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Bacterial etiology in acute hospitalized chronic obstructive pulmonary disease exacerbations

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ABSTRACT

Objectives. The most common cause of acute COPD exacerbation (AECOPD) is the respiratory tract infections. We sought to determine the bacteriological etiology of hospitalized acute exacerbations of COPD requiring hospitalization in consecutive two years. ***Methods.*** We aimed to determine the bacteriological etiology underlying in patients whom admitted to Uludag University Faculty of Medicine, Department of Pulmonary Medicine and hospitalized with AECOPD in the last two years. Medical records of the study participants were screened retrospectively and sociodemographic characteristics, routine laboratory tests and sputum culture results were analyzed. ***Results.*** A total of 242 patients hospitalized for AECOPD were enrolled. Of these 86.4% (n=209) were male. The mean age of the group was 66.6±11 years old. Sputum cultures were available in the 45 % (n=109) of the study group. The most frequent bacteria isolated from the sputum cultures of the study group were *Pseudomonas aeruginosa*, *Streptococcus pneumonia*, *Haemophilus influenzae* and *Acinetobacter baumanii*. Length of stay was longer in patients with the *A. baumanii* isolate than the rest of the group (p=0.024). Length of stay in hospital was independently associated with in-hospital mortality (OR: 1.37, 95% CI: 1.05–1.78). Isolation of *A. baumanii* and/or *Staphylococcus aureus* in sputum culture were identified as independent risk factors for prolonged length of stay in-hospital (b=0.26, p=0.008; b=15.40, p=0.003). ***Conclusions.*** Our study shows that *P. aeruginosa*, *S. pneumonia*, *H. influenzae* are common sputum isolates in AECOPD patients requiring hospitalization. Isolation of *A. baumanii* and/or *S. aureus* in sputum culture is associated with prolonged length of stay in hospital, which is an independent risk factor for in-hospital mortality.

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Keywords: Acute exacerbation; chronic obstructive pulmonary disease; sputum; bacteriology

Introduction

Chronic obstructive pulmonary disease (COPD) is a major cause of chronic morbidity and mortality worldwide. It is also common in Turkey and leads to high mortality, morbidity and frequent use of health care resources [1-3]. COPD exacerbation is an acute event characterized by a worsening of the patient's

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respiratory symptoms that is beyond normal day-to-day variations, and leads to a change in medication [4]. Common symptoms are worsening dyspnea, cough and increased sputum production. Exacerbation of COPD are important events in the course of the disease related with impairment in quality of life [5], accelerate disease progression [6], and cause substantial economic burden of COPD [7], particularly if they require hospitalization. Exacerbations of COPD requiring hospitalization are prognostic factors for poor survival in COPD [8].

Acute exacerbation of COPD (AECOPD) can be precipitated by several factors. The most common causes are bacterial or viral respiratory tract infections. *Streptococcus pneumonia*, *Haemophilus influenzae* and *Moraxella catarrhalis* were the most frequently isolated microorganisms in AECOPD patients [9, 10]. Prevention, early detection, and prompt treatment of exacerbations are vital to reduce the burden of COPD. In the present study, we sought to determine the bacteriological etiology of hospitalized acute exacerbations of COPD requiring hospitalization in consecutive two years in a large patient group. Primary and secondary study outcomes were in-hospital mortality and length of stay (LOS) in hospital.

Methods

Study Population and Definitions

COPD patients with acute exacerbation hospitalized in Uludag University Faculty of Medicine, Department of Pulmonary Medicine Inpatient Clinic, between January 2011 and January 2013 were retrospectively enrolled into the study. Medical records of the study participants were screened; demographic characteristics, comorbid diseases, routine laboratory tests, arterial blood gas analyses, sputum microscopic evaluation and bacterial culture results, antibiotic treatment choice during hospital stay, length of stay in hospital, and in-hospital mortality were analyzed. Each patient was only recruited once. Presence of pneumonia or sign of any other active infection, asthma, bronchiectasis, and presence of tuberculosis, inflammatory diseases such as connective tissue disorder, arthritis, inflammatory bowel disease and malignancy were accepted as exclusion criteria.

