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IMMUNOTROPIC EFFECTS OF NITROGENOUS METABOLITES IN PATIENTS WITH CHRONIC PYELONEPHRITIS

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Abstract

Background. We have previously shown that nitrogenous metabolites have immunomodulatory effects in healthy rats and humans as well as in patients with encephalopatia. The purpose of this study is their immunotropic activity in patients with chronic pyelonephritis. **Materials and Methods**. The object of observation were 24 men (aged 23-76 years) with chronic pyelonephritis in remission. The plasma levels and urinary excretion of uric acid, urea and creatinine and parameters of immunity twice (on admission and after 10 days of balneotherapy at the Truskavets' Spa) was performed. **Results**. Judging by the multiple correlation coefficient uricemia exhibits maximal immunotropic activity (R=0,772), followed by creatininemia (R=0,643), urea plasma (R=0,584) and creatinineuria (R=0,506) instead, urea and uric acid excretion correlate with immune parameters insignificantly (R=0,327 and 0,262 respectively). Nitrogenous metabolites together upregulate most parameters of phagocytosis by neutrophils Staph. aureus and E. coli, the level in the blood of CD8 T-lymphocytes, CIC, IgM, componentes of leukocytogram as well as entropy of leukocytogram and immunocytogram. Instead, they downregulate the relative level of lymphocytes in general and of CD4 T-lymphocytes in particular. **Conclusion**. Nitrogenous metabolites exhibit immunotropic activity in both healthy humans and in patients with chronic pyelonephritis in remission. Both common and distinctive features of immunomodulation were revealed.

Key words: **urea, uric acid, creatinine, immunity, relationships, healthy humans and patients.**

INTRODUCTION

We have previously shown that nitrogenous metabolites have immunomodulatory effects, both in healthy rats [3,4,16] and humans [10] as well as in patients with encephalopatia [9]. With regard to uric acid, it is known that the magnitude and even the sign of the correlation coefficients with the parameters of the human body depend on the state of adaptation, the presence or absence of chronic pyelonephritis, as well as its phase [5-7,18]. Therefore, the aim of this study is immunotropic activity of nitrogenous metabolites in patients with chronic pyelonephritis.

MATERIAL AND METHODS

The object of observation were 27 men (aged 23-76 years) with chronic pyelonephritis in remission. The plasma and urinary levels of uric acid (by uricase method), urea (by urease method by reaction with phenolhypochlorite) and creatinine (by Jaffe's color reaction by Popper's method) and parameters of immunity twice (on admission and after 10 days of balneotherapy at the Truskavets' Spa) was performed.

The biochemic analyzes were carried out according to the instructions described in the manual [2]. The analyzers "Pointe-180" ("Scientific", USA) and "Reflotron" (Boehringer Mannheim, BRD) were used with appropriate sets.

Immune status evaluated on a set of I and II levels recommended by the WHO as described in the manuals [11,12]. For phenotyping subpopulations of lymphocytes used the methods of rosette formation with sheep erythrocytes on which adsorbed monoclonal antibodies against receptors CD3, CD4, CD8, CD22 and CD56 from company "Granum" (Kharkiv) with visualization under light microscope with immersion system. Subpopulation of T cells with receptors high affinity (T-active) determined by test of "active" rosette formation. The state of humoral immunity judged by the concentration in serum of Circulating Immune Complexes (by polyethylene glycol precipitation method) and Immunoglobulins classes M, G, A (ELISA, analyser "Immunochem", USA). In addition, the level of IL-1 was determined (by the ELISA with the use of analyzer "RT-2100C" and corresponding set of reagents from "Diactone", France).

The set of immune parameters of saliva was IgG, IgA, secretory IgA (ELISA, analyser "Immunochem", USA) and Lysozyme. The activity of the latter was evaluated by the bacteriolysis test Micrococcus lysodeicticus (nephelometric method) [8,15].

