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Personalized Critical Care Medicine (Review)

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Персонализированная медицина критических состояний (обзор)

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Summary

Personalized medicine (PM) is a major trend in health care development in the 21st century. This area includes studying risk factors for disease development (prediction), interventions for preventing diseases (prophylaxis), individualization of diagnosis and treatment (personalization), informing the patient on disease prevention and treatment (participation). In the recent years, an intense research to introduce the personalized medicine principles into the management of critically ill patients, has been under way. This includes identification of patient groups based on genomic research, development of diagnostic tests using molecular markers, creation of novel classes of drugs based on individual patient characteristics.

The aim of the review is to summarize the available data on the implementation of the principles of PM in the routine practice of critical care institutions.

We analyzed more than 300 sources of literature from the Pubmed and Scopus databases, as well as the RSCI database. Eighty five most relevant sources were selected for the review. The paper reports data on the organization and results of implementation of PM principles and advanced technologies, such as Emergency Medicine Sample Bank (EMSB), in the daily activity of clinics providing emergency critical care. The formation of the novel PM concept focused on the treatment of critically ill patients has been discussed. The review contains detailed data on the patterns of development of specific critical illnesses such as acute cerebrovascular events, acute respiratory distress syndrome, traumatic brain injury, shock, myocardial infarction, cardiac rhythm and conduction disturbances. Medication efficacy in view of individual genetic patient characteristics has also been highlighted. No research limitations on the subject were identified.

Conclusion. The analysis of literature has demonstrated positive results of implementing PM principles in prevention, diagnosis and treatment of critically ill patients. Creation of Biobanks, development of training programs and regulatory documentation, advancing the scientific research, introduction of new methods of diagnosis and treatment will contribute to the implementation of PM principles in practical healthcare.

Keywords: personalized medicine; critical illness

Conflict of interest. The author declares no conflict of interest.

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Introduction

Individualized medical treatment strategy has been widely employed for centuries. Significant contribution to advancement of this approach was made by the founding fathers of Russian national medicine such as Matvey Mudrov, Sergey Botkin, Ivan Sechenov and others.

At the end of the twentieth century, Leo Holland (USA) formulated a trend called «Patient-Centered Diagnosis and Treatment», which marked the beginning of the era of personalized medicine (PM). In 1999, the term «personalized medicine» was proposed [1], reflecting the paradigm of 21st century healthcare [2]. The four cornerstones of PM (4P medicine) are prediction (ability to «predict» the disease), prevention (measures to prevent disease), personalization (individualized treatment), and participation (active role of the patient in the disease prevention and treatment) [3].

A paradigm shift from the «one size fits all» to individualized and targeted treatments has resulted in a greater focus on PM. Individual patient char-

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acteristics include genetic patterns and phenotype parameters (the latter include combination of physiological, biochemical, molecular, and morphological features). Unique personal characteristics are defined by such PM tools as personomics, which takes into account the human personality, preferences, values, goals, health beliefs, as well as available social support network, financial resources and individual life circumstances, which influence the response to treatment [4].

The need for the implementation of PM principles is driven by the lack of efficacy of existing treatment methods. According to Food and Drug Administration, the medications used are not effective in 75% of patients, which requires revision of the drug administration principles [5] and development of new drugs, devices and imaging technologies [6].

A survey of 153 institutions in the United States reveals considerable heterogeneity in the adoption of PM [7]. Relatively few health care providers in the United States offer PM as a part of the clinical workflow [8].

The development of PM requires elaboration of effective technologies for implementing the individualized patient care, formulating regulatory documentation, active involvement of educational institutions [9], and reducing health care costs through selection of effective therapies for the individual patient [10].

Public healthcare systems play a key role in the development of PM, as they guarantee new opportunities for patients in the implementation of individualized treatment approaches [11]. In the Russian Federation, the development of PM is regulated by the Presidential Decree of June 6, 2019 N254 «On the Strategy for the development of healthcare in the Russian Federation for the period until 2025», Orders of the Ministry of Health of the Russian Federation from April 24, 2018 N186 (the Concept of personalized medicine), from February 01, 2019 N42 (targeted program: «Development of fundamental, translational and personalized medicine»).

The aim of this review is to summarize the available evidence on the implementation of PM principles in the practice of medical institutions that treat critically ill patients.

The Role of Genetic Research in The Development of PM

The impact of PM on medical practice is largely attributed to genomic research. In this regard, expanding genetic curriculum in medical education could be the first key step to ensuring the widespread adoption of PM [12].

