# Community-Acquired Pneumonia: Immune and Metabolic Disorders Before and After Treatment

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## Abstract

Community-acquired pneumonia is one of the most common infectious diseases in the world and in the Russian Federation, having kept on being the leader among infectious causes of death. We have studied immune and metabolic disorders before and after standard therapy in patients with community-acquired pneumonia. The patients included in the study had laboratory criteria revealed indicating the presence of immune inflammation, oxidative stress, endothelial dysfunction, and activation of lipid peroxidation. The provided standard treatment does not normalize most of the changed parameters of the immune and metabolic status, which necessitates the search for methods for correcting disorders by using various combinations of immunomodulatory and antioxidant drugs in combination pharmacotherapy.

Keywords: community-acquired pneumonia, immune inflammation, oxidative stress, endothelial dysfunction, lipid peroxidation.

## 1. Introduction

Pneumonia is an infection of the distal respiratory tract, characterized by the involvement of the alveoli, small-caliber bronchi and bronchioles in the pathological process. CAP is an outpatient-acquired acute disease accompanied by symptoms of a lower respiratory tract infection (fever, cough, sputum production, chest pain, shortness of breath) and radiological signs of fresh focal infiltrative changes in the lungs in the absence of an obvious diagnostic alternative. Severe lower respiratory tract infections rank third among the main causes of death, second only to coronary heart disease, stroke and other cerebrovascular diseases [1, 2]. The leading role in the pathogenesis of community-acquired pneumonia (CAP) is played by a massive and virulent infection, a decrease in the nonspecific resistance of the organism, an imbalance of local and systemic immunity, and free radical oxidation disorders. In addition, the results of the studies carried out indicate a change in the nature of the course, the frequent development of complications and an increase in mortality in CAP [3, 4].

Community-acquired pneumonia is one of the most common infectious diseases in the world and in the Russian Federation. Among the adult population, pneumonia occurs in 5-10 patients per 1000 people. The incidence of CAP in developed countries varies from 1-11.6 ‰, among young and adult population, and 25-44 ‰ in people over 65 years [5, 6]. According to Rospotrebnadzor, the incidence of CAP in Russia in 2014 was 337.77 cases per 100 thousand of the adult population. About 400 thousand people were admitted to medical hospitals in the country; in 2014, slightly more than 40 thousand people died of pneumonia [1, 5, 7].

Medical statistics across the country underscore the severity of this problem in Russian healthcare. If we summarize and compare them with international epidemiological studies, we can state the following: approximately 1 million people are untimely diagnosed with pneumonia, and mortality from severe pneumonia has reached 10% [2, 5, 8].

Immune mechanisms have been known to play an important role in the development and resolution of almost all pathological conditions, especially infectious one, and the relationship between metabolic and immunological changes is well described. The leading role in the CAP pathogenesis is played by massive and virulent infection, a decrease in the nonspecific resistance of the organism, an imbalance of local and systemic immunity, and a violation of the processes of free radical oxidation [7, 9]. It is obvious that the fundamental in the management of CAP patients is the timely and adequate use of antimicrobial drugs as indicators of the quality of medical care. Immune dysfunctions are manifested by hypo- and/or hyperactivation processes and are one of the constituent causes of the development of the disease [4, 10, 11]. In this case, hypoactivation is associated either with a quantitative and functional insufficiency of the components of immunity, or with the absence of full activation for a specific pathogen. The development of hyperactive states is associated with an increase in the quantitative and functional characteristics of the effector components of immunity and/or a lack of suppressive factors. These dysfunctional features or their combinations underlie the development of infectious pathology [12, 13]. In this regard, the immunological assessment of the effectiveness of the routine use of standard antibiotic therapy is a general indicator of therapy. Nevertheless, there are few comprehensive studies devoted to the study of the immune and metabolic status not only before, but also after standard treatment [14-16].

The objective of the study was to establish immune and metabolic disorders before and after standard treatment in patients with community-acquired bacterial pneumonia.

## 2. Materials and Methods

Based on the results of the screening, the examination included 46 patients with community-acquired bacterial pneumonia who were receiving inpatient treatment in the pulmonary unit of the non-governmental healthcare institution “Departmental Hospital at Kursk Station, JSC Russian Railways”. Clinical observations were in the form of a controlled prospective open-label randomized trial. The general characteristics of the examined patients and the presence of comorbidities are shown in Table 1.

