ISSN: 2158-284X Volume 13, Number 1, January 2022

Scientific Research Publishing

International Journal of Clinical Medicine

ISSN: 2158-284X

https://www.scirp.org/journal/ijcm

Journal Editorial Board

ISSN: 2158-284X (Print) ISSN: 2158-2882 (Online)
https://www.scirp.org/journal/ijcm

International Journal of Clinical Medicine, 2022, 13, 1-65
https://www.scirp.org/journal/ijcm
ISSN Online: 2158-2882
ISSN Print: 2158-284X

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Volume 13 Number 1 January 2022

International Journal of Clinical Medicine (IJCM)
Journal Information

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International Journal of Clinical Medicine, 2022, 13, 1-21
https://www.scirp.org/journal/ijcm
ISSN Online: 2158-2882
ISSN Print: 2158-284X

The Pathogenetic Concept of the Diagnostic-Treatment Approach for Patients with Purulent-Septic Complications

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How to cite this paper: Ostapiuk, L. (2022) The Pathogenetic Concept of the Diagnostic-Treatment Approach for Patients with Purulent-Septic Complications. *International Journal of Clinical Medicine*, **13**, 1-21.
https://doi.org/10.4236/ijcm.2022.131001

Received: November 15, 2021
Accepted: January 7, 2022
Published: January 10, 2022

Abstract

Background: The significant improvement of immediate and long-term functional results of treating patients is the fundamental problem of modern medical science. A deep understanding of the pathogenesis is the key point in creating the management strategy for patients with various diseases. Information about the mechanisms of origin and development of purulent-inflammatory diseases and sepsis is essential for finding effective ways to prevent and treat them. **The aim of the research** is to use the method of fluorescence spectroscopy in creating the pathogenetic diagnostic and treatment model for the prevention and treatment of purulent-inflammatory diseases and sepsis, modification of treatment tactics, search for new markers of purulent-septic diseases, as well as monitoring of patients during the treatment. **Materials and methods:** The proposed approach, along with standard diagnostic methods, was used to organize the treatment process of 100 patients with purulent-inflammatory diseases, including 15 patients with sepsis, 35 with acute inflammatory abdominal pathology, 20 patients with burn injury (main group) and 35 patients with burn injury (comparison group). **Results:** The behavior of spectral-fluorescent characteristics in their dynamics has been studied, and the new markers for assessing patients' conditions have been proposed. Their effectiveness for the diagnosis of purulent-septic diseases has been proved, which advances the results of standard research methods by 24 - 48 hours. **Conclusions:** The proposed diagnostic and treatment approach is fundamentally important for diagnosis and monitoring during the treatment of patients with purulent-septic diseases. Particularly relevant is the proposal to modify the treatment process for these patients, associated with the use of infusion of donor albumin solutions.

Keywords

Purulent-Inflammatory Diseases, Sepsis, Pathogenetic Diagnostic and Treatment Model, Method of Fluorescent Spectroscopy, Albumin Infusion

1. Introduction

Over the last thirty years, much attention has been paid to the diagnosis and treatment of sepsis. Significant efforts of researchers were focused on the specific features, clinical characteristics and nature of the disease. At the same time, insufficient attention was paid to the pathogenetic assessment of the occurrence and development of purulent-septic complications. The issues of sepsis diagnosis, especially its monitoring and treatment, have not been resolved adequately. They require detailed justification as well as the quick and adequate solution by using modern scientific approaches. Particular attention should be paid to the problem of optimizing the treatment tactics and the effective monitoring of patients during the treatment. Significant efforts in this research within the proposed pathogenetic concept will be focused on the study of blood serum (BS) of surgical patients and patients with burn injury.

2. Literature Review

According to the WHO, sepsis is the dangerous dysfunction of the internal organs caused by dysregulation of the body's response to infection. Three conciliation conferences on the problem of sepsis have been held (1991, 2001, 2016) in order to discuss new strategies to solve it. Over this time, the definition of sepsis and septic shock has changed three times; periodically the international intensive care protocol was updated with the participation of dozens of leading organizations and experts [1].

In May 2017, the 70th session of the World Health Assembly adopted a resolution on sepsis. According to it, the primary attention should be focused on improving early diagnosis, finding new markers and improving treatment tactics and monitoring of patients. The changes in the definition of sepsis over the past 30 years and the main approaches to solving this problem are described in detail in the research [2]. Sepsis occurs when the body's response to the infection causes damage to its own tissues and organs and can cause the significant deterioration of the patient's condition and even his death. It is estimated to affect more than 30 million people each year and can kill 6 million people [3]. This problem is quite typical for low- and middle-income countries. According to the WHO, sepsis occurs annually in 3 million newborns and 1.2 million of children [4]. One of ten maternity deaths is due to obstetric sepsis. 95% of maternal sepsis deaths occur in low- and middle-income countries [5]. Thus, this is a global problem that requires the adoption of the effective strategy to solve it.

At the same time, since 2001, at the suggestion of Professor I. Herych (Lviv,

Ukraine), a series of studies of BS of patients with purulent-inflammatory diseases and sepsis was started within the method of fluorescence spectroscopy (MFS) [6] [7] [8] [9]. It is the most universal method in biological spectroscopy.

MFS is now successfully used in the medical practice for conducting up-to-date prospective studies based on the latest developments in molecular biology. They allow identifying certain genetic mutations in humans and their individual predisposition to the development of certain pathological conditions. The results of these studies open the way to the successful development of "personalized medicine". It means that it is possible to identify the individual risk of certain diseases for each individual and appropriate measures to prevent the possibility of their occurrence and progression. This opens vast opportunities for finding effective drugs, the so-called "gene therapy", which offers broad prospects for the treatment of various diseases, including cancer.

The method of fluorescence spectroscopy is successfully used for diagnosis in oncohematology to detect genetic mutations that cause an increased susceptibility of the human body to myeloproliferative disease [10], for the diagnosis of polycythemia and other myeloproliferative diseases, including in the dynamics [11], the study of acute lymphoblastic leukemia in children, chronic myeloid leukemia, acute promyelocytic leukemia [12], for the acute myeloid leukemia [13]. If there is a genetic mutation, the course of cancer is more aggressive. This method has also been well established for detecting genetic mutations in prothrombin and Leiden coagulation factor V, which cause an increased susceptibility of the human body to venous thrombosis, which is one of the most common vascular diseases [14].

In the framework of this research, MFS provides the study of the spectral-fluorescent characteristics of BS of patients with pyo-inflammatory diseases and sepsis, when excited BS by light with a wavelength of 280 nm. The choice of this wavelength is associated with the excitation in this area of human serum albumin molecules, which undergo conformational changes in patients with purulent-inflammatory diseases. After the preliminary study and the interpretation of the results in patients with sepsis, the study of the fluorescence spectra (FS) of BS of women with postpartum purulent-inflammatory diseases was conducted in order to prevent the occurrence of obstetric sepsis [15] [16] [17] [18]. The next step was to study the FS of BS of patients with burn trauma, which are model objects for studying the spectral-fluorescent characteristics of patients with sepsis [19]. Understanding the pathogenesis of sepsis is the key point in finding effective ways to prevent and treat it. It develops when the body's response to infection leads to damage to its own organs and tissues and can lead to significant deterioration in health and even death of the patient [20] [21].

The aim of our research is directed at performing the basic tasks of the WHO and applying a pathogenetic diagnostic and treatment model within the MFS for the diagnosis, treatment and prevention of purulent-inflammatory diseases and sepsis.

3. Data and Methodology

3.1. Data Source

The study of the BS of 100 patients with inflammatory abdominal pathology and sepsis who during 2001-2008 were treated in the purulent-septic center of Ambulance Hospital in Lviv were done. Among them, 42 (42%) were patients with aseptic pathology, 43 (43%) patients with preseptic pathology and 15 (15%) patients with sepsis. The BS of 20 patients with burns were examined during 2015-2019. They were treated at the Centre for Thermal Trauma and Plastic Surgery of 8th Clinical Hospital of Lviv. The comparison group consisted of 35 patients with severe burn injuries. The control group included 40 healthy individuals aged 21 to 55 years, with a mean age of 36 ± 1.24 years. The luminescent laboratory of the department of experimental physics at the Ivan Franko National University of Lviv provided experimental data.

Research methods: general clinical, laboratory (general blood and urine tests, biochemical blood test), instrumental examinations (electrocardiogram, X-ray, ultrasound examinations, if necessary, computed tomography (CT) or magnetic resonance imaging (MRI). In addition to standard research methods, the BS of all patients were also examined by the MFS on admission to the hospital and in the dynamics during the treatment. The measurements were performed using the aperture monochromators MDR-2 and MDR-12.

The source of excitation was the deuterium lamp DDS-400. The objects of the study were samples of BS of patients of the main and control groups. Excitation of the BS was carried out at a wavelength of 280 nm, which corresponds to the glow region of human serum albumin. Based on the obtained results for the spectral-fluorescent characteristics of their BS, possible mechanisms of sepsis occurrence and prognosis regarding its prevalence and methods of treatment are proposed and discussed. The main studied indicators were the fluorescence intensity (I_F) and the presence of a change in the position of the SF maxima (λ_{max}). The characteristic long-wave shift and the corresponding septic peak which can be found only within MFS are revealed.

3.2. Research Results

3.2.1. Pathogenetic Concept of Diagnostic and Treatment Model of Purulent-Inflammatory Diseases and Sepsis

The tactics of previous studies about sepsis were directed to the detailed external assessment of the visual state of the body. Therefore, traditional schemes were used in the treatment. At the same time, insufficient attention was paid to the microscopic processes occurring in the body of patients, in particular in the blood of patients with sepsis. Thus, this did not lead to the improvement of traditional treatment regimens. Even when conducting the biochemical analysis of blood to determine protein fractions and albumin levels, it was impossible to detect real changes in its structure in patients with purulent-septic complications. Therefore, to clarify these changes at the molecular level, it was expedient

to analyze in detail the changes in the structure of the BS in patients with these diseases. So, it was necessary to develop a new pathogenetic concept for sepsis.

Albumin molecules constantly perform transport and detoxification functions in the human body. At the same time, due to changes in the conformation of its molecule, albumin interacts with hydrophobic molecules of endotoxins, absorbs them and promotes excretion from the body. In the presence of endogenous intoxication in the body of patients with purulent-inflammatory diseases and sepsis, the interaction of albumin molecules with the products of bacterial metabolism due to the ability of albumin molecules to complex takes place. The total number of albumin molecules remains constant. At the same time, the number of complete albumin molecules in the serum samples decreases [2]. This leads to the disruption of the patient's body and requires timely implementation of effective treatment measures. However, in previous studies, the above was not taken into account, and it was not definitively clarified what this leads to. In this case, the system of albumin molecules is actually transformed into a disordered system. This requires finding possible ways to preserve the vital functions of the organism in such pathological conditions. The pathogenesis of this phenomenon has not been analyzed in our previous research [2] [6] [7] [8] [9]. Only a deep understanding of the above processes has led to the creation of the pathogenetic concept and the unconventional decision: if the complete albumin when approaching the septic state becomes less and less, so it is advisable to conduct exogenous infusions of albumin in order to replenish reserves of the body. At the same time, it is also advisable to continue traditional treatment: surgical, etiotropic (antibacterial) and symptomatic. Besides, the infusion of exogenous albumin can properly provide pathogenetic therapy while maintaining the amount of complete albumin capable of performing its basic functions. At present, it seems that this is too simple and clear solution. Attention should be paid to the importance of using physical research methods in medical practice, in particular MFS. Within the framework of MFS the fundamental changes in the spectral-fluorescent characteristics of the patient with sepsis were detected for the first time in 2001-2002. It was connected with the changes in the structure of albumin molecules in patients with this disease [2] [6] [7] [8] [9]. Two aspects of the problem of sepsis are very important: the possibility of its early diagnosis and adequate assessment of the risk of disease progression.

The above studies did not pay enough attention to in-depth pathogenetic understanding of the processes that occur in the human body in patients with purulent-septic complications at the molecular level and which were first registered within the MFS. In further research by us, taking into account the above results, the **pathogenetic concept of diagnostic and treatment model of purulent-inflammatory diseases** and sepsis was proposed. It is based on the fact that albumin molecules have the ability to complex. In the diseases which are accompanied by endogenous intoxication, part of the albumin molecules in the blood of patients are blocked by toxins. As a result, there are two types of albumin molecules in their blood: normal (concentration: X) and blocked by toxins/

pathological (concentration: $1 - X$). So, pathological albumin molecules lose the ability to perform their basic functions, namely transport and detoxification. Our proposed pathogenetic concept enabled us to understand better the processes of origin, course and treatment of sepsis.

The new definition of sepsis is to define X^*, *i.e.* the maximum minimum value of the concentration of albumin in patients with sepsis. If X is more than X^*, this ensures the viability of the organism to some extent. Then at X less X^*, exitus letalis develops. With increasing the severity of the condition of patients the possibility of synthesis of endogenous albumin in their bodies significantly reduces. In order to prevent a decrease of X, it is necessary for patients in severe condition to carry out an infusion of exogenous albumin solution to support properly the body's vital functions. During treatment, the amount of toxins in the blood of patients gradually decreases. This allows us to cancel the infusion of the donor albumin solution at a certain time. At the same time, the process of endogenous albumin synthesis is gradually normalized [15] [16] [19].

It is proposed to use MFS for diagnosis, monitoring and correction of the treatment process. The main characteristics which we study with this method are the fluorescence intensity (I_F) and the position of the maximum fluorescence band ($\lambda_{\max}$) of the BS. The main characteristics for the patients with purulent-septic complications are $I_F(X)$ and $(\lambda_{\max})(X)$. They depend on X and are determined by the following interpolation ratios for a mixture of normal and pathological proteins in the BS:

$$I(X) = I_F^a * X + I_F^t * (1 - X)$$

$$\lambda_{\max}(X) = \lambda_{\max}^a * X + \lambda_{\max}^t * (1 - X) \quad (1)$$

They describe the corresponding characteristics for normal (I_F^a, $\lambda_{\max}^a$) and pathological (I_F^t, $\lambda_{\max}^t$) albumin molecules. We also present the ratio between the lowest excited and main states and the corresponding positions of the maxima of the fluorescence bands of the BS ($\lambda_{\max}$) of normal and pathological albumin molecules. We also present the relationship between the energy differences ΔE_a and ΔE_t between the lowest excited and main states and the corresponding positions of the maxima of the fluorescence bands of the BS ($\lambda_{\max}^a$, $\lambda_{\max}^t$) of normal and pathological albumin molecules.

$$\Delta E_a = hc/\lambda_{\max}^a \; ; \quad \Delta E_t = hc/\lambda_{\max}^t \; . \quad (2)$$

where h, c, accordingly, the Planck constant and the speed of light.

Now let us focus on the most interesting of our results obtained within the MFS for patients with sepsis. The introduction of new methods of diagnosis and treatment has always been the driving force of progress in medicine. For such a search to be successful, a scientific approach, a clear statement of the task and hard work were required. To assess the possibilities of using MFS in medical practice, a series of experiments "models of the disease in vitro" was performed [2] [7] [18] [22]. As the result of a thorough analysis of the obtained results, clear trends in the spectral-fluorescent characteristics of the BS were observed.

They were likely to be present in patients with various pathological conditions and could describe changes under the influence of therapeutic measures. Understanding of these patterns and capabilities of MFS made it possible to select patients with such pathologies, in which the changes in the FS of the BS were noticeable and at the same time specific for each of them.