In a survey of individuals 18 years of age and older, many respondents cited educational resources as critical to successful implementation of PM [13]. A survey of 559 medical, pharmacy, genetics, and bioengineering students indicated positive student attitudes toward genetic testing and PM. The importance of pharmacogenomic education for more effective implementation of PM in clinical practice is emphasized [14]. Results of a population and healthcare providers survey revealed serious concerns about the protection of genetic privacy and the lack of support for a common genetic database [15]. Unprecedented opportunities are offered by population-based biobanks storing large amounts of genetic information and stimulating the development of PM [16] using the advantages of digital medicine [17]. The integration of electronic medical records and genomic research is an important aspect of PM development. The consortium network of electronic medical records and genomics data established in 2007 is funded by the National Institutes of Health (NIH) [18].

Based on a literature review of PM-related problems, the range of diagnostic methods and individual biological information, including genetic data and biomarkers, evaluation of the effectiveness of new drugs has been determined [19]. Due to advances in genetic knowledge, the patterns of clinical phenotype and individual response to drugs have gained better understanding [20].

Several national and international PM-based genomic projects have been realized based on big data analytics (complete and targeted sequencing, use of artificial intelligence), aimed at solving complex issues and developing new PM implementation programs [21].

The forecast of PM development by 2025 includes widespread genome sequencing, which will become affordable and commonly used in molecular diagnostics [22]. The Partners Health Care Personalized Medicine (introduction of genetics and genomics into research and clinical practice) program has developed the Whole Genome Sequencing (WGS) process, which is used to study both healthy individuals and patients with various diseases [23].

Both genomic and epigenomic changes, including methylation, acetylation, phosphorylation and ubiquitination of DNA and histone proteins (nucleosomes) as well as chromatin remodeling, significantly contribute to disease development. In this regard, both genetic and epigenetic diagnostic testing is required to implement the principles of PM [24].

Some urgent care centers employ various molecular assays based on genomics, transcriptomics, proteomics, and metabolomics to unravel disease mechanisms at the molecular level. However, the results of such approaches in emergency care have not been sufficiently addressed in the scientific literature [25].

Introducing PM Principles Into Critical Care Medicine

Despite certain obstacles to the implementation of PM principles in critical care medicine, there are several cases of successful implementation of measures in this direction.

The creation of the «Emergency Medicine Sample Bank» (EMSB) is an obvious success. The EMSB is a biobank of clinical data and biological samples collected from adult patients who were treated in the emergency department of a Colorado hospital, USA. EMSB is the first acute care biobank that seeks to cover all patients presenting to the emergency department. The EMSB has been integrated into the clinical workflow and serves as a powerful tool for researchers identifying new biomarkers of acute conditions, determining drug response mechanisms, and elucidating mechanisms of critical illness. Matching patient samples with data from the electronic medical record more accurately assists in identifying patient phenotypes. Combining these data with individual patient genomics allows determining the genetic basis of clinical manifestations and variability of treatment response. The authors believe that biobanks will be an important resource in emergency medicine [26].

The identification of patients with genotypic and phenotypic patterns influencing the success of diagnostic and therapeutic measures is an important principle of PM. In particular, stratification techniques based on the matching characteristics which serve as a tool for personalization of patients at risk of developing acute circulatory disorders [27] and cancer [28] have been proposed.

A new concept of PM, focused on the treatment of critically ill patients, based on four pillars, which include patient fitness and frailty assessment to determine their physiological reserve, monitoring of key physiological variables in disease and therapy, evaluation of the success of resuscitation, and integration of physiological and clinical data into an adaptive model of the patient was proposed [29].

To realize the benefits of PM it is necessary to resolve several organizational challenges such as determining the regulations for clinical trials, developing criteria for collaborative development and diagnostic standards, eliminating the incompatibility of information systems [30] by engaging the advantages of artificial intelligence [31].

An increasing number of publications covering the development, treatment and outcomes of critical conditions from the PM perspective is available. The study of acute cerebrovascular events seems promising. Cerebrovascular diseases, in particular stroke, are a major challenge for the public health. The genetic research has not yet been widely used in daily practice for stroke prevention. Currently, personalized aspects of stroke prevention are applied in an institutional care and patient education models [32]. The effective use of biomarkers allows to characterize more precisely a phenotype of patients, to trace progression of disease and response to the treatment methods.

