0-7]	0	

Comparison of days under broad spectrum, carbapenems and narrow spectrum antibiotics by Wilcoxon test. FAPP: FilmArray® Pneumonia plus Panel; SD: Standard derivation; IQR: Interquartile range

Figure 2: Sankey chart of real life treatment realized without FAPP (left column), antimicrobial therapy who would have been performed with the result of FAPP (Middle column), and the antimicrobial therapy who would have been performed following the actuals recommendations (right column). The lines are colored in red for antibiotic escalation, green for de-escalation and yellow for no changes.



No change compare to FAPP-based treatment narrower spectrum in FAPP-based treatment Broader spectrum in FAPP based treatment.

Antimicrobial Success of empiric antimicrobial therapy

The performance of the empiric antimicrobial therapy is summarized in Table 3. Optimal empiric treatment was achieved in 67% patients in the FAPP-based treatment simulation, 19% in the recommendations-based treatment simulation ($p<0.0001$) and 61% in real life ($p= 0.38$). Un-necessary broad-spectrum antimicrobial therapy was noticed in 30% of the patients with the FAPP-based treatment, as compared with 76% in the recommendations-based treatment ($p<0.0001$) and 27% in real life ($p= 0.68$). Microbiological failure was noticed in 5% of patients with the recommendations-based treatment simulation versus 3% with the FAPP-based treatment simulation with no significant difference ($p=0.37$). Whereas in real life treatment 11% of patients had a microbiological failure ($p=0.08$).

Table 3: Optimization of empiric antimicrobial therapy

	FAPP-based treatment	Recommendations-based treatment		Real life treatment	
	Percentage of patient n=100	Percentage of patient n=100	Difference with PCR	Percentage of patient n=100	Difference with PCR
Spectrum optimal to the germ	67%	19%	< 0.0001	62%	0.38
Inefficient empiric antibiotic	3%	5%	0.37	11%	0.08*
Unnecessary broad spectrum of antibiotic	30%	76%	< 0.0001	27%	0.68

*Comparison of efficiency of empiric antimicrobial therapy compared by Mc-Nemar test. * p-value adjusted for multiple test using Bonferroni's method*

Economic analyze

Finally, we conducted a cost-effectiveness analysis (table 4). The cost to avoid one day of non-optimized antibiotic was 1 121 € [-7021 ; 6794], indicating that FAPP utilization is more expensive but more effective compare to the bacterial culture alone. The sensitivity analysis conducted on the FAPP price reveals that the strategy always generate an additional cost due to a higher mean cost of probabilistic antimicrobial therapy in the FAPP group.

The financial impact of the FAPP use in our hospital for the population who will need it in one year (150 patients) is €51 322.

Table 4: Medico-economics analyses of the FAPP strategy compare to the bacterial culture alone.

	Standard bacterial culture alone	PCR and bacterial culture
	Cost (€)	Cost (€)
Total of antibiotics (a)	3431,66	3617,36
Mean (ATB) by patients	36,12	38,07
Min	3,296	5,4
Max	146,388	541,5
Standard derivation	21,86	54,85
Total (PCR) (b)	0	32319
Mean (PCR) per patient	0	340,2
Total (a+b)	3431,66	35936,36
Effectiveness	112	83
Incremental Cost-Effectiveness Ratio	$\frac{35936{,}36 - 3431{,}66}{83 - 112} = 1121$	

Discussion

In this prospective observational study, we showed that in simulated conditions, FAPP could reduce the number of days of broad-spectrum antimicrobial therapy, including carbapenems, in patients with VHAP. When compared to an empirical antimicrobial strategy based on international recommendations, FAPP had also the potential to decrease the risk of treatment failure without increasing un-necessary broad-spectrum treatment. When considering the total cost of hospitalization, the result of the cost-effectiveness ratio for FAPP was low.

Use of FAPP in this study lead to a reduction of consumption of broad-spectrum antibiotics, a reduction of days under carbapenems. It decreased the number of pneumonia episodes with ineffective empiric antimicrobial therapy from 11% to 3%, even though we couldn't show a significant difference. This strategy made possible to achieve the challenge of reserving the broad-spectrum antimicrobial therapy only to the infections that require it.

