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TIMOK MEDICAL GAZETTE

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C O N T E N T S

ORIGINAL PAPERS

REVIEW ARTICLE

THE ASSESSMENT OF THE INFLUENCE OF RELIGIOSITY AND EXISTENTIAL WELL-BEING ON THE CONSUMPTION OF ALCOHOL OF THE ADULT POPULATION OF THE ORTHODOX RELIGION

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Apstract: Background/Aim: Excessive consumption of alcohol is the important public health problem. Individual attitudes toward religion and God as well as the level of perceived meaning of one's own life are important predictors of a wide spectre of attitudes and behaviors including alcohol consumption. The research aimed to determine frequency of consumption of alcohol of adults of Orthodox religion and to estimate the correlation between the determined consumption and religiosity and existential well-being. Methods: The research is cross-sectional study implemented in the period of three months, from August 1 st 2021. to November 1 st 2021 year. The sample consisted of 103 randomly chosen adults, 57 (55,3%) males and 46 (44.7%) females, approximately 44.7 ± 10.45 years old. The instrument of the research was the Alcohol Use Disorders Identification Test (AUDIT) and two subscales of the Spiritual Well-Being Scale (SWBS): the Religious Well-Being subscale (RWB) and the Existential Well-Being Subscale (EWB). Contingency tables were used in statistical data analysis. Results: Alcohol weren't consumed by 21 (20.4%) respondents, while 82 (79.6%) consumed it with different frequency (low-risk drinking 53.4%, risky drinking 16.5%, harmful drinking 2.9% and abuse alcohol 6.8%). Moderate religiosity had 68% of respondents, low 3.9% and high 29.1%. Moderate existential well-being was achieved by 68% of respondents, high by 24.2% and low by 7.8%. Highly significant statistical correlation was determined at the level of p <0,0001 of the alcohol consumption pattern with religiosity and existential well-being of the respondents. Conclusion: Almost 80% of participants in the research consume alcohol, of which two thirds low-risk drinking. The participants with intensive religiosity as well as high existential well-being significantly less or never consume alcohol, compared to the participants who are moderately or low religiosity and existential well-being.
Keywords: alcohol, religion, existence, well-being.

INTRODUCTION

Alcohol consumption is increasingly a socially acceptable activity, favored to the level of a mandatory ritual in many social situations [1]. Globally, approximately 90% of people consume alcohol at some point in their lives, while 3-5% is women and 10% are addicted to alcohol[1]. Alcohol is a risk factor for 60 different medical conditions, and more than 4% of diseases are directly related to alcohol consumption [2]. The economic burden of alcohol consumption is estimated at more than 1% of the gross national product in middle-developed and highly developed countries [3]. Tolerance of the environment to alcohol consumption is high, so from the intake of small doses of alcohol to clinical and physical signs of intoxication, a lot of valuable time passes[4]. Society enters the scene too late, usually with its system of condemnation and isolation4. As a result, alcohol abuse causes approximately 3 million deaths each year (5.3% of deaths) [3].

Spirituality encompasses the existential need of each individual to find answers and discover the purpose of life as well as the need to believe in something greater than ourselves that connects all people with each other [5,6]. Existential well-being implies a sense of the meaning and purpose of existence, competence and the ability to accept limitations [7]. Low levels of perceived meaning of one's own life predispose to excessive alcohol consumption [8]. The content and clarity of religious norms on alcohol use and the religiosity of the individual determine the influence of religion on alcohol consumption [9]. Christianity has prescribed norms on the use of wine (not alcohol) in worship, but does not restrict moderate consumption of alcohol (strong drinks), for refreshment or health reasons [10]. The religiosity of the individual is a significant modifier of the structure of values, as well as an important predictor of a wide range of attitudes and behaviors, including alcohol consumption4.

The aim of the research was to determine the frequency of alcohol consumption and to assess the connection between the determined consumption and the religiosity and existential well-being of the adult population of the Orthodox religion in Krupa na Uni.

METHODS

The test as a cross-sectional study was conducted in a period of three months, from 01.08.2021. to 11.01.2021. The respondents were registered in the family medicine team of the Primary Health care Center of the Krupa Health Center in Uni. During the regular work in the family medicine Center, 103 adults aged 20 to 65 were selected by random sampling. The study did not include people diagnosed with alcoholism spectrum disorder or syndrome involved in treatment, rehabilitation and resocialization, people with mental illness or disorder, malignant and advanced chronic diseases. Data were collected on the basis of anamnesis, available medical documentation and filling out specific questionnaires.

The Alcohol Use Disorders Identification Test (AUDIT) was developed and recommended by the World Health Organization for the early identification of risky and harmful drinking as well as alcohol dependence [11,12]. It consists of three questions in the field of risky alcohol use (frequency of drinking, typical amount, frequency of heavy drinking), four questions in the field of harmful alcohol use (guilt after drinking, amnesia, injuries due to alcohol consumption, environmental concerns) and three questions (decreased control over drinking, increased desire to drink, morning drinking) which are scored 0-4 [11,12]. The measuring range ranges from 0 (not drinking) to 40 (alcohol abuse). A total score of 0 indicates non-consumption of alcohol, 1-7 on low-risk drinking, 8-15 on risky drinking and 20-40 on alcohol abuse [11,12]. The questionnaire has acceptable internal reliability (Cronbach's alpha coefficient 0.86) [13].

The Spiritual Well-Being Scale (SWBS) assesses two dimensions of spiritual well-being, religiosity and existential well-being [14,15]. The Religious Well-Being subscale (RWB) evaluates the relationship with God, while the Existential Welfare subscale (EWB) analyses the sense of meaning and purpose of existence, competence and ability to accept limitations [14,15. The subscales contain ten questions with answers on the Likert scale of 6 points ranging from "strongly agree" (1) to "strongly disagree" (6) [14,15]. Eight questions were written in the reverse direction and the reverse was scored [14,15]. The measuring range of the questionnaire ranges from 20 to 120, the measuring range of the subscale from 10 to 60 [14,15]. The overall questionnaire score of 20 to 40 indicates low, 41 to 99 moderate, and 100 to 120 high spiritual well-being [14,15]. The total result of the subscale from 10 to 20 is interpreted as low, from 21 to 49 as moderate and from 50 to 60 as high religiosity or existential well-being [14,15]. The subscales have acceptable internal reliability (Cronbach's alpha coefficients 0.91 and 0.84) [14,15]. For specific purposes, e.g. focusing only on religiosity and / or only on existential well-being, the authors allow individual use of subscales [14].

Contingency tables based on the nonparametric Chi square test were used to determine statistical significance. The significance level is set to 95% confidence interval. The results are presented textually and tabular, the complete work is processed in the text of the Microsoft Word processor for Windows. P values that could not be expressed to a maximum of three decimal places are shown as $p < 0.001$ [16].

RESULTS

The study included 103 adults aged 20 to 65 years. Among them were 57 (55.3%) men and 46 (44.7%) women. The mean age of the examined population was 44.7 ± 10.45 years.

Alcohol was not consumed by 21 (20.4%) participants in the study, while 82 (79.6%) consumed it with different frequency (low-risk drinking 53.4%, risky drinking 16.5%, harmful drinking 2.9% and alcohol abuse 6.8%).

Risky drinking was found in 15 (14.6%) men, harmful drinking in 3 (2.9%) and alcohol abuse in 6 of them (5.8%). Harmful drinking was not found in women, 2 (1.9%) women drank at risk and 1 (1%) abused alcohol. Males were significantly more likely to consume alcohol ($p < 0.0001$). Table 1.

Table 1: . Interrelations between a participants' gender and alcohol drinking forms according to the Alcohol Use Disorders Identification Test score

GENDER	ALCOHOL DRINKING FORMS						
	Don't drink*	Low risk drinking**	Risky drinking***	Harmful drinking ****	Alcohol abuse *****	Total	p value 1
Men	3 (2.9%)	30 (29.1%)	15 (14.6%)	3 (2,9%)	6 (5.8%)	57 (55.3%)	< 0.0001

Women	18 (17.5%)	25 (24.3%)	2 (1.9%)	0 (0,0%)	1 (1.0%)	46 (44.7%)	
Total	21 (20.4%)	55 (53.4%	17 (16.5%)	3 (2.9%)	7 (6.8%)	103 (100%)	

*AUDIT score 0; **AUDIT score 1-7; ***AUDIT score 8-15; **** AUDIT score 16-19; ***** AUDIT score 20-40; 1p according to Chi Quadrat Test.

Out of a total of 16 (15.5%) respondents aged 20 to 34, none abused alcohol, while only 1 (1%) consumed alcohol within the limits of harmful drinking. Out of a total of 49 (47.6%) respondents aged 35 to 49, none consumed alcohol within the limits of harmful drinking, while 3 (2.9%) abused alcohol. Of the remaining 38 (36.9%) respondents aged 50 to 65, 2 (1.9%) consumed alcohol within the limits of harmful drinking, while 4 (3.9%) abused alcohol. Age did not have a significant effect on alcohol consumption (p = 0.587). Table 2.

Table 2. Interrelations between a participants' age structure and alcohol drinking forms according to the Alcohol Use Disorders Identification Test score

AGE STRUCTURE	ALCOHOL DRINKING FORMS						
	Don't drink*	Low risk drinking**	Risky drinking***	Harmful drinking ****	Alcohol abuse *****	Total	p value 1
20-34 years	3 (2.9%)	10 (9.7%)	2 (1.9%)	1 (1.0%)	0 (0.0%)	16 (15,5%)	0.587
35-49 years	11 (10.7%)	28 (27.2%)	7 (6.8%)	0 (0.0%)	3 (2.9%)	49 (47.6%)	
50-65 years	7 (6.8%)	17 (16.5%)	8 (7.8%)	2 (1.9%)	4 (3.9%)	38 (36.9%)	
Total	21 (20.4%)	55 (53.4%	17 (16.5%)	3 (2.9%)	7 (6.8%)	103 (100%)	

*AUDIT score 0; **AUDIT score 1-7; ***AUDIT score 8-15; **** AUDIT score 16-19; ***** AUDIT score 20-40; 1p according to Chi Quadrat Test.

Low religiosity was found in 3 (2.9%) respondents, moderate in 70 (68.0%), while 30 (29.1%) were highly religious. The average value of the subscale of religiosity of the respondents was 41.75 (moderate religiosity) with an average deviation of 10.23. In the group of low-religious respondents, there were no respondents who do not drink and consume alcohol within the limits of low-risk drinking. On the other hand, in the group of highly religious respondents, there were no respondents who drink or abuse alcohol. A significant correlation/influence of religiosity on alcohol consumption was found among the respondents (p <0.0001). Table 3.

Table 3: Interrelations between a participants' religiosity according to po Religious Well-Being score and alcohol drinking forms according to the Alcohol Use Disorders Identification Test score

*AUDIT score 0; **AUDIT score 1-7; ***AUDIT score 8-15; **** AUDIT score 16-19; ***** AUDIT score 20-40; 1p according to Chi

RELIGIOSITY	ALCOHOL DRINKING FORMS						
	Don't drink*	Low risk drinking**	Risky drinking***	Harmful drinking ****	Alcohol abuse *****	Total	p value 1
Low2	0 (0.0%)	0 (0.0%)	1 (1.0%)	1 (1.0%)	1 (1.0%)	3 (2.9%)	< 0.0001
Moderate3	8 (7.8%)	39 (37.9%)	15 (14.6%)	2 (1.9%)	6 (5.8%)	70 (68.0%)	
High4	13 (12.6%)	16 (15.5%)	1 (1.0%)	0% (0.0%)	0% (0.0%)	30 (29.1%)	
Total	21 (20.4%)	55 (53.4%)	17 (16.5%)	3 (2.9%)	7 (6.8%)	103 (100%)	

Quadrat Test. ; RBW score 10-20; 3RBW score 21-49; 4RBW score 50-60.

Low existential well-being was found in 8 (7.8%) respondents, moderate in 70 (68.0%) and high existential well-being in 25 (24.2%). The average value of the subscale of existential well-being of the respondents was 40.36 (moderate existential well-being) with an average deviation of 10.93. In the group of respondents with low existential well-being, the largest number of respondents abuse alcohol, 5 (4.9%). There were no respondents who do not drink and

consume alcohol within the limits of low-risk drinking. On the other hand, in the groups with high existential well-being, there were no respondents who consume alcohol within the limits of risky drinking, drink harmful or abuse alcohol. A significant correlation/impact of existential well-being on alcohol consumption was found in the subjects (p <0.0001). Table 4.

Table 4: Interrelations between a participants' existential well-being according to po Existential Well-Being score and alcohol drinking forms according to the Alcohol Use Disorders Identification Test score

EXISTENTIALWELL-BEING	ALCOHOL DRINKING FORMS						
	Don't drink*	Low risk drinking**	Risky drinking***	Harmful drinking ****	Alcohol abuse ****	Total	p value 1
Low2	0 (0.0%)	0 (0.0%)	1 (1.0%)	2 (1.9%)	5 (4.9%)	8 (7.8%)	< 0.0001
Moderate3	13 (12.6%)	38 (36.9%)	16 (15.5%)	1 (1.0%)	2 (1.9%)	70 (68.0%)	
High4	8 (7.8%)	17 (16.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	25 (24.2%)	
Total	21 (20.4%)	55 (53.4%)	17 (16.5%)	3 (2.9%)	7 (6.8%)	103 (100%)	

*AUDIT score 0; **AUDIT score 1-7; ***AUDIT score 8-15; **** AUDIT score 16-19; ***** AUDIT score 20-40; 1p according to Chi Quadrat Test. ; EBW score 10-20; 3EBW score 21-49; 4EBW score 50-60.

DISCUSSION

Excessive alcohol consumption impairs the physical and mental health of the consumer and adversely affects the health and well-being of persons in his environment17. Worldwide, 32.5% of people consume alcohol (25% of women and 39% of men) [17]. The average amount of alcohol consumed is 0.73 standard drinks per day for women and 1.7 standard drinks per day for men17. A small but significant part (3.5% in developed countries) of the adult population has developed alcohol dependence, while risky and harmful drinking has been identified in a significantly higher percentage (15-40%) [18].

The average daily intake of pure alcohol in Bosnia and Herzegovina is 29 g (13.4 l of pure alcohol, of which 75.8% beer, 8.6% wine, 12.4% spirits and 3.2% other alcoholic beverages) [19]. Alcohol intoxications were recorded in 22.7% of the population (36.4% of men and 8.6% of women) [19]. Harmful drinking was found in 2.5% of the population, alcohol dependence at 3.4%. Approximately 19.6.0% of the population has health problems due to alcohol use [19]. Alcohol use is the cause of death in 4.6% of the population of Bosnia and Herzegovina (7.7% of men and 1.5% of women) [19].

In our study, 79.6% of respondents consumed alcohol (53.4% low-risk drinking, 16.5% risky drinking, 2.9% harmful drinking and 6.8% alcohol abuse). Males were more likely to consume alcohol. The age of the respondents did not have a significant impact on alcohol consumption.

Religiosity encompasses five fundamental dimensions inherent in all religions: ideological (expectation that a religious person will accept certain beliefs), experiential (expectation that a religious person will experience religious feelings), ritual (encompasses specific religious practices required of a religious person), intellectual (expectation that the religious person will be acquainted with the basic principles of his faith), consequential (includes the secular effects of religious belief, practice and experience on the religious person) [4,20].

