Pulmonary bacterial infections in patients hospitalized for COVID-19: a retrospective observational study

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Research article

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Abstract

Backround

During the COVID-19 pandemic, antibiotics use was very common. However, bacterial co/secondary infections with coronaviruses remain largely unknown, especially outside of intensive care. The aim of this study was to investigate the pulmonary bacterial infections characteristics associated with COVID-19 in hospitalized patients.

Methods

A retrospective monocentric observational study was conducted in Bichat hospital in France, between February 26 and April 22, 2020. All patients hospitalized in standard wards with COVID-19 (positive nasopharyngeal PCR and/or typical aspect on CT scan) and diagnosed with a pulmonary bacterial infection (positive bacteriological samples) were included. Bacteriological and clinical data were collected from the microbiology laboratories and the patient's medical records.

Results

Twenty-three bacteriological samples from 22 patients were positive out of 2075 screened samples (1.1%) from 784 patients (2.8%). Bacterial infection occurred with a median of ten days after COVID-19 onset. Diagnosis of pulmonary bacterial infection was suspected on the increase of oxygen requirements (20/22), productive cough or modification of sputum (17/22), or fever (10/22). Positive samples included 13 sputum cultures, one Film Array® on sputum, one bronchoalveolar lavage, six blood cultures and two pneumococcal antigenuria. The most frequent bacteria were *Pseudomonas aeruginosa* (6/23), *Staphylococcus aureus* (5/23), *Streptococcus pneumoniae* (4/23), *Enterococcus faecalis* (3/23) and *Klebsiella aerogenes* (3/23). No *Legionella* antigenuria was positive. Four out of 496 nasopharyngeal PCR (0.8%) were positive for intracellular bacteria (two *Bordetella pertussis* and two *Mycoplasma pneumonia*).

Conclusions

Pulmonary bacterial secondary infections and co-infections with SARS-CoV-2 are uncommon. Antibiotic use should remain limited in the management of COVID-19.

Backround

Over the last century, the emergence of new viral respiratory tract infections with high epidemic potential has focused global attention [1, 2]. From the Spanish Flu to the current new Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), each of these modern pandemics are responsible for numerous

deaths [3, 4]. Pulmonary bacterial infections, a key factor in the potential severity of viral infections [5], are still poorly known with Human coronavirus. Few studies investigated the co-infection and secondary infection rates. One reported up to 10% rate with *Mycoplasma, Legionella* and *Streptococcus pneumonia* in Severe Acute Respiratory Syndrome (SARS) [6] and 1% with *Mycoplasma*, *Legionella* and *Chlamydia spp*. in Middle East Respiratory Syndrome (MERS) [7]. Recent studies regarding COVID-19 reported highly variable rates of bacterial infection, up to 45% [8, 9]. However, most studies focused on intensive care patients and ventilator associated pneumonia [10, 11].

Antibiotics have been extensively used during the first outbreaks of SARS-CoV-2 [8 12]. The main reasons were symptom similarities between COVID-19 and pulmonary bacterial infections, the severity of SARS-CoV-2 pneumonia, and the lack of knowledge of the virus pathogenicity. Based on early data reported on COVID-19, it is time to question whether the broad use of antibacterials is warranted, especially in the context of rising antibiotic resistance.

Thus, a retrospective study of documented pulmonary bacterial co/secondary infections in COVID-19 hospitalized patients in standard wards was conducted. The aim of this study was to investigate the characteristics of pulmonary bacterial infections associated with COVID-19 in hospitalized patients.

Methods

Study design

A monocentric retrospective observational study was conducted in Bichat University Hospital in Paris, France, during the SARS-CoV-2 outbreak. All departments in charge of SARS-CoV-2 infected patients, except intensive care units, participated in this study. The microbiological database of the hospital's bacteriological department was screened to identify positive respiratory tract secretions sample (sputum samples, bronchial aspirations and bronchoalveolar lavages), urinary antigen (pneumococcal and *Legionella*) tests and blood cultures of hospitalised SARS-CoV-2 infected patients, between February 22 and April 22, 2020. The hospital activity based payment registry was assessed for all patients diagnosed with COVID-19, to recover positive bacterial nasopharyngeal PCR (QIAstat-Dx® or BIOFIRE® RP2.1+) for hospitalised patients during the same period. Microbiological investigations and biological samples were obtained as part of the routine patient care, at the discretion of the treating physician.