In this study, only 67% of empiric antimicrobial therapies were considered as optimal in the FAPP-guided treatment. This could potentially be explained by the protocol established to guide empiric antimicrobial therapy on the basis of PCR results. In fact, we recommended the prescription of narrow-spectrum antibiotics (amoxicillin-clavulanate or C3G) in case of negative PCR and negative Gram stain examination. We made this chose because of the possibility of false negative PCR, but this leads to the prescription of antibiotics when often, the culture is also negative.

We estimated that the implementation of FAPP would increase the medical cost by 1 121 € to avoid one day of non-optimized empiric antibiotic. This estimation was based on the consideration that all patients with VHAP would have FAPP. It is possible to reduce the cost of this new method by limiting its indication to patients at high risk of MDR pathogens.

Moreover, we only considered the impact of FAPP on the cost of antimicrobial therapy. Yet, we identified MDR bacteria requiring patient isolation in 8 episodes of VHAP, out of which 7 had no history of resistance. Since we have already demonstrated that the time-to-result was reduced by 2 days as compared to conventional cultures, it is possible that FAPP would have resulted in earlier isolation of patients and prevented the spread of MDR bacteria to other patients. Moreover, the total hospitalization cost was €55 000 per patient meaning that the additional cost associated with the use of FAPP therefore represented 0.6% of the cost of the stay.

Limits

In this study, FAPP was only available from Monday to Friday, from 8am to 6pm. The implementation of this device should be available on week-end to benefit from the rapidity of the results.

In our study, there was no difference of unnecessary broad spectrum antibiotics between the FAPP-based treatment and the real life treatment. This could be explained by the antimicrobial stewardship implemented in our center. In fact, HAP and VAP suspected in traumatic or brain injured patients, are treated with amoxicillin-clavulanate within the first 10 days of hospitalization, due to our local ecology. This led to a relatively low consumption of broad spectrum antibiotics (46% of patients in this cohort). The prescription of broad spectrum antibiotics could be more reduced in other centers.

The study was conducted before covid-19 pandemic crisis, and the SARS-cov2 is not currently detected by FAPP. The advantage of FAPP is its ability to better diagnose coinfections than standard cultures [20], which could be useful in covid-19 patients who frequently develop VAP in case of protracted mechanical ventilation. A study has already investigated the efficacy of

FAPP in 43 critically ill patients with covid-19, showing sensitivity, specificity, positive and negative predictive values of 95%, 99%, 82%, and 100%, respectively [21].

In this monocentric study, there was only 8 patients with infection due to MDR bacteria, which may seem low for VHAP, and could have minimize the effect of FAPP use. In our establishment, MDR are rarely responsible for infections. In this monocentric study, this can minimize the effect of FAPP use.

Finally, the observational design of our study did not permit to draw strong conclusions, and further multicentric studies are needed.

The optimization of empiric antimicrobial therapy is challenging in patients with VAP. In this prospective observational cohort, our results suggest that a rapid syndromic multiplex PCR to identify pathogens and resistance genes in lower respiratory tract specimens has the potential to reduce the use of broad-spectrum antimicrobial therapy without increasing the risk of treatment failure. The confirmation of our results in further interventional studies will be needed before making any recommendations for clinical practice.