Inclusion criteria were the age of patients minimum 18 years old, the diagnosis of CAP, established on the basis of characteristic epidemiological, clinical, radiological,

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and laboratory data. CAP was diagnosed according to the Russian National Guidelines for CAP and the American Thoracic Society/Infectious Diseases Society of America [7, 17, 18].

Exclusion criteria were aspiration pneumonia, atypical pneumonia, viral pneumonia, nosocomial pneumonia, pulmonary tuberculosis, primary or metastatic lung cancer, cystic fibrosis, hepatic and/or renal failure, with severe concomitant diseases, with acute respiratory distress, and medication with immunomodulatory drugs during the previous year.

The control group included practically healthy individuals (n=18), comparable to the patients by gender and age.

**Table 1: General characteristics of the examined patients**

| Clinical and anamnestic characteristics | | Enrolled patients |
|---|---|---|
| Sex (number/percent of patients) | Men | 21 / 45.7 |
| | Women | 25 / 54.3 |
| Average age (years) | | 47.03±3.2 (20-77) |
| Outpatient duration of the disease (days) | | 8,23±1,05 |
| Received antibiotic therapy during the outpatient period (number/percent of patients) | | 20 / 43,4 |
| Newly hospitalized with a CAP diagnosis (number/percent of patients) | | 46 / 100 |
| Smoking (number/percent of patients) | | 18 / 39,1 |
| Smoking index (for smokers) | | 15,7 |
| Concomitant diseases (number/percent of patients) | | 34 / 73.9 |
| Upper respiratory tract diseases (number/percent of patients) | | 11 / 23.9 |
| Characteristics of subjective and objective status at admission (number/percent of patients) | chest pain | 37 /80.4 |
| | cough | 46 /100 |
| | dyspnea (points) | 3.47±0.47 |
| | body temperature | 38±0.12 |
| | respiratory rate | 21.97±0.92 |

**Table 2: Characteristics patients by CAP severity**

| Parameters | Enrolled patients |
|---|---|
| CRB-65 (points) | 0.53±0.13 |
| SMRT-CO (points) | 0.53±0.12 |

The severity of CAP was determined in accordance with clinical guidelines [7]. To collect clinical and laboratory data, we used specially developed individual record cards, which included demographic information, diagnosis, medical history, physical data, results of laboratory and instrumental tests. The probability of death was assessed using the CRB-65 scale [7]. Patients requiring intensive respiratory support and vasopressor infusion were identified using the SMRT-CO scale [7]. To interpret these scales, the following parameters were supposed to be assessed: age, impaired consciousness, respiratory rate, systolic and diastolic blood pressure, chest X-ray data, heart rate. Assessment of the prognosis and severity of the disease was carried out upon admission of the patient, on the 3rd, 7th day of hospital treatment and upon discharge. The characteristics of the study group in relation to the severity of the underlying disease are presented in Table 2.

Evaluation of clinical and laboratory data in the main groups was carried out on the 1st and 10th day of therapy. Erythrocytes and plasma were obtained from 10 ml of heparinized blood, for which, after centrifugation, the plasma was separated, and the erythrocyte mass was subsided twice in 20 ml of 10 mM Na-phosphate buffer (pH=7.4) containing 0.9% sodium chloride and 3% dextran T-500, for 30 minutes at 37°C. After centrifugation, the supernatant was removed by aspiration, and the erythrocyte mass was subjected to additional purification on a chromatographic column through HBS cellulose.

