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STUDY PROTOCOL

Exploration of Different Rehabilitation Routes for Sepsis Survivors with Monitoring of Health Status and Quality of Life: RehaSep Trial Protocol

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ABSTRACT

Introduction: This project addresses the important problem of sepsis sequelae resulting in frequent hospital readmissions and higher mortality rate in the post-discharge period. However, neither specific diagnostic methods nor standards for rehabilitation of sepsis patients have been introduced yet. The aim of this study is to evaluate the effectiveness of two different multiparameter-monitored rehabilitation treatments in order to improve the health status and quality of life of sepsis survivors.

Methods: Decades of failed randomized controlled trials involving sepsis patients strongly suggest the need for a paradigm change. Therefore, we designed a prospective, interventional, controlled, pragmatic, patient-centred trial based on the principles of personalized medicine. Sixty post-sepsis patients after hospital discharge will be individually assigned to a control group (without intervention) and two groups with 3-month diagnostically monitored rehabilitation programs based either on the recumbent cycloergometer training or on the experimental hyperbaric oxygen therapy. In all of the patients a wide range of physiological (spirometry, ECG/cycloergometer exercise test), haematological (microscopy) and biochemical (blood tests) parameters will be assessed at hospital discharge and during subsequent 3 months in order to monitor changes of their physical capacity, immunity and degree of post-sepsis organ damage/recovery. For quality of life monitoring a novel tool—"Life After Sepsis Survey"—will be applied.

Planned Outcomes: A set of composite quantitative indices resulting from laboratory measurement data combined with the quality of life questionnaire data will constitute the primary outcomes whereas mortality rate and hospital readmission number will be counted as the secondary outcomes.

Conclusions: Critical analysis of past trials prompted us to implement multiple improvements in tools and procedures. The results of this trial will contribute to the development of rehabilitation therapy addressing not only weakness but also organ damage problems of sepsis survivors.

Trial Registration: ANZCTR (http://www.anzctr.org.au): ACTRN12618000347268, U1111-1210-6110.

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INTRODUCTION

The project addresses the issue of sepsis—"one of the oldest and most elusive syndromes in medicine" [1]. Every year, more than 30 million people worldwide are affected by this disease [2], and its incidence markedly increases.

According to the third and current definition, sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection [3].

In spite of the achievements of medicine, neither the specific diagnostic methods [4, 5] nor the standards for rehabilitation have been introduced yet [6]. As a result, frequent hospital readmissions occur in sepsis survivors [7–9]. A high mortality rate (61% within 5 years) was also noticed [10]. Moreover, the successful in-hospital stabilization of the patient's condition does not guarantee a full recovery. The patients often experience physical, mental and cognitive changes, described as the postintensive care syndrome [11, 12]. The symptoms include weakness and body wasting, polyneuropathy [11, 13], organ failure [14], chronic pain [15] or post-traumatic stress disorder features [16], strongly contributing to the reduction of daily activities [11, 12] and quality of life [10, 17]. These impairments may persist for years after hospitalization [11, 18]. At the metabolic level, a phenotype of persistent inflammation, immunosuppression and excessive protein catabolism underlies poor outcomes [19].

There is evidence [20] that exercise induces a number of physiological mechanisms of adaptation to oxidative stress. The beneficial effect of physical exercises depends on the type and intensity of exercise. Too heavy, exhausting efforts contribute to shifting of the antioxidative/pro-oxidative balance towards oxidation and adverse changes caused by excessive activity of free radicals. Only moderate, carefully selected exercises strengthen the antioxidant barrier and protect the endothelium against damage, maintaining its proper function [21]. Moreover, it has been shown that regular physical activity protects against the development of chronic inflammatory diseases [22]. Properly arranged physical exercise also contributes to the reduction of apoptosis and organ damage caused by septic shock, at least in experimental animals [23, 24].

"We used to think of sepsis as just a medical emergency, an infection that you get sick with and then recover" [12]. However, many sepsis survivors leave hospitals with such severe structural and/or functional limitations that they practically could not benefit from rehabilitation training in the therapeutically important period just after discharge. Therefore, we propose to test the effects of hyperbaric oxygen therapy (HBOT) applied as an innovative form of rehabilitation of post-sepsis patients. HBOT improves microcirculation; it can also increase oxygen supply to the ischemic tissue to reduce the extent of irreversible tissue damage [25–28]. HBOT with its immunostimulatory, angiogenic and antimicrobial effects can be also used as adjunct treatment for non-healing ulcers and problematic wounds [25].