Sputum cultures were considered positive regardless of the culture threshold if one or several bacteria were isolated from quality sample, defined by at least > 10 leukocytes/field and < 25 epithelial cells/field. Film arrays® on sputum samples, bronchial aspirations and bronchoalveolar lavages were included if one or several bacteria were found, regardless of the threshold. Data collection was further completed using the hospital electronic medical records of patients identified.

The authors evaluated the likelihood of pulmonary origin for each positive blood culture based on clinical examination, context, imaging and microbiological investigations. An acute bacterial infection was

defined as either co-infection at the symptoms onset, or secondary infection occurring during the course of illness or hospitalisation [8].

Patient inclusion

All patients with the following criteria were included:

- Patients over 18 years old hospitalised in a ward in charge of SARS-CoV-2 infection.
- SARS-CoV-2 infection diagnosed on microbiological criteria (positive PCR on nasopharyngeal swab) and/or imaging criteria (typical aspect on CT scan).
- Positive bacterial exam with either positive respiratory tract secretions sample (PCR, sputum samples, bronchial aspirations and bronchoalveolar lavages), urinary antigen (pneumococcal and *Legionella*) tests or blood culture.

Patients were excluded if they met the following criteria:

- Invasive ventilation prior to the documented bacterial exam.
- Positive blood culture with presumed extra-pulmonary origin or considered as a contamination.
- Positive respiratory tract sample considered as a colonisation.

Data collection

A standardized form on Excel was used for data collection. Data were collected on demographics, bacterial infection risk factors, clinical parameters, inflammatory biomarkers within the 24 hours following the day of the suspected infection and the previous and following values (at least 48 hours from the suspected day of infection), bacteriological samples (respiratory tract secretions samples, urinary antigen (pneumococcal and *Legionella*) and blood culture), thoracic CT scan on admission and in the 48 hours following the day of the suspected infection, specific COVID-19 antiviral and immunomodulatory treatment, empirical antibiotic therapy, duration of treatment, and final outcome at discharge from the unit.

Depending on the severity of the viral infection, patients were treated according to the local guidelines at the time of the screening and research protocols, using high dose of glucocorticosteroids (Dexamethasone) and immunomodulators (Anakinra or Tocilizumab). The imaging classification of the present study was based on the French Society of Radiology's SARS-CoV-2 classification system: mild (< 10%), moderate (10–25%), extended (25–50%), severe (50–75%) and critical (> 75%) [13]. Patients were treated by the attending physicians from the participating wards, who decided whether it was an actual infection requiring antibacterial treatment.

Statistical analysis

All continuous variables were either expressed as median and interquartile range or means and confidence intervals. Categorical variables were expressed in number and percentage. Paired samples t-

test was used to compare continuous variables among patients at different time points. All statistical analyses were performed using Excel sheets.

Results

A total of 784 patients were hospitalized with COVID-19 during the inclusion period. Forty-six among 2075 (2.2%) samples were positive for bacteria of which 23 samples were excluded. Finally, 23 samples (1.1%) from 22 patients (2.8%) were identified as secondary pulmonary infections and included in the final selection (Fig. 1). Patients' characteristics are presented in Table 1. Pulmonary bacterial infection occurred with a median of ten days after COVID-19 onset. Diagnosis of bacterial infection was suspected on the increase of oxygen requirements (20/22), productive cough or modification of sputum (17/22) and/or fever (10/22). Positive samples included 13 sputum cultures, one Film Array® on sputum (negative on sputum culture), one bronchoalveolar lavage, six blood cultures and two pneumococcal antigenuria. For any given bacterial infection, only a single positive sample was found. The most frequent bacteria were *Pseudomonas aeruginosa* (6/23), *Staphylococcus aureus* (5/23), *Streptococcus pneumoniae* (4/23), *Enterococcus faecalis* (3/23) and *Klebsiella aerogenes* (3/23). No *Legionella* antigenuria was positive. Detailed data of positive bacteriological samples are shown in Table 2.