COPD was diagnosed according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines and defined by persistent airway limitation (post-bronchodilator FEV1/FVC<0.70) in presence of ≥10 pack-years of smoking history [4]. For COPD diagnosis, previous pulmonary function tests available in the medical records were recorded. COPD exacerbation was defined as an event in the natural course of the disease characterized by a change in the patient's baseline dyspnea, cough and/or sputum that is beyond normal day-to-day variations requiring treatment with systemic steroids or antibiotics, and/or visit to emergency room or admission to hospital [4]. Acute COPD exacerbations in the previous 12 months were assessed by patients' recall of exacerbation events and according to medical records. Respiratory insufficiency was defined as an arterial oxygen tension (PaO_2) of <60 mmHg, an arterial carbon dioxide tension ($PaCO_2$) of >45 mmHg, or both [11].

Bacteriological Analyses

Sputum was collected in sterile sputum culture cups. Patients were asked to expectorate sputum in these sterile cups after washing the oral cavity and samples sent microbiology laboratory within 2 hours. Sputum was assessed macroscopically firstly: mucoid or purulent. Once the specimen reached the laboratory, first it was microscopically screened to exclude those samples with upper airway contamination. Only sputa showing fewer than 10 squamous epithelial cells and more than 25 leucocytes in at least 5 low power fields (×100) were accepted for further culture examination [9]. Sputum samples that do not fulfill these criteria were not cultured. Standard quantitative bacterial culture and identification procedures were performed as described previously [9, 12]. Blood agar was used for isolation and identification of Gram-positive organisms, MacConkey agar for Gram-negative bacteria, and enriched chocolate agar for *Haemophilus spp*. Plates were incubated at 37°C and 5% CO_2, and were checked for growth after 24 and 48 hours of incubation [12]. At least 106 colony forming units/ml indicated significant growth. In cases where multiple bacterial isolates were found in samples; the predominant species were considered as the leading pathogen.

Bacterial agents were classified as potential pathogenic microorganism (PPM) and non-PPMs. PPMs were microorganisms that cause respiratory infections such as Gram-negative rods, *Pseudomonas aeruginosa*, *Enterobacteriaceae* and *Haemophilus spp*.; Gram-positive cocci, such as *Staphylococcus*

aureus, *S. pneumonia*; Gram-negative cocci, such as *M. catarrhalis*. Non-PPMs were the microorganisms that belong to oropharyngeal or gastrointestinal flora and usually not responsible from respiratory infections (*Streptococcus viridians* group, *Neisseria spp*., *Corynebacterium spp*., *Candida spp*., and others) in immunocompetant hosts [13].

Statistical Analysis

Statistical analyses were performed using the IBM SPSS Statistics for Windows, Version 22.0 software program (Armonk, NY: IBM Corp.). Variables were investigated using visual (histograms, probability plots) and analytical methods (Kolmogorov-Simirnov / Shapiro-Wilk's test) to determine whether or not they were normally distributed. Data were expressed as mean ± SD or median (min-max) and median [interquartile range (IQR) 25 - 75] as appropriate unless otherwise specified. Categorical variables were reported as proportions. A chi-square test was used to compare proportions between two groups and a two-sample t-test for continuous outcome variables. For non-normal data Mann Whitney-U test was performed. For the multivariable analyses, possible factors identified with univariate analyses were further entered into the logistic regression analyses to determine independent predictors of in-hospital mortality. Hosmer-Lemeshow goodness of fit statistics were used to assess model fit. In a separate model, a multiple linear regression model was used to identify independent predictors of length of stay in hospital. The model fit was assessed using appropriate residual and goodness-of-fit statistics. A 5% type-I error was used to infer statistical significance.

Results

We identified a total of 242 patients hospitalized for AECOPD. Of these 242 patients, 86.4% (n=209) were male. The mean age of the group was 66.6±11 years old. Characteristic features of the study participants are presented in Table 1. Almost 61% of the study group had respiratory insufficiency at first admission.