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Annexes

Figure S1 FAPP results compared to culture results for bacterial detection

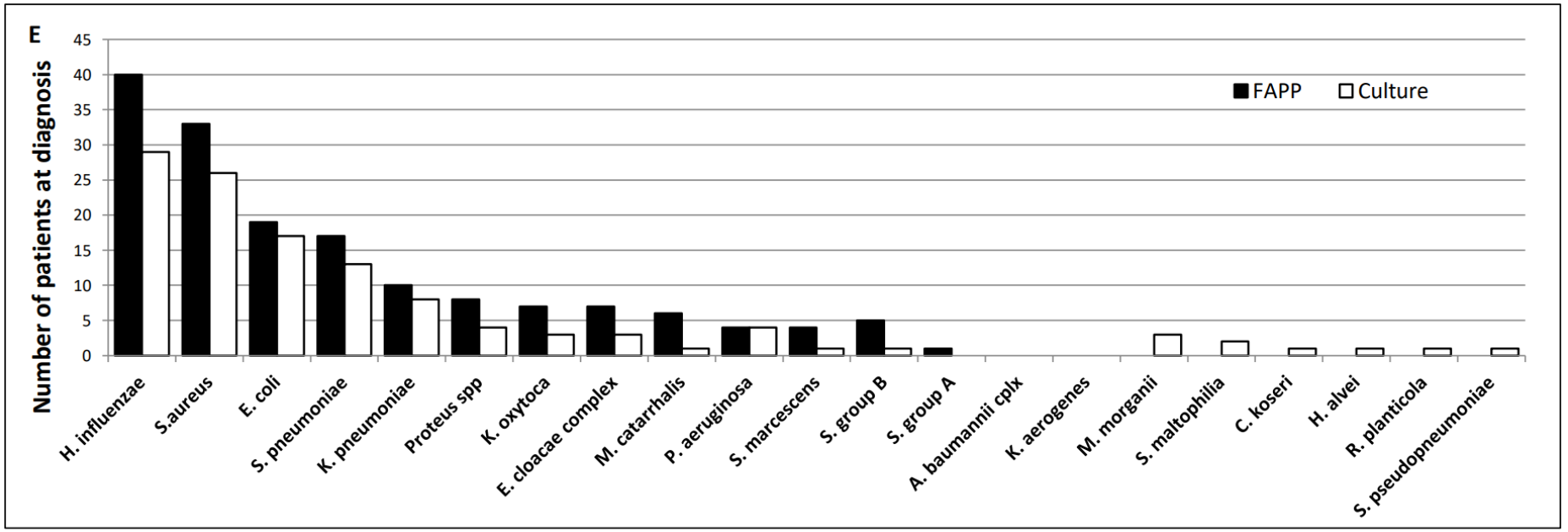

Figure S2: Sankey chart of real antimicrobial therapy realized without PCR (left column), antimicrobial therapy who would have been performed with the result of PCR (Middle column), and the antimicrobial therapy who would have been performed following the actuals guidelines (right column). The lines are colored in red for antibiotic escalation, green for de-escalation and yellow for no changes.

