Influence of Total Body Controlled Hyperthermic Perfusion on Levels of Heat Shock Proteins 70 kDa in Patients with Active Infective Endocarditis

Abstract

Development of infective endocarditis initiates a complex immunological response of the organism changing over time: the prevalence of pro-and anti-inflammatory mechanisms at the beginning is replaced by immunosuppression. A significant role in antigen presentation, cross-presentation, activation of macrophages and lymphocytes play the heat shock proteins 70 kDa (HSP).

The aim of the study was to investigate the relationship between systemic inflammatory response and HSP 70 kDa values in patients operated on under the total body controlled hyperthermic perfusion (TBCHP).

Materials and methods. The study included 18 patients with active infective valve endocarditis operated from 01.01.2016 to 01.01.2017 with the use of TBCHP. Assessment of the relationship between clinical characteristics of patients with infective endocarditis and the level of heat shock protein 70 kDa was performed preoperatively, 2 hours after TBCHP, 8 hours after TBCHP, 20 hours after TBCHP.

Results. The presence of high levels of heat shock proteins 70 kDa (5.6 ± 3.3 ng/ml) preoperatively indicated the depression of cellular and humoral immunity. Reduction in total blood plasma protein level as an indicator of catabolism was also combined with the registration of higher values of HSP70 kDa. After 2 hours after TBCHP a wide range of HSP 70 kDa levels was observed. A blood test performed after 2 hours after TBCHP showed HSP70 kDa – average level of 6.06 ± 3.8 ng/ml. Values range between 0.96 to 9.08 ng/ml. According to these data it was possible to distinguish two subgroups of patients who differ significantly in the average values of HSP70 kDa after TBCHP. There was a general tendency to reduce the values of HSP 70kDa from the initial preoperative level to the end of 20 hour after TBCHP – 5.6 ± 3.3 ng/ml and 1.6 ± 0.68 ng/ml correspondingly (p = 0.116).

Conclusion. Taking into account the previously identified preoperative relationships between HSP70 kDa level and clinical parameters of patients we may suggest that reduction of HSP 70 kDa corresponds with elimination of signs of the syndrome of persistent inflammation, immunosuppression and catabolism.

Keywords: infective endocarditis, heat shock proteins 70 kDa, persistent inflammation, immunosuppression and catabolism syndrome.
Introduction

Development of infective endocarditis initiates a complex immunological response of the organism changing over time: predominance of pro- and anti-inflammatory mechanisms in the beginning is replaced by immunosuppression [1]. Inflammation is characterized by excessive production of proinflammatory mediators, and immunosuppression – oppression of phagocytosis, presentation of antigens by monocytes, apoptosis of lymphocytes – leading ultimately to suppression of congenital and acquired immunity. This phenomenon was identified as an important late-stage mortality factor in septic patients [2, 3].

Recent studies of gene expression in septic patients have shown that inflammation and immunosuppression develop simultaneously, which is reflected in the concept of persistent inflammation, immunosuppression and catabolism syndrome (PICS) [1]. Significant role in antigen presentation, cross-presentation, activation of macrophages and lymphocytes is played by heat shock proteins (HSP) [4]. The specificity of the immune responses initiated by HSPs is related to the peptides that they accompany, and not to the HSP molecule itself [5]. HSP provide a link between congenital and acquired immunity and their presence in the circulation serves as a signal of alarm for the organism [6, 7].

The 70-kDa heat shock protein (HSP70) family of molecular chaperones represents one of the most ubiquitous classes of chaperones and is highly conserved in all organisms. Members of the HSP70 family control all aspects of cellular proteostasis such as nascent protein chain folding, protein import into organelles, recovering of proteins from aggregation, and assembly of multi-protein complexes. These chaperones augment organismal survival and longevity in the face of proteotoxic stress by enhancing cell viability and facilitating protein damage repair. Extracellular HSP70s have a number of cytoprotective and immunomodulatory functions, the latter either in the context of facilitating the cross-presentation of immunogenic peptides via major histocompatibility complex (MHC) antigens or in the context of acting as “chaperokines” or stimulators of innate immune responses [5].