MFS is extremely sensitive method, so its use is promising in the practice of health care facilities. For the successful implementation of this method, it is advisable to create portable devices for measurement of FS of BS of patients and ensure their availability in the health care facilities of research institutions. In order to implement successfully the use of this method in practice, it is necessary to create a database of spectral-fluorescent characteristics of the BS and urine of healthy people; study of the dependence of the spectral-fluorescent characteristics of their BS and urine depending on age, sex, the history of diseases; study of the correlation of the results obtained within the study of MFS, with the data of other laboratory and instrumental methods of diagnosis; conducting a series of new experimental studies to assess the suitability of MFS for diagnosis in surgical and obstetric practice. It is also necessary to create a database of the behaviour of the spectral-fluorescent characteristics of the BS of patients with different diseases of varying severity, including the dynamics on the background of treatment.

3.2.2. Study of Serum Fluorescence Spectra of Donors

The control group in this study was 40 healthy person without chronic diseases, donors aged from 21 to 55 years, whose average age was 36 ± 1.24 years. All of them did not have complaints about their health and did not have any chronic diseases. Among the members of this group were students of high educational institutions, interns, as well as persons who underwent periodic medical examinations (physicians, teachers, workers of the food industry). When people were included in the control group, screening was performed by laboratory examination (general blood test, blood sugar test, general urine test and some biochemical parameters of blood, total protein, bilirubin, urea). Persons who were found to have abnormalities, respectively, were referred to specialists for further examination, and were not involved in the control group.

FS and fluorescence excitation spectra (FES) of BS of donors and 20% donor albumin were studied. Fluorescence intensity was maximal when BS was excited by light with λ_{ex} = 280 nm, which corresponds to the natural glow of the tryptophan amino acid residue of albumin, and much lower at λ > 300 nm. Upon excitation of BS and 20% donor albumin in the region of 250 nm < λ < 280 nm FS of BS look like a λ-type curves in the region of 300 nm < λ < 450 nm.

The graphical depiction of the results of the study of the FS of donors and of 20% donor albumin is depicted in **Figure 1**. FS for these objects were found to be quite similar, although the fluorescence band of the donor is slightly wider than the fluorescence band of 20% donor albumin. The position (λ_{max}) of the fluorescence band of the donor depends on his age.

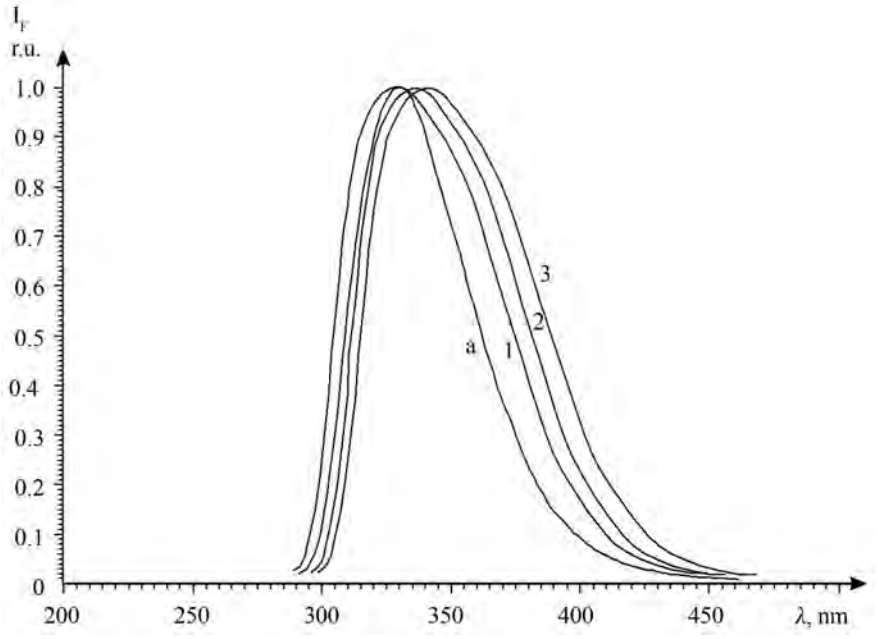


Figure 1. Fluorescence spectra of donor serum (1 - 3) and 20% donor albumin (a) (λ_{ex} = 280 nm).

In particular, λ_{max} = 328 nm corresponds to the FS of BS of young donors (1), depicted in **Figure 1**, 342.57 nm—for seniors (3), 337 nm—for the reference donor (2) and λ_{max} = 330 nm—for 20% donor albumin. It is established, that with age there is a slight shift of λ_{max} of FS BS to the long-wavelength region. The long-wavelength shift of the fluorescence maximum is probably connected with the influence of other components of the BS. The obtained results, as well as the results of the study of "*in vitro* disease models" proved the possibility of using 20% donor albumin as a standard in the study of FS of BS of patients with various diseases.

3.2.3. Study of Spectral-Fluorescent Characteristics of BS of Patients with Sepsis

The main task of this section is to study the feasibility and effectiveness of using MFS as an express highly sensitive method of diagnosis, especially early, of sepsis and purulent-inflammatory diseases. For this purpose, FS and FES of BS of donors and patients with sepsis were studied. Very important for us are the results of the study of the spectral-fluorescence characteristics of 20% donor albumin, as well as dilutions of BS with distilled water and 20% donor albumin.

The task of our research is qualitatively different from the approach used in [23]. The authors of the research, presented and discussed in [23], in their study focused on the search of specific spectral-fluorescent quantitative changes in the presence of various pathologies of physiological parameters of the organism, while we focused on the detection of spectral-fluorescent signs of pathognomonic for sepsis and purulent-inflammatory diseases constellation "serum of bacteria", *i.e.* the phenomenon of bacteremia [6].

FS were studied after exciting the BS with the light $250 \le \lambda_{ex} \le 280$ nm. Such studies were based on our hypothesis [6] about the appearance of special "bacterial proteins" in patients with purulent-septic complications, which occur during the interaction of bacteria and products of their life cycle with albumin [24].

In the study of the spectral-fluorescence characteristics of BS in patients with purulent-septic complications, two probable qualitatively significant tendencies were recorded, namely: the shift of fluorescence band maxima for patients with pre-septic pathology and sepsis in long-wave region and a significant reduction in their intensities (maximum up to 70% - 80%) of the donor unit. Both vectors of change had no correlation with the standard laboratory-biochemical parameters of conventional control of these patients, but correlated properly with the integrated clinical criteria for the severity of the patient's condition and the phenomenon of verified bacteraemia.

The revealed changes in the spectral-fluorescence characteristics of BS in patients with sepsis in most cases were preclinical in nature: they were usually recorded 24 - 48 hours before the appearance of obvious clinical and laboratory signs of a significant change in the general somatic status of patients [25]. At the same time, the structure of the FES of donors and patients with sepsis is generally similar, but the patient's intensity of the excitation spectra is much lower than that of the donor.

In vivo studies include the study of the spectral-fluorescent characteristics of BS of patients with purulent-inflammatory diseases and sepsis. Three main scenarios for the development of sepsis have been identified and described [2] [9]. We will dwell on two of them in more detail (**Figure 2** and **Figure 3**). The results of study of the BS of donor and a patient with severe sepsis caused by purulent epiduritis of the lumbosacral spine and massive retroperitoneal pelvic phlegmon, which was treated in Emergency Hospital from 28.12.2001 to 15.04.2002 are depicted in **Figure 1** and **Table 1**.

At the time of hospitalization, a critically difficult condition of the patient and verified bacteremia (blood seeding at the time of hospitalization: Staphylococcus aureus). In the BS of this patient, a long-wave peak (λ_{max} = 380 nm, I_F = 0.3) (curve 1) was detected, which was associated mainly with the glow of "pathological" albumin molecules [2] [7] [15] [22]. This curve also has a small peak in the region 335 nm. It is associated with the glow of full-fledged albumin molecules and indicates a certain resource for the survival of the patient in such a serious

Table 1. Changes in the spectral-fluorescent characteristics of the serum of a patient with sepsis.

N	*d*	1	1'	1'	2	3	4	5
Date	28.12.	28.12.	02.01.	02.01.	04.01.	12.02.	19.03.	04.06.
λ_{max} nm	340	380	380	345	345	337	349	340
***I*, r.u.**	1.0	0.3	0.09	0.15	1.07	0.46	0.39	0.79

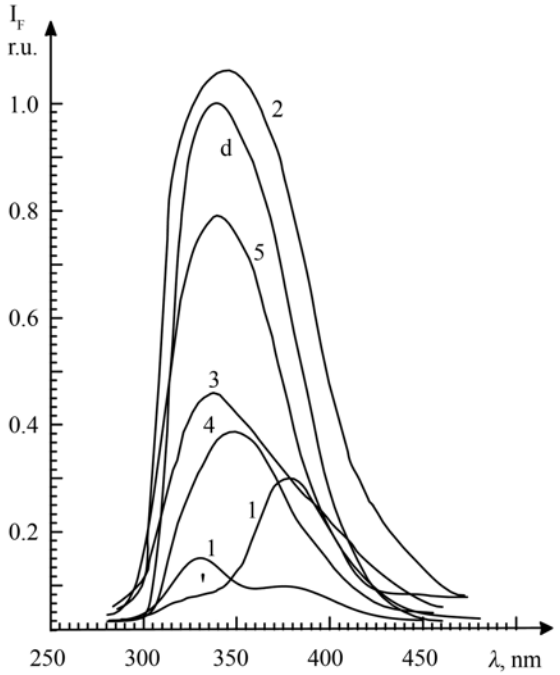


Figure 2. Fluorescence spectra of serum of the person with sepsis who was treated in Emergency Hospital in 2001-2002: 1—28.12.2001; 1'—02.01.2002; 2—04.01.2002; 3—12.02.2002; 4—19.03.2002; 5—04.06.2002 and donor blood serum (d). λ_{ex} = 250 nm (340 nm—"normal peak", 380 nm—"septic peak").

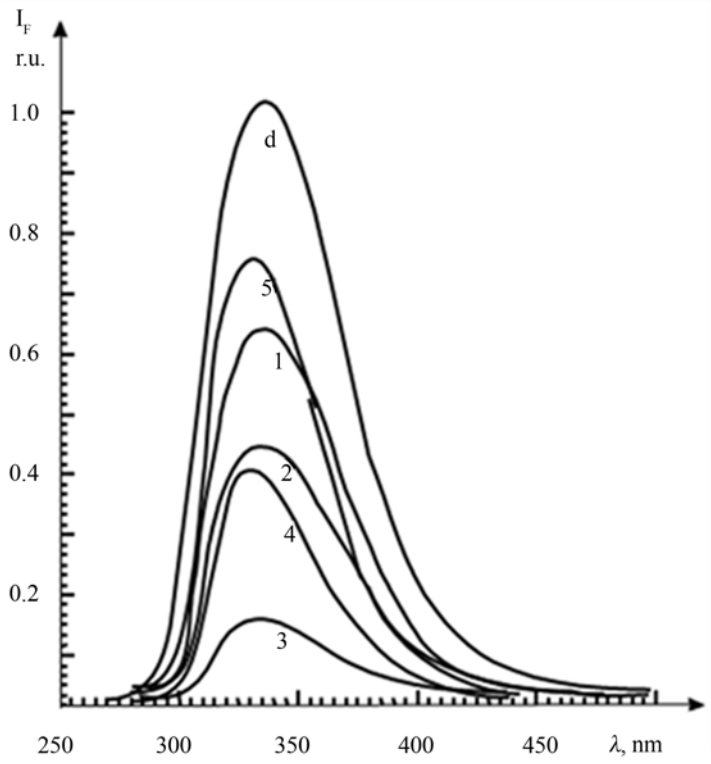


Figure 3. FS of BS of the patient with sepsis-epiduritis, was treated in Emergency Hospital in 2001-2002: 1—03.06; 2—05.06; 3—06.06; 4—07.06; 5—10.06 and donor of BS. λ_{ex} = 280 nm.

condition. As the result of the in-depth analysis of the situation described above, we modelled the behaviour scenario of FS of BS (growth of X) at 02.01 (curve 1'). The right maximum of this curve indicates a decrease in the concentration of pathological albumin, and the left shows an increase in the concentration of complete albumin in the blood of this patient.

FS of BS of patients in septic condition has a complex nature of behaviour. In particular, in the severe state, it has a two-peak structure (curves 1, 1', which reflects the presence of two varieties of albumin molecules in the BS). **Figure 2** made us possible to illustrate the successful outcome of treating, *i.e.* the patient with sepsis who was admitted to the hospital in a very serious condition. She underwent a complete clinical and laboratory examination, she was prescribed antibiotic therapy and infusion therapy in a volume of 8 - 10 litres daily. At the same time, the results of standard clinical and laboratory data were not informative enough. The patient underwent a thorough examination and surgery to remove the source of infection in the body (massive retroperitoneal pelvic phlegmon, which caused sepsis-epiduritis). Complex infusion, antibacterial, anti-inflammatory therapy was also prescribed, which contributed to the progression of this patient. Undoubtedly, this was facilitated also by her young age (33 years) and the absence of comorbidities. It is also important to note that the survival of this patient in such a serious condition was possible due to $X > X^*$. In this case, although the patient was admitted to the hospital not at the stage of formation of the septic condition, but against the background of its manifestation, MFS helped us to detect septic peak in the long-wave region (**Figure 2**, curve 1) and choose rational treatment tactics.

The suppression of bacteremia helped to reduce the number of pathological albumin molecules in the patient's blood. This in turn contributed to the process of restoring the synthesis of endogenous albumin by the liver. In the next measurement of FS of BS 4.01., (**Figure 2**, curve 2) significantly and at first glance unexpectedly increased the intensity of this band (1.07 * I_F). In fact, this process was expected.

At $X \rightarrow X^*$ the peak in the region of 380nm will increase and shift to the long-wavelength region until exitus letalis occurs. In the process of recovery, the "right" peak will decrease and gradually disappear, and the "left" curves 1, 1') gradually increases and slightly shifts to the shortwave region. The above-mentioned possible reorganization of the patient's BS in a severe condition (curve 1, and in the process of recovery curve 1', respectively) may be associated with increased bacteremia, as well as, accordingly, with a positive effect on the patient's health of treatment. Due to the subcompensated changes in the absolute quantitative and qualitative content of BS proteins at the time of the examination (biochemical studies showed total protein and protein fractions at the lower limit of normal), the rapid increase in the fluorescence band of the patient's BS cannot be interpreted by absolute hypoproteinemia, which is inherent in the fluorescence of proteins. The only possible explanation for the above phenomenon of increase in the fluorescence band of the patient's BS fluorescence may be the presence of

daily pre-infusion 8 - 10 liters during this treatment period [6] [7] [26]. Under these circumstances, a regular increase in the fluid component of the BS leads to pseudogipoproteinemia, *i.e.* a laboratory phenomenon that does not manifest with standart biuret reaction and can only be differentiated from true hypoproteinemia by a special Phillips and van Slyke technique (see [6] [7]). In our opinion, the forced excess therapeutic dilution of blood during this period caused the quenching of the fluorescence of the BS of the patient and led to the increase of the intensity of the fluorescence bands of her BS. Undoubtedly, the decrease of septic symptoms had a significant impact on the increase of the fluorescence band intensity of the BS (curve 2). Our in vitro studies of the spectral-fluorescence characteristics of standard dilutions of the donor BS with distilled water (DW) confirmed the correctness of the explanation of the reported phenomenon of the increase in the fluorescence band intensity of the BS of this patient (**Figure 2**, curve 2) [22]. Besides, the decrease in the content of BS in the samples after the addition of distilled water also led to a significant increase in the intensity of fluorescence bands. Subsequent studies of the fluorescence spectra of this patient showed, that, *i.e.* bacteremia was not completely overcome (**Figure 2**, curves 3, 4), although the long-wave septic peak disappeared, because the number of pathological albumin molecules has significantly decreased. At that time, the patient's body continued to compete between bacteremia and the compensatory capabilities of her body in combination with comprehensive treatment measures. Only the further long process of treatment under the influence of complex therapy led to the significant suppression of bacteremia and the significant improvement in the patient's condition (**Figure 2**, curve 5). At the time of the treatment of this patient the pathogenetic model had not been developed yet. Therefore, unfortunately, she was not prescribed infusion therapy with donor albumin solution. We are convinced that this procedure could significantly accelerate the process of recovery of this patient. During the treatment of patients with severe sepsis, it is necessary to examine more often samples of BS of patients in order to prevent their transition to the state $X < X^*$. In this case, it would be possible to reproduce in detail the change in the FS of patients in the state $X \to X^*$, but only at $X > X^*$. Such studies without the use of donor albumin infusions in the treatment process and with its use would help to improve our knowledge about the possibilities of optimizing the treatment process for patients with sepsis. After leaving the septic state (**Figure 2**, curves 3 - 5) during recovery, the I_F gradually increases, slightly shifting to the short-wave region. Rather interesting is the study of the behaviour of spectral-fluorescent characteristics of patients with sepsis in the case of using donor albumin infusions in the process of treatment.

