

Sphingosine-1-Phosphate (S1P) Is a Feasible Biomarker in Predicting the Efficacy of Polymyxin B-Immobilized Fiber Direct Hemoperfusion (PMX-DHP) in Patients with Septic Shock

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Purpose: The aim of this study was to identify a useful biomarker to predict the efficacy of polymyxin B-immobilized fiber direct hemoperfusion (PMX-DHP) in patients with septic shock.

Methods: The 44 patients included in this study were divided into two groups. Group A had an increase in systolic blood pressure (SBP) over 30 mmHg after PMX-DHP treatment. Group B had an increase in SBP less than 30 mmHg after PMX-DHP treatment. We evaluated the clinical characteristics and demographics of both groups. We also assessed whether the cause of sepsis affected the efficacy of PMX-DHP and compared the prognosis of both groups. Finally, we investigated whether there were any significant differences in the levels of sepsis-related biomarkers, including sphingosine-1-phosphate (S1P), between both groups before PMX-DHP in an effort to identify a biomarker that could predict the efficacy of PMX-DHP.

Results: PMX-DHP significantly increased SBP regardless of the cause of sepsis. Although there was some tendency, PMX-DHP did not significantly improve the prognosis of effective cases in comparison with non-effective cases, probably because of the limited number of patients included. Among the sepsis-related biomarkers, only S1P values were significantly different between the two groups before PMX-DHP, and S1P levels were significantly increased after treatment in the effective cases.

Conclusion: S1P levels prior to PMX-DHP can be used to predict its efficacy. In addition, continuous monitoring of S1P levels can indicate the effectiveness of PMX-DHP in patients with septic shock.

(J Nippon Med Sch 2018; 85: 39–46)

Key words: PMX-DHP, sepsis, septic shock, biomarkers, S1P

Introduction

Despite recent advances in the understanding of the pathophysiological mechanism of sepsis and strategies for its treatment, the incidence of severe sepsis with septic shock continues to rise, and sepsis-related mortality remains high¹. Both gram-negative (GNB) and gram-positive (GPB) bacterial pathogens are the most common cause of sepsis, and fungal organisms are also increasing rapidly². Lipopolysaccharide (LPS) presents in the outer membrane of gram-negative bacteria. The endotoxin, the lipid A part of LPS, is another cause for sepsis and septic

shock³. In sepsis, pro-inflammatory and anti-inflammatory responses coexist leading to immunosuppression and the host's erratic inflammatory response to the infection, which results in organ dysfunction⁴. The early identification of sepsis, cultures, source control, and application of appropriate antibiotics are crucial for a better outcome in patients⁵.

In Japan, a number of reports regarding the efficacy of direct hemoperfusion with polymyxin B-immobilized fiber (PMX-DHP) in patients with septic shock have demonstrated improved clinical outcomes including an in-

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crease in systolic blood pressure^{6,7}. Similar promising results have also been reported in Europe as well⁸. A change in biomarkers after PMX-DHP is reported to be useful to predict patient prognosis⁹.

There are several important biomarkers known to be involved in sepsis. High Mobility Group Box 1 (HMGB1), which is secreted from macrophages and monocytes, mediates inflammatory cytokines¹⁰. It is also known to trigger disseminated intravascular coagulation (DIC) and sepsis by deterioration of the coagulation system¹¹. Other biomarkers include: Anandamide (N-arachidonylethanolamine, AEA) and 2-arachidonoylglycerol (2-AG), endogenous agonists of cannabinoid receptors that are reported to be increased in patients with septic shock¹²; The plasminogen activator inhibitor-1 (PAI-1), the principal inhibitor of tissue plasminogen activator (tPA) and urokinase (uPA), which regulates the plasminogen activator to initiate fibrinolysis^{13,14}; and Protein C (PC) which regulates blood clot size and prevents the downstream coagulation pathway through the proteolytic inactivation of the procoagulant co-factors VIIIa and Va¹⁵. PAI-1 and PC activity can be a good predictor to evaluate the severity of sepsis and ongoing severe coagulopathy^{16,17}. Further, Interleukin-6 (IL-6) is one of the most common pro-inflammatory cytokines and uncontrolled activation of this cytokine is an essential contributor to the pathogenesis of septic DIC¹⁸.

