ORIGINAL RESEARCH

Analysis of Factors and T-Lymphocyte Subset Changes in Pediatric Recurrent Respiratory Infections Post-Pidotimod Treatment

Renmin Hu, MM; Chong Jin, MM; Xiang Lin, MM; Yinyin Chen, MM; Yaodong Wang, MM; Yan Guo, MD

ABSTRACT

Objective • This study aims to analyze factors contributing to recurrent respiratory tract infections (RRTIs) in pediatric patients and evaluate the efficacy of pidotimod (PI) treatment.

Methods • This study utilized a retrospective cohort design, enrolling a total of 85 children diagnosed with RRTIs between September 2020 and September 2022, alongside 54 healthy children. Logistic regression analysis was employed to identify factors contributing to RRTI occurrence. Among the participants, 40 children underwent conventional treatment (control group), while 45 received PI treatment (research group). Comparative analyses were conducted to assess clinical efficacy and adverse effects between the two treatment groups.

Results • The history of family members' smoking and parental allergy emerged as independent risk factors for RRTIs ($P < .05$, OR>1), whereas parental education level, outdoor activity, and micronutrient intake were identified as independent protective factors for RRTIs ($P < .05$, OR<1). Symptoms such as cough, fever, rhonchi, moist rales, and tonsillar enlargement resolved significantly faster in the research group compared to the control group ($P < .05$). Additionally, the research group exhibited reduced infection duration and fewer recurrent infections ($P < .05$). Following treatment, the overall treatment efficacy was superior in the research group compared to the control group ($P < .05$), with no significant difference in the incidence of adverse effects ($P > .05$). Post-treatment, levels of CD3+, CD4+, and CD4+/CD8+ were elevated in the research group compared to the control group, while CD8+ levels were lower ($P < .05$).

Conclusions • Daily outdoor activity among children, family members' history of smoking, parental allergy history, education level, and micronutrient intake emerged as independent factors influencing pediatric RRTIs. Furthermore, PI was identified as a significant treatment option for RRTIs. (*Altern Ther Health Med.* [E-pub ahead of print.])

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INTRODUCTION

Respiratory infections represent a prevalent category of infectious diseases in children, with recurrent respiratory tract infections (RRTIs) encompassing both upper and lower respiratory tract infections that manifest repeatedly in children over a specified threshold within a year.[1] Such recurrent occurrences can significantly impede the healthy growth and development of children.[2] Pediatric RRTIs typically arise due to factors such as an immature immune system, substandard living conditions, compromised air quality, and unpredictable climate patterns.[2,3]

Clinical manifestations often encompass fever, cough, and dyspnea, which, if left untreated, can escalate to respiratory failure or shock, significantly impeding the growth and development of children.[2] Studies suggest a prevalence rate of RRTIs as high as 7-10% among children aged 4-8 years.[3] In the past, clinical management strategies predominantly centered on anti-infective drug therapy, resulting in only moderate overall therapeutic effectiveness.[4] In recent years, there has been a significant increase in the number of children affected by RRTIs, highlighting the urgent necessity for effective treatment approaches to ensure the healthy development of patients.

Pidotimod (PI), functioning as an immune booster, enhances both nonspecific and specific immune responses. It

regulates, improves, and reinstates the body's immune function, making it particularly suitable for patients with compromised immune systems.[5,6] Clinically, it is commonly employed as adjuvant therapy for chronic or recurrent infectious diseases.[5] Previous data review has demonstrated the efficacy of PI in reducing the recurrence risk of pediatric respiratory infections and significantly alleviating associated symptoms.[6]

However, due to the relative scarcity of studies examining the use of PI for RRTIs, its application in clinical practice remains highly controversial.[7] Therefore, our study sought to address this gap by analyzing factors associated with pediatric RRTIs and observing symptom improvement following PI treatment. The aim was to provide valuable reference and guidance for the development of effective prevention and treatment strategies in the future management of RRTIs.

MATERIALS AND METHODS

Study Design

This study utilized a retrospective cohort design, and a total of 85 children diagnosed with RRTIs and treated at Ninghai County Maternal and Child Health Care Hospital from September 2020 to September 2022 were included in this study. Among the children diagnosed with RRTIs, 40 were assigned to receive conventional treatment, comprising the control group, while the remaining 45 received PI treatment, forming the research group. Additionally, 54 children who underwent healthy physical examinations during the same period were included for comparison. Prior to commencement, informed consent was obtained from all participants/parents, and our hospital's ethics committee granted approval for this study.