Taking into consideration that $h = 6.62 \times 10^{-34}$ Joule·second, $c = 2.99 \times 10^{8}$ m/second, $\lambda^{t}_{\max} = 380$ nm and $\lambda^{a}_{\max} \approx 330$ nm (small peak of curve 1, **Table 1**), 1 eV = 1.6×10^{-19} Joule, 1 nm = 1×10^{-9} m, on the basis of (2) we obtain

$$\Delta E_t = 3.25 \text{ eV}, \quad \Delta E_a \approx 3.75 \text{ eV} \tag{3}$$

So, $\Delta E_a \geq \Delta E_t$.

Very interesting were the results of the study of FS of BS of another patient with purulent epidural lumbar spine, complicated by sepsis, who was treated in Emergency Hospital in June 2002. A significant difference between the two cases is following. For this patient, because of the timely hospitalization and early surgical elimination of the source of infection, the progress of the septic process was much easier, which was significantly reflected in the dynamics by the changes of spectral-fluorescence characteristics (Figure 3, Table 2).

Analyzing the results, depicted in this figure, we can observe, that after the elimination of the source of infection on the background of intensive antibiotic therapy in patient with clinically mild sepsis for a certain period there was bacteremia (blood seeding 3-6.06.2002, *Kl. pneumoniae*). Five blood samples were taken for FS testing. The dynamics of FS of BS for this patient were slightly different than for the first patient: the decrease of the intensity of fluorescence bands reached maximum (0.15 I_F) only at the end of the bacteremic period (Figure 3, curves 1 - 3). At the same time, in this case, there was no significant shift of the fluorescence bands of the BS. It is possible, that in this case, the easier course of the septic process is connected with timely elimination of purulent-septic focus of infection. Subsequently, with the gradual recovery of the patient there was a significant increase in the fluorescence intensity of the BS up to 0.75 I_F (Figure 3, curve 5).

The comparison of the results of the study of FS of BS and the clinical features of sepsis in the first and second discussed above cases gives background to conclude about the similar nature of the dynamics of recovery in the "postbacterial" period. At the same time, the study of the spectral-fluorescent characteristics of the BS of these patients, in contrast to conventional methods of clinical and laboratory assessment of patients, allowed us to trace clearly the nature of the disease to recovery.

The above results indicate the main most likely scenarios of sepsis. The dynamics of changes of the spectral-fluorescent characteristics of the BS of patients with sepsis objectively reflects the clinical features of the disease, which significantly depends on the quality of diagnosis and correlates with the effectiveness of treatment tactics.

Thus, according to our studies of the BS of patients with sepsis, the decrease of intensity and shift of the fluorescence band are connected with the presence of advanced septic process and correlate with integrated indicators of clinical severity and bacteremia. The dynamics of changes of the spectral-fluorescent

Table 2. Changes in the spectral-fluorescent characteristics of the serum of a person 2 with sepsis.

N	*d*	1	2	3	4	5
Date	03.06	03.06	05.06	06.06	07.06	10.06
λ_{max} **nm**	336	336	334	333	330	331
***I*, r.u.**	1.0	0.64	0.44	0.16	0.41	0.76

characteristics of BS of these patients quite objectively reflect the course of sepsis and correlate with the effectiveness of treatment tactics.

The results of the study of FS of BS of patients with inflammatory abdominal pathology are depicted in Figure 4 and Figure 5. Some of the curves in these figures for patients in severe condition (in particular, for patients with acute pancreatitis and cirrhosis) have the two-peak structure, which is connected with the presence in their BS of two types of albumin molecules, normal and pathological in significant quantity.

One of the fundamental problems of modern medicine is the significant improvement of the immediate and long-term functional and cosmetic results of surgical treatment of patients with burns. Fundamentally important at the initial stage of the treatment process is the timely restoration of the skin after injury, when patients are not yet exhausted by the long treatment process, and the regenerative properties of the body are still preserved. It is advisable to use lyophilized xeno-implants saturated with silver nanocrystals in order to close burn wounds after their thorough cleaning under general anesthesia [27] [28]. In this case, it is also recommended to activate them with bio-galvanic current, when using auto-, xeno- and dermo-implants [29].

On the background of EI, which occurs in patients with burn injury, tissue repair in the area of inflammation and restoration of homeostasis is sharply complicated. Thus, special attention should be also paid to the problem of complications of burns: sepsis. Taking into account the above results of the study of septic complications in surgical practice, we consider it appropriate to take into

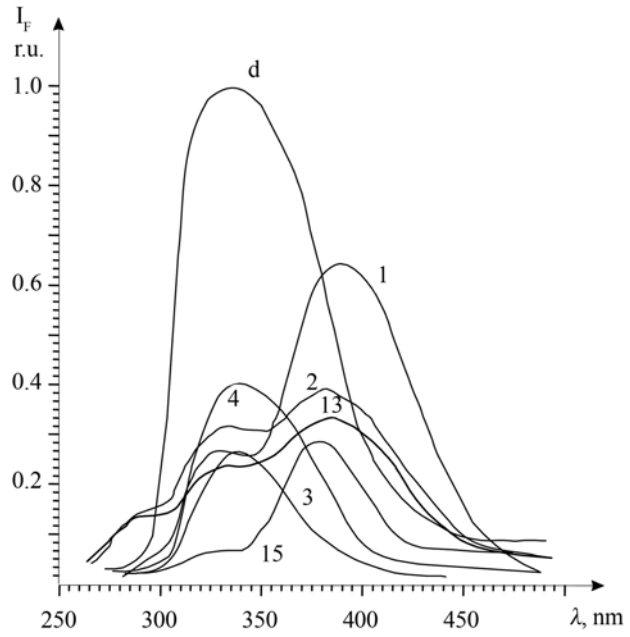


Figure 4. Fluorescence spectra of blood serum of patients with: (a) Acute pancreatitis: 1—12.02.2002; 2—12.02.2002; 3—7.06.2002; 4—19.03.2002; (b) Cirrhosis: 13—12.02.2002; (c) Sepsis: 15—28.12.2001, who were treated in Emergency Hospital in 2001-2002, and donor blood serum (d); λ_{ex} = 280 nm.

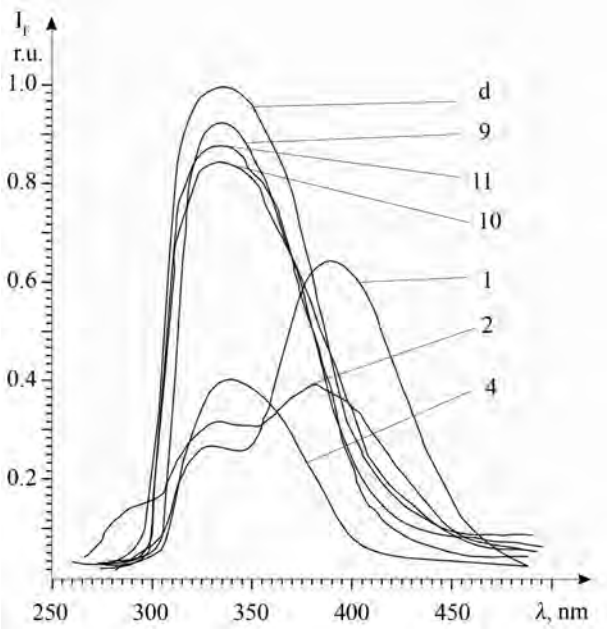
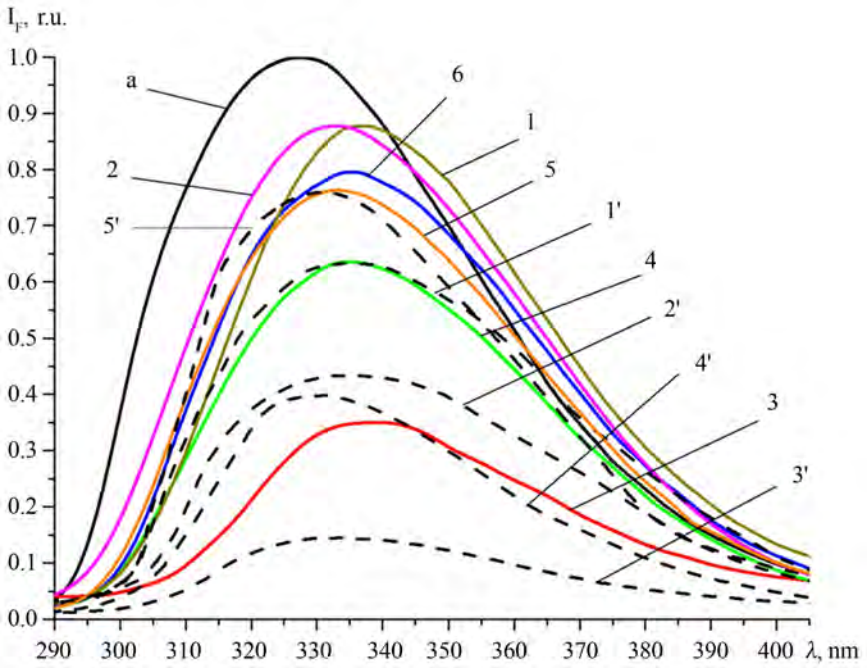


Figure 5. Fluorescence spectra of blood serum of patients with pancreatitis: 9—7.06.2002; 10—4.01.2002; 11—4.01.2002; 1—12.02.2002; 2—12.02.2002; 4—19.03.2002 and donor blood serum (d); λ_{ex} = 280 nm.

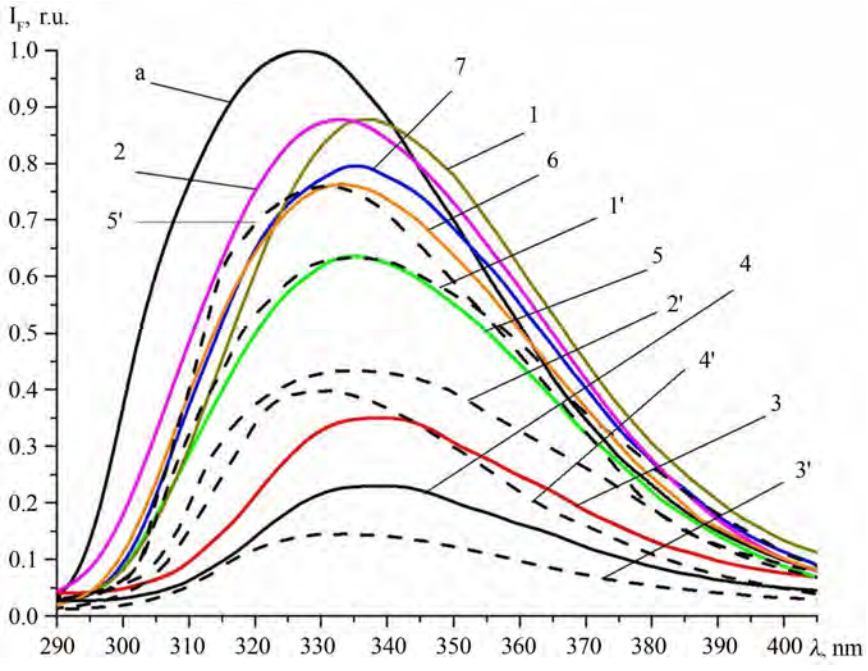
account changes at the molecular level that occur in patients with burn injuries in the case of occurrence of purulent-septic complications. In fact, severe patients with burn injuries can be the model objects during the study of septic conditions in medical practice. The timely verification of sources of infection, reliable diagnosis within the MFS and adequate treatment of patients with burn injuries can prevent their transition to the septic condition [19].

Now we shall illustrate the results of the treatment of one of the patients with the severe burn injury using the approach, proposed by us in this manuscript within the MFS. The results of studies in the dynamics of FS of BS and data for the spectral-fluorescence characteristics of the BS of patient with burn injury, who was admitted to the hospital on the 27th of June, 2015 with the area of the burn surface 38%, are depicted on **Figure 6(a)** and **Table 3(a)**.

In order to compare the spectral-fluorescent characteristics of the BS of patients with burn injury, we shall also present in the relevant figures the results of the spectral-fluorescent characteristics of the patient with sepsis, who recovered after successful treatment (**Figure 3**). Staphyloccus aureus 10^5 and Pseudomonas aeruginosa 10^6 were verified in this patient on the basis of the microbiological study. He was immediately prescribed appropriate treatment, including antibiotic therapy and infusion therapy with a volume of 2 - 3 liters daily. Due to the infusion therapy, the intensity of FS of BS compared with the fluorescence intensity of albumin (I_F = 1.00) did not decrease significantly for several days (I_F = 0.88), which correlates with the results of in vitro studies [2] [22]. At the same time, no significant shift of the FS of BS into the longwave region was recorded, despite the verification of several pathogens. At the same time, no significant



(a)



(b)

Figure 6. (a) FS of BS of the patient with burn injury, who was hospitalized at Lviv's Communal Clinical Hospital No. 8 in 2015 in dynamics during the treatment (1—3.07, 2—8.07, 3—13.07, 4—17.07, 5—20.07, 6—24.07) and a patient with sepsis (1'—03.06, 2'—05.06, 3'—06.06, 4'—07.06, 5'—10.06), who was treated in 2002 in Ambulance hospital and 20% albumin solution (b), λ_{ex} = 280 nm. (b) FS of BS of the patient with burn injury, who was hospitalized at Lviv's Communal Clinical Hospital No. 8 in 2015 in dynamics during the treatment (1—3.07, 2—8.07, 3—13.07, 4—17.07, 5—20.07, 6—22.07, 7—24.07) and a patient with sepsis (1'—03.06, 2'—05.06, 3'—06.06, 4'—07.06, 5'—10.06), who was treated in 2002 in Ambulance hospital and 20% albumin solution (b), λ_{ex} = 280 nm.

