【 ORIGINAL ARTICLE 】

# Addition of Baricitinib to COVID-19 Treatment Does Not Increase Bacterial Infection Compared to Standard Therapy: A Single-center Retrospective Study

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**Abstract:**
**Objective** The coronavirus disease 2019 (COVID-19) pandemic continues to spread across the world, and the utility of many drugs for treatment has been suggested. However, few studies have examined the efficacy and safety of treatment with baricitinib, remdesivir, and dexamethasone.
**Methods** A retrospective, cohort study of patients who were admitted to Kurashiki Central Hospital in Japan between April 6 and June 29, 2021, was conducted. Differences in patients' background characteristics, clinical outcomes, and safety were investigated in the groups with and without baricitinib treatment. The primary outcome was the bacterial infection rate, and the secondary outcome was the 28-day mortality rate. An inverse probability of treatment weighting (IPTW) analysis, including 12 covariates, was used as a propensity score analysis to reduce biases.
**Results** In total, there were 96 patients, including 43 in the baricitinib-containing therapy (BCT) group and 53 in the non-baricitinib-containing therapy (non-BCT) group. In the BCT group, the ordinal scale on admission was 2.3% with 4, 51.1% with 5, 23.3% with 6, and 23.3% with 7. In the non-BCT group, the ordinal scale was 1.9% with 3, 18.9% with 4, 58.5% with 5, 13.2% with 6, and 7.5% with 7. After adjusting by the IPTW analysis, the BCT group did not have an increased bacterial infection rate [odds ratio (OR), 1.1; 95% confidence interval (CI), 0.36-3.38; p=0.87] or 28-day mortality rate (OR, 0.31; 95% CI, 0.07-1.3; p=0.11) compared with the non-BCT group.
**Conclusion** BCT can be administered without increasing the infection risk compared with non-BCT.

**Key words:** COVID-19, baricitinib, remdesivir, dexamethasone

## Introduction

Coronavirus disease 2019 (COVID-19) was first reported in China in December 2019 (1) and has since caused a worldwide pandemic that has been forcing healthcare providers around the world to desperately find appropriate treatment (2). Many clinical trials of pharmacotherapy for COVID-19, including randomized, controlled trials, have been performed (3). Dexamethasone (DEX), remdesivir,

baricitinib, and tocilizumab are drugs proven to be effective for COVID-19 with active respiratory symptoms. Baricitinib is a reversible Janus-associated kinase-inhibitor. Combination therapy with remdesivir and baricitinib was found to be superior to treatment with remdesivir alone in the Adaptive COVID-19 Treatment Trial 2 (ACTT-2) trial (4). However, the study design of the ACTT-2 trial focused on the combination of remdesivir and baricitinib and did not allow for its use in combination with DEX.

COV-BARRIER, a phase 3 trial, showed that baricitinib,

remdesivir, and DEX therapy had a similar safety profile to that of standard care alone (5). However, COV-BARRIER excluded intubated patients, and baricitinib, remdesivir, and DEX therapy has since been used in the real-world setting for patients who did not meet the eligibility criteria of the COV-BARRIER trial.

We therefore investigated the effectiveness and safety of baricitinib-containing therapy (BCT) for patients with COVID-19 in clinical practice.

## Materials and Methods

### Study design and subjects

COVID-19 patients admitted to Kurashiki Central Hospital from April 6 to June 29, 2021, were consecutively enrolled in this study. COVID-19 was diagnosed by a positive result on either a polymerase chain reaction test or antigen test for severe acute respiratory syndrome coronavirus-2. From the patients' medical records, age, sex, underlying diseases, laboratory findings, imaging findings, bacteriological tests, severity of illness, treatment details, complications during treatment, and outcome were obtained retrospectively. In accordance with the National Institute of Allergy and Infectious Diseases ordinal scale (OS) (4), the COVID-19 patients were classified by score as follows: 1) ambulatory, no limitation of activities; 2) ambulatory, limitation of activities, home $O_2$ (oxygen) required, or both; 3) hospitalized, no $O_2$ therapy plus not requiring medical care; 4) hospitalized, no $O_2$ therapy, but requiring ongoing medical care; 5) hospitalized, given supplemental $O_2$; 6) hospitalized, requiring non-invasive ventilation or high-flow nasal cannula; 7) hospitalized, invasive mechanical ventilation or extracorporeal membrane oxygenation; and 8) death.