Of particular interest to this study, sphingosine-1-phosphate (S1P), one of the sphingolipid metabolites, is a lipid mediator that regulates a wide variety of developmental and pathophysiological systems and is involved in vascular, nervous, and immune system development¹⁹. S1P also initiates intracellular signal transduction to regulate cell growth, migration, adhesion, and survival by interaction with five G-protein coupled receptors²⁰. Since S1P maintains vascular integrity and controls cytokine secretion, extracellular S1P level is related to sepsis severity²¹. Therefore, S1P has been gaining increasing attention from researchers as a potential therapeutic or diagnostic target in sepsis.

It has been reported that PMX-DHP decreased levels of endocannabinoids, HMGB1, and the inflammatory cytokines²²⁻²⁴ mentioned above. However, the varied responses to treatment and the mechanisms as to how PMX-DHP improves sepsis still need to be elucidated²⁵. Moreover, most biomarkers were measured after PMX-DHP⁹ to evaluate its efficacy. Therefore, it is imperative to find a biomarker to assess each patient prior to PMX-DHP therapy to determine if it is a feasible modality to

treat his or her septic shock.

Since there are no standard guidelines regarding the indication of PMX-DHP for treatment of patients with sepsis, the goal of this study was to identify a useful marker to predict the efficacy of PMX-DHP on patients with septic shock.

Materials and Methods

The present study has been approved by the institutional review board, and informed consent from all patients was obtained prior to their inclusion in this study. In this retrospective study, 44 patients with septic shock were included. All patients presented with persistent hypotension that required vasopressors to maintain their mean arterial pressure (MAP) greater than 65 mmHg. Patients underwent PMX-DHP within 24 hours from admission and were divided into two groups. Group A included patients with an increased systolic blood pressure (SBP) greater than 30 mmHg after PMX-DHP treatment while group B included patients without an increase in SBP by PMX-DHP. A double-lumen catheter was inserted by the Seldinger technique into the femoral vein to establish venous access for hemoperfusion. PMX-DHP was run for 2 hours at a flow rate of 80 mL/min, and it was performed twice consecutively. An anticoagulant, Nafamostat mesylate (Torii Co., Ltd, Tokyo, Japan), was used during PMX-DHP.

First, clinical characteristics and demographics including sex, age, (Acute Physiology and Chronic Health Evaluation II) APACHE II scores, (Sequential Organ Failure Assessment score) SOFA scores, and DIC scores of all of the patients in both groups were analyzed.

Next, we evaluated whether PMX-DHP improved the SBP of the patients with sepsis; the causes of sepsis varied (surgical or non-surgical; gram-positive or gram-negative bacteria). The surgical group included patients with sepsis, such as peritonitis, who required surgical treatment. The patients with sepsis in the non-surgical group included patients who did not undergo surgery to control the cause of sepsis, such as those with pneumonia. The prognosis of patients with septic shock in both the A and B groups who underwent PMX-DHP was also analyzed.

Furthermore, we evaluated the level of sepsis-related biomarkers such as HMGB1, IL-6, AEA, 2-AG, PAI-1, protein C, and antithrombin-III (AT-III) before PMX-DHP.

Finally, we evaluated whether S1P, the lipid product of sphingosine kinases (SKs) that plays an essential role in inflammatory signaling processes as well as in disease

development and progression²⁶, can be used as an effective predictive factor of the success of PMX-DHP on patients with sepsis in terms of an increase in SBP. S1P levels were measured before and after PMX-DHP therapy in both groups. The correlations between S1P levels in both groups before and after treatment were analyzed.

S1P, endocannabinoids and F2-isoprostane were detected using a liquid chromatography tandem mass spectrometry system (Q-trap; Applied Biosystems, Foster City, CA, USA) with the isotope dilution method. The HMGB-1, IL-6, and PAI-1 levels were measured using an enzyme-linked immunosorbent assay (ELISA) (Shino-Test Corporation, Japan).

Statistical Analysis

The results were expressed as the mean ± SD. Differences in each value were analyzed by the Wilcoxon generalized test or the chi-squared test, and the Kaplan-Meier survival curves were compared using a log-rank test. A p-value less than 0.05 was interpreted to be statistically significant. IBM SPSS Statistics version 22 (IBM Corp., Armonk, NY, USA) was used for statistical analyses.