The intensity of lipid peroxidation (LPO) was assessed based on the content of acyl hydroperoxides (AHP) and malonic dialdehyde (MDA) in blood plasma and erythrocytes, the butanol-extracted stained complex formed with tiabarbituric acid. MDA and AHP was measured using TBK-Agat kit (Agat-Med, Russia), with Apel-330 spectrometer (Japan) at a wavelengths of 535 nm and 570 nm. To assess the state of the antioxidant system, we used direct/competitive enzyme-linked immunosorbent assay (ELISA) with the detection of reaction products in the wavelength range of 405-630 and ready-made commercial kits to determine the activity of superoxide dismutase (SOD) (Bender Medsystems, Austria) and catalase (Cayman Chemical, USA). Total antioxidant activity (TAA) was determined by a method based on the degree of inhibition of ascorbate and ferroinduced oxidation of Tween-80 to MDA. The level of stable nitric oxide metabolites ($CM_{ON}$) was measured using two analytical operations: measurement of endogenous nitrite and the nitrate-to-nitrite conversion with nitrite reductase, followed by measurement of total nitrite by the absorption of azo dye in the Griss reaction at 540 nm using an R&D solid-phase ELISA kit (England). In addition, the level of C-reactive protein (CRP) (Vector-Best, Russia), neopterin (IBL, Germany), erythropoietin (Biomerica, USA) was determined in blood plasma. Ceruloplasmin was determined by immunoturbidimetry using the Sentinel kit (Spain).

The content of cytokines, complement components and their inhibitors was determined in blood plasma. Interleukin 1β (IL-1β), interleukin 2 (IL-2), interleukin 4 (IL-4), interleukin 6 (IL-6), interleukin 8 (IL-8), interleukin 17 (IL-17), interleukin 18 (IL-18), interferon gamma (IFNγ), interleukin 10 (IL-10), tumor necrosis factor (TNFα), interleukin 1 receptor antagonist (IL-1RA), granulocyte macrophage colony stimulating factor (G-CSF), components complement systems (C3, C3a, C4, C5, C5a) and immunoglobulins of classes M, G, A (IgM, G, A) were detected by solid-phase ELISA using the kits

manufactured by CJSC Vektor-Best and LLC Tsitokin (Russia). When determining the inhibitors of the complement system, the concentration of factor H was established using a diagnostic kit manufactured by LLC Tsitokin (Russia) using two principles: the hemolytic method for accounting for the activation of SC and the ELISA method for detecting the terminal complex detected by specific antibodies, and the activity of the C1 inhibitor (C1-inh.) were identified by the chromogenic method by the ability to inhibit C1 esterase. All ELISA results were recorded using a Sunrise microplate photometer (Tecan, Austria).

The phagocytic activity of polymorphonuclear blood leukocytes after their isolation from the blood on the ficoll-urografin density gradient (d=1.077) was assessed by determining the phagocytic index (PI), phagocytic number (PN) and the phagocytic activity index (PAI) [19]. The activity of oxygen-dependent systems of neutrophils was assessed on a PD 303 SApel spectrophotometer (Japan) by the reduction reaction of nitroblue tetrazolium (NBT-test), spontaneous (NBT-sp.) and stimulated (NBT-st.) zymosan, stimulation index (NSI) and functional reservoir of neutrophils (NFR) [20].

In addition, immunological and metabolic parameters were studied in plasma samples and erythrocytes of peripheral blood of 18 healthy donors (38.2 ± 4.5 years) who formed a control group; the obtained results are accepted as a conditional norm.

Statistical data processing was carried out in accordance with generally accepted principles of statistical analysis. When comparing qualitative parameters, the χ2 test (chi-square) was used. To assess the reference of quantitative traits to the type of distribution, the Shapiro-Wilk test was used. To compare normally distributed values, the Student's t-test was used. The statistical significance of differences in quantitative values with abnormal distribution was assessed using the Mann-Whitney U-test and the Wilcoxon test (when comparing dependent groups). The values of normally distributed quantitative parameters are represented by the arithmetic mean (M) with an arithmetic mean error (m), and abnormally distributed ones - by the median (Me) with an interquartile range (P25; P75). The relationships were established on the basis of factor analysis, cluster analysis and the rank correlation coefficient. Differences were considered statistically significant at p<0.05.

## 3. Results and Discussion

For the correct interpretation of changes in the subjective and objective status of patients before the analysis of immune and metabolic changes, the indicators of routine prognostic scales were assessed (Table 3). According to the CRB-65 scale, a significant (p <0.05) reduction in the risk of an unfavorable outcome occurs by the 7th day and the end of therapy. The results of the SMRT-CO scale illustrate a significant decrease in the need for intensive respiratory support and infusion of vasopressors to maintain an adequate blood pressure level already by the 3rd day of therapy (p <0.05) and an increase in positive dynamics by the 7th day (p <0.01) and the final treatment (p<0.001).