Table 3. (a) Spectral-fluorescence parameters fluorescence intensity (I_F) and the position of the maximum (λ_{max}) of the fluorescence band of the patient. (b) Spectral-fluorescence parameters fluorescence intensity (I_F) and the position of the maximum (λ_{max}) of the fluorescence band of the patient.

(a)

N	*a*	1	2	3	4	5	6	1'	2'	3'	4'
Date	3.07	3.07	8.07	13.07	17.07	20.07	24.07	03.06	05.06	06.06	07.06
λ_{max} nm	327	336.1	332.2	341.1	335.1	333.1	335.1	335.2	335.2	334.1	331.6
***I*, r.u.**	1	0.88	0.88	0.35	0.64	0.76	0.80	0.63	0.43	0.14	0.40

(b)

N°	*a*	1	2	3	4	5	6	7	1'	2'	3'	4'	5'
Date	3.07	3.07	8.07	13.07	17.07	20.07	22.07	24.07	3.06	5.06	6.06	7.06	10.06
λ_{max} nm	327	336.1	332.2	341.1	341.1	335.1	333.1	335.1	335.2	335.2	334.1	331.6	331
***I*, r.u.**	1	0.88	0.88	0.35	0.27	0.64	0.76	0.80	0.63	0.43	0.14	0.4	0.76

shift of the FS of BS into the longwave region was recorded, despite the verification of several pathogens. Obviously, the intake of sufficient albumin allowed to improve significantly the work of detoxification systems of the body, which had a positive effect on the spectral-fluorescence parameters. Measurements of FS of BS after 10 days after admission to the hospital on the 13th of July, 2015 (**Figure 6(a)**, curve 3), testified to the critical moment, when there was a significant decrease in I_F to 0.35 r.u. and the shift of the FS into the longwave region by 9 nm. This condition of this patient was close to septic (**Figure 6(a)**, curves 3', 4'). This is due to the increased bacteremia in this patient. MFS revealed the deterioration of this patient's condition.

The appointment of the infusion of albumin solution with subsequent complex therapy led to the gradual improvement of the spectral-fluorescent characteristics of the BS (closer to the fluorescence parameters of albumin) in subsequent blood sampling 17.07.-24.07.2015. They correlated well with clinical indicators and the results of laboratory examinations of the patient. Therefore, he was discharged from the hospital in satisfactory condition on the 24th of July 2015.

By controlling the treatment process with the use of infusions of donor albumin solution in the case of deterioration of patient's condition, we can essentially achieve positive completion of the treatment process. The development of septic complications can be very dangerous, especially in patients with concomitant extragenital pathology. The proper organization of the treatment process using infusions of albumin solution, even for patients in serious condition is quite likely to prevent the development of septic complications.

Now we shall illustrate the possibilities of developing the septic condition for the patient, whose FS is presented in **Figure 6(a)**, which may occur with impro-

per organization of the treatment process. The scenario of a possible complicated course of the treatment process for this patient is presented in **Figure 6(b)** and in **Table 3(b)**. **Figure 6(a)** (curve 3) and **Table 3(a)** show that on the 13th of July within the MFS the decrease of the fluorescence intensity and the long-wavelength shift of the FS were recorded. If we do not take into account the data of the MFS on the 13th of July and do not prescribe the infusion of donor albumin, there will be an increase of bacteremia and within the MFS we will get a curve 4 (**Figure 6(b)**). This figure shows that the patient's condition becomes close to septic (curves 4 and 3' are quite close to each other). Therefore, he was prescribed infusion of donor albumin solution several times until his recovery. The scenario of his treatment at the final stage was under the control of the MFS. If donor albumin infusion had not been prescribed on the 17th of July, his health could significantly deteriorate. In this case, infusion therapy with the solution of donor albumin should be continued, although there was no guarantee of successful completion of the treatment process. If there is no ability to monitor the treatment process within the MFS it is necessary to monitor closely the condition of patients and timely adjust the treatment process, timely prescribing infusion therapy with the solution of donor albumin.

4. Conclusions

The deep understanding of the pathogenesis is the key point in the formation of treatment tactics for patients with various diseases. Obtaining information about the mechanisms of origin and evolution of purulent-inflammatory diseases and sepsis is extremely important for the rapid search for effective ways of their prevention and successful treatment. For this purpose, the pathogenetic concept of diagnostic and treatment model of purulent-inflammatory diseases and sepsis was proposed. It is based on the fact, that in patients with these diseases part of the albumin molecules in the blood of patients are blocked by toxins. As a result, there are two types of albumin molecules in their blood: normal (concentration: X) and blocked by toxins /pathological (concentration: $1 - X$). So, pathological albumin molecules lose the ability to perform their basic functions, namely transport and detoxification. Besides, about 6% of albumin molecules in the blood, even in healthy people, are glycosylated. At the same time, in patients with diabetes mellitus with hyperglycemia 9% - 12% of albumin molecules are in the glycosylated state. As a result, the sum of concentrations of pathological and glycosylated albumin molecules is considered pathological.

The new definition of sepsis is to define X^*, *i.e.* the maximum minimum value of the concentration of albumin in patients with sepsis. If X is more than X^*, this ensures the viability of the organism to some extent. Then at X less X^*, exitus letalis develops.

The main characteristics that we study with this method are the fluorescence intensity (I_F) and the position of the maximum fluorescence band (λ_{max}) of the BS. I_F, λ_{max} are universal markers of the severity of the condition of patients with purulent-inflammatory diseases and sepsis. They are functions of the concentra-

tions of normal (I_F^a , $\lambda_{\max}^a$) and pathological albumin molecules (I_F^t , $\lambda_{\max}^t$) (1). The peculiarities of the behaviour of these markers for purulent-inflammatory diseases, sepsis and burn injuries have been studied and illustrated. Regardless of the etiological factors of the septic condition in the patient's body, the processes that take place in it, occur in the similar scenario. The study of the biological objects within the MFS is allowed to detect pathological processes in living organisms at an early stage of their development. To overcome EI, it was proposed to use infusions of 20% solution of donor albumin. In particular, in Lviv's Communal Clinical Hospital No. 8 using treatment tactics, developed within the MFS (Ph.D. V. Savchyn, N. Tuzyuk) during the pandemic of COVID-19 in 2020-2021 more than 35 patients with burn injuries, including those in serious condition, were successfully cured even without the use of MFS.

Acknowledgements

The author is grateful to Professors Olha Bulavenko, Anatoliy Voloshinivskii, Viktor Rud and Ph.D. Vasyl Savchyn for valuable advice and guidance while preparing this publication.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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International Journal of Clinical Medicine, 2022, 13, 22-35
https://www.scirp.org/journal/ijcm
ISSN Online: 2158-2882
ISSN Print: 2158-284X

Saudi Consensus for GLP-1 RAs Switching Guidance: Consensus Report

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How to cite this paper: Alsifri, S., Elbadawi, H., Alsabaan, F., Almahfouz, A., Alyahya, K., Shesha, E., Esba, L.A., Alnais, M., Aldahash, R., Alharbi, T., Aljaser, S. and Issak, E.R. (2022) Saudi Consensus for GLP-1 RAs Switching Guidance: Consensus Report. *International Journal of Clinical Medicine*, **13**, 22-35.
https://doi.org/10.4236/ijcm.2022.131002

Received: December 9, 2021
Accepted: January 11, 2022
Published: January 14, 2022

Abstract

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) provide adequate glycemic control, weight reduction, low risk of hypoglycemia, and CV risk reduction. Their usage for type 2 DM (T2DM) is recommended mainly when hypoglycemia or weight gain should be considered, also, whenever initial therapy is failed. There are many recent updates in the treatment paradigm of T2DM. There are many types of GLP-1RAs, with a knowledge gap regarding switching between the different types. A Saudi task force gathered to develop an explicit, evidence-based consensus for switching between GLP-1RAs, when, why, and how? This article contains the expert panel's recommendations as a contribution to complement the knowledge gap in this area from the national perspective. As an alternative to intensifying therapy, switching from one GLP-1RA to another has various advantages. Improvements in glycemic control, weight loss, adherence, and medications with established cardiovascular benefits are among them. Also, switching needs to be individualized upon many discussed factors like the dose of the previous GLP1-RA and gastrointestinal adverse effects. Discussion with patients about the why and how to switch is critical.

Keywords

Glucagon-Like Peptide-1 Receptor Agonists, Switching, Type 2 DM, Glycemic Control

1. Introduction

Diabetes mellitus (DM) prevalence is rising quickly not only globally (by the year 2045 it is expected to become 9.9% with a total number of 629 Million), but also in Saudi Arabia (KSA) with its great impacts on both morbidity and mortality [1] [2].

Glucagon-like peptide-1 (GLP-1) receptor agonists (GLP-1RAs) provide effective glycemic control, weight reduction, low risk of hypoglycaemia and CV risk reduction. Both the American Diabetes Association (ADA) guidelines and the ADA/European Association for the Study of Diabetes (EASD) consensus report, recommended their usage for type 2 DM (T2DM), particularly when hypoglycemia or weight gain should be considered. In addition, they recommended their usage whenever a failure of initial therapy with metformin and comprehensive lifestyle modifications [3] [4] [5] [6].

Among the several GLP-1RAs developed, exenatide, liraglutide, semaglutide, and dulaglutide are available in the Saudi market. They have some differences in terms of their kinetics and dynamics [6]-[14]. Exenatide, liraglutide, lixisenatide, oral semaglutide are used on a daily base, either once or twice as in the case of exenatide. However, dulaglutide, exenatide extended-release and semaglutide are used once per week [15] [16].

Of all GLP-1RAs currently available, dulaglutide, liraglutide and once weekly semaglutide have demonstrated CV benefits, based on the results of several trials [9] [11] [12]. Therefore, their usage for patients with established atherosclerotic CV disease was recommended by the ADA. Also, other guidelines recommended their usage for those patients irrespective of glycemic control [3] [5] [17].

There are many recent updates in the treatment paradigm of T2DM in the light of new evidence available. There are many types of GLP-1RAs, with a knowledge gap regarding how to switch between the different types. Switching from one GLP-1RA to another may be beneficial and may delay the need to intensify therapy, thus avoiding an increase in the treatment burden. That may enable the reduction of the dose of concomitant oral anti-hyperglycemic drugs and/or insulin; therefore, improving the adherence to treatment [18].

We, a Saudi task force, gathered to develop an explicit, evidence-based consensus for switching between GLP-1RAs, when, why and how? This article has the recommendations of this expert panel.

2. Insights from Available Literature

The task force searched the medical literature for any manuscript about switch-

ing from one GLP-1RA to another. In addition to the available randomized controlled trials and real-world studies, the task force found two eminent review articles; one review by Almandoz *et al.* provided advice on switching between GLP-1RAs in clinical practice; and also did another recent review was about switching between GLP-1RAs by Jain *et al.* [18] [19].

1) GLP-1RAs have a good impact on glycemic control as well as weight reduction

Glucose-lowering efficacy differs between GLP-1RAs. That has been observed in both clinical trials and analyses of real-world data of GLP-1RA-naïve patients [20]-[27]. The differences in HbA1c and weight reduction in GLP1-RA-naïve patients are shown in **Table 1**.

In addition, switching from one GLP1-RA to another led to improved glycemic control and weight reduction in both randomized controlled trials and retrospective observational studies (**Table 2**) [28]-[35].

These studies, therefore, demonstrate that switching between GLP-1RAs can provide additional benefits in terms of glycemic control and further weight loss.

2) GLP1-RAs have cardioprotective benefits

Some GLP1-RAs have proven cardio protective benefits like OW semaglutide, liraglutide, dulaglutide. Therefore, their indications for use have been expanded in some countries to reduce the risk of major adverse CV events in adults with T2DM and established CVD [9] [11] [12] [36] [37] [38]. On the other hand, others have not proven cardioprotective benefits like lixisenatide and exenatide ER [39] [40].

Why do we need to switch from one GLP1-RA to another?

There are many drives to switch from one GLP1-RA to another. First is the need for further glycemic control and further weight reduction. The second drive to switch is the need for cardioprotection. Other motives to switch are more safety and tolerability, patients' preferences and adherence issues, and more convenient devices [18].

One of the reasons behind the reduced efficacy of GLP1-RAs is the development of increasing antibody titer as seen in an analysis of exenatide clinical trials [41].

The available GLP1-RAs have variable safety profiles. Short-acting GLP1-RAs are more likely to cause nausea and/or vomiting. Long-acting GLP1-RAs are more likely to cause diarrhea [42] [43]. Therefore, switching from one GLP1-RA to another may help alleviate these adverse effects [44].

Poor adherence reduces the effectiveness of therapy. Improved glycemic control was observed for GLP1-RAs in patients with good adherence compared with poor adherence [45] [46] [47]. First, adherence is affected by the frequency of dosing. Several studies demonstrated that as the frequency decreases, the adherence to GLP1-RA is increased [48] [49] [50]. More adherences were observed with OW GLP1-RAs than the daily-based GLP1-RAs [51] [52] [53] [54].

Table 1. HbA1c and weight reduction in GLP1-RA-naïve patients.

DURATION 6 [20]	Reduction	Liraglutide 1.8 mg	Exenatide ER 2.0 mg
	HbA1c	1.5%	1.3%-point
	Weight	3.6 kg	2.7 kg
HARMONY 7 [21]	Reduction	Liraglutide 1.8 mg	Albiglutide 50 mg
	HbA1c	1.0%	0.8%-point
	Weight	2.2 kg	0.6 kg
LIRA–LIXI [22]	Reduction	Liraglutide 1.8 mg	Lixisenatide 20 µg
	HbA1c	1.8%	1.2%-point
	Weight	4.3 kg	3.7 kg
AWARD 6 [23]	Reduction	Liraglutide 1.8 mg	Dulaglutide 1.5 mg
	HbA1c	Same	
	Weight	3.6 kg	2.9 kg
Feher *et al.* [24]	Reduction	Liraglutide 1.8 mg	Lixisenatide 20 µg
	HbA1c	Mean treatment difference [95% confidence interval (CI)] −0.3%-point [−0.56; −0.04])	
SUSTAIN 3 [25]	Reduction	OW semaglutide 1.0 mg	Exenatide ER 2.0 mg
	HbA1c	1.5 %	0.9%
	Weight	5.6 kg	1.9 kg
SUSTAIN 7 [26]	Reduction	OW semaglutide 0.5 mg	Dulaglutide 0.75 mg
	HbA1c	1.5 %	1.1%
	Weight	4.6 kg	2.3 kg
		OW semaglutide 1 mg	Dulaglutide 1.5 mg
	HbA1c	1.8%	1.4%
	Weight	6.5 kg	3 kg
SUSTAIN 10 [27]	Reduction	OW semaglutide 1.0 mg	Liraglutide 1.2 mg
	HbA1c	1.7%	1.0%
	Weight	5.8 kg	1.9 kg

Table 2. HbA1c and weight reduction after switching to another GLP1-RA.

DURATION 1 [28]	From exenatide twice daily 10 µg	To exenatide ER 2.0 mg
	Further decreases in HbA1c levels of 0.2%-point.	
LEAD 6 [29]	From exenatide twice daily 10 µg	To liraglutide 1.8 mg
	Further decreases in HbA1c levels of 0.3%-point and weight decreased by 0.9 kg.	