Parameters of phagocytic function of neutrophils estimated as described by SD Douglas and PG Quie [1] with moderately modification by MM Kovbasnyuk [6]. The objects of phagocytosis served daily cultures of Staphylococcus aureus (ATCC N 25423 F49) as typical specimen for Gram-positive Bacteria and Escherichia coli (O55 K59) as typical representative of Gram-negative Bacteria. Both cultures obtained from Laboratory of Hydro-Geological Regime-Operational Station JSC "Truskavets'kurort". Take into account the following parameters of Phagocytosis: activity (percentage of neutrophils, in which found microbes - Hamburger's Phagocytic Index PhI), intensity (number of microbes absorbed one phagocytes - Microbial Count MC or Right's Index) and completeness (percentage of dead microbes - Killing Index KI). On the basis of the recorded partial parameters of Phagocytosis, taking into account the Neutrophils (N) content of 1 L blood, we calculated the integral parameter - Bactericidal Capacity of Neutrophils (BCCN) by the formula [15]:

$$BCCN\ (10^9\ Bact/L) = N\ (10^9/L) \bullet PhI\ (\%) \bullet MC\ (Bact/Phag) \bullet KI\ (\%) \bullet 10^{-4}$$

In portion of capillary blood we counted up Leukocytogram (LCG) (Eosinophils, Rod-shaped and Polymorphonucleary Neutrophils, Lymphocytes and Monocytes). On the basis of these elements, IL Popovych's Strain and Adaptation indices were calculated [13].

We calculated also the Entropy (h) of Immunocytogram (ICG) and Leukocytogram (LCG) using IL Popovych's formulas [13,14] derived from classical CE Shannon's formula [17]:

$$hICG = - [CD4 \bullet \log_2 CD4 + CD8 \bullet \log_2 CD8 + CD22 \bullet \log_2 CD22 + CD56 \bullet \log_2 CD56]/\log_2 4$$

$$hLCG = - [L \bullet \log_2 L + M \bullet \log_2 M + E \bullet \log_2 E + PMNN \bullet \log_2 PMNN + RSN \bullet \log_2 RSN]/\log_2 5$$

Results processed by using the software package "Statistica 64".

RESULTS AND DISCUSSION

Following the accepted algorithm, we first created a matrix of correlations between nitrogenous metabolites and immune parameters (Table 1).

In the next step of the analysis, a regression model was constructed for each nitrogenous metabolite by stepwise exclusion until the maximum level of adjusted R^2 was reached.

As expected, based on the previous results, uric acid showed the maximum immunotropic activity among nitrogenous metabolites (Table 2).

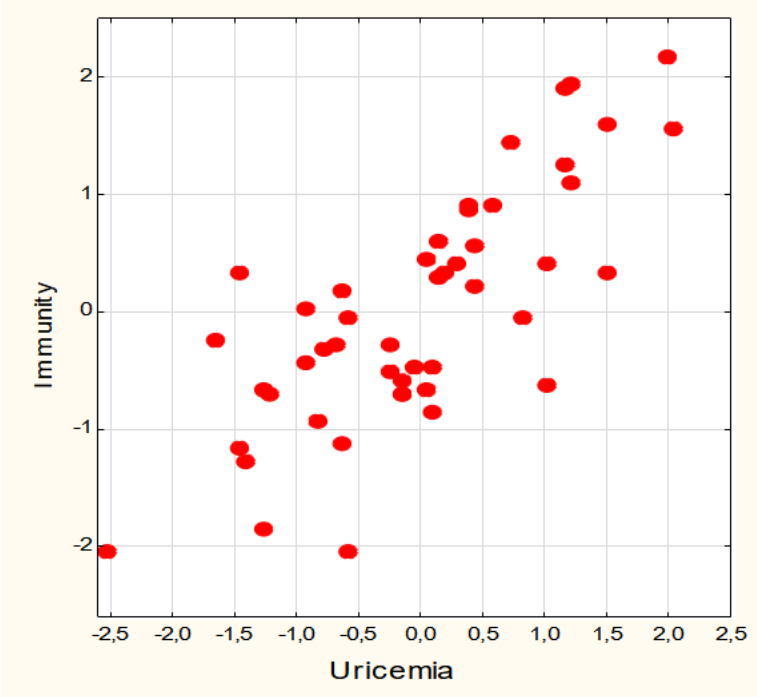
Table 1. Matrix of correlations between nitrogenous metabolites and immunity parameters in patients with chronic pyelonephritis