Religiosity is a significant modifier of the structure of values, as well as an important predictor of a wide range of behaviors and attitudes [21,22]. It allows moral values to receive a supernatural sanction that empowers them in their obligation and coercion [21,22]. It contributes to the respect of authority and institutions in general, because God, especially monotheistic, is a symbol of social authority [21,22]. It has a positive effect on self-control and resistance to negative influences [21,22]. It can answer the question of the meaning and value of life which can consequently reduce the attractiveness of alcohol consumption [21,22].

The protective influence of religiosity on alcohol consumption is also determined by the specificity of religion [10]. It is assumed that members of religious groups that are characterized by strict and clear prohibitions on alcohol consumption will resort to it to a lesser extent [10].

Islam completely forbids the production, sale, donation and keeping of alcohol in the homes of

believers [10]. On the other hand, Christianity does not have completely clear guidelines or restrictions regarding the quantity or purpose of the use of alcohol outside religious ceremonies (consumption of alcohol for refreshment or health reasons is allowed) [11].

All participants in the research were of the Orthodox faith. Moderate religiosity was found in 68% of respondents, high in 29% and low in 3%. The religiosity of the respondents had a significant impact on alcohol consumption ($p < 0.001$).

A 38-year prospective cohort study involving 1,795 children of Hindu, Islamic and Christian faiths from the island of Mauritius found that religious affiliation reduces the likelihood of drinking by adults who believe their religion promotes abstinence [10]. A survey of 526 third- and fourth-year students at eight faculties of the University of Tuzla found a strong association between all 5 domains of religious status and patterns of alcohol consumption4. A survey of 495 adults (Christians, Muslims, Buddhists, and nonreligious adults) in the United States found that nonreligious adults and Buddhists had significant positive attitudes toward alcohol use toward Christians and Muslims [23]. A study in Scotland involving 4,066 students found that non-religious students consumed significantly more alcohol (women more than 14 standard drinks per week, men more than 21 standard drinks per week) [24]. A study in Yemen among 146 adults in two centers for the treatment of alcohol and other psychoactive substance addiction found that religiosity plays an important role in the process of recovery and prevention of re-abuse [25]. A survey in Brazil among 3,007 adults in 143 cities identified a strong association between religiosity and negative attitudes toward alcohol, including limited sales time, reduced store availability, ban on advertising, tax increases, and minimum legal benefits for alcohol consumption [26].

Existential well-being is determined by the essential issues of human existence and the ability to engage in the process of creating meaning [27]. Meaning does not come from human existence itself, it is something that an adult faces and discovers[28]. Taking existential responsibility for one's life (accepting or rejecting the offered meaning) each individual comes to the consciousness of the same self [28]. The absence of meaningfulness (existential vacuum) reduces the perception of the meaning of one's own life and predisposes to potentially risky behaviors29. In addition, it causes apathy, emptiness, low self-esteem and frustration [28,29].

By consuming alcohol, an existentially frustrated adult creates the illusion of meaning, belonging and self-esteem [27].

68% of respondents had moderate existential well-being, 24.2% high and 7.8% low. The existential well-being of the respondents had a strong influence on alcohol consumption ($p < 0.001$)

A study of 151 students aged 18 to 25 in the United States identified an inverse association of existential well-being with patterns of alcohol consumption and the likelihood of attending a social event that included alcohol [30]. In addition, existential well-being is an important predictor of alcohol prevention [30]. A study of 176 adults aged 18 to 30 in Australia found significantly higher alcohol consumption in the presence of an existential vacuum [29]. A study in Canada, which included 131 adults hospitalized in a psychiatric clinic, found that an addiction treatment program contributes to the growth of meaningful life [31].

CONCLUSION

Almost 80% of the participants in the research consumed alcohol, of which two-thirds were part of low-risk drinking. Males were significantly more likely to consume alcohol. The age of the respondents did not have a significant impact on alcohol consumption.

All respondents are of the Orthodox faith. Most are moderately religious. There is a significant correlation/influence of religiosity in alcohol consumption among respondents.

Most study participants have a moderate degree of existential well-being. Participants with a high degree of existential well-being consume significantly less alcohol, compared to respondents who have moderate or low existential well-being.

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SUBCLINICAL HYPOTHYROIDISM

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ABSTRACT: Subclinical hypothyroidism (SKH) is a thyroid disorder in which the level of thyroid hormones, thyroskin and triiodothyronine in the blood is normal, but the level of thyrotropin - TSH, pituitary hormone, which regulates the work of the thyroid gland with negative feedback, is elevated. This is a biochemical diagnosis, because patients are typically asymptomatic and without signs of disease and the detection of SCC is usually accidental. Gender, age, race, geographical area, iodine status. Depending on the degree of increase in baseline TSH levels, 5-8% of patients with SCH annually have progression to clinical hypothyroidism. Iodine is chronic autoimmune thyroiditis. Existing guidelines for the treatment of SKH differ from each other, as there is conflicting evidence on the benefits of long-term levothyroxine substitution in this condition. Although there are data from several comprehensive reviews of the clinical outcomes of SKH treatment, no definitive conclusion has yet been reached on the benefits of this approach. Factors that support application of levothyroxine therapy are: clinical trial due to symptoms of hypothyroidism, patient's desire, depression, infertility / ovulatory dysfunction, progressive increase in TSH, pregnancy, or pregnancy planning, children, adolescents. Research data show that pregnant women with SCC have an increased risk of gestational diabetes, miscarriage, gestational hypertension, preeclampsia, premature birth, and the therapeutic procedure in pregnancy differs from the rest of the adult population. The approach in children with SKH, amiodarone-induced SKH and micronutrients will be briefly mentioned.

Key words: subclinical hypothyroidism, levothyroxine, pregnancy, amiodarone

INTRODUCTION

Subclinical hypothyroidism (SKH) is a common clinical condition about which there is much controversy. To date, there has been no definite consensus among thyroidologists on several aspects. First of all, the question arises whether it is necessary to do screening at SKH, ie. actively search for disorder in a wider asymptomatic population at routine periodic / preventive examinations, or find cases according to clinical indications. Another aspect of the problem is how to assess the significance of this clinical condition, as well as possible adverse effects on the cardiovascular system, metabolic parameters and mental health of the individual patient. From the first two questions the third one arises, and that is what kind of therapeutic approach to have in SKH - to treat it or not.

WHAT IS SUBCLINICAL HYPOTHYROIDISM

Subclinical hypothyroidism is a thyroid disorder in which the level of thyroid hormones (TH), thyroskin (T4) and triiodothyronine (T3) in the blood is normal, but the level of thyrotropin (TSH), a pituitary hormone that regulates thyroid function, is elevated. This is a biochemical diagnosis, because patients are typically asymptomatic and without signs of disease and the detection of SCH is usually accidental. Over time, SKH may progress to clinical hypothyroidism (KH). [1,2] SKH, depending on the duration and degree of TSH elevation, may be associated with an increased risk of cardiovascular (CV) disease and CV mortality, adverse effects on metabolic parameters, cognitive dysfunction, anxiety and depression [2,3]. Several alternative names describing the condition of SKH have been suggested such as: compensated hypothyroidism, preclinical hypothyroidism, mild hypothyroidism, decreased thyroid reserve, mild thyroid weakness [4].

WHAT IS THE PREVALENCE OF SUBCLINICAL HYPOTHYROIDISM

The estimated total prevalence of SKH in the general population is 4-10% depending on the characteristics of the examined population,

ie. gender, age, race, geographical area, iodine status [4]. SKH is more common in women and the elderly. In women, the prevalence is 8-10%, and in women older than 60, the published prevalence is up to 20% [5,6]. The prevalence is about three times higher in whites than in blacks [7]. Also, during an increase in iodine intake in a previously iodine-deficient population, there may be a slight increase in the prevalence of SKH and thyroid autoimmunity [8]. There are studies in which the prevalence of SKH in people with metabolic syndrome (MetS) is almost two and a half times higher [9]. In addition, SKH is more common in patients with Type 2 Diabetes Mellitus (DM T2) than in the healthy population and is about 10% according to some reports [10]. SKH is a relatively common condition in patients with chronic renal failure (HBI) and can be found in about 18% of patients with HBI who are not on dialysis [11]. The reported incidence of SCH in pregnant women is 2-2.5%, in some countries such as China, Belgium and northern Spain even 4-13.7%, and in children the prevalence is less than 2% [12].

Of course, in order to assess the prevalence of this condition in the population / populations, accurate registration and adequate health statistics are necessary. Estimated prevalences are often based on meta-analyzes of published articles in available databases of professional and scientific papers, in which data from limited samples of respondents are analyzed. However, differences in the estimated prevalence may also be influenced by different diagnostic criteria for this condition, e.g. use, or not, of specific serum TSH reference ranges, in this case upper limits of the reference range for individual population groups. Research shows that it is necessary to determine the distribution of concentration and range of normal TSH values, probably due to genetic factors, according to age and race, or other specific characteristics of the population, which would be used to assess the presence of thyroid dysfunction (TD) [13]. In this regard, some authors believe that the prevalence of SKH in the elderly is overestimated, because the upper limit of the reference range for TSH increases with age [14].

CAUSES OF SUBCLINICAL HYPOTHYROIDISM

The most common cause of subclinical hypothyroidism, as well as clinical, in areas with sufficient iodine intake, is chronic autoimmune thyroiditis - Hashimoto's thyroiditis (HT), atrophic thyroiditis (AT), postpartum thyroiditis (PPT) [3]. Autoimmune thyroid diseases (AITB), which include HT, AT and PPT, are 5 to 10 times more common in women than in men, the prevalence increases with age, they are more common in people with other autoimmune diseases, as well as in their blood relatives [3, 15-17].

AITB is characterized by pathological infiltration of the thyroid gland by sensitized T lymphocytes and the presence of thyroid autoantibodies in the blood - antimicrosomal antibodies / antibodies to thyroid peroxidase (TPOAb), antithyroglobulin antibodies (TgAb), prescription (TgAb) and 3 antibodies, [18], TSA [19], TSA antibodies. Determination of these antibodies in serum is one of the key diagnostic methods for the diagnosis of AITB.

On the other hand, a very common cause of SCC is iodine deficiency in the diet, because the problem of iodine deficiency areas is still pronounced worldwide [20]. Iodine is a microelement necessary for the production of thyroid hormones (TH), thyroxine (T4) and triiodothyronine (T3), which must be taken into the body through food, at least 150 μg per day.

Causes of SKH can also be iatrogenic, for example the condition after radioiodine, or surgical therapy of benign and malignant diseases of the thyroid gland, ie. diffuse toxic goiter, toxic adenoma, polynodose toxic goiter, benign and malignant atoxic nodular goiter. Also, radiation therapy to the thyroid gland can lead to radiation therapy of the neck due to non-thyroid diseases of the head and neck, including lymphoma.

Iatrogenic SKH can also be pharmacological, caused by the use of drugs for non-thyroid diseases, or diagnostics, such as iodine-rich antiarrhythmics, amiodarone, then lithium, used in psychiatry, iodine contrast agents, interferon alpha and other cytokines, tyrosine kinase inhibitors (TKI), antituberculotic Paraaminosalicylic acid (pAS), less often aminoglutethimide, which lead to SKH by various mechanisms e.g. thyroid cytotoxicity, blockade of TH production and release of excess iodine, reducing blood supply to thyroid tissue, action on type 2 and 3 deiodinases, which participate in the production of TH and their metabolites, and others [21-26]. Of course, there are also antithyroid drugs that are given in the

treatment of hyperthyroidism, ie. methimazole and propyl thyrouracil, may lead to SKH.

Infiltrative diseases, such as amyloidosis, sarcoidosis, hemochromatosis, scleroderma, cystinosis, Riddle's thyroiditis, can also affect the thyroid gland and be the cause of reduced functional reserves, ie. SKH [27,28].

As already mentioned, SKH as a consequence of AITB can often be associated with other autoimmune diseases, e.g. DM type 1, Addison's disease, rheumatoid arthritis [29-31], but also chromosomal disorders such as Down's or Turner's syndrome [32,33], which requires mandatory examination of thyroid function in patients with these diseases and syndromes.

Consumptive, or "expendable" SKH is a rare condition that occurs in patients with hemangiomas and other tumors in which type 3 deiodinase is expressed, causing accelerated degradation of T4 and T3 [34].

Finally, transient SCH can be found in patients in the recovery phase from non-autoimmune thyroiditis, subacute and painless thyroiditis, as well as during recovery from severe non-thyroid disease (NTB) [35].

THE COURSE OF SUBCLINICAL HYPOTHYROIDISM

In most patients, SKH remains stable over time. Depending on the degree of increase in the initial level of TSH, annually 5-8% of patients with SKH have a progression to clinical hypothyroidism (KH) [36]. On the other hand, thyroid function may return to normal over time in 6-35% of patients, also depending on baseline TSH levels as well as thyroid autoantibody levels [37]. In patients with elevated TPOAb, the progression of SKH to KH is 4.3% per year, and in those with normal TPOAb levels, almost twice as low, 2.6% per year [38]. Therefore, after the diagnosis of SCH, thyroid function tests (TFT) are repeated in 8-12 weeks and additional measurement of thyroid autoantibody levels is performed. If SKH persists, TFTs are repeated for 6 months during the first two years of follow-up, and then once a year if the findings are stable. In contrast, if TFTs are normal after repeated determinations and the patient has no symptoms, goiter, and elevated thyroid autoantibodies, further monitoring is not necessary [3].

DIAGNOSIS OF SUBCLINICAL HYPOTHYROIDISM

The diagnosis of SKH is made when elevated TSH values are detected in the patient (the reference range of most tests is 0.4 - 4.0 to 5 m IU/L) with normal FT4 values in the blood [39] . Bearing in mind that the diagnosis of SKH is based on the results of laboratory analyses, the specificity, sensitivity and reference values of the applied test should be taken into account, and the finding should be interpreted accordingly [40]. Although elevated serum TSH is most often a sign of primary hypothyroidism, it is important to know that measured concentrations may be elevated (usually <8 mU/L) in individuals over 65 years of age without clinical and laboratory evidence of thyroid disease [41]. Other conditions, such as post-radiotherapy of the neck, adrenal insufficiency, pregnancy, use of certain drugs (lithium, AMD), or the presence of specific antibodies in the blood (HAMA, or macro TSH) may mimic SKH [42-44]. In addition, pathological obesity due to the effect of leptin on thyrotropin releasing hormone (TRH) leads to a reversible increase in blood TSH [45]. Fluctuations in TSH concentration are expected in acute, especially severe netiroid diseases, as well as after surgical procedures - hemithyroidectomy, which should be taken into account when interpreting laboratory findings [42,46]. Laboratory diagnosis should be postponed for 2-3 months after recovery from acute diseases, due to the effects of cytokines on TSH concentration, and supplementation with biotin, which is a part of many multivitamins (especially those recommended for hair and nail health) should be stopped at least 2 days before laboratory tests, Analysis, due to interference with immunoassays [42,47,48].