Inclusion and Exclusion Criteria

Inclusion criteria were as follows: (1) a confirmed diagnosis of pediatric RRTI through laboratory and imaging examinations, alongside the presence of notable clinical symptoms;[8] (2) children with no history of congenital immunodeficiency diseases or congenital bronchiectasis; (3) with complete data availability and informed consent from participating families were considered eligible for inclusion. Exclusion criteria encompassed: (1) organ dysfunction; (2) cognitive impairment; (3) comorbidities with other respiratory diseases; (4) inability to communicate effectively; (5) medication allergies or contraindications; and (6) transfer to another hospital midway through the study.

Treatment Protocol

Conventional Treatment. Upon admission, the children received conventional treatment, which included measures such as cough and sputum relief, anti-infection therapy, and inhalation.[9] Initially, continuous low-flow oxygenation was administered, followed by inhalation of budesonide suspension (Lunanbet Pharmaceutical Co., Ltd., H20140475) containing 0.5 mg budesonide + 20 mL saline in inhalation, 10 min each time, 2 times/d, once oxygen capacity improved. Antibacterial medications, namely cefprozil, cefuroxime, azithromycin, cefetamet pivoxil, and amoxicillin, were prescribed based on the results of drug sensitivity tests conducted in children.

PI Treatment. In the research group, PI (China Resources Sanjiu (Tangshan) Medical & Pharmaceutical Co., Ltd., H20010091) was incorporated into the standard treatment regimen. Initially, 0.4 g of PI was administered twice daily (0.4 g per time, 2 times/d), which was subsequently reduced to once daily after two weeks (0.4 g per time/d after 2 weeks).

Duration of Treatment. The treatment duration for both the control and research groups spanned two months, during which participants received continuous therapy.

Efficacy Evaluation Criteria

Efficacy evaluation criteria were as follows: (1) Markedly effective: after treatment, complete resolution of all clinical symptoms was observed, with no recurrence of infections noted six months after cessation of medication; (2) Effective: pulmonary auscultation revealed a notable reduction in croup or fine moist rales, accompanied by a decrease in the frequency of infections or the absence of infections within six months after treatment cessation; (3) Ineffective: no substantial reduction in clinical symptoms or recurrence of infections was observed following discontinuation of the medication. The total effective rate of treatment was calculated as follows: Total effective rate: (Markedly Effective + Effective)/ the total number of cases × 100.

Outcome Measures

Analysis of Factors Associated with RRTI. The comparison of data between children diagnosed with RRTIs and healthy children was conducted to reveal the factors underlying the occurrence of RRTIs. This assessment aimed to identify any distinct patterns or associations that could shed light on the etiology and risk factors of RRTIs in pediatric populations.

Time to Disappearance of Clinical Symptoms. The duration required for the complete resolution of clinical symptoms, encompassing cough, fever, rhonchi, moist rales, and tonsillar enlargement, was precisely documented for both the research and control groups. This assessment was conducted to estimate the efficacy of the treatment protocols by monitoring the duration required for the complete resolution of clinical symptoms.

Duration of Infection and Recurrent Infections. The duration of infection and the frequency of recurrent infections were documented for both groups to provide a comprehensive understanding of the disease course in both groups. This assessment was aimed to evaluate the persistence of infection and the propensity for recurrent episodes, which are crucial factors in assessing the effectiveness of treatment interventions and guiding future management strategies.

Assessment of Clinical Outcomes. Clinical outcomes for both the research and control groups were thoroughly recorded. This comprehensive evaluation encompassed various

aspects of patient well-being, including symptom resolution, overall health improvement, and disease recurrence, thereby offering valuable insights into the overall therapeutic outcomes achieved through the treatment protocols employed.

Analysis of T-Lymphocyte Subsets. Fasting venous blood samples were collected from children diagnosed with RRTIs before and after treatment. Subsequently, changes in T-lymphocyte subsets, including CD3+, CD4+, CD8+, and the CD4+/CD8+ ratio, were analyzed using the NanoFCM-Flow Cytometer (Xiamen Flow Biotechnology Co., Ltd.).