	Correlations (n=48)					
Variable	CrP	UAP	CrE	UAE	Urea E	Urea P
Cr P	1,00	0,07	-0,33	-0,23	-0,23	0,51
UA P	0,07	1,00	0,08	-0,14	-0,01	0,00
Cr E	-0,33	0,08	1,00	0,32	0,46	-0,07
UA E	-0,23	-0,14	0,32	1,00	0,68	0,12
Urea E	-0,23	-0,01	0,46	0,68	1,00	0,11
Urea P	0,51	0,00	-0,07	0,12	0,11	1,00
IL-1	-0,00	-0,38	0,09	-0,06	-0,05	0,11
SIgA	0,08	0,06	0,19	-0,09	-0,19	-0,04
IgG Saliva	-0,09	-0,13	0,03	-0,01	0,09	-0,12
Lysoz Sal	0,02	0,02	0,15	-0,17	-0,28	-0,09
IgA Saliva	-0,03	-0,17	0,13	-0,05	-0,17	-0,10
PhI vs St au	0,06	0,37	0,06	-0,17	-0,05	-0,32
MC St aur	0,05	0,40	0,05	-0,17	0,01	-0,34
Killing St au	-0,33	0,26	0,23	-0,00	0,13	0,04
PhI E coli	0,11	0,24	0,04	-0,14	-0,29	-0,08
FNE	0,04	0,34	-0,00	-0,05	0,11	-0,30
IKE	-0,21	0,32	0,06	-0,05	0,04	0,07
HL	0,33	0,21	0,08	0,00	0,12	0,20
BCA	-0,24	0,36	0,24	0,03	0,15	-0,18
BCE	-0,25	0,44	0,14	0,06	0,15	-0,12
LEU	0,15	0,13	-0,05	0,12	0,10	0,11
SNN	-0,36	-0,10	0,24	0,14	0,09	-0,15
BNN	0,15	0,02	0,24	0,10	0,13	0,11
EO	0,24	0,18	-0,06	-0,01	0,14	0,31
MON	-0,02	0,27	0,21	0,04	0,03	-0,15
L%	0,32	0,00	-0,32	-0,17	-0,15	0,11
INL	-0,15	0,05	0,15	-0,16	-0,13	-0,11
INL2	0,08	0,12	0,01	-0,14	-0,03	0,21
IAP	-0,35	-0,09	0,16	0,12	-0,05	-0,26
IAP2	-0,25	0,01	0,21	0,04	-0,04	-0,27
TH	-0,06	-0,28	0,04	0,11	0,03	-0,05
TS	-0,05	0,40	-0,19	0,09	0,08	-0,11
CD22	-0,27	-0,05	-0,12	0,09	-0,02	-0,08
TA	0,08	-0,03	-0,11	0,15	-0,09	0,00
CIC	-0,15	0,21	0,10	0,06	-0,03	-0,02
IGG	-0,22	-0,08	0,17	0,04	-0,08	-0,13
IGA	0,18	0,11	0,12	0,11	-0,11	0,04
IGM	-0,08	0,08	-0,07	-0,15	-0,14	-0,19
CD56L	0,08	-0,18	0,15	-0,16	-0,09	0,13
OL	0,29	0,08	0,13	-0,15	-0,01	0,11
HIM	-0,33	0,04	-0,07	0,11	0,02	-0,14

Uricemia upregulates two parameters of phagocytosis of gram-positive and gram-negative bacteria by neutrophils as well as levels of CIC and theophilline sensitive T-lymphocytes while downregulates level og theophilline resistance T-lymphocytes. Degree of determination of uricemia immune status is 60% (Table 2 and Fig. 1).

Table 2. Regression Summary for Uricemia, µM/L
R=0,772; R^2=0,596; Adjusted R^2=0,536; $F_{(6,4)}$=10,1; $p<10^{-5}$

		Beta	St. Err. of Beta	B	SE of B	$t_{(41)}$	p-level
Variables	r		Intercpt	-2,552	0,714	-3,57	0,001
Bactericidal Capacity vs E. coli, 10^9 B/L	**0,44**	0,282	0,107	0,0008	0,0003	2,64	0,012
$CD8^+$ T-cytolytic Lymphocytes, %	**0,40**	0,323	0,109	0,0056	0,0019	2,96	0,005
Phagocytose Index vs Staph. aureus, %	**0,37**	0,354	0,107	0,0245	0,0074	3,31	0,002
CIC Serum, units	**0,21**	0,207	0,103	0,0011	0,0005	2,02	0,050
Entropy of Leukocytogram	**0,21**	0,283	0,106	0,6336	0,2367	2,68	0,011
$CD4^+$ T-helper Lymphocytes, %	**-0,28**	-0,394	0,108	-0,0070	0,0019	-3,63	0,001