Continued

CIBELES Project [30]	From another GLP-1RA	To exenatide ER
	Further decreases in HbA1c levels of 0.4%-point with no significant changes in weight.	
Visaria *et al.* [31]	From another GLP-1RA	To OW semaglutide
	Further decreases in HbA1c levels of 1.3%-point.	
REALiSe-DM [32]	From either liraglutide or dulaglutide	To OW semaglutide
	Further decreases in HbA1c levels of 0.7%-point. The mean reduction in weight was 1.6 kg following the switch.	
Watanabe *et al.* [33]	From exenatide twice daily	To exenatide ER
	Further decreases in HbA1c levels of 0.2%-point over 24 weeks. Incidence of hypoglycemia was also significantly reduced. No significant changes in weight.	
Goncalves and Bell study [34]	From liraglutide 1.8 mg	To OW semaglutide average dose 0.76
	HbA1c decreased from 7.46% ± 1.36% to 6.68% ± 1.00% The number of patients requiring insulin dropped from 16 to 13. Weight dropped from 110.6 ± 20 to 106 ± 27 kg.	
Overgaard *et al.* modeling study [35]	From another GLP-1RA	To OW semaglutide
	More reductions in HbA1c Further weigh reduction.	

Moreover, patient preference studies indicated that the injection frequency is highly considered by both injection-naïve and -experienced patients when selecting a GLP1-RA [55] [56] [57] [58] [59].

Therefore, switching from one GLP1-RA that is dosed either once or twice daily to another OW agent may improve adherence and outcomes in some patients. Despite both being OW GLP1-RAs, adherence to dulaglutide was significantly higher than exenatide ER. That indicates factors other than the frequency of dosing are also critical when considering adherence [53].

Technology-related issues are other factors affecting the decision to switch due to convenience. GLP1-RAs devices are variable. The delivery device and needle size are essential when selecting between GLP-1RAs [59]. The needle size varies between GLP1-RAs devices from large diameter (23-gauge in exenatide OW [60], 29 - 31 gauge for exenatide twice daily, and 29-gauge for dulaglutide) and a smaller diameter (32-gauge in OW semaglutide) [9] [61] [62]. A decision to switch, based on the delivery device, should only be made if a patient indicates that they have had difficulty using the injection device of their current GLP1-RA. Also, another factor is the ability to allow micro-titration (*i.e.*, titration to intermediary doses); allowing slower up-titration may help manage GI adverse effects is a significant factor [18] [63]. In addition, the degree to which the dose can be selected varies between GLP1-RA injection devices.

In the summary difference in potency, dosage frequency and adherence, duration of action see table. In general, data suggest that long-acting GLP1-RAs have greater effects on HbA1c, fasting plasma glucose, and body weight than those that are short-acting [13].

3. When to Switch from One GLP1-RA to Another?

There are several medical causes for switching. They are poor glycemic control, more weight reduction is needed, CV risk increased, or the presence of more advanced chronic kidney disease (CKD), and adverse effects. Non-medical causes are patient preference, cost, better technology, and insurance decrees [18] [19]. The following table illustrates these reasons and what to do in each (**Table 3**).

4. How to Switch from One GLP1-RA to Another?

An individualized approach should be considered [18] [19] once the decision has been made to switch from one GLP1-RA to another. Many factors should be considered; one of them is the reimbursement requirements, if any.

Consider any contraindications

Any contraindications or warnings should be considered when switching (**Table 4**).

Selecting the dose to initiate

If the patient has a history of GI adverse effects with his GLP1-RA, switch to one that enables gradual up-titration (**Figure 1**). Initiate it at the lowest dose. For example, 0.25 mg in OW semaglutide and 0.75 mg in dulaglutide. If the patient had no or minimal GI AEs with his GLP1-RA, start OW semaglutide 0.5 mg. Adjust the duration before up-titrating the new GLP-1RA according to the

Table 3. Drivers for switching and what to do in each.

When to switch	What to do
Target HbA1c is not achieved because of:	
• Poor adherence	Switch to an OW GLP-1RA
• Disease progression or lack of efficacy of the current GLP1-RA	Switch to an agent with proven better glycemic efficacy
• The development of anti-drug antibodies	Switch to different types of GLP1-RA Switch to a human GLP-1 analogue
The need for additional weight loss	The most effective GLP1-RA is OW semaglutide. [3]
Increased CV risk in T2DM	[9] [11] [13]
• Established CVD	Dulaglutide, liraglutide or OW semaglutide
• Multiple CV risk factors	Dulaglutide
More advanced CKD status: eGFR < 30 mL/min/1.73 m^2	Switch to a dulaglutide, liraglutide or OW semaglutide [9] [10] [11] [12] [63]
Adverse effects	Switch to another GLP1-RA [44]

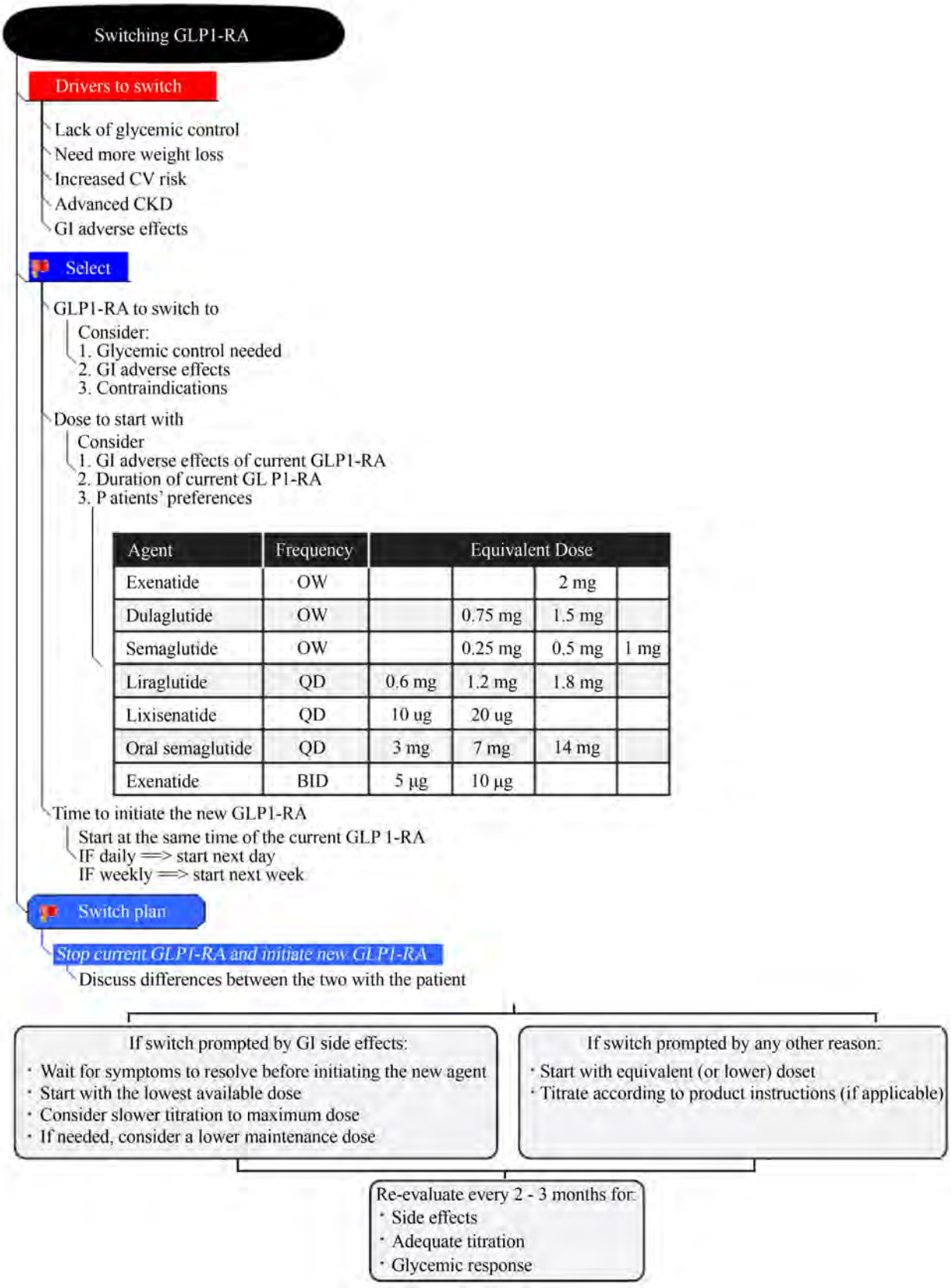

Figure 1. Switching plan to a new GLP-1RA. BID, twice daily; GI, gastrointestinal; GLP1-RA, glucagon-like peptide-1 receptor agonist; OW, once weekly; QD, once daily.

Table 4. Contraindications for switching.

GLP1-RA	Contraindication
Renal impairment	
Majority of the available GLP1-RAs except OW semaglutide, Liraglutide and dulaglutide [6]-[12] [63]	**End-stage renal disease** (estimated glomerular filtration rate [eGFR] < 15 mL/min/1.73 m^2)
Exenatide ER and exenatide twice daily [6] [8]	**Severe renal impairment** (creatinine clearance < 30 mL/min): do not use **Moderate renal impairment** (creatinine clearance 30 - 50 mL/min): use with caution
Lixisenatide [7]	Severe renal impairment
Liraglutide [12]	Renal impairment (eGFR < 60): caution in dose escalation
Dulaglutide [11]	Severe renal impairment
Diabetic retinopathy	
OW semaglutide and dulaglutide [9] [63] [64]	OW semaglutide and dulaglutide are up-titrated more slowly (every 2 - 3 months). Patients should have regular assessments for retinopathy

presence and severity of GI AEs with the previous GLP-1RA. If GI AEs were absent or minor, then up-titrate (every two weeks). If substantial GI AEs are there, then up-titrate more slowly (every four weeks). If a patient was on the current GLP1-RA for less than one month, consider him a GLP-1RA-naïve patient. If he was on it for more than one month, consider the current GLP1-RA dose when calculating the dose of the new one [9] [11] [18] [19].

Timing of the first dose of the new GLP1-RA

The first dose of the new GLP1-RA should be at the time of the next dose of the previous GLP1-RA [18] [19].

Consider concomitant therapy when initiating the new GLP1-RA

The dose of **sulphonylurea or insulin** may need adjustment when switching to reduce the risk of AEs. Sulphonylurea dose should be reduced by 50%, insulin by 20%, and close monitoring for hypoglycemia [18] [65]. Dipeptidyl peptidase-4 inhibitors should be stopped when initiating a GLP1-RA [4].

Deal with barriers to switch:

Patients may feel that they are doing well and do not need to change. In addition, they have concerns about GI AEs. Moreover, the change of devices may be a barrier for some patients. Finally, the increased cost or reimbursement issues may be present. Discuss with the patient about the benefits obtained, and reassure that GI AEs are transient. Also, emphasize that the treatment cost and burden will not be increased [15] [18].

5. Conclusion

In conclusion, switching from one GLP1-RA to another has several benefits as an alternative to intensifying therapy. These include improving glycemic control, more weight reduction, more adherence, and drugs with proven CV benefits. Also, switching needs to be individualized upon many discussed factors like the dose of the previous GLP1-RA and GI AEs. Discussion with patients about the why and how to switch is critical.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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International Journal of Clinical Medicine, 2022, 13, 36-49
https://www.scirp.org/journal/ijcm
ISSN Online: 2158-2882
ISSN Print: 2158-284X

Prevalence and Factors Associated with Burnout Syndrome among Resident Doctors at Tertiary Teaching Hospitals in Dar es Salaam, Tanzania

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How to cite this paper: Lugazia, E.R., Sway, H.C., Boniface, R.L. and Abdullah, A. (2022) Prevalence and Factors Associated with Burnout Syndrome among Resident Doctors at Tertiary Teaching Hospitals in Dar es Salaam, Tanzania. *International Journal of Clinical Medicine*, **13**, 36-49.
https://doi.org/10.4236/ijcm.2022.131003

Received: December 6, 2021
Accepted: January 11, 2022
Published: January 14, 2022

Abstract

Introduction: Burnout syndrome is prevalent to a great extent among medical residents, and this can interfere with their training and patient management. However, the extent of the problem is still unknown in our setting. This study therefore aimed at determining prevalence and factors associated with burnout syndrome among resident doctors at tertiary teaching hospitals in Dar es Salaam, Tanzania. **Method:** A cross-sectional study of resident doctors was carried out in four teaching hospitals of Muhimbili University of Health and Allied Sciences between January 2021 and March 2021. Participants were interviewed using a structured questionnaire and Maslach Burnout Inventory. **Results:** The study had 398 participants with a mean age of 35 ± 3.5 years. Overall burnout prevalence was 33.7%, as for the burnout dimensions, 205 (51.5%) respondents reported burnout in the dimension of emotional exhaustion (EE), 177 (44.5%) in the dimension of depersonalization (D), and 144 (36.2%) in the dimension of reduced personal accomplishment (RPA). Independent factors associated with burnout syndrome were: inadequate support from residency program supervisors (Odds Ratio (OR) 1.97, 95% CI: 1.23 - 3.14, p = 0.005), work-related family conflicts (Odds Ratio (OR) 3.2, 95% CI: 1.35 - 7.71, p = 0.008), stressful call perception (Odds Ratio (OR) 3.31, 95% CI: 1.90 - 5.76, p = 0.001) and each added year of study (Odds Ratio (OR) 3.46, 95% CI: 1.08 - 6.73, p = 0.009). **Conclusion:** Burnout is a problem among resident doctors in Tanzania. This could be addressed by directing preventive and intervention measures in the residency training pro-

gram. Periodic assessment is also needed to mitigate factors associated with burnout among resident doctors.

Keywords

Burnout, Resident Doctors, Emotional Exhaustion (EE), Depersonalization (DP), Reduced Personal Accomplishment (RPA)

1. Introduction

Burnout is a state of physical, mental, and emotional exhaustion arising from a continued response to chronic interpersonal stressors while at work, which in turn affects the working efficiency of a person [1]. The term was first introduced by Freudeberger and Maslach who independently studied the social issues faced by underprivileged citizens in 1970, and in 1974 it was described among health care professionals [2]. Burnout syndrome among health care professionals has become a serious health problem and the mental health of doctors is an issue of growing concern all over the world as it frequently interferes with their professional training and responsibilities [3]. Among practicing physicians, it has reached epidemic levels with a prevalence that approximates 50% [4]. The condition is also well associated with negative physiological, cognitive, psychological, and behavioral manifestations which create severe pressure on the whole health care system threatening patients' care and safety. It is not a sign of weakness, mental illness, or inability to cope with life and it can be treated, and prevented [5].

Burnout appears to be quite prevalent in both developing and developed countries and probably represents considerable economic, social and psychological costs to employees and employers in these countries. The problem of residents' burnout is widely recognized with diverse solutions implemented across developed countries. However, there is a lack of clarity about the global prevalence of burnout among medical residents due to limited evidence on residents' burnout in low-income and middle-income countries (LMIC). This affects interventions to prevent and reduce residents' burnout as most of the studies of sufficient quality have only been done in high-income countries [6].

Although the factors that contribute to residents' burnout are unclear, several studies have explored possible reasons for burnout in residency training. In these studies, residents report that time demands, workload, practice setting, lack of control over time management, work planning, work organization, specialty choice, inherently difficult job situations, sleep deprivation, problems with work-life balance and interpersonal relationships are stressors that may contribute to burnout [7] [8].