Further improvements in physical rehabilitation will require a better understanding of critical illness phenotypes and their varying recovery trajectories. Rehabilitation may then be better tailored to the individual [29].

The aim of the study is to evaluate the effectiveness of two different rehabilitation treatments in order to improve the health status and quality of life of sepsis survivors.

The other, equally important objective is to gather reliable scientific data by monitoring multiparameter changes in the health status and quality of life during important the post-discharge period.

METHODS

Study Design

This study is a prospective, observational/interventional, controlled, pragmatic, patient-centred trial based on the principles of personalized medicine.

The protocol of the study was approved by the Local Bioethics Committee at the Regional Medical Chamber in Krakow (136/KBL/OIL/2015). The research will be performed according to the Declaration of Helsinki. Informed consent will be obtained from all individual participants included in the study.

Trial Status

The trial was registered at ANZCTR (http://www.anzctr.org.au) before recruitment of the first participant (ACTRN12618000347268, first posted in December 2017).

Patient recruitment is ongoing but not completed.

Study Population

The study will be conducted with 60 patients discharged after hospitalizations for sepsis from the wards of the Ludwik Rydygier Memorial Specialized Hospital in Krakow.

The inclusion criteria will be as follows: men or women, 30–80 years of age with a documented episode of sepsis (according to the SEPSIS-3 definition).

The exclusion criteria will concern patients with sepsis and trauma, cancer or burn injury background, with leg amputations, requiring palliative care, psychiatric or with mental disability, thus unable to cooperate and/or to perform the initial cycloergometer exercise test.

By limiting the age range and applying exclusion criteria, we intend to reduce the confounding effects of age and/or malignancy or trauma on the interpretation of results.

Recruitment

Shortly before discharge from the hospital, all the potential patient candidates will be informed about the purpose and scope of the research and asked to give written consent. Then each participant will be qualified for the study collectively by the project team and collaborating hospital ward physicians after detailed examination of all available medical records and the patient's interview information. Such consultation will result in the consensus to choose the route expected as more beneficial for the patient taking into account all the circumstances. Thus the participant will be individually assigned to one of two experimental groups (E, H). The personalized rehabilitation training (E group) will be considered as the standard treatment. Hyperbaric oxygen therapy (H group) will be chosen as the alternative for patients with contraindications to exercise training (e.g. unhealed wounds, severe pains etc.) and/or predicted too low benefit from exercise therapy (see "Discussion" for further explanation). Those qualified candidates who could be included but declare (for different reasons) inability to follow the rehabilitation regimen will be offered participation in the control group (C) i.e. without our intervention nor routinely prescribed rehabilitation (which reflects the present healthcare practice with sepsis survivors).

Treatment of all the participating patients will start as soon as possible, up to a month after hospital discharge.

The study specificity is directly related to the nature of sepsis as the medical problem which occurs rather unpredictably. Of course, there are no planned hospital admissions of septic patients unlike many common chronic diseases. Consequently, the project participants, i.e. post-septic patients, generally will be included individually. In case of an insufficient number of patients who will develop sepsis within the time frame of the project, it is intended to provide additional study groups of patients treated in other clinical departments.

Rehabilitation Training Group

The patients in group E will participate in the 36 sessions (three times a week, on Monday, Wednesday and Friday, for 12 weeks) of rehabilitation program based on the semi-recumbent cycloergometer training (Kettler RE-7), which will provide a safe and comfortable approach for patients with reduced exercise capacity and a number of post-septic changes.

An exercise program administered by a physiotherapist face-to-face will be performed for 1 h and will comprise 15 min warm-up with functional strength training, 30 min cycling in a reclined position and 15 min calming-down phase with stretching and breathing relaxation exercises. The workout intensity will be selected individually according to the result of the initial

ECG cycloergometer exercise test and a 20-step scale of perceived physical exertion (the Borg scale), in which the intensity of exercise during the training will be in the range of 11–13 points, thus indicating light to moderate effort.

Hyperbaric Oxygen Therapy Group

The patients assigned to group H will be qualified by an experienced HBOT physician after a detailed examination and will undergo 36 sessions (three times a week, on Monday, Wednesday and Friday, for 12 weeks) of breathing 100% oxygen at 2.5 atm for 90 min, seated in a multiplace hyperbaric chamber under medical supervision.

In order to monitor adherence to the interventions, session attendance lists checked by the study personnel will be implemented.

Psychological support will be included if recognized as necessary.