An increase in proinflammatory cytokines was found in the blood plasma of patients with CAP prior to treatment initiation: TNFα by 4.8; IL-1β by 2.2; IL-6 by 2.9; IL-8 by 4.0; IL-17 by 1.5, and IL-18 by 2.3 times; decrease in anti-inflammatory cytokines: IL-4 by 1.8, IL-10 by 2.4, and IL-1RA by 2.3 times. The content of IFNγ, IL-2 and growth factor G-CSF was 2.1, 25.7, and 7.0 times higher, respectively, than the parameters of healthy donors. After the treatment, the concentrations of IL-4 and IL-10 returned to normal, the level of IL-17 and IFNγ did not change, and the content of the remaining investigated cytokines were corrected towards but did not reach the value of healthy donors (Table 4).

**Table 3: Changes in CRB-65 and SMRT-CO scales in patients with CAP**

| Parameters | Day of curation | | | | Statistical significance |
|---|---|---|---|---|---|
| | I. 1st | II. 3rd | III. 7th | IV. At discharge | |
| CRB-65 (points) | 0.53±0.13 | 0.33±0.11 | 0.23±0.08 | 0.2±0.07 | P I-II>0.05<br>P I-III<0.05<br>P I-IV<0.05<br>P II-III>0.05<br>P II-IV>0.05<br>P III-IV>0.05 |
| SMRT-CO (points) | 0.53±0.12 | 0.27±0.09 | 0.13±0.06 | 0.03±0.03 | P I-II<0.05<br>P I-III<0.01<br>P I-IV<0.001<br>P II-III>0.05<br>P II-IV<0.05<br>P III-IV>0.05 |

**Table 4: Plasma cytokine spectrum in patients with community-acquired pneumonia before and after standard treatment (M±m)**

| Parameters | Units of measurement | 1 | 2 | 3 |
|---|---|---|---|---|
| | | Healthy | Before treatment | After treatment |
| TNFα | pg/ml | 3.81±0.92 | 18.23±1.08*1 | 7.11±0.63*1,2 |
| IL-1β | pg/ml | 1.9±0.09 | 4.13±0.22*1 | 3.6±0.08*1,2 |
| IL-6 | pg/ml | 2.8±0.11 | 8.13±0.23*1 | 6.43±0.32*1,2 |
| IL-8 | pg/ml | 4.7±0.9 | 18.7±2.1*1 | 10.3±1.41*1,2 |
| IL-17 | pg/ml | 8.1±0.32 | 11.9±1.1*1 | 10.02±1.02*1 |
| IL-18 | pg/ml | 291.4±12.3 | 656.2±17.1*1 | 585.5±14.7*1,2 |
| IL-4 | pg/ml | 3.8±0.31 | 2.12±0.24*1 | 4.3±0.23*2 |
| IL-10 | pg/ml | 10.53±0.76 | 4.45±0.56*1 | 11.3±0.55*2 |
| IL-1RA | pg/ml | 420.9±10.4 | 181.2±11.3*1 | 220.3±9.72*1,2 |

| | | | | |
|---|---|---|---|---|
| IFNγ | pg/ml | 4.65±0.41 | 9.87±2.13*1 | 10.2±1.4*1 |
| IL-2 | pg/ml | 0.21±0.01 | 5.4±0.32*1 | 4.3±0.17*1,2 |
| G-CSF | pg/ml | 12.1±1.0 | 84.33±8.71*1 | 65.3±4.4*1,2 |
| *Note:* here and after in the tables, an asterisk (*) marks significant differences in arithmetic means (p<0.05); the numbers next to the asterisk means the group these differences in indicators are given. | | | | |

