Point-of-care multiplex molecular diagnosis coupled with procalcitonin-guided algorithm for antibiotic stewardship in lower respiratory tract infection: a randomized controlled trial

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Abstract

Objective: We aimed to show that coupling molecular syndromic respiratory panel (RP) testing with procalcitonin (PCT) measurement in the emergency department improves antibiotic (ATB) stewardship in lower respiratory tract infection (LRTI).

Methods: Open label, prospective, randomized interventional trial, conducted from 2019 to 2022 in an adult emergency department. Patients with a suspicion of LRTI were randomized into an intervention arm (PCT measurement and point of care BIOFIRE® RP2.1 plus testing, accompanied by a recommended ATB algorithm) or a standard of care (SOC) arm (PCT allowed as current practice). The primary endpoint was the duration of antibiotic exposure.

Results: 451 patients were randomized, median age 65 years (Q1-Q3: 49 – 77), hospitalization rate was 59.9% (270/451), median length of stay 5 days (Q1-Q3: 3 – 12), and 28-day mortality rate 5.3% (23/451). The median duration of ATB exposure was 6 days (Q1-Q3: 0 – 9) and 5 days (Q1-Q3: 0 – 9) in the SOC and interventional arm respectively (p=0.71). ATB was started in 29.6 % (67/226) and 33.8% (76/225) respectively (p=0.54). The BIOFIRE® RP2.1 *plus* identified at least one viral species in 112/225 patients (49.8%) of intervention arm. 212/226 (93.8%) SOC patients had PCT measurement. The adherence rate to algorithm in the intervention arm was 93.3 % (210/225).

Conclusion: Displaying PCT and real-time RP results to emergency physicians failed to significantly reduce ATB exposure in LRTI suspicions. However, the median ATB duration and rate of initiation were already low in the SOC arm using PCT measurement routinely.

Rational antibiotic (ATB) use is a major public health objective (1–4). Lower respiratory tract infection (LRTI) suspicion is the primary reason for ATB delivery in the emergency department (ED) (5,6). Procalcitonin (PCT) have been extensively studied in LRTI with numerous interventional trials having reported its usefulness for the reduction of ATB exposure (7–10). Recently, PCR-based multiplex respiratory panels (RP) have been launched on the market, and allow readily available identification of the main respiratory viruses involved in LRTIs. However, conflicting results have been reported to date on their ability to improve ATB stewardship (11–19).

The hypothesis of the PROARRAY trial is that combining PCT plasma measurement and real-time virus identification with point-of-care RP would reduce ATB exposure in LRTI suspicions presenting to the ED, compared to standard of care (SOC).

Methods

PROARRAY was an open label, prospective, single-centre, randomized interventional trial conducted in the adult ED of an academic 1600-bed hospital in Paris, France. Consecutive patients attending the ED with a LRTI suspicion (defined by at least one general symptom – among: sweats, chills, body aches and pain, or temperature >38°C – and at least one respiratory symptom among cough, sputum production, dyspnea, chest pain, or altered breath sounds at auscultation) were screened and included during week days. Exclusion criteria were: prisoner, pregnancy, no social insurance, end of life care, refusing to participate, already enrolled, and contraindication (per the discretion of the attending physician) to a nasopharyngeal swab. The patients with confirmed pulmonary tuberculosis were secondarily excluded from the intention to treat population.

After signing informed consent, included patients were randomized by clinical research assistants (CRA) into the intervention or the SOC arms through a blocked randomisation table generated using SAS® software (version 9.3 or higher, SAS Institute Inc., Cary, NC, USA). The concealment table was kept by CRA who included the patients consecutively and allocated them to the pre-randomized arm accordingly. The intervention consisted of the collection of a nasopharyngeal swab sample for immediate testing by our CRA on a FilmArray® analyzer implemented in the ED, on BIOFIRE® Respiratory Panel (RP) 2 pouch, and a blood sample sent to the laboratory for PCT measurement. The study began using the RP 2 pouch, then 2.1 *plus* when it became available in October 2020, (which included SARS-CoV-2). The BIOFIRE® Respiratory Panel 2.1 *plus* (RP2.1 *plus*) is a multiplexed nucleic acid test for the simultaneous identification of respiratory viral and bacterial nucleic acids (supplementary material 1).