Table 1
Characteristics of patients with confirmed bacterial infection

	Total **n = 22 patients**
Patients characteristics	
Age (years), median [IQR]	69 [52;84]
Male sex, n (%)	19 (86.4)
Smoking habits, n (%)	13 (59.0)
Underlying medical condition, n (%)	17 (77.3)
Chronic lung disease	9
COPD	7
Other	2
Lung bacterial colonization < 3 months	3
Immunosuppressive disease	10
Diabetes mellitus	3
Severe kidney impairment	3
Other	4
SARS-CoV-2 infection characteristics	
Positive COVID-19 PCR	22 (100%)
Empirical antibiotics, n (%)	12 (54.6)
Immunomodulatory treatment, n (%)	14 (63.6)
Corticosteroid	14
Anakinra	6
Other	2
Initial CT scan, n (%)	22 (100%)
Parenchymal involvement	
≤ 25%	11 (50.0%)
25–50%	7 (31.8%)
50–75%	1 (4.5%)

IQR: interquartile range, COPD: Chronic obstructive pulmonary disease

	Total n = 22 patients
Atypical	3 (13.6%)
Pulmonary consolidation	17 (77.3%)
Bacterial infection characteristics	
Time since COVID-19 onset (days), median [IQR]	10 [4;21]
Clinical signs, n (%)	
Increased oxygen requirements	20 (90.9%)
Productive cough or modification of sputum	17 (77.3%)
Fever	10 (45.0%)
Sepsis	2 (9.1%)
Chest Pain	1 (4.5%)
Outcome at transfer	
Discharged from hospital *, n (%)	9 (40.9%)
Death, n (%)	8 (36.4%)
Intensive care, n (%)	5 (22.7%)
IQR: interquartile range, COPD: Chronic obstructive pulmonary disease	

Table 2
Results of bacteriological samples

Pathogens	Number of positive bacteria n/23 (%)	Blood Culture	Sputum Culture	Sputum Film Array®	BAL	Pneumococcal antigenuria
Pseudomonas aeruginosa	6 (26.1%)	1	4		1	
Staphylococcus aureus	5 (21.7%)	2	3			
Streptococcus pneumoniae	4 (17.4%)	1	1			2
Enterococcus faecalis	3 (13.0%)	1	2			
Klebsiella aerogenes	3 (13.0%)		3			
Haemophilus influenzae	2 (8.7%)		1	1		
Hafnia alvei	1 (4.3%)		1			
Corynebacterium spp	1 (4.3%)	1				
Morganella morganii	1 (4.3%)		1			
Escherichia coli	1 (4.3%)		1			
Citrobacter koseri	1 (4.3%)		1			
Polymicrobial infection	5 (21.7%)		5			

Total number of pathogens exceeds total number of samples since more than one isolate have been identified in a single culture (with a maximum of three bacteria). BAL: broncho alveolar lavage

The mean level of neutrophil count before infection was 7905/mm3, at the day of infection 9546/mm3 and after 8056/mm3 (Fig. 2A). The differences were non-significant, respectively $p = 0.15$ and $p = 0.07$. Similarly, there was no difference for the mean CRP levels before (124 mg/dl), during (98 mg/dl) or after bacterial infection (78 mg/dl), respectively $p = 0.37$ and $p = 0.26$ (Fig. 2B). Leukocyte count data are not shown, and the differences were also non-significant. Lack of data prevented procalcitonin (PCT) analyses.

At admission, 11 patients (50%) had mild to moderate parenchymal involvement and 17 patients (77.3%) had pulmonary consolidation. Only ten patients (45.5%) had a CT-scan in the 48 hours following the

suspicion of secondary infection, preventing comparison between the diagnosis day and the suspected bacterial infection day. Among them, the CT scan control showed a lung consolidation appearance in five patients (50%) and the worsening of at least one previous lung consolidation in three patients (30%).