There are two categories of SKH according to the degree of TSH increase. Slightly elevated TSH, of 4–10 m IU/L, found in 80–90% of patients, and significantly elevated TSH,> 10 m IU/L [3]. After the diagnosis of TSH, the cause should be determined, ie. an etiological diagnosis should be made. Additional laboratory analyses in order to establish the etiological diagnosis are measurement of thyroid autoantibodies (TAT), TPOAb mainly due to higher sensitivity and less often TgAb, as well as ultrasound examination of the thyroid gland which can detect characteristic parenchymal changes in autoimmune thyroiditis, which is the most common cause of SKH [50].

The level of TSH in a healthy person has small variations over time, about 1/3 of the reference range, which is called its own "TSH

setpoint", which tends to increase with age [51,52]. Thus, as mentioned, in the elderly we use a wider reference range (4.0-7.0 m IU/L), i.e., a slightly elevated TSH level in the elderly is considered a physiological adaptation to aging [41].

In both healthy and SKH, TSH levels have circadian fluctuations in serum concentrations - the lowest concentration is in the early afternoon, with about 30% higher concentrations in the evening and overnight.

Delayed night peak TSH can be found in: night shift workers; those with sleep disorders; after strenuous physical activity; in mood disorders - depression [3].

Biologically inactive forms of TSH may be the reason for measured higher TSH values in some individuals [53].

Let us repeat that the level of TSH correlates with BMI and markers of insulin resistance, so the finding of TSH> 3.5 is common in obese [54].

CLINICAL CHARACTERISTICS OF SUBCLINICAL HYPOTHYROIDISM

Symptoms

By definition, SKH is an asymptomatic condition, with no clinical signs of hypothyroidism (Table 1). However, is SKH really asymptomatic? Some studies show that a small but statistically significant number of patients with SKH have more frequent symptoms of hypothyroidism than healthy ones: drier skin, poorer memory, slower thinking, weaker muscles, faster fatigue, more frequent muscle cramps, greater winter fever, deeper and hoarse voice, swollen eyes and more frequent constipation [5]. On the other hand, since the symptoms and signs of hypothyroidism are general and can occur in other conditions, some studies show that there is no improvement in symptoms in patients with SCI when levothyroxine substitution is introduced [55]. However, most patients with SCH do not have hypothyroid symptoms.

Mood and mental health disorders

Based on many studies, it seems that there may be mild disorders of declarative memory (knowledge of facts), procedural memory (skills that are performed automatically) and mood in younger people with SCC, which are improved by levothyroxine substitution [56]. However, such evidence is generally not found in the population over 65 years of age [57].

Table 1. Symptoms and signs of hypothyroidism

SYMPTOMS	SIGNS
Fatigue, weakness, suffocation	Bradycardia
Dry goat	Dry, rough skin
Feeling cold / cold	Cold extremities
Hair loss	Diffuse alopecia
Weight gain with normal, or poor appetite	Swelling of the face, hands, feet, myxedema
Constipation	Prolonged tendon relaxation time
Hoarseness	A deeper, hoarse voice
Impaired concentration, impaired memory	Efusions into serous cavities
Impaired hearing, paresthesias	Carpal tunnel syndrome
Menorrhagia, oligomenorrhea, amenorrhea	

Obesity, glycoregulation, insulin resistance, diabetes mellitus, dyslipidemia

Serum TSH levels are positively correlated with body weight [58] and it has been shown that for each unit of increase in log TSH, body weight is 2.3 kg higher in women and 1.1 kg in men [59]. In contrast, a significant decrease in body weight is associated with a decrease in TSH levels [60]. However, a sample relationship between SKH and obesity has not been shown.

SKH could reduce insulin sensitivity by reducing the number of glucose transporters in plasma membranes (cell organelle membranes) and by directly affecting insulin secretion and clearance, as is known to occur to a significant extent in hypothyroidism [61]. In patients with established diabetes mellitus (DM) type 2, a change in glycemic control may indicate SKH and long-term thyroid disorders, while the prevalence of SKH with elevated TAT in a patient with type 1 DM is up to 30% [62].

Large epidemiological studies have shown a positive correlation between TSH levels and dyslipidemia, indicating a potential impact of SKH on the lipid profile [5]. Similarly, another large study showed e.g. that an increase in TSH

levels of 1.0 m IU / L was associated with an average increase in total cholesterol levels in women of 0.09 mmol, indicating gender differences in the relationship between SCH and lipid profile. Also, the relationship between TSH levels and lipid profile is more pronounced with advancing age [63].

Cardiovascular system, heart failure and ischemic heart disease

SKH is associated with functional cardiac disorders, such as left ventricular diastolic dysfunction and decreased systolic function at rest and physical exertion [64]. Vascular abnormalities in this condition have also been shown, such as increased vascular resistance, arterial stiffness, endothelial dysfunction, and atherosclerosis [65]. Many studies point to SKH as an independent risk factor for the development of heart failure, as well as for the worsening of existing ones [64].

Some of the results of research on the impact on ischemic heart disease did not show an association between AITB and ischemic heart disease, but by re-analyzing a population-based Whickham study (66), it was found that in patients with SKH a significantly higher frequency of cardiac ischemic events and mortality due to ischemic heart disease was found. A meta-analysis of several relevant prospective studies has shown similar results [67].

Degree of TSH increase

It is not insignificant, as the results of the study show, how much TSH is elevated in SKH. We said that there are two categories of SKH according to the degree of TSH increase: slightly elevated TSH, from 4-10 m IU/L and significantly elevated. TSH> 10 m IU/L. Symptoms, manifestations, and potential complications, including endothelial, lipid, and cardiovascular disorders, are related to the degree of TSH elevation but depend, as has been said, on gender and age [68]. The results of numerous completed, as well as ongoing studies will be useful to determine both the TSH threshold and the age threshold for considering therapeutic intervention, levothyroxine substitution.

THERAPEUTIC APPROACH IN SUBCLINICAL HYPOTHYROIDISM

SKH, like KH, is treated with levothyroxine substitution. The goal of the treatment, as with KH, should be to eliminate the symptoms of hypothyroidism by achieving normalization of TSH [69].

However, since it is by definition an asymptomatic disorder in most patients, a disorder only at the blood level, two questions should be kept in mind when deciding on the treatment: what is the effect of levothyroxine treatment on long-term clinical outcomes in patients with SLE and what is the outcome of follow-up without levothyroxine treatment, on long-term outcomes in patients with SCV [70]. Existing guidelines for the treatment of SKH differ from each other, as there is conflicting evidence on the benefits of long-term levothyroxine substitution in this condition. Although there are data from several comprehensive reviews of the clinical outcomes of SKH treatment, no definitive conclusion has yet been reached on the benefits of this approach. (1). Certainly, as it was emphasized in the previous text, before starting the substitution, the TSH test should be repeated within 3 months from the diagnosis of SKH. This is important because in about 60% of patients TSH normalizes within 3 months, and in about 62% over 5 years [71,44]. On the other hand, in patients with SCC and hypothyroid symptoms, other possible causes for existing symptoms should be considered first.

According to most guides, levothyroxine substitution in SKH should be started when TSH is> 10 mIU/L, regardless of the absence of symptoms. Levothyroxine substitution should be considered in cases where TSH is between 5-10 mIU/L in repeated measurements and there are symptoms similar to hypothyroidism. However, if symptoms do not resolve after 3-4 months of levothyroxine substitution and TSH normalization, the treatment should be discontinued [70,1]. In other cases, the decision to treat SCH, when the TSH is between 5-10 mIU/L in repeated measurements, should be adjusted individually depending on age, comorbidity, degree of TSH elevation, persistence and progression of TSH elevation, TAT presence and goiter. The meaning of substitution would be based on reducing the risk of adverse CV events and possibly preventing progression to CH. It should be borne in mind that levothyroxine substitution can lead to iatrogenic subclinical / clinical thyrotoxicosis, especially in elderly patients, which in itself may be a risk of worsening CV condition and there is no evidence that substitution is useful in people

65 years of age and older [42]. Factors that support the application of left thyroxine therapy are: clinical trial due to symptoms of hypothyroidism, patient's desire, bipolar disorder, depression, infertility / ovulatory dysfunction, presence of TAT, progressive increase in TSH, pregnancy, or pregnancy planning, children, adolescents.

RECOMMENDATIONS [3]

There are two categories of SKH according to TSH level: Slightly elevated TSH - 4-10 m IU / L found in 90% of people with SKH; and TSH> 10 m IU / L

The finding of elevated TSH with normal FT4 in the first measurement should be repeated in 2-3 months, by re-measuring TSH, T4 and TPOAb

TSH and FT4 should be measured in individuals with elevated TPOAb / TgAb and / or ultrasound indicating AIT

Age-specific reference ranges should be used to diagnose SKH in the elderly population.

In patients younger than 65 years and with TSH> 10 m IU/L, even in the absence of symptoms of hypothyroidism, the introduction of L-thyroxine substitution is recommended.

In patients younger than 65 years with symptoms of hypothyroidism and TSH <10 m IU/L, a clinical trial by introducing L-thyroxine substitution should be considered.

After hemithyroidectomy, persistent SKH should be treated with L-thyroxine in order to normalize TSH.

Patients with diffuse or nodular goiter and persistent SKH should be treated with L-thyroxine in order to normalize TSH.

In patients with type 1 DM, TSH levels should be monitored once a year.

In patients with DM type 2 and unexplained deterioration of glycemic control, TSH and FT4 should be performed.

There is limited evidence that L-thyroxine substitution in younger people with SKH leads to improved mental function.

There is no evidence of beneficial effects of L-thyroxine therapy in obese individuals with TSH <10 m IU/L and normal FT4 on weight loss.

L-thyroxine therapy in SKH can lower both total and LDL cholesterol, but lipid normalization is rarely achieved.

The effect of L-thyroxine substitution on serum lipid concentrations is most pronounced in patients with TSH levels> 10 mIU/L before treatment.

The oldest elderly people, over 80 years of age, with a TSH level ≤ 10 m IU / L, should be carefully monitored, avoiding the introduction of L-thyroxine substitution.

If the hormones in the control test are normal, with a normal TAT level and the absence of goiter - no further testing is needed.

If SCH persists and L-thyroxine therapy is not started, hormones should be tested for 6 months for at least first 2 years, and then once a year.

PREGNANCY AND SUBCLINICAL HYPOTHYROIDISM

SKH in pregnancy is defined as a condition in which serum TSH is higher than the upper limit of the reference range specific to the trimester of pregnancy, while serum T4 and T3 are in the reference ranges [72,73,14,74]. It occurs in approximately 2-2.5% of pregnant women, with the number being significantly higher in some countries and as high as 13.7% in northern Spain [75].

Isolated hypothyroxinemia is defined as a serum FT4 concentration below the 2.5 percentile of the reference range (0.80 ng/dL; 10.30pmol/L), with a normal TSH concentration [72,12].

The diagnosis of SCH in pregnancy is made only on the basis of laboratory analyses, as the symptoms and signs are non-specific and very similar to problems that may be associated with lifestyle variations, or problems that result from many other conditions and pregnancy itself [72,12,74]. The reference range of TFT in pregnant women differs from the reference range of the general population, and also differs by trimesters of pregnancy. Based on published studies, mainly in Western countries, the following reference range for TSH in pregnancy is proposed: first trimester 0.1 - 2.5 mU/L; second trimester 0.2 - 3.0 mU/L, third trimester 0.3–3.5 mU/L [76-78]. However, it is advisable to determine these values for each country or region individually. It should be noted that during pregnancy there is an increase in the concentration of T4, which is highest during the first trimester of pregnancy, while this increase is significantly less during the second and third trimesters. Despite the increased binding of hormones to transport proteins, which are also increased in pregnancy, many authors believe that the reliability of the determination of free thyroxine (FT4) by standard immunoassay for FT4 is satisfactory [72,12].

As the definition of SKH is based on elevated TSH levels in combination with normal FT4 values, it would be crucial to determine the trimester-specific TH reference range. Available data from the literature indicate that in the first trimester of pregnancy the lower limit of FT4 2.5th percentile of the reference range detected by immunoassays is about (0.80 ng/dL; 10.30pmol/L) [72,12]. In order to obtain a reference value specific for the first trimester of pregnancy, some authors suggest that the normal values of total, for transport protein bound T4 (TT4), which are 5–12 mg / dL, or 50–150 nmol/L for non-pregnant women, be multiplied by 1.5 and the values thus obtained used as reference values specific to the first trimester [72,12].

Antibodies to thyroid peroxidase (TPOAb) are present in about 50% of pregnant women with SCC, and up to 80% in pregnant women with clinical hypothyroidism. In pregnant women with SCI, the determination of TPOAb is recommended in order to determine the AITB. Antibodies to thyroglobulin (TgAb) should not be neglected either. Elevated TgAbs were found in 5% of women with SKH and normal TPOAb. Women with elevated TgAb, and normal TPOAb, had significantly higher serum TSH levels compared with women without AITB. Thus, TgAb should be determined in pregnant women with negative TPOAb. After the first trimester, TAT may be negative due to immunosuppression during pregnancy, and in the presence of elevated TSH values and negative antibodies, thyroid ultrasound should be performed [72,12].

Side effects of SKH during pregnancy

Manifested clinical hypothyroidism during pregnancy is clearly associated with adverse events such as preeclampsia, eclampsia, gestational hypertension, cretinism, fetal death, and miscarriage. However, there is less evidence of complications during pregnancy and SCI. Studies dealing with this problem show conflicting results. Most studies indicate an increased risk of gestational diabetes (GD), with a positive correlation between TSH levels and the risk of GD.

Several studies have confirmed the association of SKH with miscarriages, very early embryo loss, gestational hypertension and preeclampsia. The risk of preterm birth is also present in pregnant women with SCI. Other complications that are mentioned as possible, but also quite rare, are: placental abruption, increased perinatal mortality, low Apgar score and low birth weight. However, the association between SKH in pregnancy and offspring developmental disorders has not been fully demonstrated [72,12].

Effects of SKH treatment during pregnancy

Treatment of SKH with levothyroxine is thought to outweigh the potential benefits. SKH that occurs before conception, or during gestation, should be treated with levothyroxine. In contrast, there are no studies that show the benefit of treating isolated hypothyroxinemia during pregnancy in terms of maternal obstetric complications. However, levothyroxine therapy may be considered in isolated hypothyroxinemia detected in the first trimester of pregnancy, due to its association with more favorable neuropsychological development in children. Levothyroxine therapy is not recommended in isolated cases of hypothyroxinemia detected in the second and third trimesters.

Levothyroxine therapy should be initiated in patients with TSH> 10 mU/l in the first trimester, regardless of the presence of TPOAb. Also, therapy should be initiated in pregnant women with TSH> 4 mU/L and TPOAb positive. Therapy should be considered in pregnant women with TSH of 2.5-4mU/L with positive TPOAb and in pregnant women with TSH of 2.5-10mU/L with negative TPOAb. In patients preparing for pregnancy with assisted reproductive techniques, the TSH should be <2.5 mU/L. In these patients, TSH should be determined two weeks before and two weeks after insemination and in vitro fertilization (VTO) [79].

If a decision is made to introduce substitution in pregnant women with CKD, the suggested doses of levothyroxine are: 1.20 μg / kg / day for TSH ≤ 4.2 mU / L; 1.42 μg / kg / day for TSH> 4.2–10 m IU / L and 2.33 μg / kg / day for TSH> 10 mU / L. TSH values should be checked every 4-6 weeks during the first trimester and once during the second and third trimesters.