Both PCT and RP2.1 *plus* results were reported in real-time by the clinical research assistants to the treating physicians along with recommendations based on results: to withhold or withdraw ATB if PCT<0.10 µg/L and RP2.1 *plus* assay was negative or indicated a viral respiratory pathogen only, or if PCT<0.25 µg/L and RP2.1 *plus* was positive with a viral respiratory pathogen. ATB starting was discouraged if PCT< 0.25 µg/L along with a negative RP2.1 *plus assay,* and suggested if PCT > 0.25 µg/L, whatever the RP2.1 *plus* assay was. As *per* routine practice in our ED, ATB initiation was discouraged for SOC patients having a PCT measurement < 0.25 µg/L. (usual cut-off applied in PCT-based algorithm for LRTIs) (7,8,20). The SOC was at the discretion of the emergency physician and could comprise a PCT measurement (as current practice in our ED), but no nasopharyngeal swab was performed except from October 2020 when LampPCR for SARS-CoV-2 only was requested for hospitalized patients. Because the period of inclusion partially overlapped the COVID-19

pandemic, during the first wave the inclusions were temporarily suspended between March 2020 and June 2020, as it was judged unethical not to perform SARS-CoV-2 testing in SOC arm (supplementary materials 2). Then, all screened patients first had a nasopharyngeal swab for SARS-CoV-2 PCR testing only and were excluded if positive. Secondarily, and as soon as it was available, we switched from RP 2 plus panel to RP2.1 *plus* panel (that comprised SARS-CoV-2 detection) and included COVID-19 patients (amendment submitted to and accepted by the ethical committee).

The PROARRAY trial was approved by the ethical committee on January 19th, 2019 (CPP du Sud Ouest et Outre-Mer 4, Number 18-087a), and registered on ClinicalTrials.gov under identifier NCT03840603.

Outcomes

The primary endpoint was the duration of total antibiotic exposure prescribed within 28 days (measured in days). Secondary enpoints were: protocol "failure" within 15 days of randomization (defined as worsening of LRTI and/or receipt of ATB in cases where no initial ATB treatment was administered, and/or unplanned ED's re-admission for the same complaint), hospitalization from the ED (%), number of antibiotic-free days in the first 28 days after randomization, and length of stay (LOS) in the emergency room for outpatients. Demographic data, past medical history, assessment of vital signs and symptoms at admission were prospectively collected. The final diagnosis was extracted from the conclusion of the medical file. The ED physician decision for ATB was recorded, before and after RP2.1 *plus* panel and PCT results in the intervention arm. The patients hospitalized after ED admission were followed-up until day-28 through the medical record; outpatients (and inpatients discharged before day-7) were contacted by phone on day-7 and day-28 to

record ATB treatment duration or readmission. In the intervention arm, we also recorded ATB decisions not following the algorithm (overruling), and the reason why.

Sample size calculation

In the previous published PROREAL multi-center study, the mean ATB treatment duration reported for our center was 8.3 ± 7.5 days (median: 9.0) (7). An evaluable sample of 444 patients (222 per study arm) was expected to provide 80% power to detect a difference of 2 days between the intervention and SOC arms. This assumed a common standard deviation of 7.5 days and a statistical significance set at the two-sided 5% level.

Statistical methods

Normality was tested in each arm with Kolmogorov Smirnov test in addition to visual analysis of the primary endpoint distribution. The primary endpoint was compared between the two arms (intervention and SOC) using a Student t test (assuming equal variance or not) if normally distributed, and with non-parametric Mann Whitney test if not. Antibiotic exposure status was then dichotomized as “better or equal” or “worse” than the median of SOC arm and was analyzed with a binary logistic regression adjusted on age, sex, LRTI confirmed, COPD, Immunosuppression and SOFA score. For other quantitative endpoints, same analysis as primary endpoint was done. Qualitative variables were compared between the two arms using a Chi-Square or Fisher Exact test (if the Chi-Square test was not applicable). Survival curves were plotted using the Kaplan-Meier estimator and were compared between the two arms using the log-rank test. Sensitivity analyses were performed on the following subgroups of patients: LRTI-confirmed, algorithm adherent, randomized before the first COVID-19 wave

(March 2020), ambulatory, and hospitalized. All analyses presented concern the ITT population. Statistical analyses were performed by BIOFORTIS using SAS® software version 9.4 or higher (SAS Institute Inc., Cary, NC, USA).