Finally, among the 22 patients with documented bacterial infections, nine (40.9%) were discharged from hospital, five (22.7%) were transferred to an intensive care unit and eight (36.4%) died in the standard ward. The transfer to intensive care unit occurred mostly the day of the bacterial infection suspicion. Out of these five patients, four survived after the intensive care, and one died.

A total of 496 multiplex PCRs on nasopharyngeal swab were carried out. Seven were positive including three samples later excluded due to the absence of associated SARS-CoV-2 infection (Fig. 3). Four patients (0.8%) had co-infections: two *Mycoplasma pneumonia* and two *Bordetella pertussis.* The median age was 56 years, 3 were men. The patients with whooping cough, including one with an underlying sarcoidosis under corticoids, were more severe, requiring oxygen support. *Mycoplasma pneumonia* infections were from a family cluster and mild, without any specific symptoms.

Discussion

In this retrospective study of 784 patients hospitalized in standard wards with COVID-19, only twenty-three bacteriological samples from 22 patients were positive out of the 2075 screened samples (1.1%). Additionally, only four out of 496 nasopharyngeal PCRs (0.8%) were positive for intracellular bacteria (two *Bordetella pertussis* and two *Mycoplasma pneumonia*). No legionella was found in this study.

Overall, only a very small fraction of microbiological testing revealed positive samples, leading to the positive diagnosis of secondary infection. Recent meta-analyses showed an overall prevalence of 7% of bacterial infection in hospitalized COVID-19 patients [8, 9], with 3,5% of co-infections and 14.3% of secondary infections [8]. It is noteworthy that there was a high heterogeneity including various populations (ICU and non ICU patients), antibiotics policies and microbiological samplings. Furthermore, several recent observational studies showed a bacterial infection rate between 4,7 and 6,1% [14–16], including for some of them ICU and non ICU patients and bacteremia from extra-pulmonary origin. This low rate of bacterial infection has to be confronted with the rate of antibiotic prescription in patients with COVID-19, reported as high as 72% [8, 16]. Broad spectrum antibiotics were mainly used and varied with the study. The extreme protective and cleaning measures in place for COVID-19 patient treatment can also be highlighted as a potential limiting factor in secondary bacterial infection occurrence.

The present study showed a relatively high proportion of aged men and comorbities among its patients including underlying pulmonary diseases (COPD, asthma), underlying immunosuppression factors (diabetes mellitus, kidney failure …) or immunosuppressive therapy. The lack of control group prevented any comparison to highlight potential risk factors for co or secondary infection.

Microbiological results were varied with a balanced ratio between gram-positive cocci and gram-negative bacilli. Main bacteria were *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Streptococcus*

pneumonia. This distribution contrasts with previous findings on other viruses describing a possible association between influenza virus, rhinovirus, hMPV and *S. aureus*, and *Klebsiella* spp [17]. Similarly, the same study suggested an association of regular coronavirus, parainfluenza virus and RSV infections with *Acinetobacter* spp. and *Klebsiella* spp. The previously described meta-analysis showed mainly *M. pneumonia* (42%), *P. aeruginosa* (12%) and *H. influenza* (12%) infection in SARS-CoV-2 infected patients [9]. The proportion of *M. pneumonia* was surprisingly high and very likely overestimated while relying on IgM serology [18]. Most included studies were from Asian countries, which might explain the relatively high proportion of *Acinetobacter* infection. Hugh et al. [15] and Townsend et al. [16] showed more similarities with the present study.