Sputum cultures were available in the 45% (n=109) of the study group. There were no growth in cultures of 61.5% of these patients; whereas 38.5% (n=42) of the group yielded positive on sputum cultures. The most frequent bacteria isolated from the sputum cultures of the study group were *P. aeruginosa* (n=9; 21.4%), *S. pneumonia* (n=7, 16.7%), *H. influenzae* (n=6, 16.7%), *Acinetobacter baumanii* (n=6, 16.7%), *Enterobacteriaceae* (n=4, 9.5%), *S. aureus* (n=4, 9.5%), *Escherichia coli* (n=4, 9.5%), *Klebsiella pneumoniae* (n=2, 4.8%),

Table 1. Characteristics of the Patients

Characteristics	Values
Male/female (n)	209/33
Age (mean±SD)	66.6±11
Males	68.5±10.8
Females	63.8±8.6
Comorbid disease (%)	
Diabetes mellitus	27.6
Hyperlipidemia	7.5
Hypertension	41
Obesity	8.3
Coronary artery disease	25.3
Lung cancer	20
Arterial blood gas analyses	
pH	7.38 ± 0.05
pO_2	73.2 ± 33.3
pCO_2	47.8 ± 14.7
HCO_3	27.6 ± 6.3
SaO_2	90.9 ± 9.1
Respiratory insufficiency, n (%)	131 (60.9)

n=number of patients

Stenotrophomonas maltophilia (n=2, 4.8%), and *Serratia marcescens* (n=1, 2.4%), (Figure 1).

Treatment and outcomes

The median prior admission rates of the subjects were 1 (min - max: 0 - 9). 14.9% of the group had at least two prior admissions. The mean duration of hospitalization was 9 [IQR 25-75: 7-14] days. Overall in-hospital mortality rate was 9% (n=21).

In hospital mortality was significantly higher in patients with any growth in sputum culture (78.6 % vs. 41.5%, $p<0.05$). The univariate analyses to identify variables associated with in-hospital mortality during hospitalization for AECOPD are summarized in Table 2. When baseline characteristics were compared, sex, age and most of the comorbidities except lung cancer were not different between survived and the patients died. Length of stay in hospital was significantly increased in patients died ($p=0.040$). We found that in-hospital mortality was higher in patients whom *A. baumanii* was isolated from the sputum culture than the other patients (mortality rate for *A. baumanii* group 30.8% vs. mortality rate for the rest of the group 2.1%, $p<0.0001$**).** The isolation frequency of *E. coli* and *S. aureus* were significantly higher in deceased patients when compared with the survivors ($p=0.025$, and $p=0.025$, respectively).

Patients with the *A. baumanii* isolate were significantly younger than the other patients (46±9.9 vs. 67±10.3 years old, $p<0.05$). Length of stay was longer in AECOPD patients with *A. baumanii* compared to rest of the study group (19 [min - max: 4-85] days vs. 8.5 [min - max: 1-36] days; respectively; $p=0.024$). We did not observe a significant difference in LOS duration among other bacterial isolates. We observed a higher rate of respiratory insufficiency in patients with the *A. baumanii* isolate compared to COPD patients with