**Table 5: Blood immune status in patients with community-acquired pneumonia before and after standard treatment (M±m)**

| Parameters | Units of measurement | 1 | 2 | 3 |
|---|---|---|---|---|
| | | Healthy | Before treatment | After treatment |
| $C_3$ | mg/dl | 15.0±2.0 | 0.45±0.04*1 | 0.42±0.02*1 |
| $C_{3a}$ | ng/ml | 50.1±4.3 | 21.52±0.71 *1 | 26.2±0.5*1,2 |
| $C_4$ | mg/dl | 12.1±2.7 | 0.27±0.01*1 | 0.45±0.03*1,2 |
| $C_5$ | mg/dl | 8.3±0.9 | 0.69±0.04*1 | 0.72±0.02*1 |
| $C_{5a}$ | ng/ml | 4.0±0.6 | 7.77±0.21*1 | 5.83±0.55*1,2 |
| $C_1$-inh. | ng/ml | 220.1±12.3 | 425.1±17.5*1 | 245.0±20.2*2 |
| H factor | ng/ml | 78.3±10.4 | 80.5±12.31 | 69.67±13.7 |
| IgM | mg/dl | 26.04±3.92 | 29.94±3.95 | 19.8±3.84*1,2 |
| IgG | mg/dl | 658.73±24.3 | 626.81±32.5 | 583.7±24.3*1,2 |
| IgA | mg/dl | 177.68±38.16 | 332.29±26.99*1 | 238.4±48.4*1,2 |
| PI | % | 74.3±2.3 | 66.8±1.93*1 | 73.7±1.6*2 |
| PN | abs. | 4.64±0.23 | 4.07±0.15*1 | 4.88±0.2*2 |
| PAI | - | 3.43±0.11 | 2.72±0.13*1 | 3.6±0.2*2 |
| NBT-sp. | % | 9.4±0.5 | 13.7±1.1*1 | 11.4±0.72*1,2 |
| NBT-st. | % | 22.3±2.04 | 27.8±2.0*1 | 24.1±1.7 |
| NFR | % | 12.9±1.3 | 14.1±1.2 | 12.7±1.1 |
| NSI | - | 2.37±0.12 | 2.03±0.1*1 | 2.11±0.24 |

At admission, patients with CAP had a decrease in the content of $C_3$, $C_{3a}$, $C_4$, $C_5$ components of the complement and $C_1$ inhibitor by 33.3, 2.3, 44.8, 12.0 and 1.9 times, respectively, and an increase in $C_{5a}$ and IgA by 1.9 times; the level of H factor inhibitor remained within the normal range. After the standard treatment, the concentration of $C_1$-inhibitor returned to normal, the content of $C_{3a}$, $C_4$, $C_{5a}$ and IgA were corrected towards the values of healthy donors, the level of $C_3$, $C_5$ components of the complement and H factor did not change but the concentration of IgM and IgG decreased below the donors' values (Table 5).

At the beginning of treatment, the results of a study of the functional and metabolic activity of peripheral blood neutrophils were as follows: a decrease in the activity and intensity of phagocytosis (PI, PN and PAI) compared with healthy donors, an increase in the parameters of the activity of oxygen-dependent systems of polymorphonuclear leukocytes (NBT-sp. NBT-st.), in the absence of changes in the NFR and a decrease in the NSI. After treatment, most of the studied parameters of the functional and metabolic activity of neutrophils returned to normal, with the exception of the NBT-sp. corrected test (Table 5).

Patients with CAP, before the start of treatment, showed activation of peroxidation processes in blood plasma and erythrocytes (an increase in the concentration of MDA in blood plasma and erythrocytes by 5.5 and 10.4 times, respectively, and AHP by 7.7 and 10.5 times), a decrease in antioxidant protection factors (TAA in blood plasma and erythrocytes by 1.2 times, concentration of plasma ceruloplasmin by 1.3 times, SOD activity by 1.3 and 1.5 times, respectively, and catalase by 1.7 and 1.4 times). In the blood plasma and erythrocytes, the $CM_{ON}$ level increased by 3.5 and 3.9 times, respectively. In addition, the blood plasma showed a double increase in the concentration of erythropoietin and inflammation markers, neopterin and CRP, by 1.5 and 2.6 times respectively. After the treatment, the activity of catalase in the blood plasma and erythrocytes returned to normal, in the plasma the level of ceruloplasmin and the activity of SOD. TAA of erythrocytes remained unchanged; the rest of the studied metabolic parameters shifted towards but did not reach the level of healthy donors (Tables 6, 7).

Thus, 41 (91.1%) of 45 studied parameters of the immune and metabolic status in patients with CAP at admission were changed from the values of healthy donors. It can be concluded that profound immunometabolic disorders can be considered as immune inflammation, oxidative stress, endothelial dysfunction, and activation of lipid peroxidation. It is important to note that the course of standard treatment, which included 10 days, did not normalize 70.7% of the studied laboratory immunometabolic parameters that changed before treatment and further reduced the IgM and IgG content in CAP patients below the donor values, which requires the use of combined immunomodulatory and antioxidant therapy.