The findings of the present study highlighted diagnosis difficulties. Clinical features leading to pulmonary bacterial infection suspicion can be easily confused with the usual signs of an advancing SARS-CoV-2 infection [19]. Despite sputum production seems to be an interesting sign, it has been reported in one third of SARS-CoV-2 infected patients and remains not specific of bacterial infection [20]. Additionally, bacterial infection occurrence within the COVID-19 timeframe, around the 10th day after symptoms' onset, corresponds to the classical worsening of COVID-19 symptoms [21], which adds to the difficulty of the identification of a bacterial infection. Furthermore, in the studied population, biological features did not show any difference between a potential bacterial infection and the underlying evolution of COVID-19. Imaging benefits in support of bacterial infection diagnosis should be further investigated. No distinctive marker has been highlighted in COVID-19 yet. Huang and colleagues [22] described PCT level in blood on admission in SARS-CoV-2 patients showing 75% of PCT > 0.5 ng/mL in confirmed secondary infections, whereas 69% of the other patients had a PCT level < 0.1 ng/mL. In contrast to the previous findings, Wan et al. [23] found that CRP and PCT levels on admission of severe patients were significantly higher than in the mild patients group, with no difference in documented bacterial infection rate. PCT levels could not be assessed in this study because of missing data.

The final outcome was positive in only 62% of the selected patients, with a third requiring intensive care before being discharged. Study design did not allow to claim that poor outcome in this population was the consequence of secondary bacterial infections. However this ascertainment seems consistent with the literature [24, 14], and might mainly involve patients with bacteraemia [15].

The design of this study was retrospective. Databases screening were conducted with two different methods for PCR and bacteriological samples data collection to optimise the extraction quality and limit a potential selection bias. Despite authors' endeavour, both extraction methods showed some flaws and resulted in additional exclusions during the selection process. Though all patient results were thoroughly described and analysed, there were some missing data, especially for PCT levels and CT scans, preventing further analyses.

In order to catch all potential secondary infections, no threshold was held for microbiological samples in the screening of cases. Thus, a proportion of positive samples could be the result of colonisation and not actual infection leading to an overestimation of bacterial infections. It has to be put in balance with

actual non documented infection, with no bacterial investigation or false negatives due to the large presumptive use of antibacterials or poor quality sampling. However for the latter, during a crisis and outside of ICU, only regular non-invasive microbiological samples are easily available and usable.

There is growing evidence suggesting a global overestimation of pulmonary bacterial infection in SARS-CoV-2 infected patients, resulting in an overuse of antibiotics and its consequences, mainly an increase of bacterial resistance [25]. This work supports the low prevalence of co infection and secondary infection in non ICU hospitalised patients with COVID-19. Empirical use of antibiotics are unlikely to provide significant benefit to COVID-19 patients. Systematic use of antibiotic, especially fluoroquinolones or macrolides on admission, does not seem justified. To support these findings, prospective studies are required to collect further data on the actual prevalence of bacterial infection in COVID-19 patients. Future research needs to focus on the role of antibiotics in SARS-CoV-2 infected patients, to guide its use in daily care and hopefully reduce the adverse consequences of its overuse.

Conclusion

Pulmonary bacterial secondary and co-infections with SARS-CoV2 are uncommon. Their diagnosis is difficult due to similarities with the natural course of the disease. Cough with sputum around day ten might be a sign of bacterial infection. There is a balanced ratio between gram-positive and gram-negative among involved bacteria.

Systematic use of antibiotic does not seem justified in COVID-19 management

Abbreviations

BAL
Bronchoalveolar lavage
COPD
Chronic obstructive pulmonary disease
CRP
C-reactive protein
PCR
polymerase chain reaction
PCT
procalcitonin

Declarations

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

All data were anonymised. The local Ethics Committee “Comité d’Evaluation de l’Ethique des projets de Recherche Biomédicale (CEERB) Paris Nord” (IRB00006477) approved the study and informed consent

was waived.

Consent for publication: Not applicable

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Competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Availability of data and material: Not applicable

Authors' contributions

All authors contributed to the study conception and design. ER, CD, BV extracted the data from the different databases. MH and SV collected and analysed the data. MH and SV wrote the manuscript. NP and LD supervised the study. All authors have read and approved the final manuscript.