R=0,772; R^2=0,596; $\chi^2_{(6)}$=39; $p<10^{-6}$; Λ Prime=0,404
Fig. 1. Scatterplot of canonical correlation between Uricemia (X-line) and the Immunity (Y-line) in patients with pyelonephritis

Instead, multiple correlation between uricosuria and immune parameters are insignificant (Table 3).

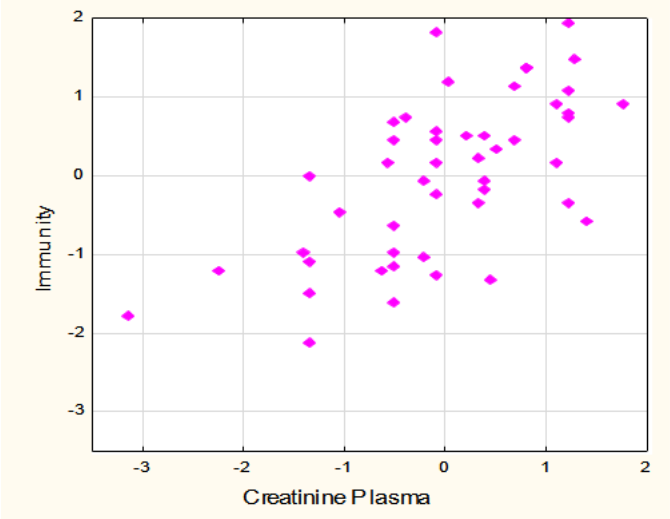
Table 3. Regression Summary for Uricosuria, mM/L
R=0,269; R^2=0,072; Adjusted R^2=0,031; $F_{(2,45)}$=1,75; p=0,185

		Beta	St. Err. of Beta	B	SE of B	$t_{(45)}$	p-level
Variables	r		Intercpt	12,62	4,88	2,59	0,013
Lysozime Saliva, mg/L	**-0,17**	-0,216	0,148	-0,039	0,026	-1,46	0,151
Pan-Lymphocytes, %	**-0,17**	-0,217	0,148	-0,045	0,031	-1,47	0,148

Creatininemia, like uricemia, upregulates entropy of Leukocytogram as well as level of Lymphocytes, while downregulates the level of Neutrophils and its killing activity against gram-positive bacteria as well as two information parameters. Degree of determination of creatininemia immune status is 41% (Table 4 and Fig. 2).

Table 4. Regression Summary for Creatininemia, µM/L
R=0,643; R^2=0,413; Adjusted R^2=0,327; $F_{(6,4)}$=4,8; p=0,0008

		Beta	St. Err. of Beta	B	SE of B	$t_{(41)}$	p-level
Variables	r		Intercpt	-268,6	311,5	-0,86	0,393
Polymorphonuclear Neutrophils, %	**-0,36**	2,244	1,368	3,853	2,348	1,64	0,108
Popovych's Adaptation Index, units	**-0,35**	-0,460	0,166	-9,275	3,338	-2,78	0,008
Killing Index vs Staph. aureus, %	**-0,33**	-0,302	0,128	-0,429	0,182	-2,36	0,023
Entropy of Immunocytogram	**-0,33**	-0,208	0,134	-119,3	76,71	-1,56	0,128
Entropy of Leukocytogram	**0,33**	0,902	0,465	280,6	144,7	1,94	0,059
Pan-Lymphocytes, %	**0,32**	1,918	1,120	3,447	2,013	1,71	0,094



R=0,643; R^2=0,413; $\chi^2_{(6)}$=23; p=0,0008; Λ Prime=0,587
Fig. 2. Scatterplot of canonical correlation between Creatininemia (X-line) and the Immunity (Y-line) in patients with pyelonephritis

The immunomodulatory activity of creatinineuria is weaker than that of creatininemia, but still significant (Table 5).