In patients with morning sickness, late levothyroxine administration may be a legitimate option. The goal of levothyroxine treatment during pregnancy is to normalize maternal serum TSH values within trimester-specific reference values.

Most cases of SKH in pregnancy are transient and recover after pregnancy. However,

pregnant women with positive TPOAb and TSH> 5 mU/L are more likely to have persistently elevated TSH, i.e. that hypothyroidism will persist after pregnancy. After delivery, the dose of levothyroxine should be reduced to the pre-conception dose. In women diagnosed with SKH during pregnancy, whose TSH is <5 mU/L and who have negative TPOAb, as well as in women whose replacement dose was less than 50 μg of levothyroxine, discontinuation of postpartum substitution may be attempted. Thyroid status checked 6 weeks postpartum, then at 6 and 12 months. In other women diagnosed with SCC after pregnancy, thyroid status should be checked 6 months and one year after delivery and the need for substitution should be determined. Levothyroxine therapy is not recommended for euthyroid women with positive antibodies [72,12]. Evidence for screening for SKH in pregnancy is ambiguous. Although there are still no well- controlled studies to justify general screening, a large number of authors recommend screening. Also, a large number of authors advocate screening only for pregnant women who are at special risk, ie. women with a history of thyroid disease, women with a family history of thyroid disease, women with goiter, women with DM type 1, women with other autoimmune diseases, women with infertility of unknown cause, women with a history of head and neck radiotherapy, women with a history of abortion and premature birth [72,12,74,80].

SUBCLINICAL HYPOTHYROIDISM IN CHILDREN

The subject of our consideration is primarily SKH in adult population, but we will make a few remarks about this condition in children. When it comes to possible prenatal impact, the results of numerous studies on the relationship between the mother's SKH and impaired neurophysiological development of the child are not consistent, as is very clear in KH [12], and further research is needed to determine the exact impact. In newborns and early childhood, especially in the first 3 years of life, THs play an irreplaceable role in the process of maturation and brain development, and the impact on linear growth persists until the closure of the pineal gland in adolescence [81]. After birth, large changes in thyroid function occur in the newborn, and the level of TSH> 5 mU / L, can be considered elevated after 1 month of age. Therefore, it is necessary, as in the elderly population, to use age-specific reference values to interpret diagnostic biochemical findings [82]. In the general pediatric and adolescent population with SCH, hormones are normalized in over 70% of them, or persist unchanged in most of the rest, for the next 5 years after the diagnosis [12]. SKH is 10 times more common in children with Down syndrome than in the general population [83]. In obese children, a TSH level of 5-7 m IU/L is likely a consequence rather than a cause of obesity [84]. In areas with sufficient iodine intake, SKH in young children is most often idiopathic (so-called persistent "Hyperthyrotropinemia" and "Non-autoimmune" idiopathic SKH), or caused by various perinatal and genetic causes. In older children and adolescents, the most common cause is AITB [12]. To date, there is insufficient evidence to recommend levothyroxine substitution in most children with SKH and TSH <10 mU/L [85].

AMIODARON-INDUCED SUBCLINICAL HYPOTHYROIDISM

Chronic therapy with amiodarone (AMD), an iodine-rich antiarrhythmic, is associated with the appearance of predictable changes in TFT, as well as the appearance of thyroid dysfunction, which is responsible for both iodine load and cytotoxicity of the antiarrhythmic [86]. According to research by the authors of this paper, amiodarone-induced subclinical hypothyroidism (AISKH) is found in the area with sufficient iodine intake in 10% of cardiac patients treated with this antiarrhythmic, more often in women, patients with enlarged thyroid gland and patients with elevated TPOAb [87]. In most patients with AISK, the condition does not progress to KH, and in a large number there is a spontaneous normalization of thyroid status, even with continued amiodarone therapy [88]. A case of amiodarone-induced thyrotoxicosis (AIT) after AISC in a patient during continued amiodarone therapy has also been described [89]. Also, during recovery from AIT, SKH may develop, transient but also permanent [87,89]. It is recommended that thyroid status be determined before initiating amiodarone therapy and monitored regularly, usually every 6 months, during therapy with this antiarrhythmic. In patients at increased risk for thyroid dysfunction, i.e. women, patients with goiter and elevated TAT, the use of another antiarrhythmic should be considered, or thyroid

status should be monitored more frequently. We believe that it is not necessary to discontinue amiodarone therapy in AISCH, but to continue regular monitoring of thyroid status [90,91].

MICRONUTRIENTS AND SUBCLINICAL HYPOTHYROIDISM

Life habits including sleep, smoking, diet, and physical activity are significant factors influencing normal thyroid function in SKH [92]. Iodine, selenium and iron are necessary for the synthesis of thyroid hormones. Hem-bound iron is part of thyroid peroxidase (TPO), which enables the incorporation of iodine atoms into tyrosine molecules in the process of synthesis of thyroid hormones [93]. Myo-inositol, as a secondary messenger of phospholipase C, also stimulates the organization of iodine and its incorporation into thyroid hormones through the inositol phosphate / Ca 2+ / diacylglycerol signaling pathway [94]. Selenium (daily requirements are 55 μg, and in pregnancy and lactation 60-70 μg) as an integral part of the enzyme deiodinase, enables the synthesis of triiodothyronine, or inactivation of thyroxine by conversion to reverse T3. In addition, selenoproteins, glutathione peroxidase, and thioredoxin reductase affect iodine organization through their effects on the concentration of reactive oxygen species, particularly H 2 O 2., [93] .

Adequate iodine intake (about 150 μg per day), as well as adequate TSH synthesis, are the basic prerequisites for the synthesis of thyroid hormones. Iodine deficiency in the diet leads to reduced synthesis of thyroid hormones, but its excessive intake has the same effect, due to the Wolff-Chaikoff effect [94]. Due to the effect on iodine organization, iron deficiency (daily requirements are about 9 mg for men and about 15 mg for menstruating women) affects thyroid status as well as myo-inositol deficiency, which, unlike iron, selenium and iodine, can still synthesize in the body from glucose, so deficits are rare [94,95] . In the case of a combined deficiency of iodine and selenium, in order to normalize the function of the thyroid gland, it is necessary to first compensate for the deficiency of iodine, and only after that the deficiency of selenium [94,96] .

CONCLUSION

SKH is a common condition and most do not require treatment, but only follow-up. There is a consensus that levothyroxine substitution should be indicated in adult patients with SCC whose TSH is ≥ 10 m IU/L. In all other cases, the assessment is individual. Recommendations regarding SCH screening vary widely among professional associations and expert groups. Overall, screening is not recommended in the general population and should be limited to people at high risk for the condition, such as patients with autoimmune diseases, positive personal or family history of thyroid disease, and those with symptoms similar to hypothyroidism. Even in asymptomatic pregnant women, opinions about the need for universal screening are divided. Most professional associations suggest targeted screening of only certain groups of patients.

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Vol. 47 (2022) No. 1 TIMOK MEDICAL GAZETTE Review article

FACTORS THAT MAY AFFECT THE SUCCESS OF THE ESOPHAGEAL VOICE AND SPEECH EDUCATION IN LARYNGECTOMIZED PATIENTS

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ABSTRACT: Introduction: The most humane, economically most justified, and according to many authors, also the first method of choice in vocal rehabilitation of totally laryngectomized patients is the use of esophageal voice and speech. While mastering this method, it is necessary to train the patients to form and use the air reservoir in the upper third of esophagus that serves as a voice activator whose airstream causes the vibrations of the pharyngoesophageal segment as the new voice generator. Objective:To investigate the factors that may affect the success of esophageal voice and speech education in clinical practice and emphasize the importance of knowing them in order to further improve this method of rehabilitation. Methods:Comprehensive review of the literature was performed by using the following databases: Google Scholar, SCIndex, PubMed and ResearchGate. The search was based on the following terminology: laryngectomy, esophageal speech, education, factors, success, treatment outcome, and their counterparts in Serbian language. Results: There are numerous factors that may affect the success of esophageal voice and speech education (anatomical-physiological, psychosocial, patient related, treatment and rehabilitation related factors, socio-demographic, physiological and others), among which the motivational status of the patient is of the greatest importance. Conclusion:There are still no clearly defined, generally accepted and comprehensive criteria for assessing the degree of success of mastered esophageal voice and speech, and consequently the lack of defined uniform factors affecting this success, positively or negatively, is present. Of the numerous observed factors, the importance of the patient's motivational status is most often emphasized.

Key words:laryngectomy, esophageal speech, factors, education, rehabilitation success.

1. INTRODUCTION

Malignant laryngeal tumors are among the most common tumors that affect the upper aerodigestive tract [1,2]. It is important to point out that they make 1-3% of all malignant tumors in human body, and 20% i.e., 25-35% of all malignant tumors of head and neck in general, where Serbia and its region Vojvodina report one of the greatest incidences in Europe [3,4]. One also needs to emphasize that it is 8 to 10 times more common in men than in women, occurring most likely at the age from 61 to 70 [4,5,6,7]. The outcome of the treatment and patient survival rate mostly depend on the stage of the tumor at the time when it is discovered [8]. However, recognition of malignant laryngeal tumors in late, advanced stage is common, despite the symptoms being present and visible even in the early stage [3,9]. Total laryngectomy is a radical and most comprehensive surgery of malignant laryngeal tumors that is applied for advanced stages of the disease, and involves complete removal of the larynx [2,10]. In physiological phonation, the role of the voice activator is performed by lungs. After the total laryngectomy, breathing is performed directly through the created permanent tracheostoma. Larynx i.e., its part – glottis, represents the voice generator, so it is obvious that the removal of the same will disable the phonation, and the change in the anatomical organization and separation of the activator from the resonator will also contribute to the change in resonance, because besides the larynx, it also depends on pharynx, nasal and oral cavity, but the trachea itself and the lungs [4,11]. The integral part of the treatment of patients with malignant laryngeal growths is certainly the voice and speech rehabilitation i.e., mastering any form of alaryngeal communication. It is important to point out the significance of the speech rehabilitation of these patients which does not only lead to the improvement of the communicational aspects, but also the psychological, social, emotional and professional ones [12,13]. There are three main

rehabilitation methods; esophageal voice and speech education, surgical implantation of voice prosthesis with the development of the tracheoesophageal voice and speech and the use of electrolarynx [4,14,15]. The most humane, economically most justified, and according to many authors, also the first method of choice in rehabilitation of totally laryngectomized patients is the use of esophageal voice and speech [4,16]. In esophageal voice, the air, placed in the upper third of the esophagus, is used as an activator and therefore, when acquiring it, it is most important to ensure the functional capacity of this air reservoir, as well as the functionality of the pharyngoesophageal segment (PE), acting as the new glottis/pseudo-glottis [12]. In esophageal voice and speech, the voice generator i.e., pseudo-glottis, is created on the same vibrational segment as in the tracheoesophageal voice and speech after the implantation of the speech prosthesis, and the difference between them is the place and the force of the activator; in esophageal voice it is the air in the esophagus whose volume is far smaller, while in the tracheoesophageal voice the activator is still the airstream from the lungs as in physiological phonation [4,12]. Besides the advantages of the esophageal voice and speech that definitely reflect in independency of prosthetic aids, free hands, economic cost-effectiveness and inconspicuousness by the environment, it is also necessary to mention the deficiencies which mostly relate to the duration of education, lower success rate, discontinuity and insufficient intensity of speech in noisy environments, very small air volumes that may be deposited in esophagus (not more than 60-70 ml), with somewhat worse melody, short duration of phrases and poorer comprehensibility of sounds from the group of nasal consonants [6,15,17]. In developed countries around the world, the most often used method for voice and speech rehabilitation in laryngectomized patients is the implantation of voice prosthesis as the gold standard in voice and speech rehabilitation in laryngectomized patients [18]. Voice prosthesis implantation in developed countries is most often primary i.e., in the same act with laryngectomy, while in the developing countries, with more patients with advanced laryngeal carcinoma and often financial inability to provide primary implantation of vocal prostheses, it is most often implanted secondarily, after an unsuccessful esophageal voice and speech education [13].

The objective of this paper was to investigate the factors that may affect the success of the esophageal voice and speech education in clinical practice around the world and in our region, obtained from the available literature data, as well as to point out the significance of observing them during vocal rehabilitation of laryngectomized patients, in order to further improve this rehabilitation method.

2. METHODS OF WORK

Comprehensive review of the literature was performed by using the following databases: Google Scholar, SCIndex, PubMed and ResearchGate. The search was based on the following terminology: laryngectomy, esophageal speech, education, factors, success, treatment outcome, and their counterparts in Serbian language, with focus on the most recent references available. This paper was created by using 30 sources, mostly research scientific papers, as well as a few professional books, meta-analyses, PhD theses but also one final paper.

3. RESULTS

3.1. Success of the Esophageal Voice and Speech Education

As there are no clear objective and subjective criteria for assessing the success rate of esophageal voice and speech, consequently a very wide range of success rates of this method of rehabilitation can be found in the literature. According to Stanković, the success rate is 86.1% [7], Krejović Trivić et al. [19] report similar rate - 86.3%, while according to Frith et al. [20], this percentage is much smaller and is only 25%. Gates [21] shares the opinion with the previously mentioned author, pointing out that the real picture of the success of education in this type of alaryngeal communication ranges from 26% to 34%. In her PhD thesis, Dragičević [4] states that 66.7% of patients achieve adequate esophageal speech.