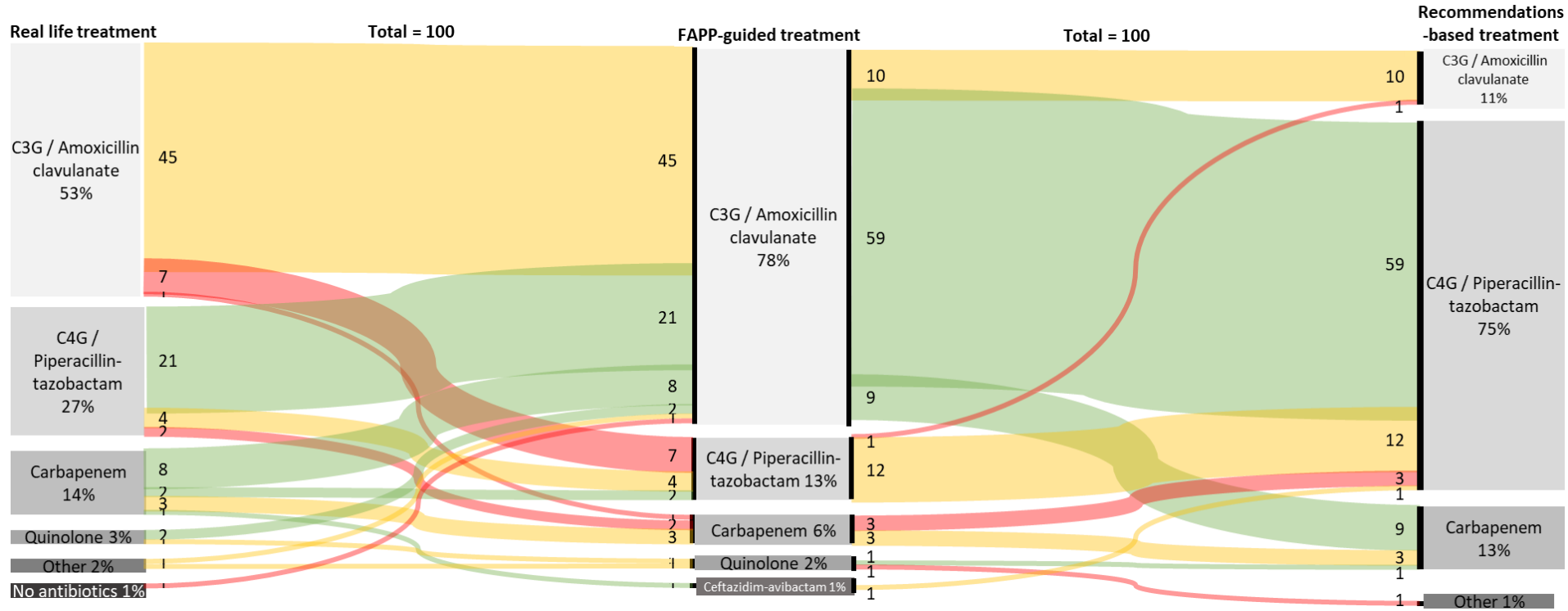

Table S1: Recommendation of enteric antimicrobial therapy guided by multiplex PCR kit results.

Multiplex PCR results		Empiric antibiotherapy recommended	
Positive for Antimicrobial resistance gene	**mecA/C and MREJ** (Methicillin resistance)	Linezolid or Vancomycin	In association, in case of **septic shock or after prior exposure to broad-spectrum** beta-lactams (cefepime, carbapenems) in case of potentially **difficult to treat bacteria**
	CTX-M (ESBL)	Meropenem or Imipenem	
	KPC, Oxa48-like* (Carbapenemases)	Ceftazidime-Avibactam + Colistine	
	NDM, VIM, IMP* (Carbapenemases)	Meropenem of Imipenem + Colistine OR Cefzazidime-Avibactam + Aztreonam	
Potentially difficult to treat bacteria	***A.baumannii***	Meropenem or Imipenem or Ceftazidime	
	E. cloacae	Cefepime	
	K. aerogenes	Cefepime	
	S. marcescens	Cefepime	
	P. aeruginosa	Meropenem or Imipenem or Ceftazidime	
Intracellular bacteria	***L. pneumophila***	Spiramycin + Levofloxacine	
	C. pneumoniae	Spiramycin	
	M. pneumoniae	Spiramycin	
Viruses	***Influenza , B***	Oseltamivir + amoxicillin/clavulanic acid	
	Others	Nothing	
Positive for others	***Proteus sp***	Amoxicillin/clavulanic acid	
	K. pneumoniae	Third generation cephalosporin	
	K. oxytoca	Third generation cephalosporin	
	E. coli	Third generation cephalosporin	
	H. influenzae	Third generation cephalosporin	
	M. catarrhalis	Amoxicillin/clavulanic acid	
	S. aureus	Amoxicillin/clavulanic acid	
	Strepto. A or B	Amoxicillin/clavulanic acid (amoxicillin if no other bacteria is identified)	
	S. pneumoniae	Amoxicillin/clavulanic acid (amoxicillin if no other bacteria is identified)	

Negative for all bacterias and resistance genes tested **	Consider direct exam : - Nothing : Amoxicillin/clavulanic acid - Gram-negative bacilli : consider ***S .maltophilia, M. morganii, C. freundii, C.koseri, H.alvei***	

* Call infectious team and test for Colistine, Tigecycline and Fosfomycine

** Call infectious team

Vu, le Président du Jury,

Professeur David BOUTOILLE

Vu, le Directeur de Thèse,

Professeur Antoine ROQUILLY

Vu, le Doyen de la Faculté,

Professeur Pascale JOLLIET

NOM : GUILLOTIN PRENOM : Florian

Titre de Thèse : POTENTIAL IMPACT ON ANTIMICROBIAL THERAPY OF RAPID MULTIPLEX PCR FOR MICROBIOLOGICAL DIAGNOSIS OF HEALTH CARE ASSOCIATED PNEUMONIA IN CRITICALLY ILL PATIENTS, A PROSPECTIVE OBSERVATIONAL CLINICAL AND ECONOMIC STUDY

RESUME

Objectif

Évaluer l'impact de l'utilisation du FilmArray® Pneumonia *plus* panel (FAPP) sur l'antibiothérapie des patients atteints de pneumonie nosocomial requérant une ventilation mécanique (VHAP) .