Control Group

Participants of the control group (C) will be only observed and diagnostically monitored with the same setting and timing as for the E and H intervention groups.

Monitoring Measurements

All the participants (assigned to groups E, H and C) will be monitored by multiparameter diagnostic measurements according to the following scheme (Fig. 1).

Blood Tests

Sets of routine laboratory tests will be ordered at monthly intervals to determine the functional changes of the patient's organs during the 3-month period after sepsis: complete blood count, WBC differential, acid–base balance, electrolytes (Na, K, Cl), Ca, Mg, hepatic function panel, renal function panel, urate, CRP, lactate, 25-OH-vitamin D, fibrinogen, INR and APTT.

These routine tests will be ordered at the certified Department of Laboratory Diagnostics of the Ludwik Rydygier Memorial Specialized Hospital in Krakow where all the blood samples will be drawn and immediately analysed.

The venous blood samples will be taken in the morning from the subjects in a fasting state, before any physiological capacity tests; the blood will be taken from HBOT- or exercise-treated patients on Mondays.

Specialized haematological and biochemical parameter tests: detailed microscopic examination of blood smears, live cell imaging of leukocyte activity, blood plasma spectrophotometric determinations of total oxidative status, total antioxidative capacity, thiol antioxidants, nitric oxide level (assessed as plasma nitrate/nitrite concentration) and measurements of myeloperoxidase enzymatic activity will be performed by the project team in the Laboratory of Blood Physiology of the University of Physical Education in Krakow.

All the blood tests in every patient will be performed at hospital discharge and after the first, second and third months.

Physiological Tests

At hospital discharge (time point 0) and after 3 months (endpoint), spirometry, ECG cycloergometer exercise test, handgrip strength and body composition analysis will also be performed with each participant.

The examinations will be contracted to the specialized medical units of the Ludwik Rydygier Memorial Specialized Hospital in Krakow.

Spirometry

Pulmonary function will be measured with the abcMED Pneumo spirometer, calibrated daily and connected to a computer with data analysis Pneumo 2005 software. Measurements will be carried out in a familiar and quiet room in the Internal Medicine Ward. Standing height and weight will be assessed. During measurements, the patient will be instructed to sit upright, and a nose clip and a non-compressible mouthpiece will be used. All the pulmonary function tests will be performed by one trained research nurse according to the American Thoracic Society/European Respiratory Society standards [30]. The following values will be assessed: forced vital capacity (FVC), forced expiratory volume in the first second (FEV1), peak expiratory flow (PEF), time to peak expiratory flow (TPEF) and