3.2. Factors That May Affect the Esophageal Voice and Speech Education

Different data can be found in the literature about the factors that may affect the success of the esophageal voice and speech education. Namely, Salmon et al.[22] group them as psychosocial and anatomic-physiologic, where the distinction occurs within these as well, into those that are positive and stimulate success and those that are negative i.e., reduce or completely halt the education success. In addition, it was also emphasized that psychosocial factors are more susceptible to control and that they can be much more influenced compared to anatomic-physiologic ones [22]. Kresić et al. [16], as well as Del Rio Valerias et al. [14] present a division of factors

into 3 groups i.e., patient-related, treatment-related and rehabilitation-related ones. Next, Singer et al. in their meta-analysis [23] label these factors as socio-demographic, psychosocial and treatment-related ones, while Frith et al. [20] group them as surgical, psychological, social and physiological. In connection to that, in positive anatomic-physiologic factors, according to Salmon [22], emphasized is the significance of soundness and mobility of the oropharyngoesophageal region i.e., function of lips, tongue and velopharyngeal mechanism in order to provide a sufficient amount of air and overcome the PE segment resistance, but also to achieve an adequate relaxation of the same which is of utmost importance if the inhalation method is used in rehabilitation. It is generally known and mentioned that upon using the esophageal voice and speech the esophagus acts as an air reservoir, and therefore, Salmon [22], but also Singer et al. in their meta-analysis [23], point out that for the success of its education, soundness of the function of all its sphincters is needed in order to enable stopping i.e. proper flow of the airstream. Stanković [7] also mentions the hearing status as a significant positive factor which affects the education success, since the adequate hearing function enables auditory control of one's own speech as well as the instructions relating to the techniques and education while, on the other side, Singer et al. [23] mention the lack of connection of this factor with the success itself. According to Dragičević [4], patients with moderately severe hearing impairment pronounce fewer number of syllables in one minute and, in line with the previously mentioned studies, the same author also mentions worse audio-vocal feedback in them. Salmon [22] points out that the age is proved to be a success predictor i.e., that younger individuals master the esophageal voice and speech with more success because they are more motivated, determined, flexible. Similarly, Singer et al.[23]mention this factor in their meta-analysis as an important one i.e., pointing out that, the older the patient is, the more pronounced the negative relatedness to education success is. Such citations are confirmed by Frith et al. [20] in their research. On the other hand, according to data from the study of Del Rio Valeiras et al. [14], patients between age 51 and 60, mostly female population, showed greater success of the esophageal voice and speech education but, however, gender- and age-related factors did not prove to be significant success predictors in this case. Same data relating to these factors were also mentioned by Dragičević [4]. With regards to gender, in their study, Keszte et al. [9] stated that in the female population there is a higher level of stress and that the feeling of stigma is more present because of the low frequency of the esophageal voice that is 60-70 Hz, which significantly differs compared to the frequency of the healthy laryngeal female voice which can reach 220Hz [9]. Accordingly, Stanković [7] provides a detail that only 33.7% of laryngectomized women accept the education of esophageal voice and speech as a possible method and, according to the study conducted by Frith et al [20], they spent much more time in rehabilitation, rating it as extremely hard. In addition, Singer et al. [23] also mention that the patients consider eructation inappropriate, and therefore all mentioned factors may affect the success. It is also important to point out the good general condition as a significant factor that will definitely enable the success and contribute to it, dictating actually the very beginning and the flow of the education [22,23]. On the other hand, according to Salmon [22], negative anatomic-physiologic factors are a combination of radiotherapy and additional surgical treatments on bigger tumors because postsurgical radiotherapy contributes to the dryness of mouth cavity, frequent inflammations, discomfort when swallowing, which all reflect on the very act of esophageal voice and speech education which is also the case in swallowing disorders as such. Singer et al. [23] mention swallowing disorders as negative predictors of unsuccessful esophageal voice and speech education which reduce it significantly. In their study, Del Rio Valeiras et al. [14] also present data supporting the idea that the quality of the voice of patients who received radiotherapy is worse compared to patients who did not, while Cocuzza et al. [18] put forward that it improves with time because the tissue itself is less flexible in early postradiotherapy period and therefore it increases with time. Negative effect of radiotherapy is recorded by Dragičević and Stanković[4,7]. According to Singer et al.[23], radiotherapy as such does not affect the success of the education. Furthermore, by introducing radiotherapy, the vocal rehabilitation process is interrupted and so the significant time period suitable for learning is lost. Salmon and Stanković [22,7] point out that in cases of extended surgical interventions, the structures that affect the esophageal speech adoption itself,

such as a part of pharynx, tongue or velum, are removed as well. In this case, the education will be aggravated and its success limited. Unlike Salmon's [22], Del Ria Valerias et al.'s [14] study provides an interesting detail that the radicalism of the surgical resection does not significantly affect the success. The same conclusion was reached by Dragičević [4] while, on the other hand, Sokal et al. [24] suggest that the patients who underwent radical surgical interventions have greater education success compared to those who only underwent laryngectomy. Unfortunately, what often happens, limiting the education, and even leading to its regression, is the recurrence of the tumor, presence of metastases and various complications. In that case, it is of primary importance to remove the mentioned and stabilize the general condition of the patient. In addition, according to Salmon [22], velopharyngeal incompetence as well as velum paresis, may negatively affect the esophageal voice and speech education by injection method. However, in such case, it is possible to use the aspiration method, but it is important to mention that the intelligibility of speech may be impaired. What might negatively affect the air intake are definitely the reduced tongue mobility and the presence of the anterior pharyngeal diverticulum. These factors contribute to that fact that the patient employs much more force than usual in order to achieve the adequate pressure level and voice whose quality is similar to one which requires less force. In their meta-analysis, Singer et al. [23] also point out good tongue mobility as the factor that positively correlates with the success. It is also important to point out the effect of the presence of esophageal stenoses as well as contraction of the inferior pharyngeal constrictor instead of relaxation, hypertonicity of the PE segment, which further lead to air retention in the hypopharynx but also its inadequate entry and exit. All the mentioned affect the success of the esophageal voice and speech education techniques [22]. The focus shifts to psychosocial factors, where among the positive ones i.e., those that accelerate the success of the esophageal voice and speech education, Salmon [22] but also Singer et al. [23] mention readiness to practice, which is more often long-lasting and intensive, presence of motivation which has been mentioned in many papers by different authors as the factor that affects the success of the education, and also the acceptance of such voice, with all its characteristics, which contributes to the increase of the level of its use in communication, and also affects the patient's self-confidence. Interestingly, personality traits are mentioned in the Salmon's [22] study as an important factor, which leads to a situation that the extroverts i.e., those who are more open for communication, have contact with more people, achieve greater success in education compared to introverts who possess opposite traits. Additionally, the support of the family was mentioned as an important factor, but also the importance of characteristics and features of the expert who conducts the rehabilitation, which all together improves and increases motivation that positively correlates with the education success. The social activity itself, according to Singer et al. [23], did not prove to be a significant factor that affects the success of the esophageal voice and speech education, while, on the other hand, personality traits of the patient are stated as significant positive factors. Besides all positive factors, negative ones are also very common, and mentioned meta-analysis as well as the study of Del Rio Valeiras et al. [14] primarily put forward the lack of motivation, presence of depression (which is often the result of the radical surgery itself i.e. laryngectomy and loss of the verbal communication function) and anxiety which impedes the success itself that was also confirmed by Singer et al. [23] in their meta-analysis. The lack of success may also be the result of the patient's inability to accept the current situation, lack of support by the family and community, but also continued use of alcohol and cigarettes, which are listed as main risk factors in occurrence of malignant laryngeal tumors, may negatively affect the education itself. However, the very use of alcoholic beverages, according to papers comprised by Singer et al. [23] in their meta-analysis, was mentioned as a factor with a lack of any relatedness to success. Factors that are put forward as patient related by Del Rio Valerias et el. [14] are his/her age and marital status at the time of treatment, level of education, employment before the intervention, current employment, place of residence, where the focus is primarily on whether it is urban or rural environment, and also the presence of some other diseases like alcoholism, depression and others. In addition, these authors also mention rehabilitation-related factors like the very technique used in rehabilitation, the starting time, as well as the number of its sessions. Singer et al. [23] found that the duration and frequency of rehabilitation as such, do not

significantly affect the very success of the education. With regards to marital status at the time of treatment and employment itself, according to Dragičević [4] and Del Rio Valerias et al. [24] they are primarily related to the motivation itself, self-confidence, amount of communication, quality of social interactions the patient has, as well as the faster adaptation to the current condition and situation. When we speak about the education-related factor, according to Bunijevac et al. [12], it does not affect the success of the education, which is also confirmed by Singer et al. [23] and Dragičević [4], but he/she can achieve it on the perception and evaluation of the quality of life and therefore the patients with higher level of education rated the quality of their lives as better in most cases [12]. According to Del Rio Valerias et al. [14], the place of residence is related to the remoteness of hospital centers where the treatment and rehabilitation take place, and therefore the life in rural areas, away from these centers, significantly complicates conducting and success of esophageal voice and speech education. In addition, Dragičević [4] mentions that the incidence rate of malignant laryngeal tumors is higher in rural areas, and so we can draw a parallel with the abovementioned. In their meta-analysis, Singer et al. [23] singled out papers that mention even 24 factors that may affect the success of the esophageal voice and speech education and emphasized their positive and negative relatedness, non-compliance and lack of relatedness with the success of education, and such factors are primarily as follows: age, socio-economic status, marital status, employment, support of the family and community, personality traits, intellectual abilities and cognitive status, motivation, psychosocial adaptability, communication behavior, social activity, mental health, use of alcohol, length and quality of rehabilitation, extended surgical interventions, stadium in which malignant tumor was identified, its location, what type of alaryngeal voice was used, patient's hearing status, presence of swallowing issues, tongue mobility, radiotherapy, postoperative complications, general physical condition of the patient. Positive relatedness to the success of the esophageal voice and speech education was found when analyzing factors that are related to the communication behavior, employment, tongue mobility, motivation, psychosocial adaptability and personality traits. It is also important to mention discordant results i.e., that in some studies factors related to intellectual abilities, cognitive status, socio-economic status and social support proved to be very significant success predictors, while in others they were not mentioned as significant ones [23]. When it comes to intellectual abilities and cognitive status, according to Dragičević [4], there is a positive correlation between this factor and perseverance in rehabilitation i.e. more intelligent patients and those with better cognitive status are more persistent in it, and this can also be associated with the fact that the mentioned strive towards establishing of the alaryngeal voice as soon as possible because in most cases they are employed and in high positions that require greater use of speech. On the other hand, according to Singer et al. [23], negative relatedness to success occurs in factors related to general physical condition of the patient, age, presence of swallowing issues, occurrence of mental health problems (most often depression), and also the occurrence of complications after the surgery, while the lack of relatedness was noticed in factors like use of alcohol, marital status, social activities, stadium and location of the tumor, hearing status, education, duration and quality of rehabilitation, extension of the surgery, radiotherapy. In the research conducted by Kresić et al. [16], the impact of motivation, gender, age, education and profession of the patient, volume of the surgical resection, time of starting and duration of the vocal rehabilitation, as well as the method used during the course on the esophageal voice and speech education, were analyzed. What is interesting is the fact that, according to this study, motivation and duration of rehabilitation are considered as factors that affect the education success, while in others such impact was not manifested, which is in line with the previously mentioned studies. In addition, mentioned is a detail that it is never too late to begin with rehabilitation, which is by all means a motivating piece of information for the patients, while Del Rio Valeiras et al. [24] stated that is should be conducted as soon as possible, emphasizing that it, as a factor, does not significantly affect the success of the education itself. In addition, what also stands out is the information that the duration will greatly depend on the individual characteristics of the patient. In their study, Frith et al. [20] came across results that are in line with the results of Del Rio Valeiras et al. [24], whereby they emphasized that the duration of rehabilitation and the time elapsed after the surgical intervention do not affect the success. In their study, Sokal et al. [24] point out that the patients

whose rehabilitation lasts longer, show greater success in esophageal voice and speech education, which is in line with the research of Kresić et al. [16]. Some authors investigated if the way of conducting the esophageal voice and speech education affects its success and in connection to that, they compared individual and group work with patients. According to Veselinović [25], individual approach has great importance in the very beginning of the education because in that period the patient is becoming familiar with and introduced to the way the air is deposited in esophagus, act of eructation and esophageal voice techniques as well as speech in general, but after that, it would be useful for him/her to join the group in which patients are similar, based on criteria like age, education, time elapsed after the surgical intervention, intellectual and cognitive status. In addition, this author points out that the approach i.e., factor related to group or individual education, does not have much impact on its success while, on the other hand, Quing et al. [26] in their research, came to the results that speak in favor of the fact that group education significantly affects the success and this is attributed to the increase in patient's self-efficacy. Namely, when this type of education is conducted, Quing et al. [26] mention that patients develop the sense of belonging, because they meet people who have an identical or at least similar problem like they do, which leads to significant increase in self-confidence and motivation, and decrease of negative emotions and other factors that limit them. In addition, there is an exchange of experience both between the patients and between their families, which is a very important factor in the overall rehabilitation process. Another factor that is being mentioned as one of those that may affect the success of the esophageal voice and speech education is the presence of the gastroesophageal reflux. In his study, Mathis [27], mentions that the lower esophageal sphincter competence disables adequate air retention, which is also contributed by the leak backward of the stomach content, and resulting in acid causing contractions of the upper esophageal sphincter, and even its spasm. The research showed that the gastroesophageal reflux does not affect the success of the esophageal voice and speech education i.e., that the skilled, less skilled or completely unskilled users of the esophageal voice and speech had the same incidence of the gastroesophageal reflux after all trials, which was also confirmed by Dragičević [4] in her PhD thesis. What stands out as important is the fact that the esophageal reflux as such occurs more often in patients who use esophageal speech in order to communicate, which brings it into connection with the eructation itself [27].

The most significant factors affecting the success in mastering the esophageal voice and speech are shown in table 1.

Table 1: Presentation of factors that affect the success of the esophageal voice and speech education

Authors	Positive effect	Negative effect	No effect
Frith C. et al. 1985.	Lower age of patients.	Higher age of patients; longer rehabilitation.	Time elapsed since the surgical resection; length of rehabilitation.
Salmon S. 1988.	Good mobility of the oro-pharyngeal-esophageal region; esophageal sphincter preservation; adequate hearing; lower age of patients; readiness of patients for intensive and long-term practicing; motivation; extroversion of patients; presence of support by the family and community.	Reduced mobility of the oro-pharyngeal-esophageal region; hyper and hypotonic esophageal sphincter; hearing impairment; higher age of patients; presence of radiotherapy; additional surgical treatments; swallowing disorders; radicality of surgical resection; velopharyngeal incompetence; velum paresis; presence of anterior pharyngeal diverticulum; presence of esophageal stenoses; introversion of patients.	
Stanković P. 1997	Male patients; adequate hearing in patients.	Female patients; attitude towards huge complexity of rehabilitation, additional resection of base of tongue and pharynx, radiotherapy	
Del Rio Valerias M. et al. 2002	Presence of motivation in patients.	Presence of radiotherapy; lack of motivation; presence of	Age of patients; radicality of surgical resection; time elapsed

		depression and anxiety in patients.	since the surgical resection; length of rehabilitation.
Singer S. et al. 2007. (meta-analysis of 56 publications)	Stable general condition of patients; preserved tongue mobility; readiness of patients for intensive and long-term practicing; motivation; personality traits.	Unstable and poor general condition of the patients; considering eructation inappropriate; presence of primary disease complications; presence of anxiety; lack of support from the family and community.	Hearing status; presence of radiotherapy; number and quality of social interactions; length and frequency of rehabilitation; use of alcohol beverages; patients' level of education.
Dragičević D. 2013	Preserved hearing; intellectual abilities; cognitive status of patients.	Moderately severe degree of hearing impairment; presence of radiotherapy; presence of gastroesophageal reflux.	Age of patients; gender of patients; level of education; radicality of surgical resection.
Kresić et al. 2015	Presence of motivation; length of rehabilitation.	Lack of motivation.	Group/individual education; gender of patients; age of patients.

4. DISCUSSION

The questionable issue and the reason why we come across different data about success, but also about factors that impact them, is dissimilarity i.e., lack of uniform criteria for its evaluation. Authors of research and meta-analyses comprised with this review used different criteria for evaluation of success, depending on their country of origin and those they considered most suitable for the evaluation itself. Different criteria also resulted in different interpretation of the factors which positively i.e., negatively affect the success.