Other factors cited in the literature include age, gender, marital status and parenting responsibilities. Concerning gender, the previous speculation had led to

the hypothesis that women residents are more prone to stress and be at a greater risk of burnout as a result of conflicts between traditional gender roles and professional practice and because of the climate of medical education which is competitive and oriented towards masculine tradition [9]. These stressors have resulted in reported incidence of psychological symptoms with feelings of becoming less humanistic, more cynical and "burning out" during residency training [10]. While previous studies done elsewhere have focused on identifying stress factors as perceived by resident doctors [11], there is insufficient information on burnout among doctors in residency training in our country. This study was therefore conducted to help us understand the prevalence and factors associated with burnout syndrome among resident doctors at Tertiary Teaching Hospitals in Dar es Salaam, Tanzania.

2. Methodology

Study setting. Data were collected from four University teaching hospitals located in Ilala district of Dar es Salaam, Tanzania. Involved hospitals were; Muhimbili National Hospital (MNH), Muhimbili Orthopaedics Institute (MOI), Jakaya Kikwete Cardiac Institute (JKCI) and Ocean Road Cancer Institute (ORCI) where the Muhimbili University of Health and Allied Sciences resident doctors do their clinical rotations.

Muhimbili National Hospital, is a national referral hospital with a bed capacity of 1500 beds, attending 1000 to 1200 outpatients per day, and 1000 to 1200 inpatients per week. Muhimbili Orthopaedics Institute, is a national specialized hospital offering Orthopedic and Neurosurgical care with a bed capacity of 362 beds, attending on average 4000 outpatients and 700 inpatients per week.

Jakaya Kikwete Cardiac Institute, is a national specialized hospital offering cardiovascular care. The Institute has 103 bed capacity attending on average 700 outpatients and 100 inpatients per week.

Ocean Road Cancer Institute, is a national specialized hospital in cancer treatment and care with a bed capacity of 270 beds attending on average 1800 outpatients and 150 inpatients per week.

Study Design. A prospective cross-sectional study was conducted.

Study population. The study population comprised of Muhimbili University of Health and Allied Sciences resident doctors (first to third year), doing clinical rotations in 4 involved teaching hospitals between January 2021 and March 2021.

Sample size. Assumptions made in determining the sample size were: prevalence of burnout syndrome among resident doctors is 55% [12], precision of 5% and confidence level of 95%. Formula for sample size calculation [13],

$$N = Z^2 P(1-P)/e^2 .$$

(N = Sample size; Z at 95% confidence level (p = 0.05) = 1.96; P = prevalence; e = precision level).

$$N = 1.96^2 \times 0.55(1-0.55)/0.05^2 = 380,$$

Taking a non-response rate of 10% into consideration, the corrected sample size was 420.

Sampling. All residents were grouped according to their specialties of training. The number selected in each department was obtained by the proportional sampling method. Enrollment was done after proper explanation to the residents about the study aim and written informed consent was obtained. The inclusion criteria were resident doctors who consented to participate.

Data collection and management. Data were collected using a structured self-administered questionnaire designed by principal investigator. It comprised of two sections, section one which consisted of socio-demographic characteristics and relevant work-related characteristics (including specialty, year of study, number of working hours per day, number of night calls per month, working relationship with colleagues, average night's sleep hours, support from supervisors, work-related family conflict, work autonomy, call perception, years of experience, sponsorship, and remuneration). Section two comprised of an adapted Maslach Burnout Inventory-Human Services Survey (MBI-HSS) designed to measure the presence of burnout (Appendix). A pilot study was conducted to ensure validity and reliability of the data collection tool. Direct scoring was used for the items in each subscale (emotional exhaustion, depersonalization and personal accomplishments) by adding together the values of the ratings. A high degree of burnout is represented by high score of emotional exhaustion (score of ≥27) and depersonalization (score of ≥13) and a low score of personal accomplishments (score of ≤33). To determine the prevalence of burnout syndrome amongst resident doctors in this study, we used the tridimensional diagnosis criteria for Burnout Syndrome using Maslach Burnout Inventory (emotional exhaustion, depersonalization and personal accomplishment). Accordingly, those who scored high on both emotional exhaustion (score of ≥27) and depersonalization (score of ≥13) plus low personal accomplishment domains (score of ≤33), were considered to have burnout. Data were double-entered into Excel (MicrosoftÂ® Excel, Seattle Washington), Statistical analysis was conducted using Statistical Package for Social Sciences (SPSS) version 23 (IBM Corp. IBM SPSS Statistics for Windows [Internet]. Armonk, NY: IBM Corp; 2017).

Data analysis. All variables were categorized and described using frequency distribution. Chi-square test was used for bivariate analysis and those variables with observed frequency less than five Fisher's exact test was applied. A variable with ($p \leq 0.05$) burnout was considered to be statistically significant. Variables that demonstrated significant bivariate association with burnout were entered into the multivariate logistic regression modal to assess independent effects. Parameter of measurement to assess association was odds ratio.

Ethical consideration. Ethical approval for the study was obtained from the Muhimbili University of Health and Allied Sciences Research Ethics Committee. An informed written consent was sought from participants.

3. Results

A total of 420 residents were enrolled in our study, from which 406 (96.6%) responded. Eight (2%) were excluded due to incomplete data. Data from 398 residents were analyzed (Figure 1).

3.1. Socio-Demographic and Work-Related Characteristics of the Participants

The participants' age ranged between 24 and 50 years with a mean age of 35 ± 3.5 years. Majorities 243/398 (61.1%) were males, 256/398 (64.3%) were married, and 256/398 (64.3%) had children. Three hundred and twenty-five (81.7%) had employment, and 277/398 (69.6%) of the residents were living outside the university campus. One hundred and fifty-nine (39.9%) residents were in their first year of training, and 100/398 (25.1%) were in their third year of training. Majorities 284/398 (71.4%) had sponsorship for their studies, 341/398 (85.7%) reported inadequate night sleep hours, 208/398 (52%) reported inadequate remuneration and over half 256/398 (64.3%) reported working more than >9 hours per day. Two hundred and six (65.8%) of residents perceived call duty as stressful, and 167/398 (42%) reported inadequate support from their supervisors (Table 1).

3.2. Prevalence of Burnout

Out of 398 residents involved in this study, burnout syndrome accounted for 134/398 (33.7%) of participants (Figure 2).

3.3. Prevalence of Burnout across Dimensions among Participants

Analyzing each sub-scale separately according to Maslach's categorization, 205/398

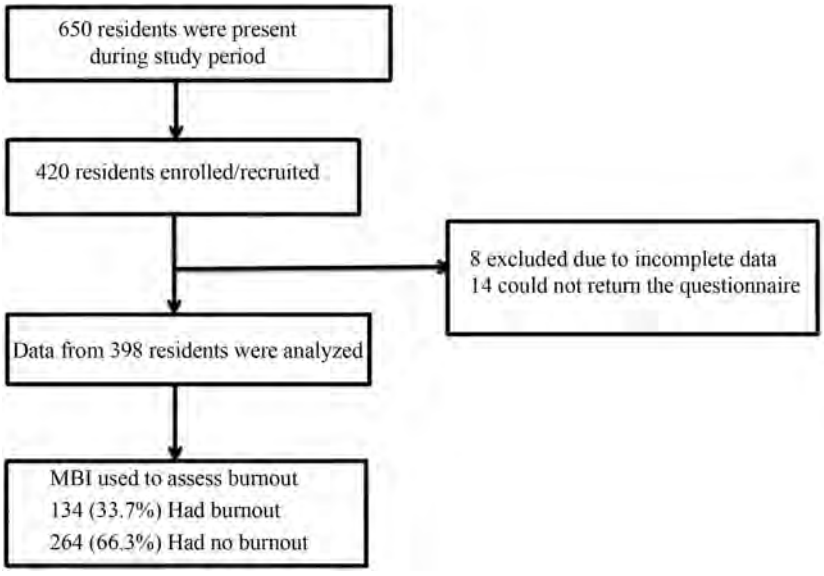

Figure 1. Schematic of residents' enrolment.

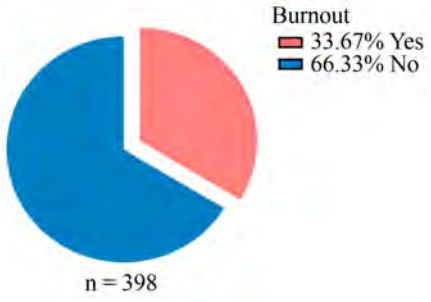

Figure 2. Proportional of residents with burnout.

Table 1. Socio-demographic and work-related characteristics of the participants.

Variable	Category	Frequency (n)	Percent (%)	Variable	Category	Frequency	Percent
Age group (years)	< 35	302	75.9	Year of residency	1st year	159	39.9
	>35	96	24.1		2nd year	139	34.9
					3rd year	100	25.1
Gender	Male	243	61.1	Sponsorship	Sponsored	284	71.4
	Female	155	38.9		Not Sponsored	114	28.6
Marital status	Married	256	64.3	Night sleep hours	Adequate	57	14.3
	Single	146	35.7		Inadequate	341	85.7
Having Children	Yes	256	64.3	Number of night shifts per month	<5 calls	234	58.8
	No	142	35.7		5 - 10 calls	121	30.4
Employment status	Employed	325	81.7	Call perception	Stressful	206	65.8
	Not Employed	73	18.3		Not stressful	136	34.2
Smoking	Yes	16	4	Remuneration	Adequate	66	16.6
	No	382	96		Not adequate	208	52.3
					No renumeration	124	31.2
Alcohol use	Yes	112	28.1	Support from supervisors	Adequate	222	55.8
	No	286	71.9		Not adequate	167	42
					No support	9	2.3
Exercise	Yes	260	65.3	Years of experience	< 5	163	41.0
	No	138	34.7		5 - 10	194	48.7
					>10	41	10.3
Chronic disease	Yes	30	7.5				
	No	368	92.5				
Accommodation	At University hostels	121	30.4				
	Outside University hostels	277	69.6				

(51.5%) residents reported burnout in the dimension of emotional exhaustion, 177/398 (44.5%) in the dimension of depersonalization, and 144/398 (36.2%) in the dimension of reduced personal accomplishment.

3.4. Factors Associated with Burnout Syndrome

The following factors were significantly associated with burnout syndrome after bivariate analysis: Third year of study accounted for majority (47%) of residents with burnout syndrome compared to first- and second-year residents (p-value 0.001), burnout syndrome was more (38.3%) among those who reported little work autonomy compared to those who reported much work autonomy (p-value 0.023). Majorities (59.2%) of those with high work-related family conflict had burnout syndrome compared to those with low and none work-related family conflict (p-value < 0.001). Those who perceived call duty as stressful had more burnout syndrome (43.1%) compared to those who perceived call duty as not stressful (p-value < 0.001), and those with inadequate supervisor's support had more burnout syndrome (46.7%) compared to those with adequate support (p-value < 0.001) (**Table 2**).

The following factors remained statistically significant after multivariate logistic regression analysis: Residents who perceived call duty as stressful were found to be 3.3 times more likely to develop burnout compared to those who perceived it as not stressful. Burnout was about twice as prevalent in residents who reported inadequate support from their residency program supervisors compared to those who reported adequate support. Burnout was 3.2 times more frequent in those who reported having high home work-related conflicts compared to those who reported none conflict. Those in their third of study were 3.4 times more likely to develop burnout compared to those who were in first year of study (**Table 2**).

4. Discussion

This study examined the prevalence and factors associated with burnout syndrome among resident doctors at tertiary teaching hospitals in Dar es Salaam, Tanzania. It revealed the prevalence of 33.7%, which is within the range of burnout syndrome among health care workers reported globally 25% - 75% [14]. It is also within the range reported in a systematic review done in Nigeria 23.6% - 51.7% [15]. Our findings are also similar to a meta-analysis study results done in Brazil in which they reported overall prevalence of 35.7% [16].

Although the prevalence reported in this study is almost similar to what has been reported in other studies done elsewhere, the implication on health services delivery in Tanzania may be more serious taking into account that, resident doctors form the major part of health care delivery across tertiary hospitals in the country due to low doctor to patient ratio situation facing the country. So, there is a risk of negative impact of burnout on patient care including medical errors, patient safety risks, and potential compromise of quality of care. For

Table 2. Factors associated with burnout syndrome.

	Burn Out				
Factor	**Yes n (%)**	**No n (%)**	**P-Value**	**Multivariate OR (95% CI)**	**P-Value**
Year of Study					
First year	39 (24.5)	120 (75.5)		1	
Second year	48 (34.5)	91 (65.5)	**0.001**	1.63 (0.96 - 3.52)	**0.046**
Third year	47 (47.0)	53 (53.0)		3.46 (1.08 - 6.73)	**0.009**
Sponsorship					
Sponsored	99 (34.9)	185 (65.1)	0.428		
Not sponsored	35 (30.7)	79 (69.3)			
Autonomy					
Much	47 (27.5)	124 (72.5)	**0.023**	1	
Little	87 (38.3)	140 (61.7)		1.20 (0.74 - 1.94)	0.445
Conflicts					
None	23 (20.9)	87 (79.1)		1	
Low	89 (35.5)	162 (64.5)	**<0.001**	1.41 (0.77 - 2.56)	**0.064**
High	22 (59.5)	15 (40.5)		3.23 (1.35 - 7.71)	**0.008**
Night shift (Calls)					
<5	76 (32.5)	158 (67.5)			
5 - 10	45 (37.2)	76 (62.8)	0.592		
>10	13 (30.2)	30 (69.8)			
Call perception					
Not Stressful	21 (15.4)	115(84.6)	**<0.001**	1	
Stressful	113 (43.1)	149 (56.9)		3.31 (1.90 - 5.76)	**0.001**
Renumeration					
Adequate	17 (25.8)	49 (74.2)			
Not adequate	71 (34.1)	137 (65.9)	0.283		
No remuneration	46 (37.1)	78 (62.9)			
Supervisor's support					
Adequate	54 (24.3)	168 (75.7)		1	
Not adequate	78 (46.7)	89 (53.3)	**<0.001**	1.97 (1.23 - 3.14)	**0.005**
No support at all	2 (22.2)	7 (77.8)		0.47 (0.09 - 2.44)	0.056
Night sleep					
Inadequate	117 (34.3)	224 (65.7)	0.507		
Adequate	17 (29.8)	40 (70.2)			

Continued

Working hours			
≤9	42 (29.6)	100 (70.4)	0.198
>9	92 (35.9)	164 (64.1)	
Experience (years)			
<5	49 (30.1)	114 (69.9)	
5 - 10	70 (36.1)	124 (63.9)	0.447
>10	15 (36.6)	26 (63.4)	

resident doctors in training there is a risk of depression, suicidal tendencies, and medical illnesses, hence the need for mental health as well as support services to this important group of doctors.

Positive predictors of burnout among resident doctors revealed in this study included work related family conflict. The residency period is highly loaded with psychological stressors [17] and the addition of work-related family conflict could lead to residents having a higher risk of becoming burned out. This was confirmed in our study by the fact that those who admitted having high work-related family conflicts were significantly associated with burnout, the same factor has been reported in other studies done elsewhere [18] [19] [20]. Inadequate support from residency program supervisors was also found to be a positive predictor of burnout among resident doctors in this study. Those who reported inadequate support from their supervisors where more likely to have burnout syndrome compared to those who reported adequate support. Other studies conducted elsewhere have reported similar findings [21] [22], in which they revealed work place social support was a major characteristic related to good performance. This is an important modifiable finding and has a greater implication in policy change.