A scheme for using biomarkers to diagnose aneurysmal subarachnoid hemorrhage has been proposed [33]. Cerebral hemodynamics is an important diagnostic biomarker in stroke. The authors have developed a simulation-based method that allows assessing cerebral hemodynamics based on the patient's vascular configuration and has high specificity and sensitivity in detecting changes in cerebral vascular perfusion [34].

The use of PM for prevention of cardiovascular diseases in women is crucial for the gender-specific medicine [35]. Based on the study of angiogenesis and neuroplasticity, modern biomarkers of post-stroke recovery have been proposed and recommended for use in clinical practice [36].

Acute respiratory distress syndrome (ARDS) is one of the life-threatening critical conditions, characterized by 40% mortality in patients of intensive care units and diagnosed based on acute hypoxemia, bilateral pulmonary infiltration and noncardiogenic pulmonary edema. ARDS has multiple clinical risk factors and mechanisms of lung damage, which in most cases can explain the lack of efficacy of pharmacological treatment. Identifying ORDS phenotypes and using this information for patient selection for clinical trials increases the chances of novel therapies being effective. Procollagen alveolar type III peptide (PCP-III) is a robust candidate biomarker among bronchoalveolar fluid proteins whose levels are associated with ARDS development and outcomes. In an observational study of 32 patients, PCP-III was highly sensitive (0.90) and specific (0.92) for the diagnosis of fibroproliferation in ARDS [37]. Its potential is used for the development of new therapeutic agents based on the mechanisms of ARDS and identification of ARDS subpopulations which can benefit from patient-specific treatment approach [38].

Identification of genetic biomarkers offers hope for the creation of effective methods of stratification, prognosis, and development of novel treatments for ARDS [39]. ARDS associated with sepsis is characterized by significant mortality. If subtypes of both sepsis and ARDS are taken into account, the prospect of a personalized approach for effective treatment of patients with these critical conditions seems promising [40].

Based on the study of blood biomarkers such as interleukins (IL-6 and IL-8), interferon gamma (IFN-γ), surfactant proteins (SPD and SPB), von Willebrand factor antigen, angiopoietin 1/2 and plasminogen activator inhibitor-1 (PAI-1), two subgroups of ARDS phenotypes (hypo- and hyperinflammatory) were identified. Patients with these

phenotypes have significantly different clinical outcomes and response to mechanical ventilation, infusion therapy and simvastatin treatment [41]. The hyperinflammatory subgroup is associated with shock, metabolic acidosis and poor clinical outcome [42–44].

Hemodynamic disturbances often are associated with adverse outcome in critical conditions. Therefore, prediction of acute hypotension development in patients is necessary for improving the intensive care performance [45].

Traumatic brain injury (TBI) is commonly associated with critical illness being one of the leading causes of mortality in young adults. In TBI, patients with similar injuries, age, and health status often show differences in recovery from trauma.

Currently, emphasis is placed on the development of a personalized approach to the treatment of TBI. Studies in model systems and the use of candidate genes in human studies have allowed to identify factors influencing the outcome in TBI. Functional outcomes after TBI vary widely among patients with «apparently similar» injuries. The presence/absence of a single nucleotide polymorphism (SNP) has been found to affect outcome after TBI. One of the well-characterized SNPs, Val66Met, is associated with the brain-derived neurotrophic factor (BDNF) gene. This SNP affects neurological function in both healthy subjects and patients with TBI [46]. The use of neuroimaging techniques has resulted in the development of tailored methods of studying brain atrophy associated with TBI [47].

The data on endocannabinoid metabolism and its therapeutic effects in traumatic brain injury have been summarized from the PM perspective [48]. The development of neuronal system models for the study of human trauma evolution using chips is under way. Three classes of chips have been identified including microfluidic, compartmentalized and hydrogel. The methods of using 3D-printing to design and produce next-generation chips created on the base of stem cells and their application in «personalized neuroscience» have been developed [49].

Shock is one of the essential issues of critical care medicine. Personalized medicine has identified subclasses of septic shock based on gene expression with phenotypic differences. Gene expression data for 100 genes with identifiable subclasses were obtained using a multiplex information RNA quantification platform and visualized using gene expression mosaics. Based on this technology, two subclasses (one of which showing decreased gene expression) characterized by different course of septic shock were reproduced. The above-mentioned subclass was independently associated with mortality, and the use of corticosteroids in such patients was also independently associated with lethal outcome [50].

The role of steroids in survival in septic shock remains controversial. Thus, the individual treatment effect of corticosteroids in adults with septic shock in intensive care units has been evaluated [51]. The data suggest that an individualized treatment strategy allowing to choose the patient for steroid therapy was successful irrespective of the potential side effects of the drugs [52].