In addition, the Japanese Ministry of Health, Labour and Welfare proposed the following COVID-19 severity classification (6): Mild, $SpO_2$ (oxygen saturation) >96%, no respiratory symptoms, no dyspnea, no pneumonia on imaging; Moderate I, $SpO_2$: 93-96%, dyspnea and pneumonia on imaging; Moderate II, $SpO_2$<93%, oxygenation required; and Severe, intensive care unit (ICU) admission or ventilator required.

### Treatment regimen and site

DEX was basically administered as either 6.6 mg intravenously daily or 6 mg orally daily for a maximum of 10 days, as in a previous report (7). Some patients were treated with high-dose methylprednisolone or with prolonged steroid administration at the discretion of the attending physician. Patients received intravenous remdesivir as a 200-mg loading dose on day 1, followed by a 100-mg maintenance dose administered daily on day 2 for a maximum of 10 days total at the discretion of the attending physician (8). Baricitinib was administered as a 2- to 4-mg daily dose for a maximum of 14 days, depending on the renal function, at the discretion of the attending physician (4).

The regimen of each treatment was left to the discretion of the attending physician. The treatment was based on the Japanese Guide for the Treatment of Coronavirus Infections (version 5.0-5.2) (6), and the general treatment policy for COVID-19 was decided through discussions between the Department of Respiratory Medicine and the ICU in our hospital. The criteria for admission to the ICU were determined to be unstable oxygenation even with a high-flow nasal cannula (HFNC) with the fraction of inspired oxygen at 70%, unstable circulation, or at the discretion of the attending physician.

### The evaluation of bacterial infections

For microbiological investigations, samples of blood, sputum, or urine were obtained for cultures.

A bacterial infection was diagnosed if certain criteria were met. Bacterial pneumonia was diagnosed based on a positive sputum culture of more than 1+ on a qualitative test, with reference to the sputum Gram stain. Hospital-acquired pneumonia (HAP) was defined as pneumonia that occurred ≥48 h after admission and did not appear to be incubating at the time of admission (9). Ventilator-associated pneumonia (VAP) was defined as a type of HAP that developed more than 48 h after endotracheal intubation. Other criteria for HAP and VAP were also added to the present study, consisting of new shadows during COVID-19 treatment and significant detection of bacteria according to the above criteria in lower respiratory tract specimens. Three respiratory physicians, including two who were infectious disease specialists, made the decision regarding HAP or VAP while blinded to the patients' treatment group. Bacteremia was defined based on a positive blood culture (excluding contaminated normal skin flora). Urinary tract infection was defined based on a positive urinary culture, $10^5$ on a quantitative test, and >5 white blood cells/high-power field (HPF, ×400) on the urinalysis.

### Outcomes

The primary outcome was the bacterial infection rate during treatment for COVID-19. The secondary outcome was the 28-day mortality rate from the date of COVID-19 infection. A subgroup analysis examined the bacterial infection rate and the 28-day mortality rate in the patients with OS values of 5-7 (patient groups with oxygen demand for more advanced devices than nasal oxygen).

### Statistical analyses

Nominal variables are expressed as numbers and percentages, and continuous variables are expressed as medians and the interquartile range. Nominal variables were analyzed using Fisher's exact test, and continuous variables were analyzed using the non-parametric Mann-Whitney U test.

For comparisons of the bacterial infection rate and 28-day mortality between the BCT group and the non-BCT group, propensity score (PS) methods were used to reduce bias and the effects of patients' confounding factors on treatment out-

comes. The PS was defined as the probability that a patient would be assigned to a particular therapy based on the patients' baseline covariates. Inverse probability of treatment weighting (IPTW) was selected for the PS analysis, as it was reported to result in a lower mean squared error when estimating the effect of treatment (10). The PS of bacterial infection was estimated by a multivariate logistic regression analysis involving the following 10 covariates: age, sex, hospitalization in the intensive care unit on admission, intubation on admission, OS on admission, diabetes mellitus, chronic kidney disease, chronic obstructive pulmonary disease, C-reactive protein level, and albumin level. The PS of 28-day mortality as estimated by the multivariate logistic regression analysis involved the following 12 covariates: age, sex, hospitalization in the ICU on admission, intubation on admission, OS on admission, heart disease, diabetes mellitus, chronic kidney disease, chronic obstructive pulmonary disease, C-reactive protein level, albumin level, and lymphocyte count. These covariates were selected based on previous reports analyzing prognostic factors for COVID-19 (11-14).