The current study also found that senior residents in their third year of study were more likely to develop burnout, similar findings were reported by Dhusia *et al.* [21]. The increased experience usually accounts for higher working hours, increased workload and it is a time when they are working on their dissertations in our settings, combining all those, puts much pressure on them and may exacerbate the syndrome. Residents who perceived call duty as stressful in this study were more likely to develop burnout compared to those who perceived it as not stressful. Our results are in line with a systematic review done in Nigeria by Ogunsuji *et al.* [15], which reported perception of call duty as stressful to be positive predictors of burnout among resident doctors. This can be due to the fact that night calls are associated with heavy workload especially handling emergencies, sleep deprivation and few staffs normally present during night shifts in our hospitals.

There are some key limitations in this study: firstly, the study was conducted at tertiary teaching hospitals in Dar es Salaam region. Therefore, it may be diffi-

cult to generalize the findings to doctors across the country, and hence it may not reflect what is happening in other centers. Secondly, data collectors not collecting all data and so some are missing. Thirdly, information bias from participants and data collectors may have affected the quality of data.

5. Conclusions

The study has shown that burnout is prevalent among resident doctors in our setting and it has illuminated some factors that influenced burnout among resident doctors in residency training. There is therefore a need for directing preventive and intervention measures in the residency training program. Periodic assessment is also needed to mitigate factors associated with burnout among resident doctors.

What Is Known about This Topic?

- Burnout among medical doctors is a global phenomenon.
- Burnout can hinder optimal healthcare delivery.
- Healthcare providers are in prolonged exposure to job stressors.

What This Study Adds

- This study provides valuable insight into the burden of burnout syndrome among resident doctors in Tanzania hospitals.
- It also points out the need for support services to resident doctors in Tanzania.

Authors' Contributions

Edwin Rwebugisa Lugazia, Happiness Charles Sway, Respicious Lwezimula Boniface and Asha Abdullah conceived and designed the study. Happiness Charles Sway undertook the data collection and statistical analysis and wrote the first draft of the manuscript. All authors contributed to the intellectual content and approved the final manuscript.

Acknowledgements

We are grateful to the management and workers of Muhimbili National Hospital, Muhimbili Orthopaedic Institute, Jakaya Kikwete Cardiac Institute and Ocean Road Cancer Institute for their cooperation. This work was supported by Muhimbili University of Health and Allied Sciences (MUHAS).

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Appendix

A questionnaire

Prevalence and Factors Associated with Burnout Syndrome among resident Doctors at Tertiary Teaching Hospitals in Dar es Salaam, Tanzania

Serial number: _____

PART I: Socio-demographic and professional characteristics

1. Age … (years)

2. Gender

Male Female

3. Marital status

Married Single Widowed Separated

4. Do you have children?

Yes No

5. Employment status

Employed Not employed.

6. Do you smoke?

Yes No

7. Do you take alcohol?

No Yes

8. Practice of physical exercise

Yes No

9. History of any chronic disease?

Yes No

10. Accommodation status

At MUHAS hostels Outside MUHAS hostels

11. Year of study

1st year 2nd year 3rd year

12. Speciality/Department …

13. Studies sponsorship

Sponsored (Government/Private) Not sponsored (Self sponsorship)

14. Work related Autonomy?

Little Much

15. Work /studies related family conflicts

High Low None

16. Relationship with co-workers/colleagues

Good Bad

17. Average working hours per day…

18. Average night's sleep hours…

19. Number of days on calls per month

Less than 5 5 - 10 More than 10

20. How do you perceive call duties?…

Stressful Not stressing

21. How is your remuneration?

Adequate Not adequate No remuneration at all.

22. Perception of support from the supervisors

Adequate Not adequate No support at all.

23. Number of years working in the health care profession…

PART II:

MBI–Human Services Survey							
How Often	**0**	**1**	**2**	**3**	**4**	**5**	**6**
	Never	**A few times a year or less**	**Once a month or less**	**A few times a month**	**Once a week**	**A few times a week**	**Every day**

How Often

0 - 6 Statements

1. I feel emotionally drained from my work.
2. I feel used up at the end of the workday.
3. I feel fatigued when I get up in the morning and have to face another day on the job.
4. I can easily understand how many my recipients feel about things.
5. I feel treat some recipients as if they were impersonal objects.
6. Working with people all day is really a strain for me.
7. I deal very effectively with the problems of my recipients.
8. I feel burned out from my work.
9. I feel I'm positively influencing other people's lives through my work.
10. I've become more unsympathetic toward people since I took this job.
11. I worry that this job is hardening me emotionally.
12. I feel very energetic.
13. I feel frustrated by my job.
14. I feel I'm working too hard on the job.
15. I don't really care what happens to some recipients.
16. Working with people directly puts too much stress on me.
17. I can easily create a relaxed atmosphere with my recipients.
18. I feel very happy working closely with my recipients.
19. I have accomplished many worthwhile things in this job.
20. I feel like I'm at the end of my rope.
21. In my work, I deal with emotional problems very calmly.

International Journal of Clinical Medicine, 2022, 13, 50-56
https://www.scirp.org/journal/ijcm
ISSN Online: 2158-2882
ISSN Print: 2158-284X

Study on the Changes and Correlation of Related Immune Factors before and after Chemotherapy in Non-Small Cell Lung Cancer

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How to cite this paper: Zhang, J.J., Song, D.B., Dong, Y., Bai, L., Gao, D.Q., Zhang, S.L., Guo, Y., Li, F.B., Yu, X.L. and Li, Q.S. (2022) Study on the Changes and Correlation of Related Immune Factors before and after Chemotherapy in Non-Small Cell Lung Cancer. *International Journal of Clinical Medicine*, **13**, 50-56.
https://doi.org/10.4236/ijcm.2022.131004

Received: December 20, 2021
Accepted: January 16, 2022
Published: January 19, 2022

Abstract

Objective: To investigate the changes of related immune cytokines (Dendritic Cells (DC) cells, $CD4^+$, $CD8^+$, Th17, IgG, IgM, IgA) in patients with non-small cell lung cancer (NSCLC) before and after chemotherapy. **Methods:** Eighty-five NSCLC patients who were treated in the Oncology Department of the Affiliated Hospital of Chengde Medical College from December 2018 to February 2021 were selected as the research objects, and the patients were analyzed at different time points (before chemotherapy, after the first chemotherapy, and after the second chemotherapy) Changes in the expression levels of DC cells, $CD4^+$, $CD8^+$, Th17, IgG, IgM, IgA in peripheral blood, and explore their correlation. **Results:** Before chemotherapy, after the first chemotherapy, and after the second chemotherapy, the peripheral blood $CD4^+$ and $CD8^+$ were significantly increased, and the Th17, IgG, IgM, and IgA levels gradually decreased. The difference was statistically significant. But there was no obvious change in DC cells. **Conclusion:** There is no significant change in DC cells in peripheral blood of NSCLC patients before and after chemotherapy. $CD4^+$ and $CD8^+$ are significantly increased, Th17, IgG, IgM, and IgA levels are all decreased, which is a manifestation of impaired immune function of patients after chemotherapy.

Keywords

Non-Small Cell Lung Cancer, Chemotherapy, Immune-Related Factors

1. Introduction

Lung cancer currently accounts for the first place in the incidence and mortality

of malignant tumors among adults in my country [1]. NSCLC as the main type of lung cancer, has a 5-year survival rate of only 15%, while the 5-year survival rate of patients with clinical stage I is as high as 80% to 90% [2]. Therefore, early diagnosis and treatment are an important part of improving the prognosis of patients. However, the early stage of NSCLC has no obvious clinical symptoms. Most patients are in the advanced stage of the disease at the time of diagnosis, and have lost the opportunity for surgical treatment. They can only use radiotherapy, chemotherapy, and targeted therapy. Targeted therapy is generally only suitable for patients with sensitive gene mutations [3], and the indications for radiotherapy are also relatively limited [4], so chemotherapy is still the main treatment method, and it plays an important role in controlling disease progression and prolonging survival. However, the side effects of chemotherapy are large, which reduces the patient's quality of life. How to reduce the side effects of chemotherapy and improve its anti-tumor effect is a hot topic of research in recent years. The proposal and gradual application of immunotherapy have brought some optimistic changes to the treatment of tumors. Immunotherapy mainly works by stimulating the immune factors in the human body. In order to explore the relationship between chemotherapy and various immune factors as well as various immune factors, we conducted this study and look forward to helping patients.

2. Objects and Methods

2.1. Research Objects

A total of 85 NSCLC patients who were treated in the Oncology Department of the Affiliated Hospital of Chengde Medical College from December 2018 to February 2021 were selected as the research objects. There were 48 males and 37 females. The age ranged from 30 to 78 years old, with an average age (62.21 ± 6.15) years old. There were 22 cases of lung squamous cell carcinoma, 57 cases of lung adenocarcinoma, and 6 cases of lung adenosquamous carcinoma. TNM staging: 23 cases in stage III and 62 cases in stage IV. Inclusion criteria: 1) NSCLC at the first visit and confirmed by histopathology, TNM staging is based on the AJCC staging standard (8th edition) [5]; 2) Age 18 to 80 years; 3) Pathology and imaging there is no indication for surgery in the scientific assessment; 4) KPS score ≥ 60 points; 5) The expected survival time is more than 3 months. Exclusion criteria: 1) Patients with surgical indications requiring surgery. 2) Patients with severe heart, lung, liver, kidney and other vital organ dysfunctions who cannot tolerate chemotherapy.

2.2. Chemotherapy

The chemotherapy regimen is cisplatin/carboplatin + pemetrexed/gemcitabine/paclitaxel. Dosage: pemetrexed 500 mg/m^2, gemcitabine 1250 mg/m^2, paclitaxel 175 - 200 mg/m^2, cisplatin 75 mg/m^2, carboplatin AUC = 6, intravenous drip administration, 21 days as a cycle.

2.3. Research Methods

All patients were drawn with 10 ml of fasting venous blood in the morning before chemotherapy (T1), on the 21st day after the first chemotherapy (T2), and on the 21st day after the second chemotherapy (T3). Separate the core for 20 minutes (centrifugation radius 14 cm), take the supernatant and place it in a refrigerator at −80˚C for later use. The enzyme-linked immunosorbent assay was used to detect the levels of DC cells, $CD4^+$, $CD8^+$, Th17, IgG, IgM, and IgA in the serum. Each factor detection kit was purchased from Kangtai Heyuan Biotechnology Co, Ltd. (Beijing).

2.4. Statistical Analysis

The data analysis of this study was carried out using SPSS 22.0. Measurement data conformed to a normal distribution and expressed as mean ± standard deviation, using t test, measurement data using χ^2 test, and Pearson correlation analysis of the correlation between DC cells and $CD4^+$, $CD8^+$, Th17, IgG, IgM, IgA at each time point. All P values are two-sided tests, and $P < 0.05$ indicates that the difference is statistically significant.

3. Results

1) The patient's general information, including age, gender, pathological type, and TNM staging are comparable. See Table 1 for details.

2) $CD4^+$ and $CD8^+$ were significantly increased before chemotherapy, after 1 cycle of chemotherapy, and after 2 cycles of chemotherapy, Th17, IgG, IgM, and IgA levels gradually decreased, and each factor was significantly different at different time points ($P < 0.05$). See Table 2 for details.

3) Pearson correlation analysis showed that: at different time nodes (before chemotherapy, after the first chemotherapy, after the second chemotherapy), the peripheral blood DC cells of patients had no correlation with other factors. See Table 3 for details.

4. Discussion

For patients with advanced lung cancer, chemotherapy is one of the most commonly used treatment methods [6]. The chemotherapy regimen containing cisplatin is the first-line chemotherapy regimen for advanced lung cancer, but after its treatment, there will be more serious complications due to its side effects, which affects the quality of life and limits its clinical application to a certain extent [7]. Nowadays, the development of tumor science is gradually developing

Table 1. Basic clinical data of patients.

age	Gender (Male/Female)	Pathological type (squamous cell carcinoma/adenocarcinoma/ adenosquamous carcinoma)	Stage (III/IV)
62.21 ± 6.15	48/37	22/57/6	23/62

Table 2. Changes in the levels of peripheral blood DC cells, $CD4^+$, $CD8^+$, Th17, IgG, IgM, IgA over time.

parameter	DC cells	$CD4^+$ (%)	$CD8^+$ (%)	Th17	IgG	IgM	IgA
T1	1.57 ± 0.219	27.32 ± 2.02	26.23 ± 2.21	3.42 ± 0.26	12.31 ± 1.12	1.53 ± 0.21	1.62 ± 0.14
T2	1.50 ± 0.225	29.18 ± 2.57	31.89 ± 3.48	3.28 ± 0.17	11.01 ± 1.02	1.25 ± 0.12	1.16 ± 0.11
T3	1.53 ± 0.231	33.98 ± 2.71	33.34 ± 4.04	2.53 ± 0.29	10.58 ± 1.25	0.98 ± 0.14	0.97 ± 0.12
P value	0.405	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Comparison within the group (P value)							
T1 vs. T2	0.252	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
T1 vs. T3	0.600	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
T2 vs. T3	0.375	<0.001	<0.001	0.006	<0.001	<0.001	<0.001

Table 3. Correlation between DC cells and various factors at each time node.

parameter	DC cells (T1)		DC cells (T2)		DC cells (T3)	
	r	P	r	P	r	P
$CD4^+$ (%)	−0.036	0.754	0.039	0.773	−0.254	0.094
$CD8^+$ (%)	0.067	0.7	−0.001	0.992	0.278	0.066
Th17	0.105	0.437	−0.083	0.529	0.035	0.715
IgG	0.099	0.505	0.177	0.228	−0.084	0.562
IgM	0.078	0.412	0.045	0.315	0.097	0.213
IgA	0.101	0.395	0.056	0.574	0.045	0.075

towards the internal environment and human autoimmunity, and how to stimulate the human body environment and autoimmunity in the process of anti-tumor treatment is particularly important [8] [9].

At present, immunotherapy has become a new treatment method for tumors. [10] [11] [12] Compared with chemotherapy, immunotherapy has stronger specificity and fewer side effects, and it also has a corresponding impact on the quality of life of patients. Decrease, so the research of immunotherapy has attracted much attention. Due to the extensive targeting of chemotherapy, it kills tumor cells and also destroys the body's own immune system. The impact of different immune factors is unknown. When chemotherapy and immunotherapy work together, the human body has a synergistic or antagonistic effect, or dif-

ferent timings have different coordination effects. The optimal timing of combination therapy is unclear [13] [14]. Therefore, it is of great significance to study the changes of various immune factors before and after chemotherapy and their correlation.

DC cells are the most popular antigen-presenting cells in recent years. With the deepening of research, it has been discovered that cells are the most powerful antigen-presenting cells in the human body. A large number of studies have shown that [15] [16], DC cells play an irreplaceable role in the body's immune response, so anti-tumor research is also closely related to DC cells.

Cellular immunity is considered to be an important mechanism of the body's anti-tumor [17], and the cells that exert immune effects are mainly T lymphocytes. T lymphocyte subsets include $CD4^+$ helper T cells and $CD8^+$ suppressor T cells. $CD4^+$ cells assist cellular immune response and humoral immunity. $CD8^+$ cells mainly inhibit the synthesis and secretion of antibodies and T cell proliferation. The relative distribution of $CD4^+$ and $CD8^+$ cells reflects the body Anti-tumor immune status.