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Figures

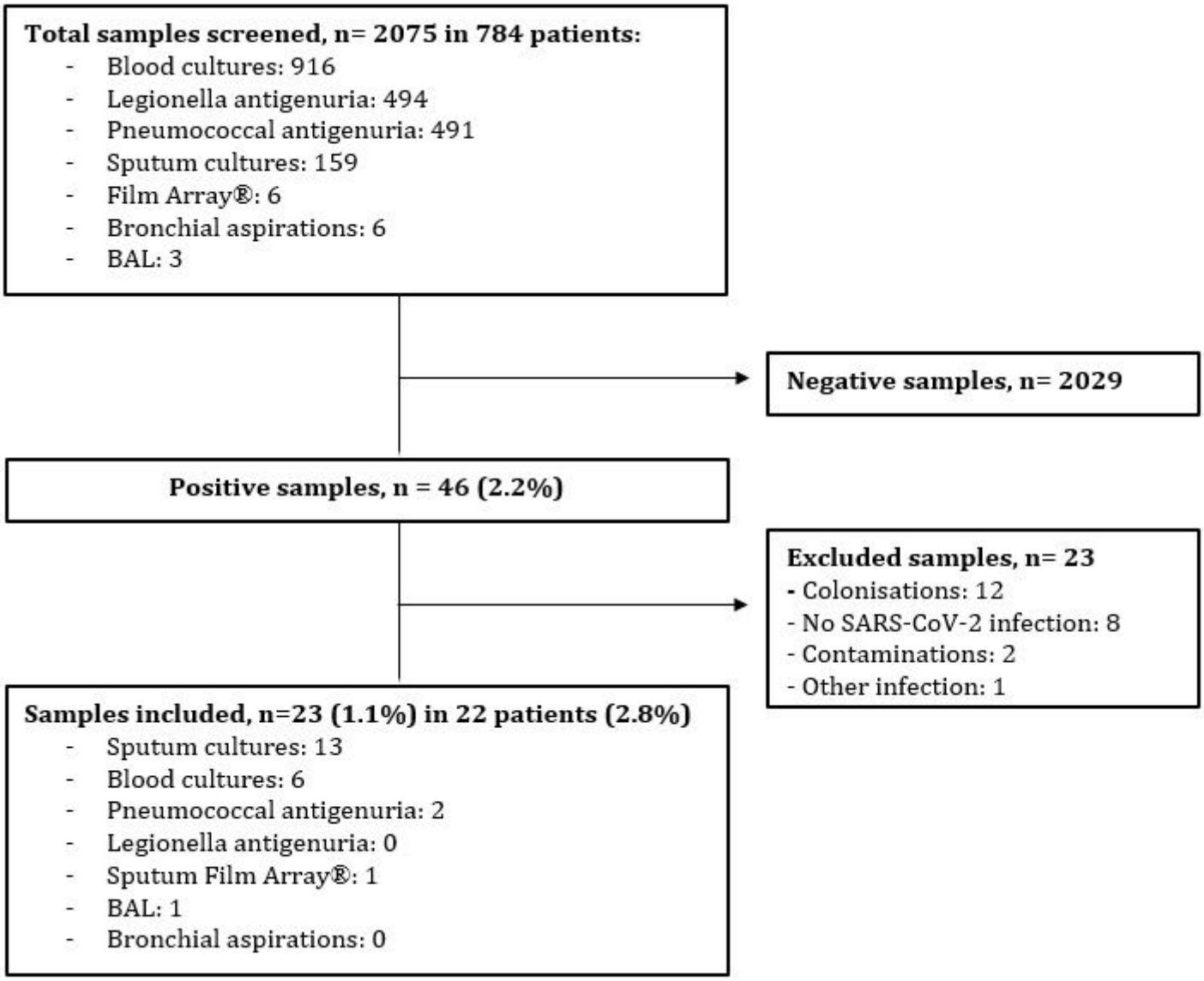

Figure 1

Flow chart of bacteriological samples

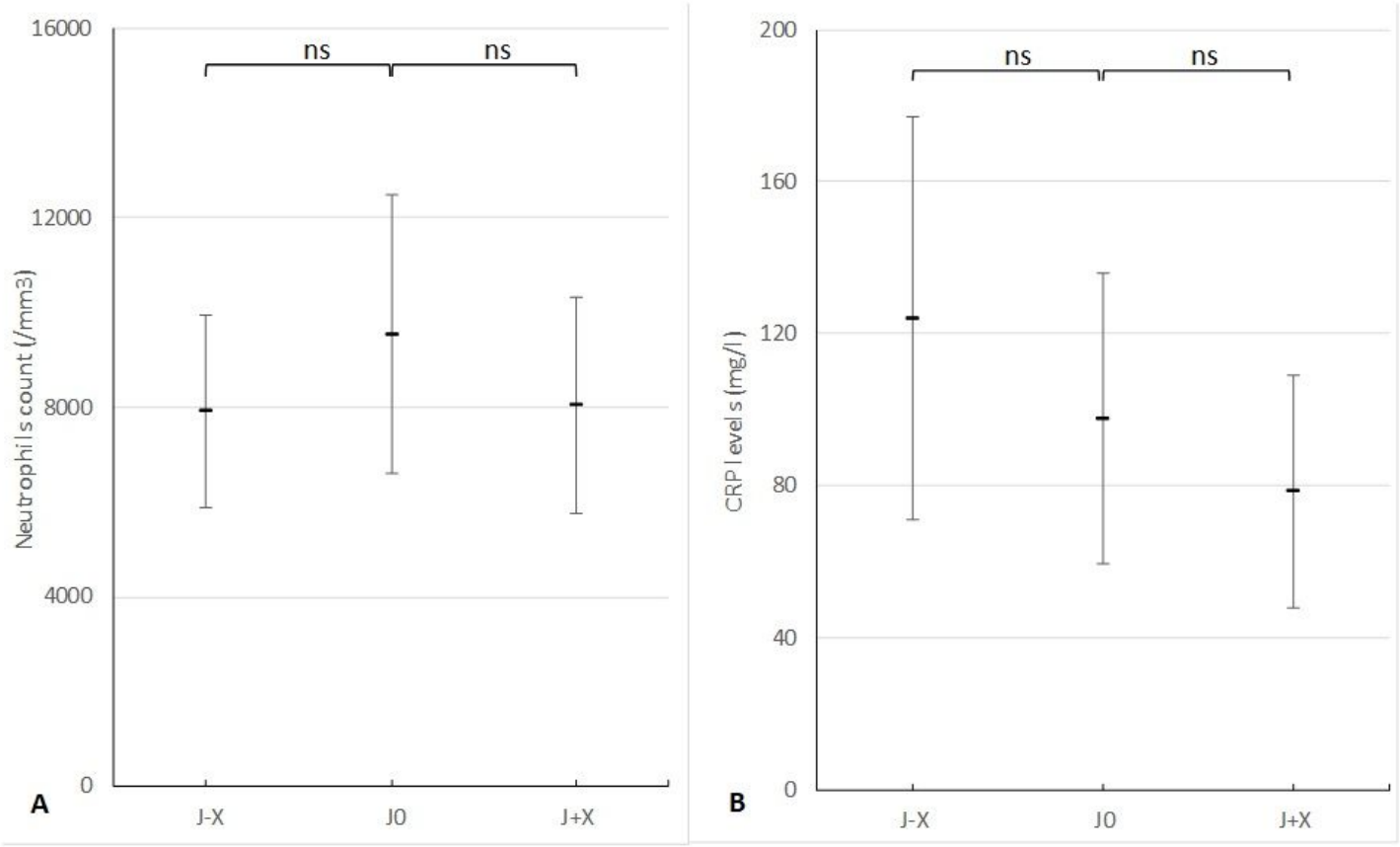

Figure 2

Variation of polynuclear neutrophils count (A) and CRP levels (B) before (J-X), at the onset (J0) and after (J+X) secondary bacterial infection