Criteria that have most often been mentioned in literature relate to satisfactory phonation when needed, length of air insufflation, short latency between inhalation and beginning of phonation, good intelligibility [4,28]. When it comes to overall impression, Stanković [7] provides a five-level scale, which evaluates the quality of esophageal voice i.e. evaluates the parameters related to the quality, roughness, clarity, weakness of the voice and vocal strain, and the levels are as follows: 1. excellent – full automatism in speech production; 2. good – continuous speech with occasional soundlessness of certain syllables; 3. mediocre – the technique is present, but without longer continuity; 4. Poor- production of short phrases only and 5.very poor/failed - production of only certain two-syllable and multi-syllable words or no sound at all. The same scale was also used by Mumović et al. [28] as well Vekić et al. [29].

According to Kresić et al. [16], excellent success in esophageal voice and speech education was achieved by patients who have fully automatized it, while the success rated as good implies establishing continuous speech with soundlessness of certain syllables, which matches Stanković' [7] criteria. Somewhat more elaborately defined criteria are found in Veselinović et al.'s [13] paper, where the success is rated as excellent in cases when a patient has the ability to spontaneously and effortlessly produce esophageal voice and speech in every communication situation, which is fully automatized and with a steady rhythm and melody, barely noticeable, deprived of the noise of cannula, and without too much unnecessary gesturing. On the other hand, one finds a definition arising from the fact that the education is considered successful if the patient has the ability to communicate with his/her environment in any way, and that such communication is also socially acceptable. In addition, the criterion of success is, on one hand, also rated based on whether the patient uses the learnt voice and speech at all, what their qualities are, whether he/she uses such way of communication as the only one while, on the other, it is rated by estimating phonation parameters like intelligibility, pitch, loudness, speed, but also the satisfaction of the patient with his/her own voice and speech [4]. Criteria for assessment of success used by Del RioValeiras et al. [14] imply three levels i.e., good success of the esophageal voice and speech education is achieved when a person always uses it, it is medium if the person uses it sometimes and poor if he/she does not use it at all.

From the above said, we can realize that by watching the criterion which implies that the patient spontaneously and effortlessly produces esophageal voice and speech in every communication situation, in a fully automatized way and with a steady rhythm and melody, barely noticeable, deprived of the noise of cannula, and without too much unnecessary gesturing, the success can be characterized as significantly smaller compared to one whose criterion is that the patient can communicate in

any way that is socially acceptable, and therefore the factors that affect it will be observed differently [4,13].

Besides the lack of consistent criteria, the reasons for divergence of results and different recording of the impact of individual factors on the success itself are also the use of different measuring instruments, which are often not standardized i.e., rules for their use, scoring and interpretation of data are not defined beforehand [23]. It is preferable to use the objective analysis which reduces the probability that it will produce its own conclusion, different processing and interpretation, which will definitely affect the improvement of success evaluation, but the perception of the factors' impact as well. However, its drawback is that it requires the use of voice sample only, but not speech [4,23]. When speaking about the instruments for self-assessment by the patients, a problem arises, implying different perception of the quality of voice and speech, and therefore the success of the education. For that reason, the esophageal voice and speech that was rated as excellent according to a therapist's evaluation, the patient shall consider unsatisfactory because he/she makes the comparison against the former, premorbid characteristics, while, on the other hand, voice and speech that were rated as very poor by a therapist, could be very satisfactory and excellent to the patient because for him/her the quality is not of primary importance. In connection to that, according to Dragičević et al. [30], patients who use esophageal voice and speech as a method of alaryngeal communication, rated its quality significantly worse compared to those who use tracheoesophageal voice and speech. In addition, disagreement with regards to the impact of factors on the success of education also results from inclusion of small number of examinees in the studies, and therefore the results cannot be largely generalized with regards to the entire population of laryngectomized patients who were educated for the use of esophageal voice and speech. What has been put forward as significant is also the need for a multi-variant analysis in order to perceive the manifestation and realization of the impact of factors on one another [23].

5. CONCLUSION

When taking into account all effects of the total laryngectomy and loss of numerous laryngeal functions on a person, among which is the most important one for them – phonation function, esophageal voice and speech education represents the most natural and humane type of reestablishment of verbal communication, despite the fact that in developed countries it has been completely replaced by the primary implantation of vocal prosthesis, especially in last 30 years. As pointed out, there are still not clearly defined, generally accepted and comprehensive criteria to evaluate to what extent the esophageal voice and speech education was successful, and this results in different understanding of the same, and then different understanding of positive i.e., negative impact of different factors. Despite the abovementioned, most of the conducted studies examining the factors that may affect the success of the esophageal voice and speech education, speak in favor of the fact that the patient's motivation is the key to the same. In all other factors, different data were obtained, and in some cases, they do affect the success, but in some, their impact is completely absent.

What needs to be done in the future is to clearly define the success criteria, but also define and apply standardized instruments in order to enable more adequate examination of the success of the esophageal voice and speech education, and compare the results of different studies. In addition, an evaluation with objective assessments of various voice and speech parameters on representative sample of participants is required.

6. LITERATURE

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Vol. 47 (2022) No. 1 TIMOK MEDICAL GAZETTE Review article

CAN WE TREAT URGENT MEDICAL CONDITIONS WITHOUT ADEQUATE DRUGS?

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Summary: Emergency Medicine does not represent a simple collection of various medical conditions, but rather an urgent approach to life threatening conditions. This urgent approach progresses as fast as the science in medicine does. Modern protocols for treatment of injured and ill patients are introduced, demanding more and more knowledge and skills as well as more modern equipment and wider spectrum of drugs. However, innovations are not followed by changes within the lists of medications set by National Health Insurance Fund of Serbia (NHIFS). Paper describes drugs necessary for adequate pre-hospital treatment that are not available to the physicians due to administrative barriers. On one hand, there are drugs from B list that are necessary for treatment, and are approved for use by NHIFS at hospital level only. The use of any of these drugs at pre-hospital level may lead to severe penalties to the physician in case of complications or adverse reactions in a patient following the treatment. On the other hand, there are drugs from D list which are also necessary for the urgent treatment of patients with life threatening conditions, according to latest recommendations. These drugs may be applied at pre-hospital level, but their procurement is complicated due to NHIFS regulations and that's why some of them may rarely be used (Propafenone and Magnesium sulfate). We particularly emphasize that one of the most effective drugs for the conversion of heart rhythm, Adenosine (6 mg/ml and 10mg/ml ampoule), is not registered in the Republic of Serbia and therefore cannot be used at pre-hospital level. Through these exclusive administrative barriers adequate treatment is rendered impossible while the system of urgent treatment of patients with life threatening conditions at pre-hospital level is degraded.
Key words: Emergency medical care, urgent medical conditions, treatment protocols, drugs

History of the development of Emergency Medicine

Emergency Medicine does not represent a simple collection of various medical conditions, but rather an urgent approach to life threatening conditions. It includes decision making and undertaking rapid measures in order to prevent death or deterioration of an existing life threatening condition in a patient. It is a particular medical specialty the primary task of which is urgent recognition, treatment and prevention of unexpected life threatening illness or injury in a patient. [1]

Emergency Medical Care (EMC) is a special area of health care arranged at primary health care level, organized in order to undertake necessary and immediate medical interventions so that deterioration or permanent damage caused by life threatening conditions could be avoided. [2] Unlike the First Aid measures provided by a layman, in our settings Emergency Medical Care is provided by a health professional specially trained for the treatment of these conditions

First records on provision of EMC were detected on papyrus dated 700 years B.C. Further historical records from various periods in time clearly show that EMC was present and

available with various types of organization and was improved through centuries. In 1955 external defibrillator was used for the first time and in 1958 artificial ventilation (mouth to mouth) was described followed by description of external heart compression in 1960. However, EMC was still provided by interns, physicians with other medical specialties and hastily trained staff at that time. Introduction of innovations in pre-hospital treatment of injured and ill patients lead to the development of separate medical specialty –urgent medicine. First Chair of Urgent Medicine was founded in 1971 at Medical Faculty in California. [3,4,5,6] In Former Yugoslavia, first Chair of Urgent Medicine was founded in 1979 at Medical Faculty of Sarajevo. Much later on, in 1991, Chair of Urgent Medicine was founded at Medical Faculty in Belgrade, followed by Medical Faculties in Nis, Novi Sad, Ljubljana and Zagreb in 1993, 1994, 2007 and 2010, respectively.

Implementation of protocols for treatment of life threatening conditions was as quick as was the progress of Urgent Medicine as a separate medical specialty. One of the first protocols implemented during the 70s of the XX century, was the so called Advanced Cardiac Life Support protocol. [7] After that, protocols for the treatment of trauma in the field settings, acute myocardial infarction, acute stroke, periarrest arrhythmias and many other were introduced. [8,9,10,11,12] Evidence based protocols are being updated annually. Urgent Medicine specialists are trying to implement new protocols in Serbia that have not been used previously. [13] Improvement and use of new protocols necessitates provision and use of modern equipment and wider spectrum of drugs. However, National Health Insurance Fund of Serbia (NHIFS) annually sets the lists of registered medications that they will cover for.. [14] Innovations in treatment of life threatening conditions are not followed by changes within the official lists of medications set by NHIFS, which may lead to lower quality in treatment compared to the best recommended one.

There are five official lists of medications set by NHIFS:

A List – Drugs prescribed by physicians and issued based on official physician's prescription form

A1 List - Drugs prescribed by physicians and issued based on official physician's prescription form, which have therapeutic parallel to the drugs from A List

B List – Drugs issued on order and applied during a treatment in outpatient clinics or hospital

C List – Drugs with special regime of prescribing

D List – Drugs without a license for use in Serbia, but necessary in diagnostic and therapy – unregistered drugs [14]

B and D lists contain drugs which are necessary for pre-hospital treatment of patients according to latest recommendations, but which are, for various reasons, unavailable to urgent medicine physician working in the departments for EMC.

Drugs from the B List unavailable for pre-hospital treatment

A total of nine drugs necessary for pre-hospital treatment are currently on the B List and their use is exclusively allowed in hospital facilities. These are:

Pantoprazole, 40mg, bottle
Streptokinase, 1.500.000 units bottle
Hydroxyethyl starch, Sodium chloride 6% 500ml bottle and 10% 500ml bottle
Urapidil 25/5ml or 50mg/10ml ampoule
Oxytocin 5 or 10 IJ/ml ampoule
Propofol 10mg/ml ampoule
Midazolam 5mg/5ml or 15mg/3ml ampoule
Flumazenil 0,5mg/5ml or 1mg/5ml ampoule
Protamine sulfate, 50mg/5ml bottle

First drug from the B List, unavailable for pre-hospital treatment is Pantoprazole. Gilbert and associates in 2001 published a meta-analyses on comparison of efficacy of proton pump inhibitors versus H2 antagonists in patients with bleeding gastric ulcer. Results showed that the use of proton pump inhibitors reduces the risk of long-term and repeated bleeding from gastric ulcer. [15] Intravenous drug administration almost instantly causes reduction of acidity of gastric content, preventing further damage at the sight of ulcer niche. [16,17] Masjedizadeh and associates conducted a prospective randomized study in 2014 and concluded that the use of Pantoprazole is equally efficient regardless of whether the dosage was high (80mg during the first hour, followed by 8mg/h the next three days) or low (40mg during the first hour, followed by 4mg/h the next three days) and administered as continuous intravenous infusion. [18] This clearly showed the need for the use of proton pump inhibitors as soon as

possible in patients with bleeding ulcers in gastrointestinal tract. In our settings, ampoules are available only at hospital level, so that in vast majority of cases drug cannot be used during the first hour of bleeding when the patient is far away from the hospital. The use of Ranitidine in these situations is inadequate substitute for the use of Pantoprazole and therefore bleeding is prolonged, patient's condition deteriorated and in some cases life threatening.

Plasma expanders Hydroxyethyl starch, Sodium chloride 6% and 10%, so called Hetasorb®, are a group of drugs that are also unavailable for pre-hospital use. In case of hypovolemic shock when compensation of volume is necessary, solutions of sodium chloride are needed and these are also unavailable and are not on any of the lists issued by NHIFS. According to the National Guidelines for good clinical Practice, issued by the Ministry of Health of Serbia, Ringer Lactate, 0,9% NaCl is recommended for pre-hospital diagnosis and treatment of urgent medical conditions for compensation of volume in hypovolemic shock and hypertonic solution is a third option [19]. Fluid compensation is the first therapeutic measure in trauma patients with hypovolemic shock. There is no evidence from the literature showing that fluid compensation is better with one type of solution than another. Advantage of colloids is faster and more long-term maintenance of volume of circulating fluid, absence of tissue edema or acid base status disorder. [20] Advantage of hypertonic salty solutions is quick increase in circulatory fluid volume. They are most valuable when used together with colloids. [21] Team for EMC is the first responder to severely injured patients. In case that team has no colloids or hypertonic salty solutions at their disposal when dealing with the injured patient in pre-hospital settings, they can undertake all necessary measures to preserve life of trauma patient with hypovolemic shock. [22]

Urapidil is another drug that is missing for pre-hospital use. This drug is also on the B List, but can be administered only in hospitals settings. Urapidil administration is most important in case of preeclampsia. It reduces blood pressure in 80% of cases when used as isolated drug intravenously. It has no adverse effects on the mother or child. However, if used too fast it can cause hypotension. [22,23] Use of this drug is justified in hypertension crisis as well as in a case of ischemic and hemorrhagic stroke with hypertension crisis. [24] Drug is not available for pre-hospital use just like Sodium nitroprusside or Labetalol which are recommended by National Guidelines of Good Clinical Practice for pre-hospital diagnosis and treatment of urgent medical conditions issued by the Ministry of Health. Therefore, there is no possibility of adequate care in case of hypertension in preeclampsia.

Oxytocin is another drug missing in pre-hospital care of urgent medical conditions in gynecology and obstetrics, besides Urapidil. It can be used in pre-hospital settings during the third labor age in order to shorten the period of expulsion of the placenta, consequently reducing the blood loss. Besides that, it can be used in infusion of crystalloids in case of heavy bleeding after delivery. [19,25] Abundant bleeding after delivery represent urgent medical condition when over 500 ml of blood is lost. Frequently, place of delivery is remote from adequate hospital facility. In case of expulsion of the placenta after delivery or if the bleeding is abundant, lack of oxytocin in pre-hospital settings may represent a big problem.

Propofol is also one of the drugs unavailable for pre-hospital use according to the NHIFS. Its administration is limited to the hospital settings. Propofol is a general anesthetic used intravenously for the induction and preservation of general anesthesia, sedation of the patient during mechanical ventilation and other diagnostic and therapeutic procedures. It has sedative, hypnotic, anticonvulsive and antiemetic characteristics. It is recommended for sedation before intubation in patients with severe asthma particularly if bronchospasm is expressed. [26,27,28] Propofol is recommended in patients with severe cranial injuries without hypovolemic shock in order to reduce intracranial pressure. [29] Mackay and associates published the research in 2001 showing that urgent medicine physicians are equally capable as anesthesiologists to take care of and intubate a patient in short term anesthesia. Therefore, urgent medicine physicians can safely use intravenous sedatives and neuromuscular blockers in pre-hospital settings. [30]

Midazolam is reserved for the use in hospital settings and is also on the B List, although the most EMC departments in Serbia have this drug at their disposal. In case of pre-

hospital use followed by complications or adverse events in a patient receiving the drug, physician may be exposed to severe judicial penalties. Midazolam is a benzodiazepine with sedative, hypnotic, anticonvulsive and muscle relaxation characteristics. Sedative and hypnotic effects occur quickly and last shortly, making this drug a good choice for short term sedation when pre-hospital intubation is difficult. [26, 31] Edward and associates conducted a research in 1999 showing that the use of this drug is justified in pre-hospital settings when intubation is difficult and also if performed by paramedics. [31] Considering the fact that in our country urgent medicine physicians work in pre-hospital settings there is no justification for the exclusive use of Propofol and Midazolam there. The two remaining drugs will be described in a separate chapter due to the fact that they are antidotes, a group of drugs extremely important for pre-hospital use in urgent medical conditions.