Assessment of Adverse Reactions. The occurrence of adverse reactions, such as vomiting and gastrointestinal disturbances, during the course of treatment in both groups, was documented to assess the tolerability and potential side effects associated with the treatment regimens.

Statistical Methods

The data analysis was conducted using SPSS 22.0 statistical software (International Business Machines, Corp., Armonk, NY, USA), while GraphPad Prism 7 (GraphPad Software, San Diego, CA, USA) was utilized for graphical representation. Counting data were presented as rates [n (%)] and compared using the chi-square test (χ^2). Measurement data were expressed as mean ± standard deviation ($\bar{x} \pm s$), with intergroup comparisons performed using the *t* test. Paired *t* tests were employed for within-group comparisons before and after treatment. Logistic regression analysis was employed to identify correlation factors. A significance level of $P < .05$ was considered statistically significant.

RESULTS

Univariate Analysis of Factors Affecting RRTI

Statistical analysis revealed no significant differences in age, gender, place of residence, or pet ownership between children diagnosed with RRTI and their healthy counterparts ($P > .05$). However, children with RRTI exhibited lower parental education levels, decreased outdoor activity, and deficiencies in micronutrients such as iron (Fe), calcium (Ca), and zinc (Zn) compared to healthy children. Additionally, a higher prevalence of smoking among family members and a history of parental allergies were observed in the RRTI group compared to the control group ($P < .05$), see Table 1.

Multifactor Analysis of the Influence of RRTI

Subsequently, logistic regression analysis was conducted with RRTI as the independent variable and the previously identified factors as covariates. The results indicated that smoking among family members and a history of parental allergies were independent risk factors for RRTI ($P < .05$, OR > 1), whereas parental education level, outdoor activity, and adequate intake of micronutrients served as independent protective factors ($P < .05$, OR < 1), see Table 2 and 3.

Effect of PI on Clinical Symptoms

After treatment, the observation of clinical symptom disappearance times in both groups revealed a significantly shorter duration for the resolution of cough, fever, rhonchi, moist rales, and tonsillar enlargement in the research group compared to the control group ($P < .05$). These findings suggest that the therapeutic effect of PI on symptom improvement in RRTI was notably more pronounced, see Figure 1.

Effect of PI on Duration of Infection and Frequency of Recurrent Infections

Statistical analysis revealed that the duration of infection and the frequency of recurrent infections in the research group were (3.51 ± 1.58) days and (2.80 ± 0.84) times, respectively. Moreover, both the duration of infection and the

Table 1. Univariate Analysis of Factors Affecting RRTI ($\bar{x} \pm s$)

Variables	Healthy Children (n=54)	RRTI (n=85)	χ^2	*P* value
Age	4.52±2.14	4.63±1.99	0.315	.754
Boy/Girl	30/24	43/42	0.327	.568
Urban/Rural	47/7	80/5	2.099	.147
Parental Education Level (>High School/ ≤High School)	42/12	46/39	7.958	.005
Daily Outdoor Activity (None/0-2h/>2h)	6/32/16	42/36/7	25.090	<.001
Pet Ownership (Yes/No)	11/43	24/61	1.084	.298
Smoking From Family Members (Yes/No)	22/32	53/32	6.208	.013
Parental Allergy History (Yes/No)	13/41	42/43	8.866	.003
Fe (mmol/L)	8.09±0.82	7.47±0.88	4.224	<.001
Ca (μmol/L)	1.71±0.11	1.56±0.21	4.771	<.001
Zn (μmol/L)	83.43±6.71	76.91±6.54	5.659	<.001

Note: Values are presented as mean ± standard deviation for continuous variables and as frequency for categorical variables. Statistical significance was determined using the chi-square test (χ^2) for categorical variables and the *t* test for continuous variables, with $P < .05$ considered statistically significant.

Abbreviations: Fe, Iron, Ca, Calcium, Zn, Zinc.

Table 2. Assignment Table for Categorical Indicators and Blood Mineral Levels

Indicators	Assignment
Parental education level	>High School=0/≤high School=1
Parental education level	None=0/0-2h=1/>2h=2
Smoking from family members	No=0/Yes=1
Parental allergy history	No=0/Yes=1
Fe (mmol/L)	No assignment required
Ca (μmol/L)	No assignment required
Zn (μmol/L)	No assignment required

Note: Assignments are represented by numeric values corresponding to the given categories for each indicator.