Méthodes

Les prélèvements respiratoires de cent patients adultes atteints de VHAP ont été testés à l'aide du FAPP, et cultivé selon les techniques courantes. Les cliniciens en charge des patients n'avait pas connaissance des résultats de la FAPP. L'antibiothérapie empirique basées sur les résultats de la FAPP ont été simulées rétrospectivement par des experts indépendants en aveugle selon un algorithme prédéfini et comparées à 1) celles qui ont été prescrites dans la vie réelle selon les protocoles locaux, et 2) celles qui auraient été prescrites, si les recommandations internationales ERS/ESICM/ESCMID/ALAT avaient été suivies sans les résultats de la FAPP. Le critère d'évaluation principal était le nombre de jours d'antibiotique à large spectre. Les critères d'évaluation secondaires étaient les taux d'échec du traitement microbiologique et le ratio coût-efficacité.

Résultats

La durée médiane d'antibiothérapie à large spectre était de 0 [0-1,25] jour dans la simulation basée sur la FAPP, contre 2 [0-6] jours dans la vie réelle ($p < 0,0001$) et 2 [2-3,25] jours dans la simulation basée sur les recommandations ($p < 0,0001$). L'antibiothérapie empirique aurait été inefficace dans 3 % des cas avec les résultats du FAPP, alors qu'il a été inefficace dans 11 % des cas dans la vie réelle ($p=0,08$) et 6 % des cas avec la simulation basée sur les recommandations ($p=0,37$). Le ratio coût-efficacité était de 1 121 € [-7021 ; 6794] pour éviter un jour d'antibiotique non optimisé, indiquant que l'utilisation du FAPP est plus efficace et plus coûteuse.

Conclusions

Nos résultats suggèrent que l'utilisation du FAPP chez les patients atteints de VHAP a le potentiel de réduire l'utilisation d'une thérapie antimicrobienne à large spectre sans augmenter le risque d'échec du traitement.

MOTS-CLES

PNEUMONIE ASSOCIEE AU SOIN ; PNEUMONIE ACQUISE SOUS VENTILATION MECANIQUE, PCR MULTIPLEXE; ANTIBIOTHERAPIE EMPIRIQUE

Titre de Thèse : POTENTIAL IMPACT ON ANTIMICROBIAL THERAPY OF RAPID MULTIPLEX PCR FOR MICROBIOLOGICAL DIAGNOSIS OF HEALTH CARE ASSOCIATED PNEUMONIA IN CRITICALLY ILL PATIENTS, A PROSPECTIVE OBSERVATIONAL CLINICAL AND ECONOMIC STUDY

Abstract

Objective

To evaluate the impact of the implementation of syndromic multiplex FilmArray® Pneumonia *plus* Panel (FAPP) on the antimicrobial treatment of patients with mechanically ventilated hospital-acquired pneumonia (VHAP).

Methods

Respiratory fluids from one hundred adult patients with VHAP were tested using FAPP. Conventional cultures were performed in parallel. Clinicians in charge of the patients were left blinded to the FAPP results. Antimicrobial therapies based on FAPP results were retrospectively simulated by independent blinded experts according to a predefine algorithm and compared to 1) those that were prescribed in practice according to local guidelines, and 2) those that would had been prescribed, if international ERS/ESICM/ESCMID/ALAT recommendations had been followed without FAPP results. The primary end-point was the number of days of broad-spectrum antimicrobial therapy. Secondary endpoints were rates of microbiological treatment failure, and cost-effectiveness ratio.

Results

The predicted median duration of broad-spectrum antibiotics was and 0 [0-1.25] day in the FAPP-based simulation, versus 2 [0-6] days in real-life ($p < 0.0001$) and 2 [2-3.25] days in the recommendations-based simulation ($p< 0.0001$). Microbial treatment failure was predicted for 3% of cases with FAPP results, versus observed in 11% in real life ($p=0.08$), and 6% with the recommendations-based simulation ($p=0.37$). The incremental cost-effectiveness ratio was 1 121 € [-7021 ; 6794] to avoid one day of non-optimized antibiotic, indicating that FAPP utilization is more effective and more expensive.

Conclusions

Our results suggest that using FAPP in patients with HAP has the potential to reduce the use of broad-spectrum antimicrobial therapy without increasing the risk of treatment failure.

MOTS-CLES

Ventilated associated pneumonia ; Heath care associated pneumonia, Multiplex PCR; Empiric antimicrobial therapy