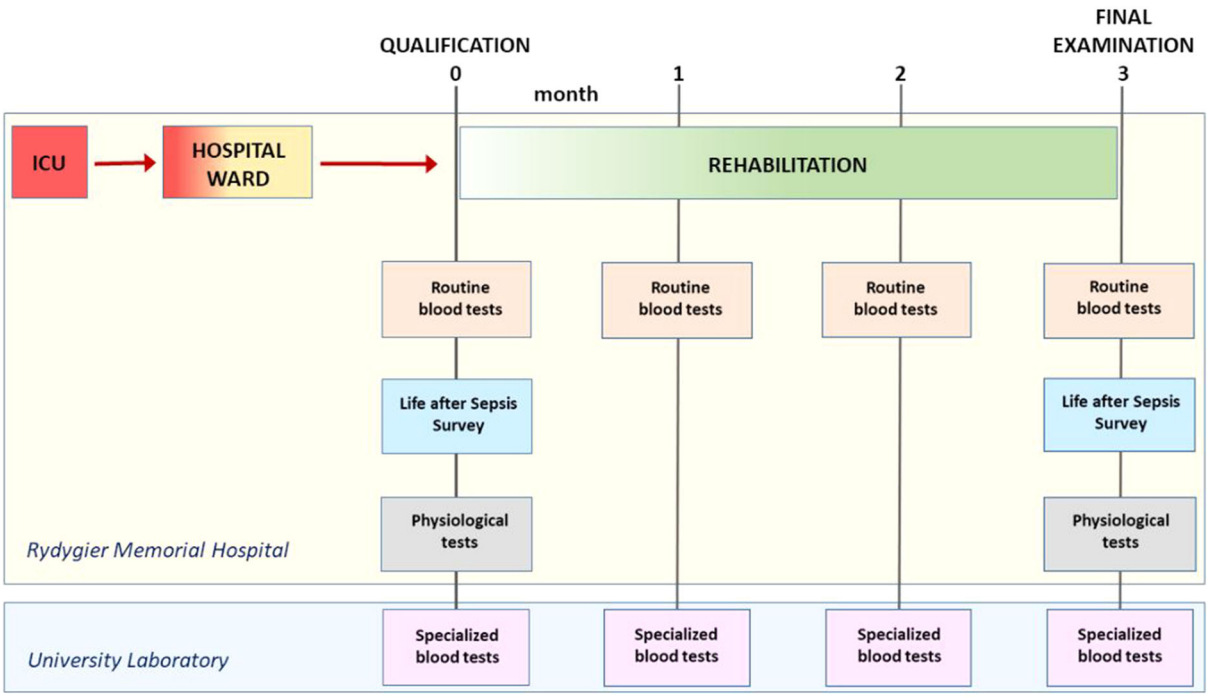

Fig. 1 Scheme of the proposed course of treatment

forced expiratory time (FET). The highest of three successful measurements will be taken for analysis. The results will be expressed as the percentage of a predicted value.

ECG Cycloergometer Exercise Test

Exercise testing, supervised by a clinical cardiologist, will be performed on an electromagnetically controlled semi-recumbent cycloergometer (Kettler RE-7). The test comprises a 3-min rest period followed by a progressive exercise test of up to seven steady-state stages each lasting 3 min, starting at a 25-W workload and with a 25-W increment. The test will be terminated when the participant is unable to maintain a cadence of 60–70 revolutions per minute or desires to stop. The exercise intensity will be regarded as the total work amount (in kilojoules) achieved at stop time. ECG and heart rate will be monitored throughout exercise using a 12-lead ECG CardioTEST ASPEL test system. Blood pressure will be measured manually before and after the exercise test.

Handgrip Strength Test

The handgrip strength (in kilograms) will be measured twice for each hand alternately, using an electronic hand dynamometer (Camry EH101). The participant will be asked to sit or stand up, with an elbow extended and arm hanging down not touching the body with the wrist in a neutral position, and squeeze the dynamometer with each hand as hard as possible for 5 s. For the primary analyses, we will use the maximum values achieved by a patient.

Body Composition Analysis (BCA)

The body composition parameters such as fat mass (FM) and fat-free mass (FFM), total body water (TBW), extracellular water (ECW), intracellular water (ICW) and skeletal muscle mass (SMM) will be analysed using the seca mBCA 525 portable Bioelectrical Impedance Analysis medical instrument comprising an electronics unit with touchscreen monitor linked by Wi-Fi to the measuring mat. The mBCA 525 is designed for measurements in the supine position and will be operated using eight adhesive

gel electrodes placed at defined anatomical sites on the dorsal surfaces of the hand, wrist, ankle and foot according to the manufacturer's instructions. The eight-electrode technique enables segmental bio-impedance measurement with high accuracy.

In addition, basic measurements of height, weight and waist circumference will be made before the BCA test.

Photography

Photographic documentation of wound healing will be performed for patients with wounds, undergoing HBOT.

Quality of Life Assessment

At hospital discharge (time point 0) and after 3 months (endpoint) each patient will complete the specialized "Life After Sepsis Survey" to assess post-sepsis problems with respect to physiologic, functional and mental capacities, treatments received and satisfaction with the healthcare received during the hospitalization period. The survey was developed as part of the Sepsis Survivors Engagement Project (SSEP) [31]. For the purposes of this study it will be translated and adapted from the original version into Polish.

Planned Outcomes

Primary Outcomes

- Blood test composite outcome: changes of haematological and biochemical diagnostic indices measured by routine and specialized methods
- Physiological capacity composite outcome: changes of physiological indices measured by
  - ECG cycloergometer exercise test [time to exhaustion, total work (in kilojoules)]
  - Spirometry [FEV1 (in litres), FVC (in litres), PEF (in litres), TPEF (in seconds), FET (in seconds)]
- Change in the quality of life as assessed with the specialized "Life After Sepsis Survey" questionnaire

Secondary Outcomes

- Mortality rate of the study participants as compared to the rate for the sepsis survivors population
- Hospital readmission number of the study participants due to secondary infection/sepsis within 3 months after hospital discharge as verified by medical records

Data Collection

Data security and confidentiality will be ensured by the appropriate measures.

Material patient-related records such as sample tubes, microscopic slides, electronic files, data sheets and questionnaires will be stored using coded IDs. Patients' personal-sensitive records will be stored separately, in a locked cabinet accessible only to the two project investigators.

All the data acquired from measurements, observations, documentation etc. will be digitalized and stored in the dedicated database. Password protection and multiple backup procedures will be applied to maintain a high level of data safety and security.