Results

Population

From July 17th, 2019 to June 10th, 2022, 828 patients were screened and 451 randomized (226 in SOC arm, 225 in Intervention arm), constituting the intention to treat population (ITT). 10/451 (2.2%) prematurely withdrew and 14/451 patients (3.1%) of the ITT population presented major deviations to the protocol and were therefore excluded from the per protocol population (PP) (figure 1). The main descriptive characteristics of the population are represented in table 1. A small majority of patients were men (56.5%) and the median age was 65 years (Q1-Q3: 49 – 77). The majority of the population reported at least one significant medical past history, with cardio-vascular history being the most prevalent. Community acquired pneumonia (CAP) and COVID-19 were the most frequent LRTIs in the population. Among all LRTI suspicions, 25.5% (115/451) had an alternative final diagnosis (table 1). 270/451 patients (60%) were hospitalized, 39/413 (9.4%) in intensive care units, and the 28-days mortality rate was 5.3% (23/432) (table 2).

Exposure to ATB

The median number of days of antibiotic exposure prescribed (primary endpoint) was 6 days in SOC (Q1-Q3: 0 – 9) and 5 days in Intervention arm (Q1-Q3: 0 – 9), a difference that was not statistically significant (p=0.71) (table 2).

In the ER, 168/451 patients (37.2%) were started antibiotic (SOC arm: 67 (29.6%), intervention arm: 76 patients (33.8%) *p*=0.54) or maintained (for patients already on antibiotics: 14 (6.2%) and 11 patients (4.9%) respectively).

Sensitivity analyses on subgroups showed no significant difference on antibiotic exposure between both arms: LRTI-confirmed subjects, patients randomized before March 2020, patients following the algorithm recommendations in the Intervention arm, ambulatory patients only and hospitalized patients. The time to ATB discontinuation is represented in figure 2 where no significant difference was shown (*p*=0.65). There were 100 patients (47.2%) in the SOC and 108 (50.5%) in the intervention arm for whom the ATB exposure was below the SOC median (6 days) (*p*=0.58). After binary logistic regression, ATB exposure status was not significantly different between groups (OR = 1.12; 95%CI = [0.75; 1.66]).

The protocol failure rate (as defined in method section) was not different in SOC and intervention arm: 17/168 (10.1%) and 26/179 (14.5%) respectively (*p*=0.21).

Other outcomes

The median LOS in the emergency room for outpatients was significantly lower in the intervention arm compared to SOC (5.68 *versus* 6.47 hours respectively, *p*=0.04). Conversely, hospital admission rates (134/226 (59.3%) *vs* 136/225 (60.4 %), *p*=0.80), ICU admission rates (23/226 (11.1%) *vs* 16/225 (7.8 %), *p*=0.26), total length of stay in hospital (5.5 days (Q1-Q3: 0 – 13) *vs* 4.0 days (Q1-Q3: 0 – 11), *p*=0.50), and number of days of isolation (0 days (Q1-Q3: 0 - 6) *vs* 0 days (Q1-Q3: 0-4), *p*=0.68)) were not significantly different between SOC and intervention arms respectively.

Virus distribution and PCT concentrations

The distribution of the viruses identified by the RP2.1 *plus*, and the corresponding concentrations of PCT are represented in supplementary material 3. Among patients in Intervention arm, 112 (49.8%) had an RP2.1 *plus* test positive for at least one virus species. Of them, only 25 (22.5%) had PCT concentrations above the 0.25 µg/L threshold, including 9 SARS-CoV-2 and 5 Influenza virus.

Algorithm adherence

Taking into account both PCT and RP2.1 *plus* results (intervention arm only) there were 15 (6.7%) overruling decisions for ATB (7 of them having a negative RP2.1 *plus* test). The main reasons reported for overruling were imaging evocative of pneumonia (chest X-ray and/or thoracic CTscan) and identification of another infectious source (mainly urinary tract).