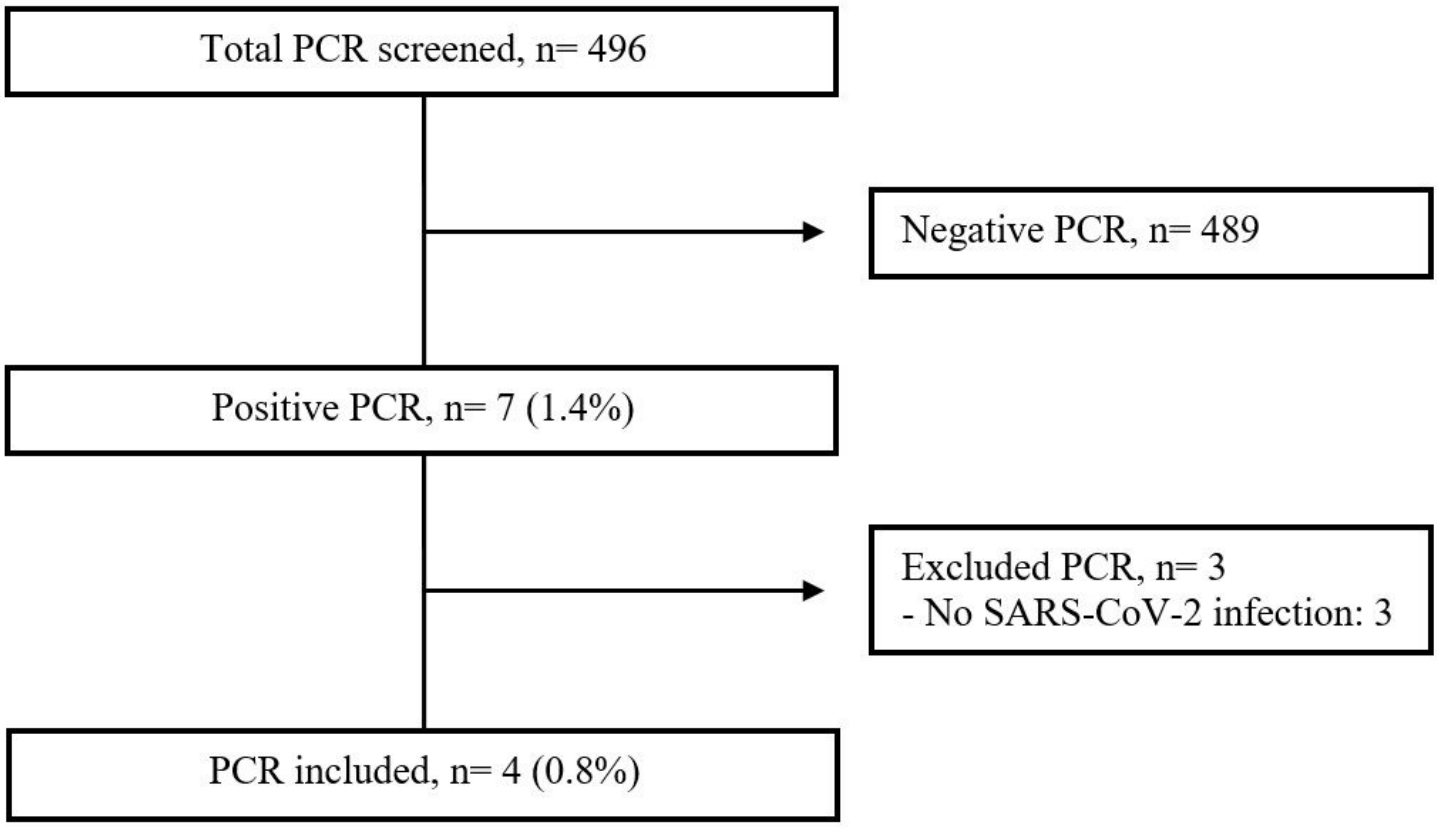

Figure 3

Flow chart of bacterial multiplex PCR on nasopharyngeal swab