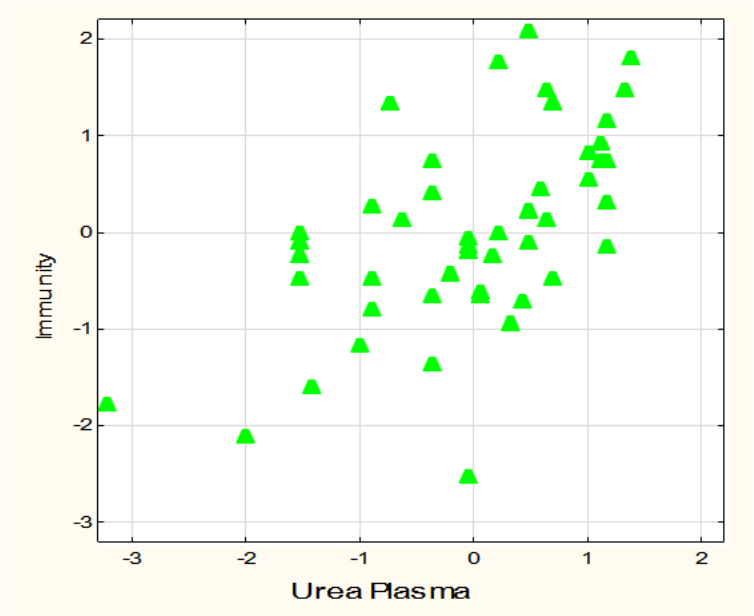
Table 5. Regression Summary for Creatinineuria, mM/L
R=0,506; R^2=0,256; Adjusted R^2=0,147; $F_{(6,4)}$=2,35; p=0,049

		Beta	St. Err. of Beta	B	SE of B	$t_{(41)}$	p-level
Variables	r		Intercpt	0,077	7,44	0,01	0,992
Pan-Lymphocytes, %	**-0,32**	-0,329	0,168	-0,1696	0,0865	-1,96	0,057
Bactericidal Capacity vs St. aur, 10^9 B/L	**0,24**	-0,280	0,214	-0,0350	0,0267	-1,31	0,198
Rod-shaped Neutrophils, %	**0,24**	0,249	0,144	0,9491	0,5494	1,73	0,092
Killing Index vs Staph. aureus, %	**0,23**	0,315	0,169	0,1281	0,0687	1,86	0,069
Monocytes, %	**0,21**	0,255	0,149	0,5507	0,3218	1,71	0,095
Secretory IgA Saliva, mg/L	**0,19**	0,168	0,152	0,0094	0,0085	1,11	0,275

Immunotropic effect of urea was minimal among the studied nitrogenous metabolites (Tables 6 and 7, Fig. 3).

Table 6. Regression Summary for Urea Plasma, mM/L
R=0,584; R^2=0,342; Adjusted R^2=0,280; $F_{(4,4)}$=5,6; p=0,0011

		Beta	St. Err. of Beta	B	SE of B	$t_{(43)}$	p-level
Variables	r		Intercpt	10,09	1,19	8,46	10^{-6}
Microbial Count for St. aur., Bac/Phag	**-0,34**	-0,394	0,132	-0,050	0,017	-2,99	0,005
Popovych's Adaptation Index, units	**-0,26**	-0,341	0,130	-0,631	0,240	-2,62	0,012
IgM Serum, g/L	**-0,19**	-0,146	0,132	-0,499	0,448	-1,11	0,272
Eosinophils, %	**0,31**	0,288	0,125	0,223	0,097	2,30	0,026



R=0,584; R^2=0,342; $\chi^2_{(4)}$=18; p=0,001; Λ Prime=0,658
Fig. 3. Scatterplot of canonical correlation between Urea Plasma (X-line) and the Immunity (Y-line) in patients with pyelonephritis

Table 7. Regression Summary for Urea Excretion, mM/L
R=0,327; R^2=0,107; Adjusted R^2=0,068; $F_{(2,45)}$=2,70; p=0,078