Discussion

The hypothesis of the PROARRAY trial was that combining PCT measurement with point-of care RP would reduce ATB exposure compared to SOC. In the results we report here, this intervention did not improve ATB exposure compared to SOC (which included routine PCT measurement). Of note, in this cohort we report a low rate of ATB initiation (32.7%) among patients with a LRTI suspicion, whereas several surveys have reported much higher rates ranging from 44 to 83% (5,19,21–23). To our knowledge, the PROARRAY trial is the largest

having studied PCT in conjunction with RP intervention, and the only conducted both before and during the COVID-19 pandemic period.

ATB stewardship and rational use in LRTI can be achieved with the help of host response biomarkers to infection like PCT, and direct identification of the causative pathogen like RP (20,24-25).. However, conflicting results have been reported about the place and efficiency of those RP in ATB stewardship, with a majority of studies being observational and not randomized (14,17,19,26,27). Moreover, very few have studied the combination of both PCT-algorithm and RP (11,12,16). In a north-American trial on adult LRTI patients admitted in wards (with the exclusion of CAP), Branche et al. failed to report a significant difference in ATB use between a SOC arm and the combination of PCT and RP (16). However, subgroup analyses revealed that fewer subjects with positive results of viral testing and low PCT values were discharged with ATB (20% vs 45%; p=0.002) and that shorter antibiotic duration was observed among algorithm-adherent intervention patients (64% of intervention arm) versus non-intervention patients (2.0 vs 4.0 days; p=0.004). In this PROARRAY trial, adherence to the algorithm was very high (89.6%), even in SOC arm for PCT which was currently used. Indeed, our emergency physician team had a 15-years long experience with PCT-guided algorithm (7,20,24), which may have contributed to the lower median ATB duration (6.0 days) observed than hypothesized (9.0 days), and to the low rate of ATB initiation reported here (32.7%). In other words, we cannot exclude that using in current practice a PCT algorithm may partly explain the apparent absence of added effect of RP on ATB stewardship.

In this study, we confirm the feasibility of point-of-care RP2.1 *plus* testing in the ED, for readily available information at the bedside. In a LRTI trial conducted in Argentina with

adults and children, Echavarria et al. reported significantly more frequent ATB withholding in the FilmArray arm (Biofire RP2) compared to immunofluorescence assay and a median time to result of 1 hour 52 minutes and 26 hours 40 minutes respectively (13). The RP2.1 *plus* test positivity rate of 49.8% in PROARRAY was high and therefore informative, similar to what has been reported previously (16,27). Moreover, the Biofire RP2.1 *plus* panel has also been used as a room triage tool. With the restricted number of beds downstream the ED, it may help in organizing isolation. Finally, displaying to outpatients (and therefore general practitioner) the result of RP before leaving the ED may strengthen adherence to not start ATB.

PCT has been reported to be helpful to diagnose viral LRTI, by using its negative predictive value for a bacterial etiology (28). We confirm here that the large majority of LRTI-suspected patients for which RP2.1 *plus* identified a viral species, had PCT concentrations below 0.25 µg/L (77.5%) (Supplementary material 3). Among the 25 patients above this cut-off, 14 had SARS-CoV-2 or Influenza infections. High PCT concentrations have been reported among those with viral infections, in case of bacterial superinfection or of major inflammatory syndrome related to the cytokine storm observed in several COVID-19 (29–31).

The PROARRAY trial has strengths and limitations. As strengths, we acknowledge the prospective and randomized design, the large population size covering 3 winter seasons and the COVID-19 pandemic, and finally the high rate of algorithm adherence, as it was reported to be an independent variable associated with ATB duration reduction (7). As limitations: firstly, PROARRAY is a single center trial and we cannot exclude a center bias. Secondly, the use of PCT measurement in the SOC group as current practice, limits the interpretation of the respective part of PCT and RP in ATB stewardship. However, as PCT measurement has

been implemented for 15 years in our ED, we thought that it would have been unethical to prohibit PCT measurement in SOC arm. Thirdly, the intervention took place at the ED level and we had no control on ATB prescription or RP ordering in medical wards or external primary care, after patients left the ED. Therefore, we cannot exclude that several patients in SOC arm may had benefited from RP ordering in wards.

In conclusion, the combination of PCT measurement and point-of-care RP2.1 *plus* panel in patients attending the ED for LRTI suspicion did not improve the ATB exposure compared to a SOC already practicing a PCT algorithm for ATB stewardship.