All p values were two-sided, and p values of ≤0.05 were considered significant. All statistical analyses were performed with EZR [Jichi Medical University Saitama Medical Center (15)], which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria, version 4.1.0). More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics.

## Results

In total, 96 hospitalized patients with COVID-19 were enrolled. The clinical characteristics of patients in both groups at baseline are shown in Table 1. There were no significant differences in the age, sex, do-not-intubate or do-not-attempt-resuscitation status ratio, symptom duration until hospitalization, and underlying diseases between the BCT and non-BCT groups. The body mass index (26.6 kg/m$^2$ vs. 23.5 kg/m$^2$; p=0.04) and OS at admission (5.0 vs. 5.0; p=0.01) were significantly higher in the BCT group than in the non-BCT group.

The clinical laboratory data of both groups at baseline are also shown in Table 1. Hemoglobin A1c (HbA1c) (6.1% vs. 5.8%; p=0.04), alanine aminotransferase (36 U/L vs. 24 U/L; p=0.04), and lactate dehydrogenase (442 U/L vs. 338 U/L; p=0.02) were significantly different between the BCT and non-BCT groups. The ICU admission rate, intubation rate, and causes of death of both groups are shown in Table 1. The ICU admission rate (56.1% vs. 24.5%; p=0.006) and the intubation rate (51.2% vs. 13.2%; p<0.001) were significantly higher in the BCT group than in the non-BCT group. In both groups, the cause of death was mostly COVID-19.

Primary and secondary outcomes are shown in Table 2. The bacterial infection rate [odds ratio (OR), 1.1; 95% confidence interval (CI), 0.36-3.38; p=0.87] did not differ significantly. Causative infectious organisms are listed below.

*Staphylococcus epidermidis* was the most common bacterial pathogen causing bacteremia, *Staphylococcus aureus* (all cases were methicillin-sensitive *S. aureus)* was the most common bacterial pathogen causing bacterial pneumonia, and *Escherichia coli* was the most common bacterial pathogen causing urinary tract infection (some patients were duplicated). The 28-day mortality rate (OR, 0.31; 95% CI, 0.07-1.3; p=0.11) also did not differ significantly.

The causes of treatment interruptions with baricitinib are shown in Table 3. There were 11 patients who did not complete baricitinib for 14 days (3 because their general condition improved, 2 discontinued because of bacteremia or VAP, and 1 each due to discharge home, liver dysfunction, oral candida, or urinary tract infection).

The standardized mean differences (SMDs) of the 10 covariates are shown in Table 4 before and after adjusting by the IPTW analysis for the primary outcome. The SMDs of the 12 covariates are shown in Supplementary Material 1 for the secondary outcome (28-day mortality). After adjusting by the IPTW analysis, there were no significant differences in the bacterial infection rate or 28-day mortality rate (Table 5). In a subgroup analysis of the OS 5-7 group, the bacterial infection rate and 28-day mortality rate did not differ significantly (Supplementary Material 2).

## Discussion

The present study showed that baricitinib could be used without increasing the infection risk compared with non-BCT according to an IPTW analysis. In addition, the 28-day mortality showed a trend toward a lower mortality in the BCT group than in the non-BCT group, although the difference was not significant.

The baseline characteristic data showed that the BCT group had a higher OS and a higher body mass index, indicating a higher severity of disease and a higher risk of developing severe disease. On baseline laboratory findings, the BCT group had worse control of diabetes mellitus and higher lactate dehydrogenase values. However, the bacterial infection rate did not increase. Adverse events requiring discontinuation of baricitinib were not frequent, showing an acceptable incidence. In terms of disposition, the ICU admission rate and intubation rate were markedly higher in the BCT group than in the non-BCT group, but there was no significant difference in the mortality rate. In addition, there were no deaths due to infections other than COVID-19 in the BCT group. A subgroup analysis limited to OS 5-7 (patients requiring oxygenation) showed trends similar to the main analysis, regardless of the IPTW analysis findings (Supplementary Material 3).