The importance of finding the relationship between the clinical data of patients with IE and the level of 70-kDa HSP is associated with the use of total body controlled hyperthermic perfusion (TBCHP) during surgical interventions. In the implementation of the therapeutic effect of hyperthermia, the activation of the immune system plays an important role both due to the direct effect of temperature increase on the immunocytes and, as a result of the synthesis of heat shock proteins, activating action on immunocompetent cells. TBCHP in surgical treatment of patients with IE modifies the production of HSP, which through the intranuclear transcription factor (NF-kβ) regulates the activity of the cellular and humoral immune response.
The objective of the study was to investigate the relationship between systemic inflammatory response and HSP 70 kDa values in patients operated on under the total body controlled hyperthermic perfusion.

Materials and methods
The study included clinical data of 18 patients with active infective valve endocarditis, which were consecutively hospitalized, examined and operated with the use of TBCHP in SI “National Amosov Institute of Cardiovascular Surgery of NAMS of Ukraine” from 01.01.2016 to 01.01.2017. The diagnosis of IE was established according to the clinical criteria of Duke University. The average age of patients was 46.2 ± 3.4 years (20.0 – 66.0 years). The criteria for exclusion from the study group were: viral hepatitis B, C, drug addiction, the presence of antibodies to the human immunodeficiency virus.

The causative agent of IE was identified in 10 (55.6%) cases. The bacteriologic spectrum of pathogens included: Gram-positive cocci – 8 (44.4%) cases (Staphylococcus aureus – 1 case, Staphylococcus epidermis-3 cases, Enterococcus faecalis-3 cases), fungal microflora – 2 (11.1%) cases (Candida).

Fever during hospitalization was recorded in 12 (66.7%) cases. The average value of maximum body temperature rises during hospitalization was 38.3 ± 0.2 (37.2 – 39.3°C).

Patients were operated with the use of total body controlled hyperthermic perfusion. After moderate hypothermia (t = 28°C), surgical correction was carried out; warming to initial temperature; total controlled hyperthermic perfusion – increasing of the body temperature to 39°C with the exposure 30 min. Cooling of the patients to normothermia was performed in passive way.

The analysis of the plasma level of HSP-70 kDa was carried out with the help of the “BCM Diagnostics” test system by the method of enzyme immunoassay, which is based on the specific antigen-antibody reaction.

In accordance with the study protocol, measurement of the 70-kDa HSP level was performed in the following stages: before surgery (HSP-1), 2 hours after hyperthermia (HSP-2), 8 hours after hyperthermia (HSP-3), 20 hours after hyperthermia (HSP-4), 14 days after operation (HSP-4*).

Results
The average value of plasma concentration of HSP-1 was 5.6 ± 3.3 ng/ml (1.04 – 12.52 ng/ml). The ratio of male and female patients was 16 (88.9%) and 2 (11.1%) cases, respectively. At the same time, the average age of men was more than in women – 48.4 + 3.3 and 28.0 + 8.0 years respectively (p = 0.055). Correlation between gender and level of HSP-1 was not found.
Analysis of the relationship between HSP-1 levels and the results of bacteriological studies of blood showed that the highest values of HSP-1 corresponded to two cases of fungal infection – 9.49 + 1.2 ng/ml; for gram-positive pathogens the level of HSP-1 was – 5.42 + 0.9 ng/ml; in cases of negative bacteriological studies, the level of HSP-1 was 6.13 + 0.7 ng/ml (FiO₂ = 0.7, p = 0.613).