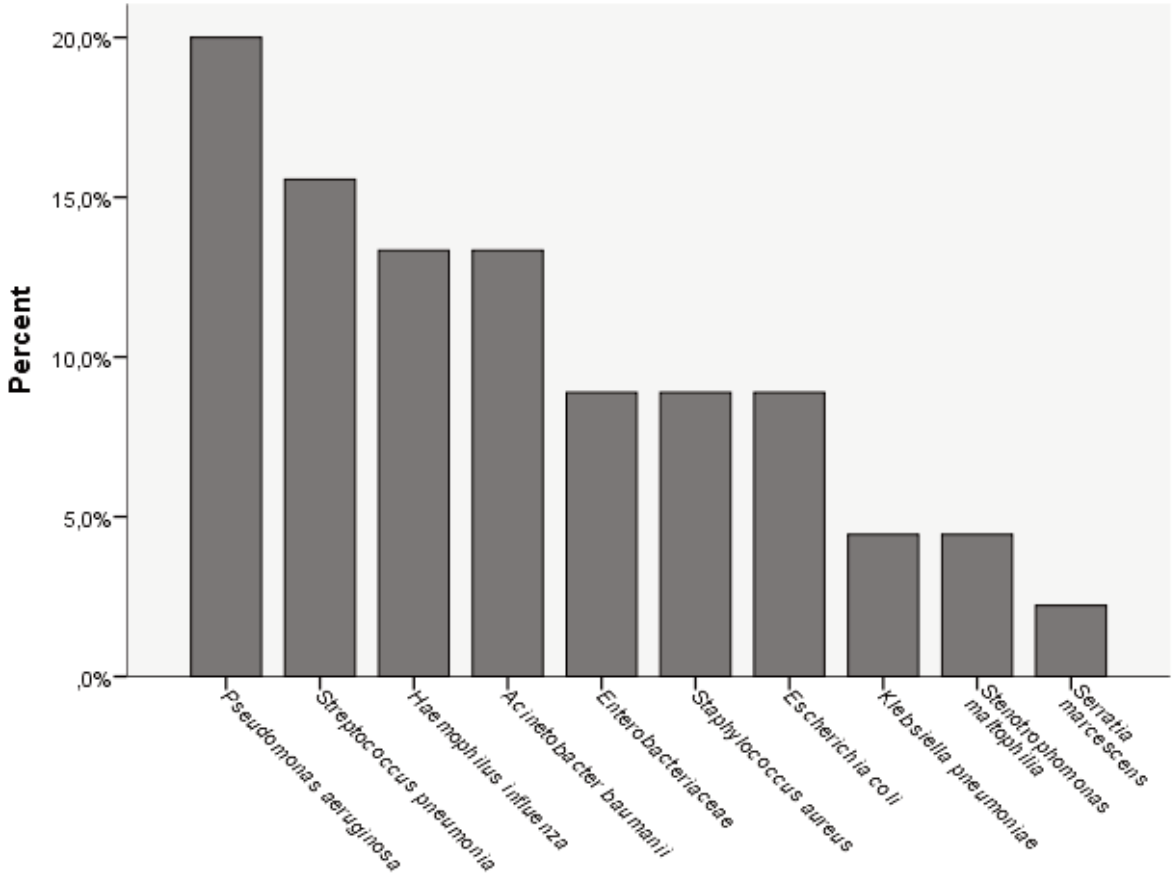

Figure 1. Distribution of potentially pathogenic microorganisms yielded on sputum culture of hospitalized COPD patients with acute exacerbation.

Table 2. The univariate analyses to identify variables associated with in-hospital mortality during hospitalization for AECOPD

	Survived (n=221)	Died (n=21)	*p*
Age; *years*	66.9 ± 11.1	63.4 ± 9.2	0.163
Sex, Males; *n*	181	20	0.210
LOS, *days*	9 [7 - 13]	14 [7 - 19]	0.040
Comorbidities; *n (%)*			
Diabetes mellitus	31 (27.4)	2 (25)	0.881
Hyperlipidemia	8 (100)	0 (0)	0.401
Hypertension	49 (90.7)	5 (9.3)	0.749
Obesity	9 (8.9)	0 (0)	0.409
Coronary artery disease	29 (27.9)	0 (0)	0.104
Lung cancer	16 (76.2)	5 (5.7)	0.010
# of previous hospitalizations	0.83 ± 1.24	0.81 ± 1.28	0.454
Repiratory insufficiency; *n (%)*	121 (61.4)	10 (55.6)	0.623
Sputum isolates; *n (%)*			
PPM			
Haemophilus. influenzae			
Streptococcus pneumonia	6 (6.4)	0 (0)	0.331
Pseudomonas aeruginosa	8 (8.5)	1 (7.1)	0.863
Acinetobacter baumanii	2 (2.1)	4 (30.8)	< 0.0001
GNEB			
Escherichia coli	2 (2.1)	2 (14.3)	0.025
Enterobacteriaceae	4 (4.3)	0 (0)	0.432
Serratia marcescens	1 (1.1)	0 (0)	0.698
Klebsiella pneumoniae	2 (2.1)	0 (0)	0.582
Stenotrophomonas maltophilia	2 (2.1)	0 (0)	0.582
Staphylococcus aureus	2 (2.1)	2 (14.3)	0.025
Non-PPM	17 (8)	4 (19)	0.092

n=number of patients, LOS=length of stay in hospital, # represents number of, PPM= potentially pathogenic organism, GNEB=Gram-negative enteric bacilli

other isolates (p=0.043). Rate of respiratory rate were not different among patients stratified according to isolation of other bacteria.