The ACTT-2 trial showed that the efficacy of the combination of baricitinib and remdesivir was superior to that of remdesivir alone in shortening recovery time and accelerating improvement in the clinical status of COVID-19 patients. In addition, baricitinib plus remdesivir did not increase infections or infestations, including septic shock,

**Table 1.   Baseline Clinical Characteristics of the BCT and Non-BCT Groups.**

| | BCT n=43 | Non-BCT n=53 | p value |
|---|---|---|---|
| Age, y | 69.0 (57.5-75.5) | 69.0 (57.0-82.0) | 0.39 |
| Male sex | 27 (62.8%) | 34 (64.2%) | 1.0 |
| DNI/DNAR | 5 (11.2%) | 15 (28.3%) | 0.08 |
| BMI, kg/m$^2$ | 26.6 (22.9-28.0) | 23.5 (22.3-25.8) | 0.04 |
| Symptom duration before admission, days | 8.0 (5-11) | 6.0 (3-9) | 0.15 |
| **Ordinal scale on admission** | **5.0 (5-6)** | **5.0 (5-5)** | **0.01** |
| 3 | 0 | 1 (1.9%) | |
| 4 | 1 (2.3%) | 10 (18.9%) | |
| 5 | 22 (51.1%) | 31 (58.5%) | |
| 6 | 10 (23.3%) | 7 (13.2%) | |
| 7 | 10 (23.3%) | 4 (7.5%) | |
| Japanese severity classification of COVID-19 | | | 0.06 |
| Mild | 0 | 4 (7.5%) | |
| Moderate I | 1 (2.3%) | 4 (7.5%) | |
| Moderate II | 27 (62.8%) | 36 (67.9%) | |
| Severe | 15 (34.9%) | 9 (17.0%) | |
| **Previous coexisting disease** | | | |
| Hypertension | 26 (60.5%) | 31 (58.5%) | 1.0 |
| Heart disease | 8 (18.6%) | 10 (18.9%) | 1.0 |
| Diabetes mellitus | 16 (37.2%) | 15 (28.3%) | 0.39 |
| Chronic obstructive pulmonary disease | 12 (27.9%) | 18 (34.0%) | 0.66 |
| Interstitial lung disease | 1 (2.3%) | 1 (1.9%) | 1.0 |
| Chronic kidney disease | 2 (4.7%) | 7 (13.2%) | 0.18 |
| Stroke | 5 (11.6%) | 5 (9.4%) | 0.75 |
| Cancer | 7 (16.3%) | 9 (17.0%) | 1.0 |
| Liver disorder | 2 (4.7%) | 3 (5.7%) | 1.0 |
| **Laboratory data** | | | |
| Hb, g/dL | 14.2 (13.1-15.3) | 13.4 (11.8-15.7) | 0.08 |
| WBC, /μL | 6,600 (5,400-10,250) | 5,900 (4,700-9,700) | 0.26 |
| Neut, % | 84.0 (78.9-89.8) | 82.0 (73.3-87.4) | 0.14 |
| Lym, % | 11.7 (6.7-15.0) | 13.1 (7.6-18.3) | 0.16 |
| PLT, /μL | 19.3 (14.6-25.0) | 18.5 (14.4-21.5) | 0.33 |
| HbA1c, %* | 6.1 (5.9-6.7) | 5.8 (5.6-6.5) | 0.04 |
| CRP, mg/dL | 5.9 (3.5-9.2) | 4.6 (1.4-9.7) | 0.15 |
| TP, g/dL | 6.3 (6.0-6.7) | 6.4 (6.1-6.7) | 0.28 |
| ALB, g/dL | 3.0 (2.8-3.3) | 3.2 (2.9-3.5) | 0.12 |
| AST, U/L | 51 (41-70) | 43 (28-71) | 0.25 |
| ALT, U/L | 36.0 (28-59) | 24 (17-53) | 0.04 |
| LDH, U/L | 442 (359-533) | 338 (237-496) | 0.02 |
| Cre, mg/dL | 0.80 (0.66-0.98) | 0.91 (0.64-1.36) | 0.21 |
| BUN, mg/dL | 20（17-25) | 18 (14-29) | 0.31 |
| eGFR mL/min/1.73 m$^2$ | 71.5 (52.6-82.5) | 55.8 (41.1-79.2) | 0.16 |
| Na, mmol/L | 137 (134-139) | 136 (134-139) | 0.46 |
| K, mmol/L | 4.0 (3.8-4.3) | 4.1 (3.8-4.4) | 0.49 |
| BNP, pg/mL** | 22.5 (9.1-36.8) | 18.3 (9.4-40.7) | 0.74 |
| CPK, U/L | 138 (51-268) | 132 (73-341) | 0.49 |
| T-Bil, mg/dL | 0.5 (0.4-0.7) | 0.5 (0.4-0.8) | 0.76 |
| **ICU admission, n (%)** | **23 (56.1%)** | **13 (24.5%)** | **0.006** |
| **Intubation, n (%)** | **21 (51.2%)** | **7 (13.2%)** | **<0.001** |
| **Cause of death** | **n=7** | **n=14** | |
| COVID-19, n (%) | 6 (85.7%) | 12 (85.6%) | |
| Lung cancer, n (%) | 1 (14.3%) | 0 | |
| Septic shock, n (%) | 0 | 1 (7.2%) | |
| Bacterial pneumonia, n (%) | 0 | 1 (7.2%) | |
| **Treatment** | | | |
| No medical treatment | 0 | 8 | |
| Remdesivir | 0 | 1 | |
| Dexamethasone | 0 | 22 | |
| Dexamethasone+remdesivir | 0 | 22 | |
| Dexamethasone+remdesivir+baricitinib | 43 | 0 | |