Analysis of the characteristics associated with temperature reactions showed that the highest levels of HSP-1 were in those patients who had the disease without chills – 8.65 + 1.07 ng/ml (p = 0.002). In case of chill in the history of disease and the presence of fever during hospitalization, significantly lower HSP-1 levels were recorded – 4.23 + 0.63 g/ml and 4.77 + 0.8 ng/ml, respectively. Since all the patients were hospitalized for surgical treatment, the absence of chills and fever cannot be interpreted as a state of cure or recovery. A possible explanation is the persistent infection or the hyporeactive or areactive course of the disease itself (Table 1).

Table 1. Analysis of the relationship between plasma levels of HSP-1 and the temperature reactions

| Data                                      | n  | %     | HSP-1     | χ² | p     |
|-------------------------------------------|----|-------|-----------|----|-------|
|                                           |    |       | M         |    |       |
|                                           |    |       | Sd        |    |       |
| Chills in medical history:                |    |       |           |    |       |
| no                                        | 7  | 38.9  | 8.65      | 3.8| 0.002 |
| yes                                       | 11 | 61.1  | 4.23      |    |       |
| Fever at hospitalization:                 |    |       |           |    |       |
| no                                        | 6  | 33.3  | 8.39      | 2.6| 0.020 |
| yes                                       | 12 | 66.7  | 4.77      |    |       |
| Chills in the hospital:                   |    |       |           |    |       |
| no                                        | 13 | 72.2  | 6.22      | 0.4| 0.697 |
| yes                                       | 5  | 27.8  | 5.48      |    |       |

The correlation between the plasma levels of HSP-1 and the immunogram data revealed a negative correlation with the absolute number of leukocytes (r = -0.409, p = 0.130) and the absolute number of monocytes (r = -0.605, p = 0.017). A distinctive negative relationship was revealed for the parameters of the humoral immunity: CD19 + B-lymphocytes (X1) (r = -0.453, p = 0.068), CD19 + B-lymphocytes (abs) (r = -0.545, p = 0.036), immunoglobulin A (R = -0.604, p = 0.010). A negative relationship at the trend level was observed for CD16 + natural killers (r = -0.361, p = 0.155). In the analysis of the cellular immunity, a positive correlation was found for the percentage of CD3 + T lymphocytes (%) (r = 0.478, p = 0.052), CD8 + T suppressors (%) (r = 0.413,
p = 0.099). In addition, a positive relationship was found between HSP-1 and the reserve capacity of monocytes (r = 0.667, p = 0.003) and the level of total myeloperoxidase (abs.) (R = 0.607, p = 0.063).

The obtained data made it possible to calculate the dependence of the preoperative level of HSP on the initial values of B-lymphocytes and immunoglobulin A by the method of linear repression (Fig. 1).

Linear regression of HSP-1 from B-lymphocytes and immunoglobulin A was calculated by the formula:

\[ X_3 = 13.2096 + (-0.3930) \times X_1 + (-1.5391) \times X_2, \]

\[ X_1 - \text{B-lymphocytes} \]
\[ X_2 - \text{immunoglobulin A} \]
\[ X_3 - \text{initial value of the HSP}. \]

The determination coefficient of the obtained model was \( R^2 = 54.28\% \) and the sensitivity of \( S^2 = 2.1950 \), respectively.

Correlation analysis of the plasma level of HSP-70 kDa and biochemical blood data revealed a negative correlation with protein levels (\( r = -0.533, p = 0.028 \)) and K+ (\( r = -0.444, p = 0.074 \)).

Analysis of the baseline level of HSP 70-kDa with clinical data of IE patients suggests that persistent inflammation, immunosuppression and catabolism syndrome or its components can be predicted by measuring 70-kDa HSP levels. In this regard, for the studied group of patients, both the evaluation of the dynamics of HSP values in the early
postoperative period, and the normalization of the parameters of cellular and humoral immunity, indicating the recovery of patients, are fundamental. The particular interest is devoted to the dynamics of HPS values in the postoperative period in connection with the intraoperative application of TBCHP.