Sample Size

One of the aspects of this study's novelty is that there are no data from similar previous studies enabling us to perform a precise and formal sample size calculation. Our target sample size of 60 patients was chosen to be large enough for such preliminary research and also for feasibility.

Data Analysis

The final statistical analysis of the collected data will be performed at the end of the trial using a number of analytical techniques. Analysis with repeated measurements with a grouping factor [two-way analysis of variance (ANOVA) with repeated measurements] will be particularly justified in the case of the analysis of planned data sets which will be balanced with a constant number of repeated measurements and a negligible number of missing observations. Since

there will be several results (in number equal to the number of measurement situations) from each of the tested patients, it will be possible to evaluate the variability associated with the individual variation of the subjects and the variability associated with the different measurement situations in groups (E, H, C), as well as the interactions between them.

Evaluation of the survey results describing the quality of life of patients will be based on Poisson regression analysis. This analysis allows one to evaluate the dependencies between variables in cases when the dependent variable (answer) assumes in its nature the realizations in the form of a set of discrete data. An alternative method to assess the quality of life will be an analysis of canonical correlation. It will provide a list of quantitative variables with specific weights indicating their participation/impact on the quality of life assessment.

In any case, to avoid data redundancy and to group correlated variables and extract only the representatives of variables, an autocorrelation analysis will be performed. Finally, all variables will be included in the interpretation of the final results.

Survival analysis will be performed to assess the survival of patients in all groups (E, H, C).

The analysis will be carried out using the R program together with selected libraries, i.e. stat, ggplot2, CCA [32–35].

DISCUSSION

Design Rationale

The need for implementation of rehabilitation for post-sepsis patients as the key to their recovery is strongly expressed [36–38], and new research studies with the aim to deepen our understanding of long-term functional impairments are highly recommended [37].

Decades of failed randomized controlled trials (RCTs) involving patients with sepsis strongly suggest the need for a paradigm change. Therefore, we designed a prospective, interventional, controlled, pragmatic, patient-centred trial based on the principles of personalized medicine.

Regarded as the highest scientific standard, a traditional RCT is typically a well-controlled study with carefully selected populations under ideal conditions. This makes it difficult to translate results to the real-life practice [39]. RCTs are a "crowned" standard among medical researchers. Indeed, we admit that RCTs are perfectly suited to preclinical studies on laboratory animals. However, RCTs bear many flaws that render them incongruent with the reality of patients with sepsis in the healthcare environment. In our opinion, trials involving septic or post-septic patients just by assuming a randomization pattern become destined for failure. Some respected sepsis researchers have already presented similar points of view [40–42].

Randomization vs. personalization patient-related issues we thoroughly considered encompass the following points:

- Ethics—it is extremely difficult or impossible to strictly accord with randomization, the use of which would result in delivery of inappropriate treatment to some patients while depriving others of the appropriate treatment; for instance, it would be unethical to randomly assign sepsis survivors with unhealed wounds.
- Safety—for aforementioned reasons and with typically narrow-range or nominal (e.g. questionnaire only) health monitoring, the RCTs might compromise participants' safety.
- Blinding—combined with randomization might evoke patients' distress, disappointment, distrust and distraction which eventually would jeopardize participant adherence/retention; sepsis survivors are afflicted persons bearing difficult/traumatic memories and interaction with them should be cautious and sympathetic; in this context, a personalized, unblinded approach will certainly facilitate a trusting and participating attitude of the patients that may turn out to be an important ingredient to increase the probability of therapeutic success.
- Feasibility—it is intertwined with all the aforementioned issues and affected by them; after all, it should be remembered that nowadays, trials are carried out in a difficult

legal environment; trialists are simply dependent on patients' trust and willingness to cooperate and their consent obtained is only conditional; the first example is the current problem of access to patients' medical documentation and records: here, without active patient/family involvement we could not even start the best (theoretically) planned, blinded RCT.

Consequently, when designing our study we assumed a patient-centric, supportive approach with the ultimate aim to improve sepsis survivors' health status and quality of life to the most realistic extent, i.e. to achieve progress, steady state, or just slow down a regress—either may be success for a given patient.

It was essential to establish an efficient network of collaborating experienced partners within the hospital: the management, department heads, ward physicians, medical technologists, nurses and technicians. A series of meetings and negotiations were held and formal agreements signed.

Critical analysis of past trials prompted us to introduce multiple changes and improvements in tools and procedures.