The presence of immune inflammation in the subjects is confirmed by an increased level of TNFα, IL-1β, IFNγ, IL-17, a marker of cellular immunity activation neopterin, an increase in the level of $C_{5a}$ fragment released upon activation of the complement system - an active chemotactic and vasodilating factor with anaphylactogenic.

**Table 6: Metabolic parameters in patients with community-acquired pneumonia before and after standard treatment (M±m)**

| Parameters | Units of measurement | 1 | 2 | 3 |
|---|---|---|---|---|

| | | Healthy | Before treatment | After treatment |
|---|---|---|---|---|
| MDA | µmol/l | 0.92±0.03 | 5.1±0.28*1 | 3.5±0.12*1,2 |
| AHP | c.u. | 0.21±0.04 | 1.61±0.11*1 | 0.71±0.05*1,2 |
| Catalase | mcat/l | 21.7±0.27 | 12.86±0.48*1 | 21.95±0.47*2 |
| SOD | c.u. | 16.97±0.34 | 13.35±0.59*1 | 20.37±0.67*1,2 |
| TAA | % | 37.95±0.8 | 31.78±0.58*1 | 39.19±0.45*2 |
| Ceruloplasmin | g/l | 0.32±0.04 | 0.24±0.03*1 | 0.34±0.03*2 |
| Neopterin | pg/ml | 6.02±0.15 | 4.06±0.11*1 | 5.12±0.2*1,2 |
| CRP | mg/dl | 3.7±0.27 | 9.54±0.69*1 | 6.7±0.13*1,2 |
| $CM_{NO}$ | µmol/l | 1.68±0.14 | 5.82±0.27*1 | 3.93±0.1*1,2 |
| Erythropoietin | IU/l | 3.72±1.41 | 7.6±1.24*1 | 2.6±0.29*1,2 |

**Table 7: Red blood cell metabolic parameters in patients with community-acquired pneumonia before and after standard treatment (M±m)**

| Parameters | Units of measurement | 1 | 2 | 3 |
|---|---|---|---|---|
| | | Healthy | Before treatment | After treatment |
| MDA | mmol/l | 0.32±0.03 | 3.34±0.1*1 | 2.14±0.09*1,2 |
| AHP | c.u. | 0.14±0.02 | 1.47±0.09*1 | 0.87±0.06*1,2 |
| TAA | % | 33.4±1.4 | 27.4±1.5*1 | 28.5±1.32*1 |
| SOD | c.u. | 19.23±1.62 | 12.41±1.02*1 | 16.7±0.89*1,2 |
| Catalase | mcat/l | 11.5±1.31 | 8.4±0.56*1 | 10.3±1.2*2 |
| $CM_{NO}$ | mmol/l | 1.12±0.04 | 4.34±0.12*1 | 3.02±0.2*1,2 |

Activity and participating in reactions of inflammation and hypersensitivity with the absence of a compensatory increase in the inhibitor (H factor) or even its decrease (C1-inh.) [16, 21, 22].

The development of oxidative stress (prooxidant and antioxidant imbalance, in which prooxidants predominate) is evidenced in our studies by an increase in the concentration of LPO products (MDA, AHP), $CM_{ON}$ and CRP (a systemic inflammatory response marker) in blood plasma and erythrocytes, a significant decrease in antioxidant protection (TAA, SOD activity, catalase) [23, 24].

Endothelial dysfunction in CAP patients is evidenced by an increase in the vasodilating (ON) factor, an increased level of proinflammatory cytokines (TNFα, IL-1, IL-17), neopterin and CRP [11, 22, 25-27].

The results indicate that confirmed laboratory immunometabolic disorders in patients with CAP, indicating the presence of immune inflammation, oxidative stress, endothelial dysfunction, and activation of lipid peroxidation. This justifies the need for intervention in the pathological process, restoration of normal lung tissue activity, and reduction of disabling consequences. The provided standard treatment does not normalize most of the changed parameters of the immune and metabolic status, which necessitates the search for methods for correcting disorders by using various combinations of immunomodulatory and antioxidant drugs in combination pharmacotherapy [13, 28].

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