Abbreviations: Fe, Iron; Ca, Calcium; Zn, Zinc.

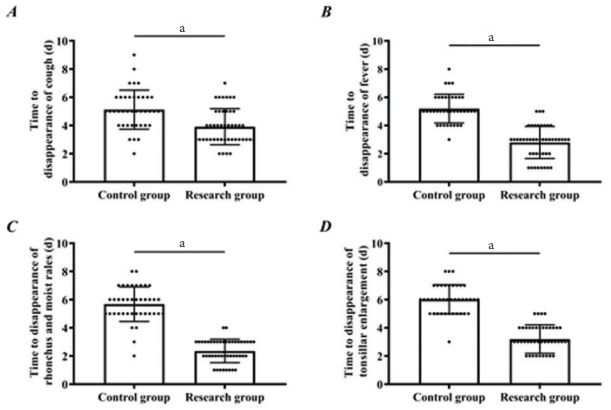
Table 3. Multifactorial Analysis of RRTI Influence

Indicators	B	S.E.	Wald χ^2	*P* value	OR	95%CI
Parental education level	0.426	1.262	14.620	<.001	0.426	0.264-1.114
Parental education level	1.126	0.846	12.881	<.001	0.292	0.084-0.763
Smoking from family members	0.891	1.887	8.931	<.001	2.161	1.542-3.945
Parental allergy history	0.712	1.066	10.162	<.001	1.871	1.062-5.063
Fe(mmol/L)	1.622	1.631	5.874	<.001	0.262	0.062-0.557
Ca(μmol/L)	1.840	1.912	12.633	<.001	0.426	0.164-1.300
Zn(μmol/L)	0.726	0.652	14.094	<.001	0.559	0.284-1.065

Note: β: Beta coefficient representing the change in the outcome variable for a one-unit change in the predictor variable, S.E.: Standard Error of the estimate, Wald χ^2 - Wald Chi-square statistic testing the significance of the predictor variable, *P*: Probability value indicating the significance of the predictor variable, OR: Odds Ratio estimating the likelihood of the outcome variable occurring, 95% CI - 95% Confidence Interval around the Odds Ratio.

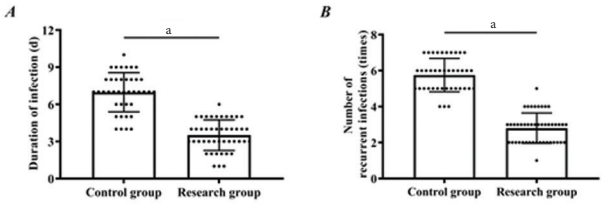
Abbreviations: Fe, Iron; Ca, Calcium; Zn, Zinc.

Figure 1. Impact of PI on Clinical Symptoms. (A) Time to Disappearance of Cough; (B) Time to Disappearance of Fever; (C) Time to Disappearance of Rhonchus and Moist Rales; (D) Time to Disappearance of Tonsillar Enlargement. The figure illustrates the duration taken for the clinical symptoms of cough, fever, rhonchus and moist rales, and tonsillar enlargement to resolve following treatment with PI.



[a]$P < .01$, the significance level indicates statistical significance.

Figure 2. Impact of PI on Duration of Infection and Number of Recurrent Infections. (A) Duration of Infection (B) Number of Recurrent Infections. The figure demonstrates the effect of PI on the duration of infection and the frequency of recurrent infections.



[a]$P < .01$ indicates statistical significance.

Table 4. Comparison of Clinical Efficacy between Control and Research Groups [n (%)]

Group	n	Markedly Effective	Effective	Ineffective	Total Effective Rate
Control Group	40	18(45.00)	14(35.00)	8(20.00)	80.00
Research Group	45	25(55.56)	18(40.00)	2(4.44)	95.56
χ^2					4.936
P value					.026