Drugs from the D List unavailable for pre-hospital treatment

Drugs from the D List, necessary for urgent medical care in life threatening conditions can be divided in two groups. The first group is comprised of drugs unregistered in Serbia, but available in EMC departments. These are: Atropine sulfate, Aminophylline, Glucose 50% and Naloxone hydrochloride. The second group is comprised of drugs that are unavailable but necessary for work in EMC. These are Propafenone ampoule 35mg/10ml and Magnesium sulfate 20%, 100 ml. bottle. Propafenone is member of Ic group of antiarrhythmics. It blocks sodium channels leading to slowing down the heart rhythm. It is used for therapy of supraventricular and ventricular tachycardia, and the most significant use is for therapy of Wolf-Parkinson-White syndrome. [32] Lately, it has been more frequently used in pre-hospital settings for conversion of atrial fibrillation, lasting less than 48 hours, into sinus rhythm. It is equally efficient as Amiodarone, but provides the effect faster. [33] It is equally efficient for the control of speed of ventricular response in case of fast supraventricular arrhythmias. [34]

Regardless of excellent recommendations it is not registered in Serbia so that it is not available to urgent medicine physicians for pre-hospital use.

Just like Propafenone, Magnesium sulfate is not available either. This drug is used during pregnancy in case of preeclampsia, eclampsia or intoxication for the prevention of convulsions. [35] It is also recommended in case of Torsades des pointes prolonged Q-T interval. [36] Intravenous administration is justified in case of severe asthma attack. [37] All of these are life threatening conditions where adequate therapy is needed as soon as possible. Delay in provision of proper therapy especially in case of eclampsia with convulsions may have fatal consequences in a pregnant woman or offspring. This is the reason why Magnesium sulfate should be provided to EMC teams for pre-hospital use.

Unregistered drugs in Serbia, not present on any of the lists

There are drugs unregistered in Serbia and not recognized by NHIFS as necessary for therapy neither at pre-hospital nor at hospital level. These drugs are not present on any of the lists issued by the NHIFS despite the fact that Global or European recommendations consider them necessary in certain urgent medical conditions. These are:

Adenosine, 3mg/ml ampoule

Biperiden, 5mg/ml ampoule

Carbo medicinalis (tablets, granules or suspension in sorbitol).

Adenosine is an antiarrhythmic. It is efficient for conversion of supraventricular tachycardia into a sinus rhythm. It represents first choice among drugs for the therapy of supraventricular rhythm disorders as stated in the recommendations from 2003, as well as in the recommendations from 2010 when periarrest arrhythmias are considered. [38,39] It was recommended by the Working Group for the creation of National Guidelines for Good clinical Practice in pre-hospital diagnostic and treatment of urgent medical conditions. [25 40] Adenosine acts faster, has shorter effect, is safer for use in pregnancy, has less adverse events than other antiarrhythmic drugs. [38,41,39] Gausche and associates published the study in 1994 showing Adenosine effective and safe to convert supraventricular tachycardia in pre-hospital use by paramedics. [42] This means that there are no limits for the procurement of the drug and its pre-hospital use by urgent medicine physicians.

Biperiden is the second unregistered drug. It is anticholinergic that is used

intravenously in therapy of: Parkinson disease (especially for rigors and tremors), iatrogenic extrapyramidal syndrome, nicotine poisoning and poisoning caused by organic compounds of phosphorus. [43] Having in mind the fact that EMC teams use Haloperidol in pre-hospital settings to treat various agitated states and also deal with intoxications with expressed extrapyramidal syndrome, Biperiden (for intravenous use) availability is necessary.
The remaining drug is an antidote and will be described in separate chapter.

Antidotes

Antidotes physically or chemically react with toxic substance or pharmacologically and biochemically correct the disorders caused by toxic substance that entered the organism. Antidotes are divided into specific and non-specific. Specific antidotes act on certain toxic substance while non-specific have neutralizing effect on a large number of toxic substances. [43,44] Principles of pre-hospital care of an intoxicated patient are summarized as ABCDE approach, followed by detoxification that encompasses prevention of toxic substances absorption, acceleration of its elimination, and the use of antidotes. [40,43,44] First two measures in detoxification may be applied, while the third one, use of antidotes, is most frequently unavailable in pre-hospital settings. Intoxications occur in farmers working in remote areas far away from hospitals. Time of the transport in such cases is significantly longer than usual and EMC teams are not in the position to undertake all the measures so that life could be saved and damage to the vital organs reduced to a minimum. [45] Some antidotes are unavailable such as:

Flumazenil, 0,5mg/5ml or 1mg/5ml ampoule
Protamine sulfate 50mg/5ml bottle
Glucagon syringe 1mg/1ml.

Carbo medicinalis (tablets, granules or suspension in sorbitol).

Flumazenil is specific benzodiazepine antagonist used in case when the effect of benzodiazepine needs to be reduced or interrupted quickly. [26,46] This drug has a short half-life of elimination, around an hour, so that after the initial dose slow intravenous infusion has to be continued. It is very efficient in benzodiazepine overdose, but it is not recommended in mixed intoxications or as a routine drug in differential diagnosis of coma. [47,48] It is indicated for hemodynamically stable patients who received or deliberately took high doses of benzodiazepines. In such a case, the drug has low frequency of side effects and is considered safer than intubation and mechanical ventilation in patients whose breathing is compromised. [46,47,49] This drug is on the B List, however its use is reserved for hospitals.

Protamine sulfate is also a specific antidote. This drug is used in case of heparin overdose. It is efficient in case of overdose by non fractionated and low molecular heparin. It is applied when heavy bleeding occurred after heparin overdose. Therapy should be started immediately in order to stop the bleeding and reduce the risk of death. [26,50] This drug is not registered in Serbia and is on the D List, so that it can be procured for special indications only

Glucagon is also unavailable for pre-hospital use. This drug is applied in case of hypoglycemia and as a specific antidote in case of β-blocker and calcium channel antagonist intoxication. [26] In case of β-blocker intoxication the drug is applied in high dosage as an antidote of first choice, while in case of calcium channels antagonist intoxication it can be used only in extremely difficult cases when recommended antidotes become ineffective. [51,52] β-blocker intoxication do not occur frequently, but are potentially life threatening requiring urgent use of antidotes. High doses applied intravenously may be life saving. [53] Glucagon is on the A List so it is available to the EMC teams.

Beside specific ones, Carbo medicinalis as an unspecific antidote is also unavailable. Prevention of toxic substances absorption has an important and unavoidable role in the process of treatment of intoxicated patients. Potential benefit of Carbo medicinalis use in cases of intoxication is well known since the 1830s. During the last twenty years its use has been essential in case of intoxication occurred within one hour. [53,54,55] A team of EMC arrives at proper location of the incident most frequently within one hour. However, additional time is needed for pre-hospital treatment and transport to a hospital facility so that one hour is frequently exceeded. Greater benefit could be achieved in case of Carbo Medicinalis availability to EMC teams for pre-hospital care because within one hour complete absorption of the toxic

substance in the digestive tract would be prevented.

CONCLUSION

Emergency Medical Care most frequently deals with life threatening conditions. Due to unavailability of certain drugs there is no possibility of adequate treatment according to modern protocols. Through administrative barriers created by making drugs unavailable or allowed for exclusive use at hospital level, adequate treatment is rendered impossible, while the system of urgent treatment of patients with life threatening conditions at pre-hospital level is degraded.

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TIMOK MEDICAL GAZETTE

Vol. 47 (2022) No. 1 Review article

PARADIGM CHANGE IN THE TREATMENT OF CHRONIC HEART FAILURE ACCORDING TO ESC GUIDE 2021 - NEW INNOVATIVE DRUGS IN FOCUS

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Summary: Medical, primarily drug therapy directed by the New ESC Guide or Guidelines for Patients with Heart Failure (HF) brings significant innovations and changes in the treatment paradigm, from the gradual introduction of drugs to the simultaneous introduction of 5 main classes of drugs. Treatment of heart failure with reduced left ventricular ejection fraction (HFrEF) and symptoms of class II-New York Heart Association (NYHA) -dispnea at higher exertion and higher NYHA classes, now includes angiotensin receptor inhibitor neprilysin (ARNI) as a substitute for angiotenzin convertase enzyme inhibitor(ACEI). Another significant innovation is the addition of SGLT-2 inhibitors (SGLT2i = sodium-glucose channel cotransporter-2 inhibitors). SGLT2i: dapagliflozin or empagliflozin are now in the first line of therapy for heart failure, along with the introduction of beta-blockers (BB), ACEI or ARNI, mineralocorticotide receptor inhibitors (MRAs) and Henle's loop diuretics in fluid retention as recommended in Class I. Sacubitril-valsartan, a combined neprilysin and angiotensin inhibitor (ARNI), was introduced in the reduced left ventricular ejection fraction (HFrEF) and showed an additional reduction in CV mortality and hospitalization due to HFrEF compared to the ACE inhibitor enalapril. Dapagliflozin and empagliflozin reduce the risk of cardiovascular mortality or hospitalization due to HF in patients with HF and reduced left ventricular ejection fraction <40% (HFrEF), but empagliflozin has recently shown an effect in HFpEF with an ejection fraction of 65% of 40%.

Key words: heart failure, pharmaceuticals, left ventricular ejection fraction, heart failure with reduced left ventricular ejection fraction (HFrEF), heart failure with perserved left ventricular ejection fraction (HFpEF), hypertension, kidney disease, myocardial ichaemia, natriuretic peptide

The key points from the European Society of Cardiology (ESC) Guide for the Diagnosis and Treatment of Acute and Chronic Heart Failure (HF) from 2021 [1] are presented, as well as some views from the American ACC / AHA Guidelines from 2022 [2]:

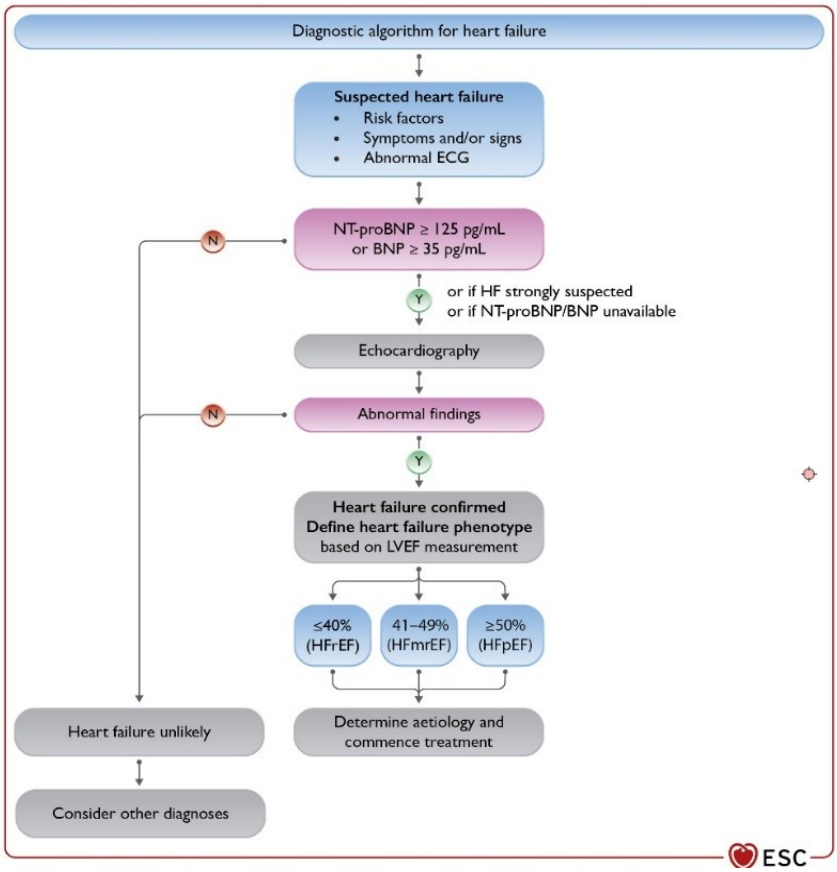
Heart failure (HF) nomenclature with left ventricular ejection fraction (LVEF) of 41-49% has been revised in HF with mildly reduced EF (HFmEF). HF with LVEF ≤40% remains HF with reduced EF (HFrEF), and HF with LVEF ≥50% remains HF with preserved EF (HFpEF).

Table 1. Heart failure (HF) nomenclature from ESC guideline 2021

Type of HF		HFrEF	HFmrEF	HFpEF
CRITERIA	1	Symptoms ± Signs[a]	Symptoms ± Signs[a]	Symptoms ± Signs[a]
	2	LVEF ≤40%	LVEF 41–49%[b]	LVEF ≥50%
	3	-	-	Objective evidence of cardiac structural and/or functional abnormalities consistent with the presence of LV diastolic dysfunction/raised LV filling pressures, including raised natriuretic peptides[c]

All patients with suspected HF should have: electrocardiogram, transthoracic echocardiogram, X-ray of thorax (lung and heart), complete blood count, urea, creatinine, electrolytes, thyroid hormones, glycosylated hemoglobin (HbA1c), lipid status, iron analysis, peptide (BNP / NT-proBNP). Magnetic resonance imaging of the heart is recommended in patients with poor acoustic window for ultrasound of the heart or in patients with suspected infiltrative cardiomyopathy, amyloidosis , hemochromatosis, dilated non-compaction cardiomyopathy or myocarditis [1]. The new diagnostic algorithm for heart failure (HF) is shown in Figure 1.

FIGURE 1. DIAGNOSTIC ALGORITHM FOR HEART INSUFFICIENCY (HF) ACCORDING TO THE NEW ESC GUIDE 2021.