The blood test, performed 2 hours after TBCHP, showed that the average value of HSP-2 was of 6.06 ± 3.8 ng/ml. Values ranged from 0.96 to 9.08 ng/ml. The analysis, conducted 8 hours after TBCHP, indicated that the average value of HSP-3 was 4.23 ± 3.05 ng/ml. Values ranged from – 0.24 to 5.14 ng/ml. A blood test, performed 20 hours after TBCHP, showed that the average value of HSP-4 was 1.60 ± 0.68 ng/ml. Values ranged from 0.26 to 2.94 ng/ml.

We have performed a graphical assessment of the dynamics of HSP values at all stages of the study (Fig. 2). The results of the analysis showed:

1. There was a general tendency to reduce the values of HSP-70 kDa, starting from the initial pre-operative level and ending with the fourth measurement stage (20 hours after TBCHP). Taking into account the previously revealed relationships between HSP-1 and clinical data of patients, it was possible to assume that the decrease in the level of HSP corresponded to the elimination of persistent inflammation, immunosuppression and catabolism syndrome signs.

2. Two hours after the TBCHP, there were significant fluctuations in the performance of the HSP-2 (from 0.96 to 9.08 ng/ml). The systematization of these data maked it possible to distinguish two subgroups of patients, which differed significantly in the mean values of HSP-2.

![Figure 2. Dynamics of HSP levels at all stages of the study](image)

Stages: 1 – before surgery; 2 – after the operation (2 hours); 3 – after the operation (8 hours); 4 – after the operation (20 hours).
Analyzing data, we have found that for high values of HSP-2, lower previous values (HSP-1) and subsequent values (HSP-3) are characteristic, as well as again a relative increase in HSP-4 values. A part of the observations registered the reverse dynamics – for lower values of HSP-2, higher previous values (HSP-1) and subsequent values of HSP-3 were characteristic. Thus, in accordance with the dynamics of the HSP, we have formed two subgroups, with the boundary between these groups being the value of HSP-2 (within the limits of 5–6 ng/ml). The data of all observations were systematized into two subgroups. Subgroup 1 included all observations with HSP values ≥ 6 ng/ml, and all observations with HSP values <6 ng/ml are assigned to subgroup 2. For each of the subgroups, graphs of the dynamics of the average HSP values were plotted, which showed significant differences at the HSP-2 level (Fig. 3, 4).

![Figure 3. The dynamics of the HSP values for subgroup 1 (n = 6) (HSP ≥ 6.0 ng/ml)](image)

![Figure 4. The dynamics of the HSP values for subgroup 2 (n = 12) (HSP < 6.0 ng/ml)](image)

The peculiarity of the analysis was that if we similarly split into groups according to the values of the HSP-1, i.e. on the initial level, then we
would not get such regularities, since the close values of the HTS-1 varied in different directions. Thus, in this analysis, it could be assumed that the qualitative and quantitative changes in HSP were due not to its initial value, but to other factors, the presence of which led to the fact that 2 hours after hyperthermia, we got either a significant increase in HSP or a decrease in it.

Analysis of the oxygen-dependent killing data indicated a decrease in the intensity of intracellular metabolism of neutrophils in the second sub-group, which was manifested by a significant decrease in the level of myeloperoxidase (p = 0.048), a significant decrease in the level of superoxideidion of neutrophils (p = 0.089) and a significant increase in the level of hydrogen peroxide (p = 0.090) (Fig. 5).

![Figure 5. Comparative analysis of oxygen-dependent killing data between subgroups 1 and 2](image)

When assessing the parameters of the immunological status, an increase in leukocyte levels (p = 0.126) and neutrophil levels (p = 0.112) in the second subgroup was revealed at the level of the trend. There was a significant increase in the apoptotic activity of neutrophils in the first group (p = 0.137) (Fig. 6).