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Author contributions

LV: conceptualization, methodology, investigation, review and editing original draft.

MC: conceptualization, investigation, review and editing original draft.

DB: resources and validation of Biofire ® tests, editing original draft

IC and EH: investigation (patient inclusion, data collection)

AA: formal analysis, data curation, editing original draft, visualization

PH: conceptualization, methodology, investigation, writing original draft and editing, visualization, supervision, funding acquisition.

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Table 1 : Subjects characteristics at baseline

Variable	Standard of Care (n=226)	Intervention (n=225)	P value
Gender			0.42 (†)
Male	132 (58.4)	123 (54.7)	
Female	94 (41.6)	102 (45.3)	
Age at inclusion			0.42 (‡)
Mean (SD)	63.2 (19.3)	61.7 (19.5)	
(Min ; Max)	(19.0 ; 99.0)	(20.0 ; 99.0)	
Median (Q1 ; Q3)	66.0 (49.0 ; 78.0)	65.0 (49.0 ; 76.0)	
Past medical history	203 (89.8%)	199 (88.4%)	
ENT/Oculars	26 (11.5%)	25 (11.1%)	
Cardio-vascular	129 (57.1%)	119 (52.9%)	
Locomotors/Rheumatologic	43 (19.0%)	47 (20.9%)	
Endocrine/Hematologic	53 (23.5%)	55 (24.4%)	
Respiratory	78 (34.5%)	79 (35.1%)	
Neurologic/Psychiatric	49 (21.7%)	56 (24.9%)	
Gastro-intestinal	66 (29.2%)	61 (27.1%)	
Dermatological	9 (4.0%)	5 (2.2%)	
Metabolic	38 (16.8%)	35 (15.6%)	
Immunological	9 (4.0%)	7 (3.1%)	
Nephro-urological	41 (18.1%)	40 (17.8%)	
Gynecological	17 (7.5%)	25 (11.1%)	
Allergy	3 (1.3%)	3 (1.3%)	
Other	47 (20.8%)	42 (18.7%)	
Systolic Blood Pressure (mmHg)			0.78 (‡)
N	226	225	
Mean (SD)	121.1 (20.4)	121.7 (20.5)	
Median (Q1 ; Q3)	119.5 (106.0 ; 134.0)	120.0 (107.0 ; 136.0)	
Diastolic Blood Pressure (mmHg)			0.98 (‡)
Mean (SD)	70.7 (14.1)	70.7 (15.0)	
Median (Q1 ; Q3)	70.0 (61.0 ; 80.0)	71.0 (59.0 ; 80.0)	
Missing	1	0	
Heart rate (bpm)			0.25 (‡)
Mean (SD)	96.5 (19.2)	98.0 (17.3)	
Median (Q1 ; Q3)	95.5 (83.0 ; 109.0)	99.0 (85.0 ; 111.0)	
Respiratory Rate (breaths/min)			0.37 (‡)
Mean (SD)	24.8 (6.4)	24.6 (6.9)	
Median (Q1 ; Q3)	24.0 (20.0 ; 30.0)	24.0 (20.0 ; 28.0)	
Missing	37	33	
Temperature (°C)			0.77 (‡)
Mean (SD)	37.7 (1.0)	37.8 (1.0)	
Median (Q1 ; Q3)	37.7 (36.9 ; 38.5)	37.8 (36.9 ; 38.5)	
SpO2 (%)			0.21 (‡)
Mean (SD)	94.4 (3.9)	93.7 (4.4)	
Median (Q1 ; Q3)	95.0 (93.0 ; 97.0)	95.0 (92.0 ; 97.0)	
Symptoms			
Sweats	37 (16.4)	31 (13.8)	
Chills	69 (30.5)	53 (23.6)	
Body aches and pain	70 (31.0)	75 (33.3)	