Humoral immunity is an important line of defense for the body's immunity. IgM, IgA, and IgG constitute the main antibodies of humoral immunity, which were once studied abroad as indicators for judging prognosis [18]. Th17 plays an important role in tumor immunity and can help tumor cells achieve immune escape and immune tolerance, so as not to be eliminated by the body's immune system [19].

Our research found that in the course of chemotherapy, as the cycle of chemotherapy increases, there is no significant change in DC cells in the peripheral blood. $CD4^+$ and $CD8^+$ are significantly increased, and Th17, IgG, IgM, and IgA levels are all decreased, which may be one of the mechanisms by which the patient's immune function is suppressed. Therefore, it is very necessary to improve the body's immunity and increase immunotherapy in the early stage of chemotherapy. At the same time, the mechanism by which DC cells are not affected is still unclear and needs to continue to be studied, but it is not excluded that DC cells participate in tumor-related pathways and are continuously activated by tumor-related factors without being affected by chemotherapy. If DC cells can be found to participate in tumor response targets, there may be better anti-tumor therapies. At the same time, there is no correlation between DC cells and other factors, and further research is needed to prove that, after all, the human body is the product of a variety of internal environmental chemical reactions, and a single non-correlation does not mean that it is absolutely irrelevant. This study needs to continue to expand the sample size and extend the research period to further confirm this conclusion.

5. Conclusion

There was no significant change in DC cells in peripheral blood of NSCLC patients before and after chemotherapy. $CD4^+$ and $CD8^+$ were significantly in-

creased, Th17, IgG, IgM, and IgA levels were all decreased. DC cells were not related to other factors, which may be the patient's immune function One of the frustrating mechanisms.

Fund

S & T Program of Chengde (201804A030).

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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International Journal of Clinical Medicine, 2022, 13, 57-65
https://www.scirp.org/journal/ijcm
ISSN Online: 2158-2882
ISSN Print: 2158-284X

What Factors Influence the Choice of Anesthesiology in a Moroccan Medical School?

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How to cite this paper: Hachimi, A., Rachda, S., El-Alaoui, M., Bouebazebi, L.B., Belmaati, R., Essafti, M., Saroukh, F.-E. and Amine, M. (2022) What Factors Influence the Choice of Anesthesiology in a Moroccan Medical School? *International Journal of Clinical Medicine*, **13**, 57-65.
https://doi.org/10.4236/ijcm.2022.131005

Received: October 28, 2021
Accepted: January 21, 2022
Published: January 24, 2022

Abstract

Objective: To determine factors influencing anesthesiology choice among resident doctors at the medical school of Marrakech. Materials and Methods: We have conducted a descriptive cross-sectional study based on an anonymous questionnaire. Results: A total of 406/672 questionnaires were returned, with a female/male sex ratio of 1.07. The duration of the training (OR: 3.3; CI 95%: 1.74 - 6.23; $p < 0.001$), intellectual challenge (OR: 3.02; CI 95%: 1.69 - 5.37; $p < 0.001$), doctor-patient relationship (OR: 2.22; CI 95%: 1.02 - 4.84; p: 0.04), and financial aspects (OR: 2.14; CI 95%: 1.09 - 4.21; p: 0.02) were independent factors that influenced the choice of anesthesiology. Conclusion: we recommend the succeeding: 1) Support students in their choice; 2) Correct misconceptions about certain specialties; 3) Promote clinical clerkship; 4) Encourage mentorship; 5) Increase the salary of at-risk specialties.

Keywords

Anesthesiology, Career Choice, Influencing Factors, Resident Doctor

1. Introduction

Any health policy with good performance indicators and responsiveness to critical situations is conditioned by the availability of human resources in sufficient quantity and quality. The Moroccan Ministry of Health has published a health map that gives an overview of the healthcare workers in 2019 for 35,478,393 inhabitants [1]. In the public sector, the number of doctors was 12,034, including 3857 general practitioners, 7559 specialist doctors, 458 dentists, and 160 phar-

macists. Morocco faces a shortage of medical specialists in the public sector. This sector has counted only 492 pediatricians, 456 gynecologists, 439 anesthesiologists, 402 radiologists, 350 traumatologists, 344 visceral surgeons, 330 ophthalmologists, 309 cardiologists, 255 nephrologists, 222 psychiatrists, 211 dermatologists, and 185 urologists. For some specialties, the situation is alarming, particularly for neurosurgery (134 physicians), oncology (107 physicians), hematology (63 physicians), nuclear medicine (47 physicians), and critical care medicine (42 physicians).

According to social background, many factors affect anesthesiology choice as a career; these factors vary from one country to another. In a sizeable Brazilian cohort among 4601 medical students, Guilloux *et al.* [2] identified the factors that impacted the decision to pursue anesthesiology as a career: gender male ($p = 0.000$), other medical doctors in the family ($p = 0.014$), prefer to work in the hospital ($p = 0.002$), prestige ($p = 0.018$), and the social responsibility ($p = 0.030$).

It would be interesting to know the criteria determining the career choice to provide well-founded elements for decision-makers to correct the imbalance in the distribution of different specialties. Consequently, we surveyed resident doctors of the Faculty of Medicine and Pharmacy of Marrakech to highlight the factors influencing anesthesiology choice.

2. Materials and Methods

2.1. Setting

The setting of this study was the Faculty of Medicine and Pharmacy of Marrakech, Morocco. It produces general practitioners and surgical/medical specialists. The medical curriculum includes three cycles; the first lasts two years, the second lasts three years, and the third lasts two years, followed by 2-year internship and residency programs of varying lengths of time according to specialty. The residency program is also accessible for non-intern students after the three cycles and thesis defense.

2.2. Study Design

We performed a cross-sectional observational study on the residents' perceptions to determine factors influencing their choice over four months (June to September 2019). We included all residents of our institution in grades 1 through 4/5 in a self-administered survey. We conceived and adapted the questionnaire based on the Murdoch *et al.* study [3]. It comprehended two sections; the first contained socio-demographic data and information about specialty and the second contained factors influencing their choice. It was distributed at clinical training wards by a resident doctor. We used a 5-Likert scale ranging from strongly disagree (1) to strongly agree (5).

Reliability coefficients for the questionnaires were determined, resulting in an alpha Cronbach (α) of 0.817.

2.3. Statistical Analysis

The data were analyzed using the SPSS 10.0 software package (IBM, Armonk, NY). Statistical analysis was descriptive, univariate, and multivariate. Qualitative variables were presented by numbers (n) and percentages (%), and quantitative variables by means (m) and standard deviations S.D. (±). For comparing categorical variables, we used: Fisher Exact test or Chi-square test in univariate analysis and binary logistic regression in multivariate analysis for anesthesiology. A p-value of <0.05 was considered significant.

2.4. Ethical Aspects

Ethically, participation was voluntary and anonymous, and the confidentiality of the information collected during the study was guaranteed. We afforded information notes to all participants before filling the questionnaire.

3. Results

Of the 672 questionnaires distributed, 406 were returned (60.4%). The mean age was 29 ± 2.2 years, and the female/male sex ratio was 1.07. **Table 1** summarizes the remaining socio-demographic characteristics of the 406 resident doctors.

In the univariate analysis, duration of the training ($p < 0.001$), interest in the practice of procedures ($p < 0.001$), intellectual challenge ($p = 0.01$), and financial aspects ($p = 0.03$) were the influencing factors. In the multivariate analysis, duration of the training, intellectual challenge, doctor-patient relationship, and financial aspects were independent factors that influenced anesthesiology choice. Besides, the participants did not choose it because of the absence of a mentor model, overloading work, and lack of time for family (**Table 2**).

4. Discussion

In Morocco, we have had 1.2 anesthetists/100,000 inhabitants, according to the recent statistics in 2019 [1]. However, the goal of the World Health Organization, the World Federation of Societies of Anesthesiologists, and the Lancet Commission on Global Surgery is at least 20 SAO (surgeon-anesthetist-obstetrician) per 100,000 population by 2030 to ensure safe anesthesia [4] [5].

Factors affecting the choice of anesthesiology as a career vary from one country to another and according to social background. In our context, these factors were duration of the training (four years for medical specialties compared to surgical ones), intellectual challenge, doctor-patient relationship, and financial aspects. Oku *et al.* [6], in Nigeria among 105 graduating medical students at the University of Calabar, stated that the predictors for choosing anesthesia were personal interests in 81%, future job opportunities in 63%, the requirement of specialized skill in 62%, and influence by a mentor in 30%. Among 183 undergraduate final-year students of the University of Ghana School of Medicine and Dentistry, Abdul-Rahman *et al.* [7] showed that causes for not choosing anesthesia were anesthesia is "boring and not interesting", "complex and difficult to understand", "delicate and risky" and very "demanding".

Table 1. Socio-demographic characteristics of the 406 participants.

Variables		Number (n)	Percentage (%)
Geographic origin	Rural	49	12
	Urban	357	88
Home medical school	Marrakech	366	90
	Others	40	10
Marital status	Single	274	67.5
	Married	132	32.5
Father's education level	Illiterate	24	6
	Primary	21	5
	Secondary	24	6
	High school	53	13
	University	284	70
Mother's education level	Illiterate	61	15
	Primary	42	10
	Secondary	32	8
	High school	49	12
	University	222	55
Parents' profession	Healthcare worker	69	17
	Physician	35	51 (35/69)
Year of the residency study	First	162	40
	Second	101	25
	Third	61	15
	Fourth	65	16
	Fifth	17	4
Specialty	Obstetric Gynecology	37	9
	Anesthesiology	32	8
	Traumatology	20	5
	Ophthalmology	20	5
	Pediatrics	20	5
	Cardiology	20	5
	Visceral surgery	20	5
	Radiology	20	5
	Biology	16	4
	Endocrinology	16	4

Continued

	Gastrohepatology	16	4
	Oncology-Radiotherapy	16	4
	Psychiatry	12	3
	Urology	12	3
	Neurosurgery	12	3
	Nephrology	12	3
	Dermatology	12	3
	Maxillo-facial surgery	12	3
	Ear nose and throat	12	3
	Neurology	12	3
	Pneumology	12	3
	Hemato	9	2
	Pathology	9	2
	Rheumatology	9	2
	Internal medicine	9	2
	Others	9	2

Table 2. Independent factors for the choice of anesthesiology.

Factors	Odds ratio	95% CI	p
Duration of the training	3.3	1.74 - 6.23	<0.001
Doctor-patient relationship	3.02	1.69 - 5.37	<0.001
Intellectual challenge	2.22	1.02 - 4.84	0.04
Financial aspects	2.14	1.09 - 4.21	0.02
Influence of mentor model	0.20	0.07 - 0.57	0.003
Work overload	0.25	0.12 - 0.54	<0.001
Time for the family	0.22	0.10 - 0.46	<0.001

In Punjab and among 185 post-graduate students and consultants, Asad *et al.* [8] indicated that the most frequent factors that influenced the choice were the opportunity to do procedures in 65.9%, promotion prospects in 58.4%, time for family in 58.4%, the chance of an overseas job in 55.7%, the diversity of clinical specter in 54.6%, and intellectual challenge in 50.8%. In Saudi Arabia at the King bin Abdulaziz University for Health Sciences and among 236 medical students in the 5th and 6th years, Alkhilaiwi *et al.* [9] mentioned that lifestyle in 30%, influence from family/peers in 19%, patient care aspects in 17%, fundamental science/research aspect in 15%, and financial aspect in 14% affected the decision for anesthesiology. In India, among 190 post-graduate anaesthesiology students at

the UCMS and GTB Hospital-Delhi, Tyagi *et al.* [10] reported that income in 67.7%, the opportunity to perform procedures in 64.1%, the diversity of clinical specter in 63.8%, the chance of overseas work in 57.2%, time for family in 53.7%, intellectual challenge in 51.6%, and the inaccessibility of other specialties in 50% were the affecting factors.

In Brazil, Guilloux *et al.* [2] conducted a national survey among 4601 new medical school graduates in 2015. They noted that the factors that impacted the decision to pursue anesthesiology as a career were gender male (RR: 1.394; 95% CI: 1.234 - 1.574; p = 0.000), other medical doctors in the family (RR: 1.431; 95% CI: 1.081 - 1.896; p = 0.014), prefer to work in the hospital (RR: 4.583; 95% CI: 1.632 - 12.871; p = 0.002), prestige (RR: 1.312; 95% CI: 1.052 - 1.637; p = 0.018), and the social responsibility (RR: 1.297; 95% CI: 1.026 - 1.638; p = 0.030).

In Scotland, using a mixed-method design including a questionnaire survey and qualitative interviews among 42 new registered core and Acute Care Common Stem anesthesia trainees, Moore *et al.* [11] observed that the most critical determinants were the quality of training, personal health, senior support, staffing level, sustainability of working conditions, the morale of the team, future job prospects, and the equity of payment. In the USA, among 55 residents in the anesthesiology residency at Mayo Clinic in Rochester in 2011, Augustin *et al.* [12] found that the most important reasons for choosing anesthesiology were a "hands-on" specialty in 49%, acute critical care in 33%, opportunity to perform invasive procedures in 31%, immediate gratification in work in 31%, and the involvement of physiology and pharmacology in practice in 21%.

This study had some limitations. First, it was monocentric. A national survey could be interesting to compare with other countries. Secondly, we used the questionnaire as a method for this study. A mixed-method design with qualitative reviews can clarify further item details. Thirdly, our subjects were resident doctors. A survey including medical students of the first cycle is interesting given that some traits could be changed over the years.

5. Conclusion

We recommend the succeeding: 1) Support students in their choice; 2) Correct misconceptions about certain specialties; 3) Promote clinical clerkship; 4) Encourage mentorship; 5) Increase the salary of at-risk specialties.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Appendix: Questionnaire

A) Socio-demographic characteristics:

1) Age: …years Gender: M ☐ F ☐

2) Geographic origin: urban ☐ rural ☐

3) Faculty of medicine: Faculty of Marrakech ☐ Other faculties ☐

4) Marital status: Married ☐ Single ☐

5) Father's education level: illiterate ☐ Primary ☐ Secondary ☐ High school ☐ University ☐

6) Mother's education level: illiterate ☐ Primary ☐ Secondary ☐ High school ☐ University ☐

7) Do your mother or father is a healthcare worker? No ☐ Yes ☐, if yes: Physician ☐ Other ☐

8) Year of the residency training: 1st ☐ 2nd ☐ 3rd ☐ 4th ☐ 5th ☐

9) Specialty: …

B) Criteria influencing the choice: Please rate each of the following items on a scale from 1 to 5 (1-Strongly disagree, 2-Disagree, 3-Neither disagree nor agree, 4-Agree, 5-Strongly agree) regarding their influence on your choice.

	1	2	3	4	5
Hospital training completed during the externship					
Content and quality of teaching of lectures					
Attended workshops, round tables and conferences					
Training during the intership					
Duration of the residency training					
Prestige and status of the specialty					
Intellectual challenge					
Desire practice in academic setting					
Enjoy tending to patients' social and psychological needs					
Interest in procedures and surgical techniques					
Occupational risks (radiation, infectious diseases					
Medico-legal risks					
The pedagogical approach of the teachers of the department					
Ward atmosphere (organization, medical and paramedical staff, etc.)					
Shift pace and workload					
Flexible working hours					
Availability of employment in the liberal sector					
Assignment at the end of the specialty training					
Financial aspects					

Continued

Your spouse's career and location
Personal profile (stress, etc.)
Socio-economic level (requirement of significant investment)
Influence of someone (parents, relatives, friends)
Life experience/Emotional shock
Health reason
Lifestyle

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