The obtained data indicate a greater degree of activation of the systemic inflammatory response in patients of the second sub-group. One of the possible causes of activation of neutrophil apoptosis in patients of the first subgroup is the realization of the effector function of cytotoxic T-cells and natural killer-cells (NK-cells). Cytotoxic T-lymphocytes can initiate cell death by activating receptors on the surface of target cells.
Correlation analysis of interrelation of HSP levels in each of the subgroups was carried out with an absolute number of leukocytes, red blood cells and protein. For subgroup 1, a negative relationship was established between the level of HSP-1 with the absolute number of natural killers \( r = -0.809, p = 0.097 \) and the level of the blood protein \( r = -0.793, p = 0.060 \). There was also a negative correlation between the level of HSP-3 and red blood: erythrocytes \( r = -0.885, p = 0.016 \), hemoglobin \( r = -0.878, p = 0.021 \) and hematocrit \( r = -0.907, p = 0.012 \).

For subgroup 2, a negative relationship was established between the level of HSP-1 and the values of monocytes \( r = -0.644, p = 0.045 \), B-lymphocytes (CD19 +) \( r = -0.678, p = 0.031 \), and also at the trend level with NK-cells (CD16 +) \( r = -0.526, p = 0.097 \).

A general trend was observed in decrease the HSP 70 kDa values from the initial preoperative level to the end of 20 hours after TBCHP – 5.6 ± 3.3 ng/ml and 1.6 ± 0.68 ng/ml, respectively \( p = 0.166 \).

The comparative analysis of the immunogram indices at the pre- and postoperative stages (2 hours after hyperthermia) revealed that in the postoperative period there was a significant increase in the level of leukocytes \( p = 0.007 \) and neutrophils \( p = 0.002 \). These data indicate an intensification of the systemic inflammatory response, and a significant decrease in the immunoregulatory index CD4 + / CD8 + \( p = 0.001 \) on a significant depletion of the immune system.

In contrast, when evaluating the results of a comparative analysis of the immunogram data at the pre- and postoperative stages (14 days after hyperthermia), no significant differences between the levels of
leukocytes and neutrophils were revealed. However, signs of activation of the humoral link of immunity were registered – an increase in the levels of CD19 + (p = 0.132). Activation of the cellular system of the immune system was represented by a significant increase in CD3 + T-lymphocytes (p = 0.056); significant increase in the content of CD8 + T-suppressors (p = 0.006) and natural killers of CD16 + (p = 0.086). Immunoregulatory index on day 14 after surgery was significantly lower than baseline – 1.27 (p = 0.037), but did not exceed normal limits.

The correlation analysis between the values of HSP and blood indices at all stages of the study showed that the initial negative relationship between the level of HSP-1 and blood leukocytes (r = −0.464, p = 0.059) and the level of HSP-1 and neutrophils (r = −0.469, p = 0.058) to the 14th day of the postoperative period was leveled – (r = −0.172, p = 0.495) and (r = −0.132, p = 0.603), respectively. The revealed negative relationship between the level of HSP-2 and the level of erythrocytes (r = −0.537, p = 0.026), HSP-2 and hemoglobin level (r = −0.564, p = 0.018), HTS-2 and hematocrit (r = −0.634, P = 0.006) at the time of discharge from the hospital is not recorded (Table 2).

**Table 2. Results of the correlation analysis between the values of HSP and blood levels at all study stages**

| Data                               | HSP-1 preoperative | HSP-2 2 hours post/op | HSP-3 8 hours post/op | HSP-4 20 hours post/op | HSP-4* 14 days post/op |
|------------------------------------|--------------------|-----------------------|-----------------------|------------------------|------------------------|
|                                    | r  p               | r  p                  | r  p                  | r  p                   | r  p                   |
| Leucocytes (x10⁹/l) (abs.)         | -0.464 0.059       | -0.095 0.716          | -0.177 0.483          | -0.207 0.410           | -0.172 0.495           |
| Neutrophils (abs.)                 | -0.469 0.058       | -0.087 0.739          | 0.055 0.829           | -0.098 0.851           | -0.132 0.603           |
| Erythrocytes (x10¹²/l) (abs.)      | -0.061 0.818       | -0.537 0.026          | -0.200 0.427          | -0.364 0.138           | 0.161 0.524            |
| Hemoglobin (g/l)                   | 0.037 0.888        | -0.564 0.018          | -0.377 0.123          | -0.386 0.114           | 0.341 0.167            |
| Hematocrit                          | 0.067 0.806        | -0.634 0.006          | -0.437 0.070          | -0.441 0.067           | 0.237 0.344            |
| Protein (gr/l)                     | -0.425 0.089       | -0.031 0.904          | -0.209 0.422          | 0.051 0.863            | 0.154 0.615            |