HBOT

Hyperbaric oxygen therapy will be explored for the first time as a rehabilitation treatment for sepsis survivors. Thus, we will provide a new opportunity for continuation of therapy for some of the patients with contraindications for exercise training (e.g. unhealed wounds) within the important "therapeutic window" for rehabilitation just after hospital discharge. Although in the standard HBOT regimen the treatment sessions are administered daily (five times per week), in our design the sessions will be scheduled on alternate days (three times per week) in order to offset the transient effects of oxidative stress so as to improve the treatment tolerance and patient safety.

Physiological Tests

The most commonly used test for evaluation of physical capacity after critical illness is the Six-Minute Walk Test (6MWT). However, we regard it as unsuitable for patients with temporary disabilities, who are unable to walk on their own and use a wheelchair for the first weeks after hospital discharge. The primary reason we excluded the 6MWT is that it would exclude some of our patients who otherwise might benefit from rehabilitation. Alternatively, more instrumental approaches are also frequently applied, for better objectivity.

A typical cardiopulmonary set-up commonly used in clinical trials comprises electrocardiograph electrodes and a gas exchange mask as the measuring devices combined with a treadmill as the exercising device. This is obviously inadequate for usually long-term critical care sepsis survivors suffering from dyspnoea and muscle wasting; firstly, because of breathing through a mask; secondly, because of a moving treadmill—both of which become confounding factors. In some other common set-ups with a classic bicycle saddle the problem with balance remains.

Therefore, we will implement the more patient-friendly design comprising a semi-recumbent cycloergometer with a wider seat and a comfortable backrest. Here, the patient will breathe freely and the cycling time and electronic total work readings will constitute superior, unconfounded indices of the exercise capacity. The same cycloergometer model will be used both for the test and exercise training. In addition, we will use spirometry for more accurate measurement of pulmonary function.

In general, the majority of chosen physical capacity evaluation methods are in accordance with the recent expert consensus statement [43]; one exception is the use of body composition analysis which was ranked as unimportant. However, considering its practicality, feasibility and the range of data obtained, we decided to use this measurement, especially given that we will apply the latest generation equipment, certainly not available at the time of the aforementioned consensus process. Moreover, other investigators are also using body composition and hand grip strength measurement in their protocol in an ongoing trial [44].

Quality of Life Assessment

For quality of life monitoring we will introduce, for the first time in a clinical trial, a novel tool—the "Life After Sepsis Survey". This questionnaire, developed in collaboration with sepsis survivors themselves [31], is the most specific and suitable tool available today. Our study will further contribute to its validation by using it repeatedly and verifying with patients' medical records.

STRENGTHS AND LIMITATIONS

Advantages

The distinguishing feature of this project is that in the course of the study all the participating patients will be diagnostically monitored at the detailed, multiparameter level that will allow for individual, timely adjustments of any ongoing treatment and definitely increase the overall patient safety.

Furthermore, all the rehabilitation procedures will be carried out in the same hospital, where the patients had undergone sepsis treatment, in cooperation with their hospital doctors.

An additional advantage is the location of both the hyperbaric chamber and the exercise room within the hospital complex: they are easily accessible by ambulance and away from the common traffic routes that is also very important in terms of secondary infection prevention in post-sepsis patients who are frequently vulnerable and immunocompromised. These potential dangers will be also avoided by planning the independent ambulance transport (to be contracted as an external service) for the patients coming for the rehabilitation sessions.

It should be emphasized that our project fulfils multiple aspects of a recent (May 2017) resolution of the World Health Organization (WHO) that recognized sepsis as a global health priority [45].

Limitations

Besides our study qualities we are aware also of its limitations. Although we strive to set up our interventions as completely as possible, we were not able to include state-of-the-art nutritional care accompanied by microbiological monitoring. Also, initially planned immunophenotype monitoring turned out to be infeasible.

CONCLUSIONS

No trials concerning development of the individual rehabilitation model monitored by multiparameter diagnostics have been reported so far.

The results of this trial will contribute to development of rehabilitation therapy addressing not only weakness but also organ damage problems of sepsis survivors.

Now, not waiting for the future, it is high time to start realization of the undertaking designed in conformance with the personalized medicine paradigm.

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Compliance with Ethics Guidelines. The protocol of the study was approved by the Local Bioethics Committee at the Regional Medical Chamber in Krakow, Poland (136/KBL/OIL/2015). The research will be performed according to the Declaration of Helsinki of 1964, as revised in 2013. Informed consent will be obtained from all individual participants included in the study.

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