Results

There were 25 cases and 19 cases in groups A and B, respectively, and each group had a variety of underlying causes of sepsis, as shown in **Table 1**. Peritonitis (18 cases) was the leading cause of sepsis, followed by pneumonia (13 cases).

Table 1 Underlying diseases

Underlying disease	The number of cases
Peritonitis	18 (41.0%)
Pneumonia	13 (29.5%)
Pyothorax	4 (9%)
Gas gangrene	2 (4.5%)
Meningitis	1 (2.3%)
Others	6 (13.6%)

Table 2 Characteristics of the patients and disease severity (effective cases vs non-effective cases)

Characteristics	Effective cases	Non-effective cases	p value
Number of patients	25	19	
Sex (male/female)	14/11	15/4	NS
Age (mean±SD)	61.3±14.4	61.5±12.4	NS
APACHE II score (mean±SD)	27.3±8.2	26.7±9.3	NS
SOFA score (mean±SD)	11.6±4.6	11.6±4.8	NS
DIC score (mean±SD)	5.2±1.9	4.2±2.0	NS
SBP before PMX-DHP (mean±SD)	95.1±15.7	104.9±23.9	NS

Patients' characteristics are shown in **Table 2** and there were no statistically significant differences in their background (sex, age, APACHE II score, SOFA score, DIC score, and SBP before PMX-DHP). Notably, the APACHE II scores and SOFA scores of both groups did not show any differences, suggesting that there were no significant differences in terms of severity of their illness (**Table 2**).

Next, we evaluated whether the SBP was improved in surgical and non-surgical septic cases. PMX-DHP significantly improved SBP in both surgical and non-surgical patients. Intriguingly, the p value for surgical cases was a hundred times lower than that of non-surgical cases (**Fig. 1**). It is interesting to note that PMX-DHP improved the SBP of patients with septic shock regardless of the causative organism (gram-negative or positive bacteria) and PMX-DHP was significantly more effective in increasing SBP in patients with a GNB infection (**Table 3**). There were no statistical significances between patients' survival rate and all of the sepsis biomarkers, including S1P after PMX-DHP (data not shown). Although patients with an increased SBP after therapy tended to have a better clinical outcome, PMX-DHP did not significantly improve the prognosis of effective cases (i.e. group A that had an increased SBP greater than 30 mmHg) as compared to non-effective cases (i.e. group B without an increase in SBP) (**Fig. 2**).

In an attempt to evaluate whether there is an efficacy predictor of PMX-DHP therapy for patients with sepsis, we compared values of sepsis-related biomarkers, including IL-6, HMGB-1, AEA, 2-AG, S1P, PAI-1, and protein C, between group A and group B before PMX-DHP therapy. **Table 4** shows that while other biomarkers for septic DIC did not show any significant difference between the 2 groups, the values of S1P were significantly lower in group A (group A: 71.0 ± 110.0 ng/mL vs group B: 174.1 ± 167.8 ng/mL, p=0.0193). Furthermore the differences in S1P level before and after PMX-DHP were analyzed between the two groups (delta S1P was obtained by sub-