This study was conducted on a group of patients with IE, i.e. at different periods of disease there were all the pathogenetic components of sepsis: bacteremia (fungemia), a syndrome of the systemic inflammatory response, a focus of infectious valve destruction. With an average
duration of the disease 2.4 ± 2.2 months the length of the temperature period was 1.8 ± 1.2 months. For the indicated time intervals, various regimes of antibiotic therapy were repeatedly applied, which did not lead to eradication of the pathogen (presence of fever in the hospital, positive bacteriological studies). At the same time, all patients had valve destruction and needed cardiosurgical intervention. Thus, we observe a joint influence of three negative factors: prolonged persistence of the inflammatory process, valvular regurgitation and heart failure. Registration of higher levels of HSP-1 in cases of absence of chills in medical history and fever in the hospital is the first evidence of depletion of the body’s defenses. Signs of suppression of cellular and humoral immunity are combined with the high levels of HSP-1, and decrease in the level of total plasma protein, as one of the indicators of catabolism, is also combined with the registration of higher values of HSP-1. Thus, at the prehospital stage, high levels of HSP-1 can serve as markers of persistent inflammation, immunosuppression (depletion of reserve capabilities of the body after prolonged antigenic stimulation) and catabolism syndrome.

In the early postoperative period, an increase in the activity of the systemic inflammatory response syndrome and inhibition of the cellular immune system are recorded. The disappearance of signs of the syndrome of the systemic inflammatory response and restoration of the parameters of cellular and humoral immunity are observed by the 14th day of the postoperative period.

Surgical removal of the intracardiac focus of infection and normalization of hemodynamics help reduce the activity of the systemic inflammatory response, eliminate signs of persistent inflammation, immunosuppression and catabolism, whose biochemical marker is 70 kDa heat shock protein.

**Conclusions**

1. The initial mean value of 70-kDa HSP in patients with IE is 5.6 ± 3.3 ng/ml (0.1 – 12.2).
2. High levels of HSP-1 are combined with the main signs of persistent inflammation, immunosuppression and catabolism syndrome.
3. Surgical intervention under conditions of hyperthermal perfusion tends to decrease the level of HSP 70 kDa in the postoperative period (p = 0.166).
4. In the early postoperative period, an increase in the activity of the systemic inflammatory response syndrome and inhibition of the cellular part of the immune system are recorded. The disappearance of signs of the syndrome of the systemic inflammatory response and restoration of the parameters of cellular and humoral immunity is observed by the 14th day of the postoperative period.
Вплив гіпертермічної перфузії на рівні білків теплового шоку 70кДа у хворих з активним інфекційним ендокардитом

Резюме. Розвиток інфекційного ендокардиту ініціює комплексну імунологічну реакцію організму, що змінюється в часі: поширеність про- і протизапальних механізмів на початку замінюється імуносупресією. Значення роль у презентації антигену, крос-презентації, активації макрофагів і лімфоцитів відіграють білки теплового шоку 70 кДа (БТШ).

Метою дослідження було вивчення взаємозв'язку між системною запальною реакцією та величиною 70 кДа БТШ у пацієнтів, оперованих в умовах загальної контролюваної гіпертермічної перфузії (ЗКГП).