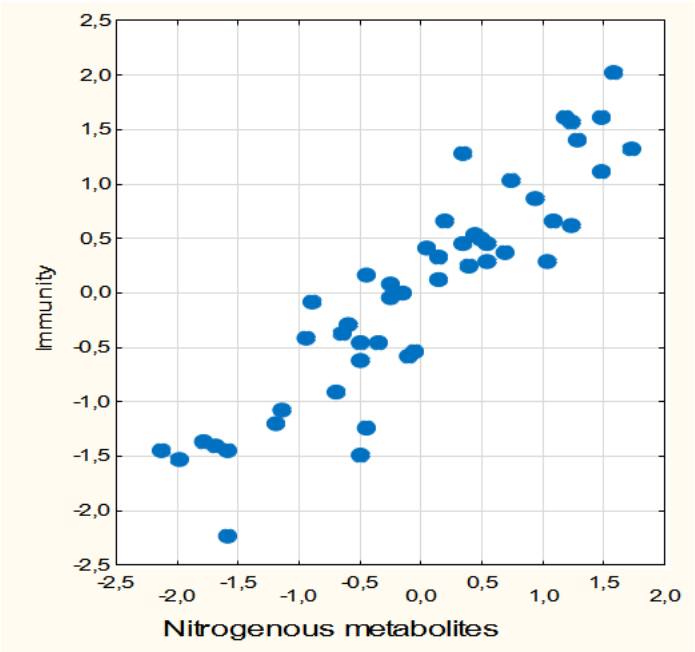
		Beta	St. Err. of Beta	B	SE of B	$t_{(45)}$	p-level
Variables	r		Intercpt	3711	1703	2,18	0,035
Phagocytose Index vs E. coli, %	**-0,29**	-0,192	0,163	-23,1	19,7	-1,18	0,246
Lysozime Saliva, mg/L	**-0,28**	-0,185	0,163	-4,38	3,86	-1,14	0,262

At the final stage, the canonical correlation between the parameters of nitrogenous metabolites, on the one hand, and the parameters of immunity, on the other hand, was analyzed. The program identified only one significant pair of canonical roots. Nitrogen root receives the maximum factor load from uricemia, much smaller, but unidirectional - from the

excretion of creatinine and urea, and similar in strength, but opposite in sign - from their plasma levels (Table 8).

Table 8. Factor load on canonical roots of nitrogenous metabolites and immunity parameters in patients with chronic pyelonephritis

Left set	Root
Uric acid Plasma	0,883
Creatinine Excretion	0,305
Urea Excretion	0,265
Uric acid Excretion	0,024
Urea Plasma	-0,320
Creatinine Plasma	-0,278
Right set	**Root**
Bactericidal Capacity vs E. coli, 10^9 B/L	0,543
Microbial Count for Staph. aureus, Bac/Phag	0,504
Bactericidal Capacity vs Staph. aur, 10^9 B/L	0,496
Phagocytose Index vs Staph. aureus, %	0,250
$CD8^+$ T-cytolytic Lymphocytes, %	0,431
Killing Index vs Staph. aureus, %	0,340
Monocytes, %	0,322
CIC Serum, units	0,226
Phagocytose Index vs E. coli, %	0,155
Entropy of Leukocytogram	0,139
Entropy of Immunocytogram	0,115
IgM Serum, g/L	0,106
Eosinophils, %	0,092
Popovych's Adaptation Index, units	0,022
Polymorphonuclear Neutrophils, %	0,018
Secretory IgA Saliva, mg/L	0,017
Rod-shaped Neutrophils, %	0,009
$CD4^+$ T-helper Lymphocytes, %	-0,243
Pan-Lymphocytes, %	-0,117
Lysozime Saliva, mg/L	-0,031



R=0,909; R^2=0,827; $\chi^2_{(120)}$=170; p=0,0017; Λ Prime=0,0062

Fig. 4. Scatterplot of canonical correlation between Nitrogenous Metabolites (X-line) and the Immunity (Y-line) in patients with chronic pyelonephritis

All but not three immune parameters are subject to upregulation. The degree of determination of the immune status of this sample of patients with nitrogenous metabolites is 83% (Fig. 4).

A more detailed analysis of this and previous samples in a comparative aspect will be the topic of the next article.

ACKNOWLEDGMENT

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ACCORDANCE TO ETHICS STANDARDS

Tests in patients are conducted in accordance with positions of Helsinki Declaration 1975 and directive of National Committee on ethics of scientific researches. During realization of tests from all participants the informed consent is got and used all measures for providing of anonymity of participants.

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