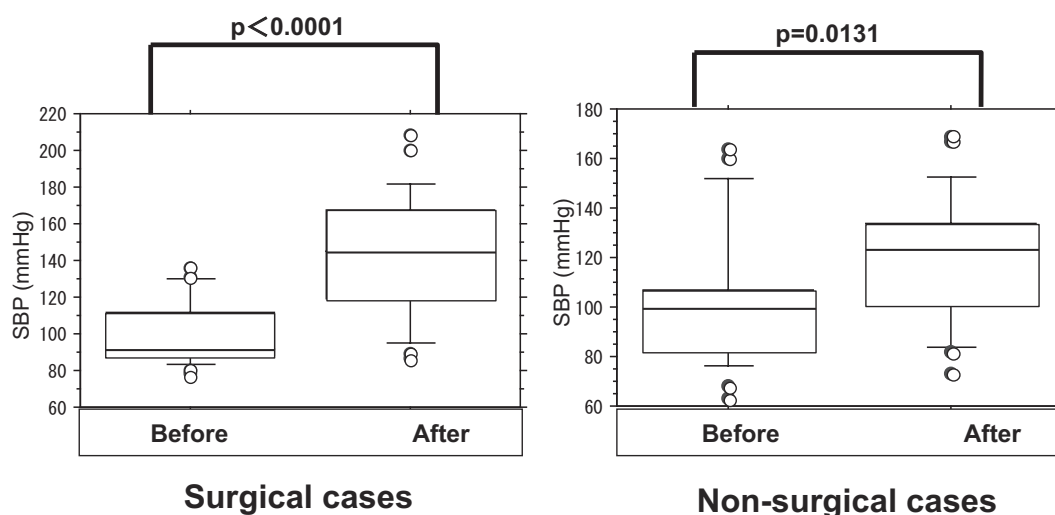


Fig. 1 The change in systolic blood pressure after polymyxin B-immobilized fiber direct hemoperfusion (PMX-DHP) based on surgical or non-surgical causation.

PMX-DHP significantly improved systolic blood pressure in both surgical and non-surgical patients.

Table 3 Increase in systolic blood pressure (SBP) by polymyxin B-immobilized fiber direct hemoperfusion (PMX-DHP) based on causative organisms

Causative organism	Increase in SBP (greater than 30 mmHg)	No increase in SBP (greater than 30 mmHg)	p value
Gram positive bacteria	5	8	0.043
Gram negative bacteria	22	9	

tracting S1P levels after PMX-DHP from the levels before treatment). It is notable that S1P levels were significantly increased in Group A that had a significant increase in SBP after PMX-DHP therapy (Fig. 3).

Discussion

The change in the hemodynamics and the conditions of a patient during severe sepsis are very dynamic and complex, which makes adjunct therapy for sepsis, other than controlling the causative lesion, greatly variable. Since sepsis tends to involve deterioration of multiple organs and coagulation systems, its treatment is very complicated and the strategy varies depending on each institution²⁷. The mortality of patients with severe sepsis in the first 24 hours after admission to the intensive care unit (ICU) is 30–40% before ICU discharge¹⁷. Furthermore, almost half of these patients that are diagnosed with sepsis within 24 hours of their admission die during their hospital stay^{28,29}. Therefore, in patients with sepsis, early diagnosis and immediate management largely contribute to their outcome. Even though compliance of Early Goal Directed Therapy (EGDT) and guidelines based on the Sur-

viving Sepsis Campaign is still low, it remarkably improves the prognosis of patients with severe sepsis if appropriately followed^{30,31}.

PMX-DHP was developed and advanced in Japan. It has been utilized to successfully control endotoxemia in patients with septic shock⁶. Although PMX-DHP was not included in EGDT due to limited evidence of its efficacy at the time, some previous studies have shown that PMX-DHP significantly improved mortality of patients with severe sepsis due to intra-abdominal gram-negative infections with increases in MAP, decreases in vasopressor requirement, improved P/F ratios, and improved SOFA scores when compared to the conventional therapy group^{32,33}. Sepsis is often caused by an unwanted complication during the course of surgical or non-surgical patients who were treated for other critical illnesses^{17,34}. Our data showed that PMX-DHP was effective in both surgical and non-surgical cases. These findings suggest that even though source control is essential for sepsis treatment especially in patients who require surgery, supplemental therapy like PMX-DHP may be able to expedite improvement of severe sepsis conditions.

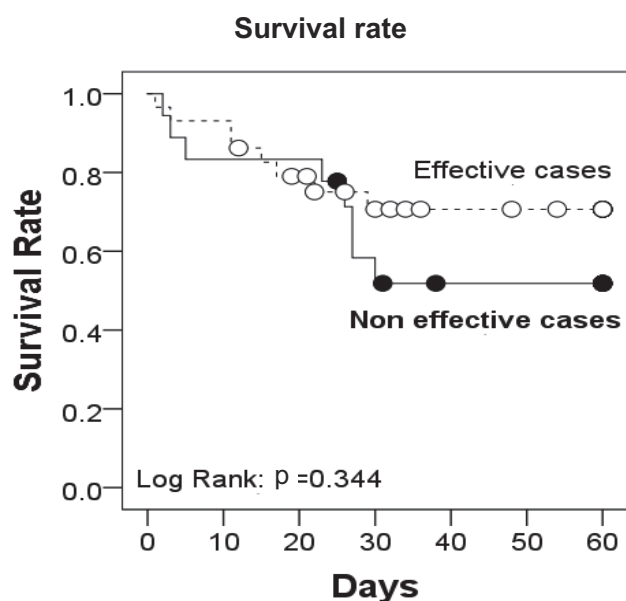


Fig. 2 Effective cases vs Non effective cases (more than 30 mmHg SBP increase)