Матеріали та методи. Дослідження включало дані 18 пацієнтів з активним інфекційним ендокардитом, що пройшли лікування з 01.01.2016 по 01.01.2017 р. з використанням ЗКГП. Оцінювання взаємозв'язку між клінічними характеристиками хворих з інфекційним ендокардитом і рівнем білка теплового шоку 70 кДа проводили передоперативно, через 2, 8 і 20 годин після ЗКГП.

Результати. Наявність високих рівнів білків теплового шоку 70 кДа (5,6 ± 3,3 нг/мл) на передоперативному етапі вказувало на зниження клітинного і гуморального імунітету. Зниження загального рівня білка плазми крові, як показника катаболізму, також поєднувалося з реєстрацією вищих значень HSP70 кДа. Через 2 години після ЗКГП спостерігали широкий діапазон рівнів HSP 70 кДа. Аналіз крові, проведений через 2 години після ЗКГП, показав середній рівень HSP70 кДа – 6,06 ± 3,8 нг/мл. Значення становили від 0,96 до 9,08 нг/мл. За цими даними можна було виділити дві підгрупи пацієнтів, які значно відрізнялися за середніми значеннями HSP70 кДа після ЗКГП. Спостерігалась загальна тенденція до зниження значень БТШ 70 кДа від початкового дооперативного рівня до кінця 20-ї години після ЗКГП – 5,6 ± 3,3 нг/мл і 1,6 ± 0,68 нг/мл відповідно (p = 0,116).

Висновок. Ураховуючи раніше визначені передоперативні зв'язки між рівнем БТШ і клінічними показниками пацієнтів, можна припустити, що зменшення HSP 70 кДа відповідає усуненню ознак синдрому персистенції запалення, імуносупресії та катаболізму.

Ключові слова: інфекційний ендокардит, білки теплового шоку 70 кДа, синдром персистенції запалення, імуносупресії та катаболізму.

REFERENCES
1. Mira JC, Brakenridge SC, Moldawer LL, Moore FA. Persistent Inflammation, Immunosuppression and Catabolism Syndrome. Crit Care Clin. 2017;33(2):245–58. https://doi.org/10.1016/j.ccc.2016.12.001
2. Hawkins RB, Raymond SL, Stortz JA, Horiguchi H, Brakenridge SC, Gardner A, Efron PA, Bihorac A, Segal M, Moore FA, Moldawer LL. Chronic Critical Illness and the Persistent Inflammation, Immuno-suppression, and Catabolism Syndrome. Front Immunol. 2018;9:1511. https://doi.org/10.3389/fimmu.2018.01511

3. Qu B, Jia Y, Liu Y, Wang H, Ren G, Wang H. The detection and role of heat shock protein 70 in various nondisease conditions and disease conditions: a literature review. Cell Stress Chaperones. 2015;20(6):885–92. https://doi.org/10.1007/s12192-015-0618-8

4. Chen Y, Wang L, Kang Q, Zhang X, Yu G, Wan X, Wang J, Zhu K. Heat Shock Protein A12B Protects Vascular Endothelial Cells Against Sepsis-Induced Acute Lung Injury in Mice. Cell Physiol Biochem. 2017;42:156–68. https://doi.org/10.1159/000477308

5. Radons J. The human HSP70 family of chaperones: where do we stand? Cell Stress & Chaperones. 2016;21(3):379–404. https://doi.org/10.1007/s12192-016-0676-6

6. Halbach JL, Wang AW, Hawisher D, Cauvi DM, Lizardo RE, Rosas J, Reyes T, Escobedo O, Bickler SW, Coimbra R, De Maio A. Why antibiotic treatment is not enough for sepsis resolution: an evaluation in an experimental animal model. Infect Immun. 2017; 85(12). pii: e00664-17. https://doi.org/10.1128/IAI.00664-17

7. Stortz JA, Murphy TJ, Raymond SL, Mira JC, Ungaro R, Dirain ML, et al. Evidence for persistent immune suppression in patients who develop chronic critical illness after sepsis. Shock. 2017;49(3):3–8.

Стаття надійшла в редакцію 12.08.2019 р.