Data are presented as medians and interquartile ranges or n (%).

*Missing n=11. **Missing n=15.

ALB: albumin, ALT: alanine aminotransferase, AST: aspartate aminotransferase, BCT: baricitinib-containing thera-
py, BMI: body mass index, BNP: brain natriuretic peptide, BUN: blood urea nitrogen, COVID-19: coronavirus dis-
ease 2019, CPK: creatine phosphokinase, Cre: creatinine, CRP: C-reactive protein, DNAR: do not attempt resuscita-
tion, DNI: do not intubate, eGFR: estimated glomerular filtration rate, Hb: hemoglobin, HbA1c: hemoglobin A1c,
ICU: intensive care unit, K: potassium, LDH: lactate dehydrogenase, Lym: lymphocytes, Na: sodium, Neut: neutro-
phil, PLT: platelet, T-Bil: total bilirubin, TP: total protein, WBC: white blood cell

**Table 2.   Bacterial Infection Rate, Coinfection Causative Pathogens, 28-day Mortality, and Usage of Antibiotics.**

|  | BCT n=43 | Non-BCT n=53 | p value |
|---|---|---|---|
| Bacterial infection | 11 (25.6%) | 9 (17.0%) | 0.30 |
| Causative organism |  |  |  |
| Bacteremia |  |  |  |
|   Number of patients, n | n=2 (duplicate) | n=2 (duplicate) |  |
|   *Staphylococcus epidermidis* | 2 |  |  |
|   *Enterobacter aerogenes* |  | 1 |  |
|   *Klebsiella pneumoniae* | 1 |  |  |
|   *Proteus mirabilis* |  | 1 |  |
|   *Staphylococcus aureus* |  | 1 |  |
| Bacterial pneumonia |  |  |  |
|   Number of patients, n | n=9 (duplicate) | n=4 (duplicate) |  |
|   *S. aureus* | 4 | 3 |  |
|   *Haemophilus influenzae* | 3 | 1 |  |
|   *Pseudomonas aeruginosa* | 1 | 1 |  |
|   *Escherichia coli* | 1 |  |  |
|   *Klebsiella* spp. | 1 |  |  |
|   *Streptococcus pneumoniae* |  | 1 |  |
| Urinary tract infection |  |  |  |
|   Number of patients, n | n=2 (duplicate) | n=5 (duplicate) |  |
|   *E. coli* | 1 | 3 |  |
|   *Enterococcus faecalis* |  | 2 |  |
|   *Enterobacter aerogenes* |  | 1 |  |
|   *Klebsiella pneumoniae* | 1 |  |  |
|   *Morganella morganii* |  | 1 |  |
|   *Proteus mirabilis* |  | 1 |  |
|   *Stenotrophomonas maltophilia* | 1 |  |  |
| 28-day mortality, n (%) | 3 (7.3%) | 13 (24.5%) | 0.02 |
| Usage of antibiotics | 20 (46.5%) | 18 (34.0%) | 0.29 |

Data are presented as n (%).
BCT: baricitinib-containing therapy

**Table 3.   Causes of Treatment Interruptions with Baricitinib.**

| Cause | Baricitinib suspended |
|---|---|
| Improved general condition | 3 |
| Bacteremia | 2 |
| Ventilator-associated pneumonia | 2 |
| Discharge | 1 |
| Liver dysfunction | 1 |
| Oral candidiasis | 1 |
| Urinary tract infection | 1 |

pneumonia, and sepsis (4). However, this trial did not allow baricitinib plus DEX, and to our knowledge, few articles have compared the incidence of infectious complications between BCT and non-BCT populations.