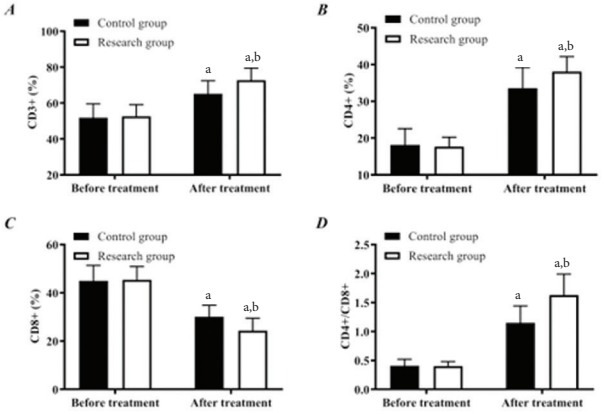
Note: The table compares the clinical efficacy of treatment between the control and research groups. The numbers represent counts, with percentages shown in parentheses. A chi-square (χ^2) test was conducted to determine the statistical significance, yielding a χ^2 value of 4.936 with a corresponding *P* value of .026.

number of recurrent infections were significantly lower in the research group compared to the control group ($P < .05$), see Figure 2.

Comparison of Clinical Efficacy

After treatment, the total effective rate of treatment was 95.56% in the research group and 80.00% in the control group. Notably, the total effective rate of treatment was significantly higher in the research group compared to the control group ($P < .05$), see Table 4.

Figure 3. Impact of PI on T-Lymphocyte Subsets. Note: (A) CD3+; (B) CD4+; (C) CD8+; (D) CD4+/CD8+ The figure illustrates the impact of PI on various T-lymphocyte subsets, including CD3+, CD4+, CD8+, and CD4+/CD8+.



[a]comparison with the values before treatment ($P < .05$)
[b]comparison with the control group ($P < .05$)

Table 5. Comparison of Adverse Reactions between Control and Research Groups [n (%)]

Group	n	Vomiting	Gastrointestinal Reaction	Diarrhea	Total Incidence (%)
Control Group	40	2(5.0%)	1(2.5%)	1(2.5%)	4(10.0%)
Research Group	45	1(2.2%)	1(2.2%)	1(2.2%)	3(6.7%)
χ^2					0.311
P value					.577

Note: The table presents the comparison of adverse reactions observed in the control and research groups during treatment. The numbers represent counts, with percentages shown in parentheses. A chi-square (χ^2) test was conducted to determine the statistical significance, resulting in a χ^2 value of 0.311 with a corresponding *P* value of .577.

Effect of PI on T-Lymphocyte Subsets

Before treatment, no statistically significant differences were observed in the comparison of CD3+, CD4+, CD4+/CD8+, and CD8+ levels between the two groups of children ($P > .05$). However, following treatment, levels of CD3+, CD4+, and CD4+/CD8+ were elevated in both groups, with significantly higher levels noted in the research group compared to the control group ($P < .05$). Conversely, CD8+ levels were lower in the research group compared to the control group ($P < .05$), see Figure 3.

Comparison of Adverse Reactions

During treatment, the incidence of adverse reactions was 10.0% in the research group and 6.7% in the control group. However, the disparity in the total incidence of adverse reactions was not statistically significant ($P > .05$); see Table 5.

DISCUSSION

Pediatric RRTIs represent a prevalent clinical condition among children, with younger age groups being particularly susceptible.[9] Recent trends indicate a steady increase in the incidence of RRTIs over the years, posing significant challenges to children's health and development.[10] However, reliable prevention and treatment strategies to mitigate the

occurrence of RRTIs have been lacking. Therefore, comprehending the potential risk factors associated with RRTI bears significant clinical relevance for devising future preventive and therapeutic strategies.[11] Conversely, due to the incomplete understanding of RRTI pathogenesis, there exists considerable controversy surrounding the selection of treatment modalities for this condition.[11,12]

PI is a high-purity dipeptide that stands out as the sole clinically available immune-boosting medication, holding promising potential for the management of RRTI.[13] Therefore, in the present study, we investigated the therapeutic efficacy of PI on RRTI, providing valuable insights for future management approaches. Initially, logistic regression analysis revealed that children's daily outdoor activity, family members' smoking history, parental allergy history and education level, as well as micronutrient levels, were all independent factors influencing pediatric RRTI. Previous studies have also demonstrated the significant association of these factors with RRTI occurrence,[14,15] thereby reinforcing the findings of our current findings.