Myocardial infarction is one of the common life-threatening critical conditions. Research based on personalized medicine is underway to unravel the pathogenesis of circulatory disorders in the coronary artery system and to identify the diagnostic molecular markers. Epigenome changes have been shown to elucidate some mechanisms of coronary heart disease (CHD) pathogenesis. The «network medicine» combines standard clinical signs and noninvasive cardiac imaging tools with epigenetics for in-depth molecular phenotyping of CHD. In particular, this approach is used to develop new drugs based on natural components.

Several clinical trials have focused on the evaluation of circulating miRNAs (e.g., miR-8059 and miR-320a) in the blood in combination with imaging parameters such as the coronary calcifications and the degree of coronary artery stenosis [53].

Rhythm and conduction abnormalities can also be life-threatening. Atrial fibrillation (AF) is the most common cardiac arrhythmia. Despite advances in surgical technologies, antiarrhythmic drugs remain the mainstay of treatment of symptomatic AF. However, the response varies considerably among patients: more than half of patients who received rhythm control therapy have recurrent AF within a year.

The limited success of rhythm control strategy could be partially due to individual differences in disease mechanisms and the inability to predict response to medications in individual patients. Studies of AF over the past decade have shown that susceptibility to AF therapy could be due to genetic regulation. Increased predisposition to AF has been found to be associated with the chromosome 4q25 locus. Screening of candidate genes regulating cardiac potassium and ion channel function in probands and families with early-onset AF revealed several rare variants. Screening of DNA isolated from cardiac atria has identified a mutation of the GJA5 gene underlying abnormal electrical connections between cardiac cells. Based on meta-analysis, more than 10 loci relevant to the development of AF were identified [54].

A study of 6,567 Caucasian patients found an association between the incidence of atrial fibrillation and greater height in women [55].

Potassium channel genes have been shown to be associated with the risk of AF. Their enhanced function leads to a faster repolarization current

and a shorter effective refractory period which increases cellular excitability and susceptibility to arrhythmias. Mutations in sodium channel subunit genes have also been associated with AF. A single-nucleotide polymorphism in SCN10A has been found to be associated with the early-onset AF [56].

Possible interactions between obstructive sleep apnea (OSA), atrial fibrillation (AF) and connexins have also been revealed. Epidemiological studies show that OSA is associated with increased incidence and progression of coronary heart disease, heart failure, stroke, and arrhythmias, especially AF. The role of connexins in AF is now relatively well established. Understanding the biology and regulatory mechanisms of connexins in OSA at the transcriptional, translational, and posttranslational levels will allow to elucidate the role of connexins in the development of OSA-induced AF [57]. Increased susceptibility to AF can be explained by various risk factors modifying left atrial tissue [58].

Atrial fibrillation is characterized by structural and electrical remodeling of the heart. Atrial fibrosis, a hallmark of structural atrial remodeling, is a complex multi-factorial process involved in the occurrence and maintenance of AF [59]. Atrial models have been developed that include detailed atrial anatomy, tissue ultrastructure, and the pattern of fibrosis distribution. Use of atrial models has given important insights into the mechanisms underlying AF by demonstrating significance of atrial fibrosis and altered atrial electrophysiology in the initiation and maintenance of AF [60]. Recent data demonstrate a hereditary component underlying AF [61].

Critical conditions are often accompanied by deadly infectious complications. Advances in diagnostics have minimized the frequency of «blind» antibiotic prescription without proper laboratory evaluation. Molecular diagnostics, in turn, have been improved by nanobiotechnology and are coupled with improved delivery of antimicrobial agents. Sequencing the microbial and viral genomes and studying the genetic susceptibility of patients makes it possible to develop individualized approaches to their treatment [62].

Critically ill patients are often prescribed with enteral or parenteral feeding. Personalized nutrition in general may be a more effective way of changing lifestyle than other measures. A study [63] evaluated the effects of a 10-week personalized nutrition system on lifestyle and health outcomes. The intervention reduced calorie, carbohydrate, sugar, total and saturated fat intake. A reduction in body weight, fat content, and hip circumference was registered in the studied cohort. Health improvements were most pronounced in the altered phenotype subgroup, indicating that a personalized nutrition program may be particularly effective for behavior change in target groups with impaired health.

To develop personalized nutrition, the concept of «system flexibility» has been introduced, involving real-time assessment of metabolism and other processes. Genetic variants and performance measures were integrated into this systemic approach to provide a strategy for a balanced assessment of individual nutrition [64].