Possible factors identified with univariate analyses (length of stay in hospital, lung cancer, presence of sputum *A. baumanii*, *E. coli* or *S. aureus* isolates, non-PPM) were further entered into the logistic regression analyses to determine independent predictors of in-hospital mortality. Only, increasing length of stay in hospital was independently associated with in-hospital mortality (Table 3).

In a separate model, a multiple linear regression model was used to identify independent predictors of length of stay in hospital. Isolation of *A. baumanii*, *S. aureus*, and PaO_2 levels were identified as significant risk factors for prolonged length of stay in-hospital (Table 4).

Discussion

The underlying etiology of acute COPD exacerbations is often infectious and mostly related with a bacterial and/or viral infection. *H. influenzae*, followed by *S. pneumonia* and *M. catarrhalis* were the

Table 3. Factors independently associated with in-hospital mortality of AECOPD

	B	SE	Wald	*p*	OR	95%CI OR
Length of stay in hospital, days	0.31	0.13	5.34	0.020	1.37	1.05 – 1.78
Escherichia coli in sputum	3.98	2.77	2.07	0.150	53.75	0.24–12178.00
Staphylococcus aureus in sputum	3.36	1.80	3.4	0.063	28.74	0.84–985.59

SE=standard error; OR=odds ratio; CI=confidence interval

Table 4. Factors affecting length of stay in-hospital in AECOPD

	Univariate Regression				*Multivariate Regression*			
Variable	**B**	**SE**	**β**	***P***	**B**	**SE**	**β**	***p***
Age, years	16.49	3.25	-0.11	0.09	-	-	-	-
Sex	12.52	1.46	-0.07	0.29	-	-	-	-
Lung Cancer	0.50	2.20	0.022	0.82	-	-	-	-
PCO_2	0.07	0.04	0.13	0.06	-	-	-	-
Pseudomonas aeruginosa	3.19	3.34	0.09	0.34	-	-	-	-
PO_2	0.03	0.02	0.12	0.07	0.04	0.02	0.17	0.06
Acinetobacter baumanii	16.94	3.67	0.41	<0.0001	10.92	4.05	0.26	0.008
Staphylococcus aureus	18.69	4.56	0.37	<0.0001	15.40	4.97	0.31	0.003

β=unstandardized regression coefficient; SE=standard error of the coefficient; β=standardized coefficient

most frequent bacterial isolates in sputum samples of COPD patients with exacerbation [10, 14]. Besides, non-fermentative Gram-negative bacilli (*P. aeruginosa*, *S. maltophilia, A. baumanii*) were reported as the leading causative pathogens for severe COPD exacerbations that require mechanical ventilation [15].

This retrospective study of bacterial isolates associated with AECOPD in a tertiary hospital in Bursa, Turkey found that potential bacterial pathogens were isolated from sputum in approximately 40% of the patients. This isolation rate is in accordance with previous studies reporting an isolation rate of 32 % to 51 % performed in similar settings [16-19]. Our results demonstrated a predominance of *P. aeruginosa*, *S. pneumonia*, *H. influenzae*, and *A. baumanii* as the most common sputum isolates in AECOPD patients requiring hospitalization. Microbial patterns observed in our study correspond to mostly to *P. aeruginosa* in 21.4%, Gram-negative enteric bacilli (GNEB) in 26.2%, *A. baumanii* in 16.7%, and *S. aureus* in 9.5%. Community acquired pathogens (*S. pneumonia*, *H. influenzae*) were responsible in 31% of the total isolates. Our findings are in accordance with Miravitlles *et al.* [10] reports including *H. influenza*, *P. aeruginosa*, and *S. pneumonia* as the most frequent isolates in sputum samples of COPD patients with exacerbation [11]. Interestingly, we observed *P. aeruginosa* as the leading pathogen isolated from sputum samples of COPD patients with exacerbation. Moreover, rates for isolation of *A. baumanii* was high and noteworthy (as high as *H. influenzae* isolation rates, 16.7% for both isolates) in our study. To the best of our knowledge, our study is one of the first reports showing A. *baumanii* as a remarkably frequent isolate in sputum samples of hospitalized COPD patients with exacerbation. Recently, Dai *et al.* [20] reported that *Pseudomonas*, followed by *A. baumanii*, *Klebsiella*, *E. coli* and *S. pneumonia* in bacteriologic analyses of sputum in patients with hospitalized AECOPD patients [20]. Moreover, Li *et al.* [19] reported *Pseudomonas* as the most common pathogen in patients with COPD exacerbation. Besides Soler *et al.* [21] reported a high rate of Gram-negative bacteria and *Pseudomonas/Stenotrophmonas spp*. isolates in respiratory samples of COPD patients with severe exacerbations. Previous studies have demonstrated a significant variation in the relative incidence of specific pathogens in AECOPD, which may relate to patient inclusion criteria, settings and environmental or epidemiological factors [10, 19-22]. Nearly 15% of our study group had at least two prior admissions in the previous year before enrollment into this study. Moreover, 61% of the overall study participants had respiratory insufficiency at first admission. We suggest that high prior admission and respiratory insufficiency rates may reflect a study group mainly including severe COPD patients, which can be an explanation for the relatively high *P. aeruginosa*, GNEB, *A. baumanii* and *S. aureus* isolation rates observed in our study. We observed a significantly higher respiratory insufficiency rate for patients with *A. baumanii* isolates. Infections due to *P. aeruginosa*, GNEB, *A. baumanii* and *S. aureus* are of special concern in terms of treatment as these pathogens would require specific and prolonged antimicrobial treatment.