The comparison of survival rate between effective (group A: an increase in systolic blood pressure (SBP) greater than 30 mmHg) and non-effective cases (group B: an increase in SBP less than 30 mmHg) after polymyxin B-immobilized fiber direct hemoperfusion (PMX-DHP). Although effective cases tended to appear to have a better prognosis, PMX-DHP did not significantly improve the prognosis of effective cases as compared to non-effective cases.

Although group A tended to have a better prognosis than group B, unlike a previous report³³, our data did not show statistically significant correlation between the patients' prognosis and an efficacy of PMX-DHP in terms of an increase in SBP, possibly due to the low number of patients included in this study.

In the past PMX-DHP was said to only be effective against bacteremia caused by GNB, because PMX-DHP was originally designed to adsorb endotoxin to treat patients with septic shock. However, more recent studies support that it also has a beneficial effect on GPB through removal of activated monocytes and neutrophils³⁵. In fact, our data showed PMX-DHP increased SBP in patients with sepsis caused by both GPB and GNB, although it was significantly more effective in patients with a GNB infection. Our data suggest that PMX-DHP improves patients' hemodynamic status not only through endotoxin adsorption but also through improvement of aberrant inflammatory cytokines and mediators. Some other previous studies have also shown that PMX-DHP was effective in the reduction of endocannabinoids, high mobility group protein 1 (HMGB1), and inflamma-

tory cytokines^{6,24,36}. Thus, PMX-DHP has been reported to improve such biomarkers involving progression of severe sepsis. However, the efficacy of PMX-DHP on patients with sepsis varies. Therefore, it is imperative to find a useful marker to predict the efficacy of the therapy.

Various factors contribute to the severity of sepsis, and S1P is one of the best potential target molecules to treat sepsis because this biologically active metabolite of plasma-membrane sphingolipids has a wide range of functions that are related to sepsis onset and progression. The plasma concentrations of apoM (apolipoprotein M), a carrier for S1P, decrease dramatically during sepsis reflecting the severity of the disease³⁷ and there is a positive correlation between plasma apoM and S1P³⁸. S1P levels are also significantly decreased in patients with sepsis and are inversely associated with disease severity²¹. Further, its value represents an aberrant inflammatory reaction in sepsis³⁹. Since S1P protects endothelium resulting in prevention of vascular leakage and regulates vascular integrity^{40,41}, low S1P levels may cause capillary leakage and deterioration of tissue perfusion leading to organ failure in severe sepsis. Furthermore, low S1P levels are related to LPS induced severe lung injury⁴². Therefore, it is reasonable to focus on the plasma S1P level to evaluate the efficacy of sepsis treatment. Our data revealed that S1P levels were significantly lower in patients in Group A with increased SBP after PMX-DHP prior to therapy, and interestingly they were markedly increased after therapy as compared to patients without an increase in SBP after therapy. These findings imply that PMX-DHP increased the SBP of patients in Group A with severe sepsis by reducing sepsis-related chemical mediators and was also able to increase S1P after therapy. We do not know whether the effect of PMX-DHP on S1P is direct or indirect. Inconsistent with previous studies^{21,37,42}, there were no significant differences in the severity of sepsis between group A and group B in the present study despite the fact that S1P levels were significantly lower in group A than in group B. It might be possible to say that S1P can be more sensitive in reflecting the severity of sepsis than other scores such as APACHE II and SOFA. Otherwise S1P can be a very sensitive predictor for therapeutic efficacy of PMX-DHP regardless of the clinical condition of patients with sepsis. Furthermore, S1P level is known to be regulated by its synthesis by sphingosine kinases and degradation mediated by mediators including S1P phosphatases, lipid phosphate phosphatases, and S1P lyase⁴³. Indeed, Hemdan et al. reported that administration of 4-deoxyipyridoxine, an inhibitor of S1P-lyase,

Table 4 The value of sepsis related biomarkers before polymyxin B-immobilized fiber direct hemoperfusion (PMX-DHP) (effective cases vs non-effective cases)