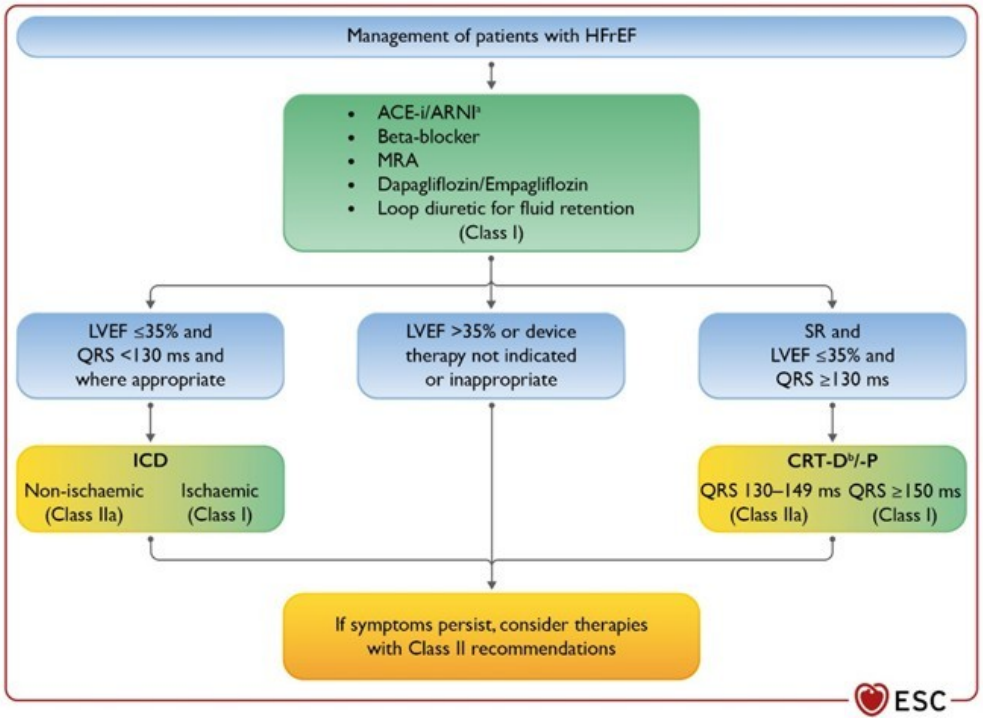
LEGEND: Heart failure with reduced left ventricular ejection fraction (HFrEF)
Heart failure with mildly reduced left ventricular ejection fraction (HFmrEF)
Heart failure with preserved left ventricular ejection fraction (HFpEF)
Available at www.escardio.org/guidelines (doi: 10.1093/eurheartj/ehab368)

Medical, primarily drug therapy directed by the New ESC Guide, ie guidelines for patients with heart failure (HF) with reduced ejection fraction (HFrEF) brings significant innovations and changes in the treatment paradigm, from the gradual introduction of drugs to the simultaneous introduction of 5 main classes of drugs.

Treatment of heart failure with reduced left ventricular ejection fraction (HFrEF) and symptoms of class II-New York Heart Association (NYHA) -dispnea at higher exertion and higher classes, now includes angiotensin receptor inhibitor neprilysin (ARNI) as a substitute for angiotenzin convertase enzyme inhibitor(ACEI). Another significant innovation is the addition of SGLT-2 (Sodium Glucose channels Cotransporter-2) inhibitors, dapagliflozin or empagliflozin in first-line therapy for heart failure, simultaneously with

the introduction of beta-blockers, ACEI or ARNI, mineralocorticoid receptor inhibitors and diuretics. class I. (picture 2)

Figure 2. Treatment of patients with HEART INSUFFICIENCY WITH REDUCED EJECTION FRAGMENT (HFrEF) according to the ESC guide from 2021



Legend ACE-I = angiotensin converting enzyme inhibitor; ARNI = angiotensin receptor-neprilysin inhibitor; ARB = angiotensin receptor blocker; BB = beta-blocker; CRT-D = pacemaker for cardiac resynchronization with a defibrillator; CRT-P = pacemaker for cardiac resynchronization; Available at www.escardio.org/guidelines (doi: 10.1093/eurheartj/ehab368)

Excessive neurohumoral activation antagonists, beta-adrenergic receptor blockers, and renin-angiotensin-aldosterone system antagonists have shown a reduction in CV mortality in HFrEF in a number of clinical randomized studies and have been the primary therapy for heart failure for some time. These drugs achieved the following beneficial effects: slowing the progression of left ventricular remodeling, reducing discomfort, improving endurance and quality of life in all symptomatic categories from NYHA class II to NYHA class IV. Eplerenone as a selective mineralocorticoid aldosterone receptor antagonist is recommended for NYHA class II, while for severe class III-IV patients with beta-blockers and ACEIs or sartans, a non-selective mineralocorticoid aldosterone receptor antagonist beparon (beta blocker) should be added with . In decompensated patients with severe congestion, Henle's loop diuretics remain a pillar of therapy.

In the treatment of heart failure with reduced LVEF (HFrEF), sacubitril-valsartan, a combined neprilysin and angiotensin inhibitor (ARNI), was introduced in previous 2016 ESC guidelines, which showed an additional reduction in CV mortality and hospitalizations due to HFrEF compared to the ACE inhibitor enala .

Dapagliflozin and empagliflozin reduce the risk of cardiovascular mortality or hospitalization due to HF in patients with HF and reduced left ventricular ejection fraction <40% (HFrEF) [1] but empagliflozin has also recently shown an effect in HFpEF [65% ejection] .
In patients with HFrEF and NYHA class II to III symptoms, ARNi is recommended to reduce morbidity and mortality (class 1A) [3-7].
In patients with previous or current symptoms of chronic HFrEF, the use of ACEi is useful in reducing morbidity and mortality when ARNi is not feasible (class 1A) [8-15].

In patients with previous or current symptoms of chronic HFrEF who are intolerant to ACEi due to cough or angioedema and when the use of ARNi is not feasible, the use of ARBs is recommended to reduce morbidity and mortality [16-20].
In patients with previous or current symptoms of chronic HFrEF, in whom the introduction of ARNi is not feasible, treatment with ACEi or ARB gives high economic viability [2,21-27].
ARNi is contraindicated in concomitant ACEi or within 36 hours of the last dose of ACEi, or in patients with a history of angioedema.

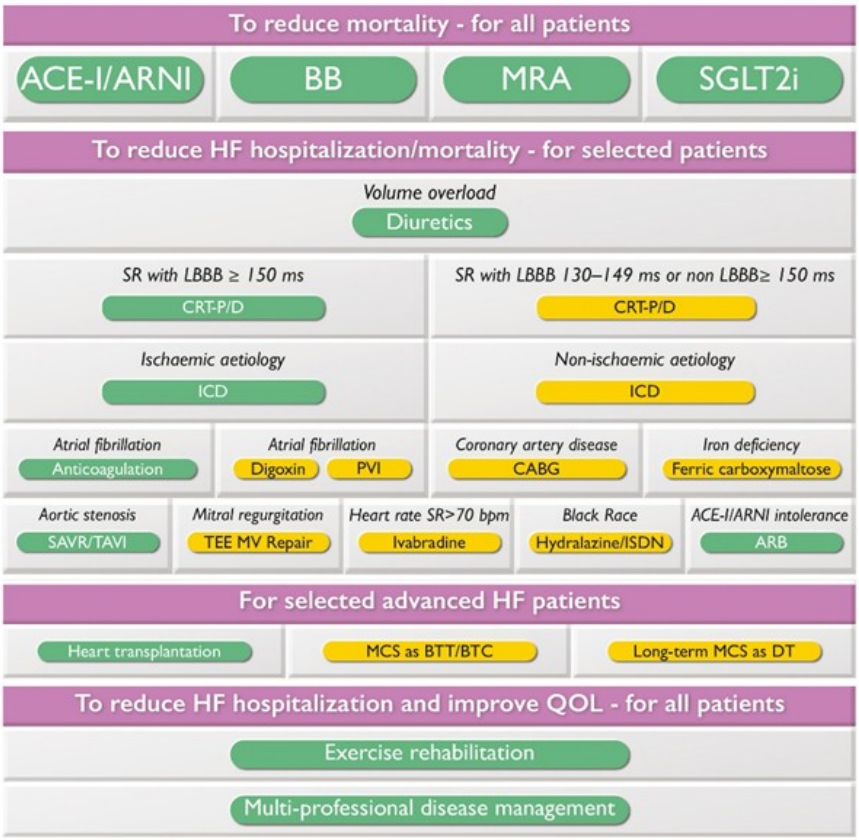
Recommendations for the administration of empagliflozin and dapagliflozin that reduce cardiovascular mortality or hospitalization due to HF in patients with HF and reduced left ventricular ejection fraction <40% (HFrEF)
In patients with symptomatic chronic HFrEF, SGLT2i is recommended to reduce hospitalization due to HF and cardiovascular mortality, regardless of the presence of type 2 diabetes [28,29] and thus introduced SGLT2i therapy has good economic justification [30,31].

Recommendations for HF with MILDLY reduced EF (HFmrEF)
In patients with HFmrEF, SGLT2i may be helpful in reducing hospitalizations for HF and cardiovascular mortality [32]. Among patients with current or previous symptomatic HFmrEF (LVEF, 41% –49%), the use of ARNi, ACEi or ARB and MRA and evidence-based beta blockers for HFrEF may be considered adequate for use to reduce the risk of hospitalization for HF and cardiovascular mortality , especially among patients with LVEF at the lower end of this spectrum [33-40].
Recommendations for HF with preserved EF (HFpEF) according to the ACC / AHA guide from 2022 (ref 2)

1. Patients with HFpEF and hypertension should be titrated with antihypertensive drugs in order to achieve the target blood pressure in accordance with published guidelines of clinical practice for the prevention of morbidity [41-43].
2. In patients with HFpEF, SGLT2 inhibitors may be useful in reducing HF hospitalizations and cardiovascular mortality [44].
3. In patients with HFpEF, treatment of atrial fibrillation (AF) may be helpful in improving symptoms.
4. In selected patients with HFpEF, mineralocorticoid receptor (MRA) antagonists may be considered effective in reducing hospitalizations, especially among patients with LVEF at the lower end of this spectrum [45-47].
5. In selected patients with HFpEF, the use of ARBs may be considered to reduce hospitalizations, especially among patients with LVEF at the lower end of this spectrum [48,49].

Implantable cardioverter-defibrillators (ICDs) are recommended for the primary prevention of sudden cardiac death in symptomatic ischemic or non-ischemic cardiomyopathy with LVEF ≤35% despite 3 months of optimal targeted therapy (GDMT) if 1-year survival is expected. ICD is not recommended within 40 days of myocardial infarction (MI) or for patients with NIHA class IV symptoms who are not candidates for advanced therapy.
Cardiac pacemaker resinchronization (CRT) therapy is recommended for symptomatic HFrEF with EF <35% in sinus rhythm with left bundle branch block (LBBB) for 150 ms despite GDMT. It is also recommended for HFrEF with EF <35% regardless of the symptoms or duration of heart failure if there is a high degree of atrioventricular (AV) block with the need for a pacemaker. (FIGURE 3)

FIGURE 3. Strategic review of care for patients with heart failure and reduced left ventricular ejection fraction (HFrEF)



LEGEND: b.p.m = beats per minute; BTC = bridge to transplant candidate; BTT = bridge to heart transplant; CABG = surgical coronary artery bypass grafting; CRT-D = defibrillator pacemaker resynchronization; CRT-P = pacemaker for cardiac resynchronization; DT = definitive therapy; ICD = implantable cardioverter-defibrillator; ISDN = isosorbide dinitrate; LBBB = block of the left branch of the His bundle; MCS = mechanical circulation support; MV = mitral valve; PVI = radiofrequency isolation of pulmonary veins; SAVR = surgical replacement of the aortic valve; SR = sinus rhythm; TAVI = transcatheter replacement of the aortic valve; TEE MV repair = transcatheter MV reconstruction from edge to edge.
Color code for recommendation class: green for recommendation class I; Yellow for recommendation class IIa. The figure shows the management options with Class I and IIa recommendations. See special tables for those with Class IIb recommendations.
Available at www.escardio.org/guidelines (doi: 10.1093/eurheartj/ehab368)

For HFmEF, diuretics are recommended to alleviate or eliminate congestion. ACE inhibitors / angiotensin receptor blockers / ARNI / beta-blockers / mineralocorticoid receptor antagonists may be considered as adjunctive therapy to reduce mortality and hospitalization (Class IIa recommendation).

Diagnosis and treatment of factors that contribute to heart failure (hypertension, kidney disease, etc.) and the use of diuretics are recommended for patients with heart failure with preserved left ventricular ejection fraction (HFpEF). Specific therapies have not been shown to reduce mortality in HFpEF. However, after the release of the ESC guide (August 2021), a new registration study Emperor-preserved (2) appeared, where empagliflozin showed improvement in the clinical outcome of treatment in patients with heart failure and preserved LVEF> 40%. A pooled analysis of the effects of empagliflozin 10 mg daily with pre-existing drug therapy for heart failure was performed on 9,718 Emperor-reduced and Emperor-Preserved patients. These two studies were comparable so that a wide range of left ventricular ejection fraction from 25% to 65% was obtained. Studies have shown that empagliflozin reduces the risk of hospitalization due to heart failure in a wide range of ejection fraction values by up to 65%, and its efficiency is

reduced in patients with LVEF> 65%. There is also a beneficial effect of empagliflozin on symptoms and endurance effort consistently with an ejection fraction of less than 65%. Further analysis found that the size of the therapeutic response to empagliflozin did not depend on the size of LVEF in the range of 25% to 65%, with a similar reduction in HF hospitalization risk to LVEF size in subgroups <30% and 40-50%, and in the subgroup with preserved left ventricular ejection fraction> 50%. An important fact from these studies is that empagliflozin reduces the risk of worsening glomerular filtration (GFR) in HF along the entire spectrum of the ejection fraction of LVEF, both with reduced, slightly reduced and preserved LVEF from 25% to 65% (2).

For all patients with HF, enrollment in a multidisciplinary HF program, at home or at the clinic, is recommended. For the prevention of HF, Class I recommendations include: appropriate hypertension treatment, statin use, when indicated, SGLT2 inhibitors in diabetics at high risk for or with cardiovascular disease, and counseling to discontinue, consume alcohol and drugs, and treat obesity.
For acute decompensated HF, routine use of inotropic drugs is not recommended in the absence of cardiogenic shock, and routine use of opioid-morphine is also not recommended for cardiogenic pulmonary edema. Routine use of an intra-aortic balloon pump in cardiogenic shock after myocardial infarction is not recommended.
Additional Class I recommendations for hospitalized patients with acute HF include the introduction of targeted oral therapy and the careful elimination of pre-discharge volume overload (congestion) with early follow-up within 1-2 weeks of hospital discharge.

For patients with atrial fibrillation (AF), routine use of anticoagulants for CHA2DS2-VASc ≥2 in men and ≥3 in women is recommended, preferably with direct-acting oral anticoagulants (NOAC), except in the presence of a prosthetic mechanical valve or moderate or severe mitral stenosis. Recommended. Emergency cardioversion is recommended for patients with HF AF who are hemodynamically compromised. Rhythm control, including radiofrequency catheter ablation, should be considered in AF patients who have symptoms.

For patients with HF and severe aortic stenosis, transcatheter / surgical replacement of the aortic valve using the Heart Time approach is recommended. For patients with HF with secondary mitral regurgitation, percutaneous edge-to-edge mitral valve repair should be considered if severe symptoms persist despite appropriate guided therapy (GDMT). For patients with secondary mitral regurgitation and coronary artery disease requiring revascularization, coronary by-pass and mitral valve surgery should be considered.
Patients with cancer who are being considered for cardiotoxic chemotherapeutic drugs and who are at risk of cardiotoxicity should ideally be evaluated by a cardio-oncologist before starting therapy.
Tafamidis is a Class I recommendation in patients with TTR-type amyloidosis with symptoms of NIHA class I-II.
All patients with HF should be periodically examined for iron deficiency anemia. Administration of ferric carboxymaltose should be considered in symptomatic, outpatient patients with HF and anemia due to iron deficiency and EF ≤45% or hospitalized patients with HF with EF ≤50%.

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