The other aim of our study was to evaluate the potential relationship between causative bacterial agents for AECOPD and LOS in hospital. Despite, isolation of *A. baumanii*, *E. coli* or *S. aureus* in sputum, accompanying lung cancer, and length of stay in hospital were identified as possible risk factors for in-hospital mortality on univariate analyes; logistic regression analyses revealed that only increasing

length of stay in hospital was independently associated with in-hospital mortality. Our results demonstrated that exacerbations associated with *A. baumanii* resulted in a significantly longer LOS in hospital, higher rates for respiratory insufficiency and in-hospital mortality. Nakau *et al*. [22] also identified *A. baumanii* to be associated with prolonged hospitalization in AECOPD. It was also identified as an independent risk factor for prolonged in-hospital stay with *S. aureus* and arterial oxygen tension. Therefore, we suggest that bacterial infectious phenotypes seem to associate with LOS and in-hospital mortality in AECOPD. But we were not able to explore all of the possible risk factors that may cause prolonged stay in hospital and mortality in our study because of its retrospective design. Further research is warranted to explore the impact of all possible risk factors in LOS and in-hospital mortality in AECOPD with special consideration to bacterial infectious etiology.

The Limitations of the Study

This study has several limitations. Firstly, our study population included only hospitalized AECOPD events and for that reason, we are unable to evaluate bacteriological profile of milder exacerbations that do not require hospitalization. Secondly, because of the retrospective design of the present study; we were unable to fully evaluate potential factors such as severity of the airflow obstruction, chronic corticosteroid use, recent antibiotic therapy, factors related with respiratory insufficiency and referral to intensive care unit, etc., which may effect in-hospital mortality. Thirdly, we did not isolate sputum specimens for viral etiology. On the other hand, present study shows that isolation of *A. baumanii* was associated with younger age and adverse clinical outcome in terms of length of stay, higher rates for respiratory insufficiency and in-hospital mortality. Although, we did not explore *A. baumanii* positive sputum culture as an independent risk factor for increased in-hospital mortality; we have shown that *A. baumanii* positive sputum culture is an independent risk factor for prolonged LOS in hospital. Further larger scale prospective studies are warranted to explore the impact of all possible risk factors in LOS and in-hospital mortality in AECOPD with special consideration to bacterial infectious etiology.

Conclusions

In conclusion, present study demonstrates that *P. aeruginosa*, and *A. baumanii* are frequent bacterial isolates in addition to community acquired pathogens (*S. pneumonia*, *H. influenzae*) in AECOPD patients requiring hospitalization. In addition, this study indicated that *A. baumanii* or *S. aureus* positive sputum cultures are independent risk factors for prolonged LOS in hospital. Prolonged length of stay in hopital is an independent risk factor for in-hospital mortality in hospitalized acute exacerbations of COPD.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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