The treatment based on personalized medicine also takes gender differences into account. The terms «sex» and «gender» are often misused as synonyms. Sex implies anatomical and physiological differences, while gender includes mental, cultural and social differences. Consideration of sex and gender differences is important for effective disease prevention, identification of clinical signs, outcome prediction and therapy optimization [65].

Pharmacogenomics of critical conditions. Pharmacogenomics is the most important element in dealing with PM issues. Difficulties in implementing the principles of pharmacogenomics are related to gene variability. For example, CYP2D6 has several alleles that determine different rates of drug metabolism, which can change the therapeutic effect [66] and influence individual treatment response and drug toxicity manifestations [67]. Clinical implementation of personalized therapy based on pharmacogenomics is still limited. In Korea, an assessment of physicians' knowledge of personalized therapy based on pharmacogenomics was conducted. Fifty-three percent of physicians reported insufficient knowledge of pharmacogenomics. The main obstacle to its clinical implementation was the high cost of genetic testing and the lack of education of medical professionals and clinical experts in pharmacogenomics [68].

It is unclear whether pharmacogenomics data can be used to predict emergency department hospitalization. A cohort study has shown that traditional risk factors, such as age and self-perceived health, are much more likely to predict emergency department hospitalization and treatment than pharmacogenomic information (69). At the same time, pharmacogenetic testing can help identify patients at increased risk for drug toxicity. A step-by-step approach to pharmacogenetic testing in primary care has been developed, involving identification and education of patients, ordering of pharmacogenetic tests, and interpretation of their results [70].

Clopidogrel and CYP2C19 variants are the first example of a drug-gene interaction. Clopidogrel is an antiplatelet agent used in acute coronary syndrome (ACS). Studies have shown that certain variants of the CYP2C19 gene are associated with altered function of enzymes involved in clopidogrel metabolism, which puts patients with acute coronary syndrome at risk for thrombotic complications [71].

Pharmacogenetics is used to develop individualized treatments specific to people from different

ethnic or racial groups with varying degrees of genetic diversity. Genetic differences can alter the therapeutic efficacy of drugs. Pharmacogenetic studies in mixed ethnic groups have identified candidate genes, the best of which is the gene encoding the ARDB2, the target receptor for beta-agonist therapy [72].

In 2015, the IGNITE (Introducing Genomics into Practice) network created an online resource toolkit on genomic medicine implementation, allowing users to create targeted guidelines for introducing genomic medicine, including pharmacogenomics [73].

Multiple driver genes can cause «resistance» to individual drugs. New personalized driver genes and combinatorial drug identification algorithm (CPGD) have been developed. The results showed that the new technology is more efficient compared to existing synergistic combinatorial strategies [74].

Adverse drug reactions (ADRs) are an important and frequent cause of ineffective treatment. Genetic predisposition to adverse reactions is an emerging challenge in various areas of medicine. Improved genotype-phenotype correlation using novel laboratory methods and the introduction of artificial intelligence can contribute to personalized prediction of adverse reactions, selection of the optimal drug and its dose for each patient [75].

Drug candidates demonstrating well-defined pharmacokinetic and pharmacodynamic profiles often fail to confirm their efficacy in phase II and III clinical trials. A system (QSP platform) based on a drug development strategy has been proposed and implemented at the University of Pittsburgh Drug Discovery Institute. This platform addresses the issues of biological heterogeneity and the evolution of resistance mechanisms, which present a major obstacle in drug development, and involves a paradigm shift from conventional medicine to personalized medicine [76].

Studies of individualized efficacy of pharmacological drugs in critical conditions, such as asthma [77], thrombotic complications [78], COVID-19 infection involving in silico analysis (computer models) [79], are being conducted.

The personalized medicine is a constantly evolving area. One of the novel directions is theranostics which includes the creation of pharmacological preparations that can be used to resolve diagnostic and medical problems in an integrated manner. In particular, several preparations for tailored diagnosis and treatment of central nervous system diseases have been developed from the theranostics position [80]. Our studies of molecular markers in ischemic and hemorrhagic strokes have revealed individualized changes in their serum level during the disease course [81, 82].

Conclusion

Literature data analysis demonstrates the positive results of implementing personalized medicine principles in the prevention, diagnosis and treatment of critically ill patients. Creation of biobanks, development of training programs and regulatory documentation, intensification of scientific research, introduction of new diagnostic and therapeutic methods will promote the implementation of personalized medicine principles in practical health care.

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