Characteristics	Effective cases	Non-effective cases	p value
IL-6 (pg/mL)	29,766.5±41,769.3	18,992.4±38,071.2	NS
HMGB-1 (ng/mL)	15.3±17.1	6.9±10.4	NS
AEA (ng/mL)	664.2±797.5	414.6±272.0	NS
2AG (ng/mL)	17.2±31.5	9.1±8.9	NS
S1P (ng/mL)	71.0±110.0	174.1±167.8	0.0193
PAI-1 (ng/mL)	159.5±54.5	135.0±69.8	NS
Protein C (%)	31.3±10.7	46.9±38.8	NS

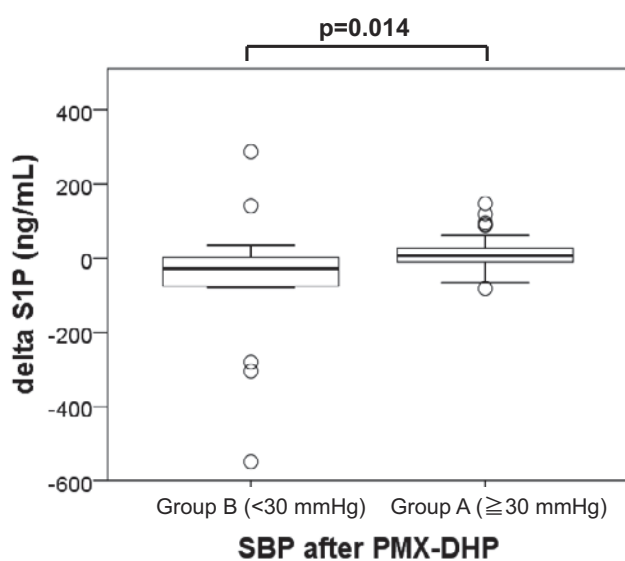


Fig. 3 Change in S1P level after the PMX-DHP in patients with or without increase in SBP

The change in sphingosine-1-phosphate (S1P) level after polymyxin B-immobilized fiber direct hemoperfusion (PMX-DHP) in patients with or without increased systolic blood pressure (SBP). The delta S1P was obtained by subtracting S1P levels after the PMX-DHP from S1P values before treatment. The delta S1P was significantly higher in patients with an increased SBP after PMX-DHP, which means that PMX-DHP increased the S1P value significantly more in effective cases as compared to ineffective cases.

improved recovery from sepsis in mice models⁴⁴. Thus, PMX-DHP might be able to capture inhibitory mediators of S1P such as S1P lyase resulting in an increase in S1P level and improvement of SBP. However, detailed investigations are warranted to elucidate the detailed mechanism of this phenomenon.

The present study has some limitations to be noted. The study was performed in a single institution with a small sample size. Since patients had various etiological backgrounds, discrepancy could exist in each group.

Moreover, the efficacy of PMX-DHP might be affected by prior hemodynamic status. Fluid volume, dose of catecholamine given, and timing depended on each physician's decision, so each patient had a different hemodynamic condition before initiating PMX-DHP.

Thus, further studies with increased sample size, appropriate adjustment of patients' background, and robust institutional protocol for PMX-DHP are required to improve the limitations of the current study.

In the present study, we evaluated biomarkers that are relevant to the status of sepsis. Our data analysis revealed that S1P was the only marker included in this study that could predict significant efficacy of PMX-DHP. Moreover, the present study also showed that S1P levels were increased when PMX-DHP improved patients' SBP. Therefore, S1P may be useful to monitor the efficacy of PMX-DHP as well. Our data showed for the first time that low plasma S1P level in patients with sepsis could be a very useful predictor for successful PMX-DHP therapy.

Conclusion

Although PMX-DHP has limited evidence to date for sepsis treatment, several positive results have been shown. Due to its pathophysiological complexity, it is very difficult to evaluate the efficacy of adjunctive treatment for sepsis. Our data suggests that S1P can be a useful biomarker to predict the efficacy of PMX-DHP for patients with septic shock.

Acknowledgement: We would like to thank Dr. Janet Markman for editing the manuscript.

Conflict of Interest: The authors declare no conflict of interest.

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(Received, June 7, 2017)

(Accepted, November 24, 2017)