Baricitinib was originally approved for the treatment of rheumatoid arthritis (16). Serious adverse events, including infections, through week 24 were more frequent with baricitinib and placebo than with adalimumab. Therefore, the combination of baricitinib and DEX may increase the risk of infection. In the present study, BCT did not increase the risk of bacterial infections, such as bacterial pneumonia,

bacteremia, or urinary tract infection, and was able to be continued by adding antibiotics for infections that newly developed, even if bacterial infections occurred.

COV-BARRIER excluded patients with OS 7 (intubated) at the start of treatment. In the present study, 23.3% of the BCT group patients had OS 7, but our findings were still similar to those of COV-BARRIER. In addition, COV-BARRIER excluded cases with a history of steroid administration, and higher corticosteroid doses [>20 mg per day (or prednisone equivalent) administered for >14 consecutive days in the month before study entry] were not permitted unless indicated per standard of care for a concurrent condition, such as asthma, chronic obstructive pulmonary disease, or adrenal insufficiency. However, in the present study, it was possible to include data without such restrictions, and the same trend as in COV-BARRIER was seen. When a patient developed exacerbation of lung shadows during COVID-19 treatment, it was difficult to differentiate between COVID-19 exacerbation and bacterial pneumonia. In the present study, three physicians, including one respiratory specialist and two who were both respiratory and infectious disease specialists, made the decision regarding HAP or VAP while blinded to which treatment group the patients

**Table 4.  Standardized Mean Differences before and after Propensity Score Analysis for Bacterial Infection.**

| Covariate | Standardized mean difference | |
|---|---|---|
| | Before IPTW | After IPTW |
| Age | 0.12 | 0.07 |
| Sex | 0.03 | 0.08 |
| Hospitalization in intensive care unit on admission | 0.62 | 0.04 |
| Intubation on admission | 0.83 | 0.07 |
| Ordinal scale on admission | 0.72 | 0.05 |
| Diabetes mellitus | 0.19 | 0.07 |
| Chronic kidney disease | 0.30 | 0.07 |
| Chronic obstructive pulmonary disease | 0.13 | 0.002 |
| C-reactive protein | 0.04 | 0.02 |
| Albumin | 0.32 | 0.06 |

IPTW: inverse probability of treatment weighting

**Table 5.  Bacterial Infections and 28-day Mortality with BCT before and after IPTW Analysis.**

| | Before IPTW analysis | | After IPTW analysis | |
|---|---|---|---|---|
| | OR (95%CI) | p value | OR (95%CI) | p value |
| Infectious disease rate | 1.68 (0.62-4.6) | 0.30 | 1.10 (0.36-3.38) | 0.87 |
| 28-day mortality rate | 0.21 (0.05-0.70) | 0.02 | 0.31 (0.07-1.3) | 0.11 |

IPTW: inverse probability of treatment weighting

belonged. The present results suggest that the combination of steroids and baricitinib may be used safely in the short term without increasing the incidence of infectious diseases, including HAP and VAP. COV-BARRIER showed a reduction in the 28-day all-cause mortality with treatment. However, after adjusting based on the IPTW analysis, the present study did not show a reduction in the 28-day mortality. Since the 28-day mortality tended to be better in the BCT group than in the non-BCT group, we believe that the reason for the lack of a significant difference in the present study was due to the small number of cases.

Several limitations associated with the present study warrant mention. First, it was a retrospective study conducted with a small sample size in a single center. In particular, the lack of significant differences in 28-day mortality or other outcomes might have been attributable to the small sample size. Second, treatment was dependent on the discretion of the attending physician. Third, some patients received limited treatment intensity due to the code status of "do not intubate and do not attempt resuscitation". Finally, three physicians, including one respiratory specialist and two who were both respiratory and infectious disease specialists, made decisions regarding HAP or VAP. However, it was still difficult to strictly distinguish between worsening COVID-19 and HAP or VAP.

## Conclusion

Baricitinib was able to be used without increasing bacte-

rial infections, which has been a previous concern with BCT.

**The authors state that they have no Conflict of Interest (COI).**

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