Variable	Standard of Care (n=226)	Intervention (n=225)	P value
Cough	139 (61.5)	151 (67.1)	
Sputum production	56 (24.8)	67 (29.8)	
Dyspnea	164 (72.6)	161 (71.6)	
Chest pain	46 (20.4)	43 (19.1)	
Auscultation altered sounds	61 (27.0)	50 (22.2)	
Main diagnosis			
CAP	67 (29.6)	62 (27.6)	0.62 (†)
AECOPD	11 (4.9)	20 (8.9)	0.09 (†)
Acute bronchitis	12 (5.3)	12 (5.3)	0.99 (†)
Asthma decompensation	4 (1.8)	5 (2.2)	0.75 (†)
Flu	4 (1.8)	30 (13.3)	<0.0001 (†)
COVID-19	53 (23.5)	38 (16.9)	0.08 (†)
Influenza-like illness	15 (6.6)	11 (4.9)	0.43 (†)
Heart or respiratory failure	16 (7.1)	18 (8.0)	0.71 (†)
Other extra respiratory infection	42 (18.6)	27 (12.0)	0.05 (†)
Pulmonary embolism	2 (0.9)	2 (0.9)	1.00 (†)
LRTI confirmed?			0.17 (†)
Yes	162 (71.7)	174 (77.3)	

Modalities of qualitative variables are presented as n (%).
SBP: systolic blood pressure. Bpm: beat per minute. SpO2: pulse peripheral oxygen saturation. CAP: community acquired pneumonia. AECOPD: acute exacerbation of chronic obstructive pulmonary disease. ICU: intensive care unit. NA: not available. LOS: length of stay
(†): Chi-square test was used; (‡): Mann-Whitney U test was used

Table 2: Outcomes according to the group

Variable	Standard of Care (n=226)	Intervention (n=225)	P value
Primary outcome			
Number of days of antibiotic exposure prescribed during the 28 days follow-up			0.71 (‡)
Patients N	212	214	
Missing	14	11	
Mean (SD)	6.25 (6.99)	6.06 (7.00)	
(Min ; Max)	(0.00 ; 28.00)	(0.00 ; 28.00)	
Median (Q1 ; Q3)	6.00 (0.00 ; 9.00)	5.00 (0.00 ; 9.00)	
Secondary outcomes			
Initiation of an antibiotic therapy in the first 28 days after inclusion			0.54 (†)
Yes	67 (31.3)	76 (34.1)	
Missing/NA	12	2	
Initiation of an antibiotic therapy outside ED			0.36 (†)
Yes	54 (25.2)	48 (21.5)	
Missing/NA	12	2	
Hospital Admission			0.80 (†)
Yes	134 (59.3)	136 (60.4)	
Missing	0	0	
ICU admission			0.26 (†)
Yes	23 (11.1)	16 (7.8)	
Missing/NA	18	20	
Length of stay in the ED for non-admitted patients (hours)			0.036 (‡)
Mean (SD)	6.68 (2.69)	5.98 (2.13)	
(Min ; Max)	(0.05 ; 18.85)	(0.88 ; 14.05)	
Median (Q1 ; Q3)	6.47 (4.98 ; 8.02)	5.68 (4.60 ; 7.07)	
Length of stay in hospital, included ICU (in days)			0.51 (‡)
N	222	216	
Mean (SD)	7.8 (8.6)	7.1 (8.2)	
Median (Q1 ; Q3)	5.5 (0.0 ; 13.0)	4.0 (0.0 ; 11.0)	
Missing	4	9	
All-cause mortality (in the first 28 days after randomization)			0.54 (†)
Yes	13 (6.0)	10 (4.7)	
Missing/NA	9	10	
PCT measurement (µg/L)			0.84 (‡)
N	212	222	
Mean (SD)	0.87 (3.43)	1.43 (6.67)	
Median (Q1 ; Q3)	0.12 (0.06 ; 0.45)	0.12 (0.06 ; 0.43)	
Missing	14	3	
Identification of at least one specific virus in the ED			
Yes	NA	112 (49.8)	

Modalities of qualitative variables are presented as n (%). SBP: systolic blood pressure. Bpm: beat per minute. SpO2: pulse peripheral oxygen saturation. CAP: community acquired pneumonia. AECOPD: acute exacerbation of chronic obstructive pulmonary disease. ICU: intensive care unit. NA: not available. LOS: length of stay

(†): Chi-square test was used; (‡): Mann-Whitney U test was used

Figure 1: flow chart of PROARRAY trial

Figure 2: Survival curves of time-to-antibiotic discontinuation