Among these identified factors, we posit that outdoor activities contribute significantly to enhancing children's physical fitness and strengthening their immune systems.[16] Research has substantiated that parental smoking induces respiratory motor fatigue and diminishes respiratory defenses in fetuses, subsequently reducing the ability to clear impurities from the respiratory tract in children post-birth.[17] Passive smoking resulting from family members' tobacco use is known to increase children's vulnerability to RRTIs, as residual pathogens from smoke exposure can exacerbate the onset of such infections.

Additionally, genetic studies have revealed a predisposition to RRTIs among children with a parental history of allergies, likely attributed to genetically mediated alterations in immune function.[18] Moreover, the impact of parental education level on susceptibility to RRTIs may arise from educated parents instilling rational behaviors and cultivating a hygienic environment for their children. This behavior, in turn, reduces direct exposure to pathogens.[19]

Furthermore, micronutrients play a crucial role as essential nutrients in the human body, particularly during the growth and development stages of children.[20] Deficiencies in micronutrients such as calcium, iron, and zinc can result in diminished activity of immune cells, macrophages, and granulocytes, leading to various adverse outcomes, including anemia, compromised immune function, and impaired bone development. These factors collectively elevate the risk of RRTIs.

PI, a novel immunomodulator, has become increasingly prevalent in clinical practice. Despite lacking direct antibacterial or antiviral properties, it exerts a stimulating influence on both specific and nonspecific immune functions. PI serves therapeutic purposes by boosting the antiviral capabilities of the body's natural killer cells through the cellular immune pathway [21]. Studies have confirmed that administering PI treatment to children with RRTI enhances treatment efficacy and accelerates symptom relief.[22]

Our study further substantiates this finding, as evidenced by the significantly higher total treatment efficiency observed in the research group. Moreover, the time to disappearance of clinical symptoms and the duration and frequency of recurrent infections were notably reduced, indicating the excellent therapeutic effect of PI on RRTI. This outcome may be attributed to the beneficial impact of PI on regulating the balance of T-cell populations and activating NK cells in affected children.[23]

The T-lymphocyte subset comprises crucial immune cells in the body, such as CD3+, CD4+, and CD8+, which essentially reflect the body's immune function. This assertion is supported by the observed higher levels of CD3+, CD4+, and CD4+/CD8+ in the children receiving PI treatment compared to those in the control group after treatment. Conversely, CD8+ levels were lower in the PI-treated group than in the control group, indicating the significant modulating effect of PI on immune function. This finding is consistent with the findings of Fu et al.,[24] further supporting our results.

Additionally, the high bio-efficacy of PI can enhance neutrophil phagocytosis in the affected organism, ultimately enhancing lesion chemotaxis and providing better protection against pathogen growth and invasion.[25] The lack of significant differences in adverse reaction incidence between the two groups of children also indicates that PI displays a high safety profile and merits promotion in clinical practice.

Study Limitations

However, it is important to acknowledge the limitations of this study. The relatively small sample size may introduce bias into the results, limiting the generalizability of our findings. Additionally, the study highlighted regional variability in RRTI prevalence,[26] indicating the need for a more extensive sample to enhance the comprehensiveness and representativeness of our results. Furthermore, further in-depth investigations are warranted to fully explain the therapeutic mechanism of PI. Subsequently, efforts should focus on developing and implementing strategies for the prevention and treatment of RRTI to offer a more reliable clinical reference.

CONCLUSION

In conclusion, our study highlights the significant role of various factors such as children's outdoor activity, family members' smoking history, parental allergy history, education level, and micronutrient status in pediatric RRTI. Importantly, our findings underscore the effectiveness of PI as a treatment for RRTI, demonstrating its ability to improve patients' T-lymphocyte subsets and overall immune function while maintaining a high level of safety. These results suggest that PI holds promise for clinical application and widespread promotion in the management of pediatric RRTI. However, further research with larger sample sizes and deeper exploration of PI's therapeutic mechanisms are warranted to provide more robust clinical guidance for the prevention and treatment of RRTI.

COMPETING INTERESTS
The authors report no conflict of interest.

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None.

AUTHOR CONTRIBUTIONS
Renmin Hu and Chong Jin contributed equally to this work and are co-first authors.

AVAILABILITY OF DATA AND MATERIALS
The data that support the findings of this study are available from the corresponding author upon reasonable request.

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