IOSUD - UNIVERSITATEA „DUNĂREA DE JOS” DIN GALAŢI
Școala Doctorală De Științe Biomedicale

DOCTORAL THESIS ABSTRACT

BICARBONATE IONIZATION IN HYPERHIDROSIS – ANALYSIS OF IMPROVING THE QUALITY OF LIFE OF CHILDREN

PhD student name,
FLORENTINA (NĂSTASE) CRĂCIUN

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Seria M: Medicină Nr. 11
GALAŢI, 2024

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INTRODUCTION

Sweating is a physiological process essential for survival, by which the body maintains thermal balance. The term "Excessive Sweating" is difficult to define. Instead of quantifying the amount of sweating, we try to define the amount that limits daily activities, causing social, physical and emotional discomfort and that has an impact on the quality of life.

Hyperhidrosis is not defined by the amount of sweat, but by dysfunctional, unexpected and uncontrollable sweating. In daily practice, qualitative measurement of hyperhidrosis is preferred, so any secretion that significantly interferes with individual activities should be regarded as abnormal.

Over time, multiple scales have been developed to quantify the impact of hyperhidrosis on everyday life. Some of them are disease-specific, others are dermatological-specific, while some studies have used general quality-of-life measurement scales. Although there are a few, some have only been used in studies where they have been validated. The most frequently encountered in the assessment of the quality of life in patients with hyperhidrosis are the Hyperhidrosis Disease Severity Scale, the Dermatology Life Quality Index and the Hyperhidrosis Quality of Life Questionnaire, which can be used simultaneous.

Although it is a relatively common disease, it is underdiagnosed and underevalueted, both by the patient and by medical professionals. In the specialized literature we find many studies that propose measuring and quantifying the impact on patients, comparing them before and after various treatments, their main results are performed on adults. Less common are those that include mixed groups, children - adults, and those on children-only groups are very rare.

Through studies 1 and 2, retrospective studies over a period of 10 years, we aimed to obtain information about the epidemiological data and their correlation with the period when the treatment was performed, about the affected areas, the genetic factor involved and about the addressability to the treatment, emphasizing during the 3 years that overlapped with the COVID-19 pandemic.

Through study 3, we aimed to form an exclusive group of children, aged up to 18, to subjectively evaluate the severity of hyperhidrosis and its impact on quality of life, by means of the Hyperhidrosis Disease Severity Scale and the Children Dermatology Life Quality Index, and then to compare the data obtained after performing 10 sessions of ionization with bicarbonate at the palmar and/or plantar level.

In this study we did not measure sweat objectively, because objective tests only provide measurements for a limited moment, not data for the whole day. That's why we chose to use subjective scales to measure the child's perception of the effects of hyperhidrosis.

Through study 4, we aimed to objectify the results of the ionization, by photographing the amount of sweating before performing the treatment in only one limb and then comparing it with the images obtained after the treatment, and comparing the sweating in the treated limb with the contralateral, untreated one.

Through these 4 previously mentioned studies, we want to raise an alarm on the impact of hyperhidrosis on children and their subsequent development, an impact much underestimated, but which can be significantly improved by means of ionization with bicarbonate.

CHAPTER 1
ANATOMY AND PHYSIOLOGY NOTIONS

1.1 ANATOMY OF THE SKIN

The skin is the largest organ of the body, with a weight between 6 and 10 kg, which represents approximately 12-15 % of body weight and a surface area of approximately 1.8 m^2 (1,2). This represents the boundary between the environment and the organism (3), acting as a barrier against infectious organisms and harmful chemicals, as well as against the loss of electrolytes and water (4–7). The thickness varies depending on the topographical area, from 0.5-4 mm, being thinner on the face, eyelids and thicker on the dorsal region, palms, soles and scalp. Skin color varies depending on: geographical area, race, blood circulation at the level of the dermis and the amount of skin pigment - melanin (8).

1.2 PHYSIOLOGY OF SWEAT GLAND

The human body contains approximately 2-4 million sweat glands (9,10). These glands are divided into three main types based on anatomical distribution, function, structure, secreted substances and secretory mechanism: eccrine, apocrine and apoecrine (11–15).

1.2.1 CLASSIFICATION OF SWEAT GLAND

1. Eccrine sweat glands were discovered and described in 1833 and 1834, but they received their current name 100 years later (12). There are 3 million of them, about 80% of all sweat glands (9,16). They are derived embryologically from the surface epithelium (16), not from the folliculosebaceous unit (10,13). The development of sweat glands begins at the gestational age of 28 weeks, and an increase in the active-inactive ratio ends at the age of 2.5 years. The surrounding thermal environment influences the degree of activation during this period, therefore the concentration of active glands is higher for those who live in warm climate areas and lower for those who live in cold areas (17). Eccrine glands produce a hypotonic, odorless, transparent secretion with a watery consistency (9,16), being functional early, starting from the age of 2-3 their number is finalized for the rest of life. As the skin stretches, with growth, their density decreases, resulting in a higher density in children than in adults and a lower density in obese than normal-sized people (17).

2. Apocrine sweat glands were discovered in 1844 and named as such in 1922 (12). They are located in limited areas in the armpit, urogenital region and nipples (11,16,18). They are also present in a modified form in the eyelids and external auditory meatus (11,14). Apocrine glands are less numerous than eccrine ones (13,16), the ratio of eccrine glands/apocrine glands is 1:1 at the axillary level, and in the other body areas they are in a ratio of 10:1 (10).

This type of sweat glands is present from birth, but before puberty the glands are small and inactive (19). After activation, with puberty, they grow in size, surpassing the eccrine ones and begin to secrete a viscous, oily substance containing cholesterol, lipids and steroids (11), being under the control of adrenergic fibers (16).

3. Apoecrine sweat glands have been described recently since 1987 and represent a mixed form of glands (12). As their name suggests, they have properties in common with apocrine and eccrine glands, being more similar to eccrine ones by the duct through which they secrete directly onto the body surface and by the secreted substance which is watery,

salty (12,14). They secrete continuously, with a higher rate of secretion compared to other sweat glands and with a higher rate of response to cholinergic and adrenergic stimuli. The only area of the body where they appear is the armpit, developing during puberty from the eccrine glands (11).

4. Sebaceous glands are not sweat glands, but they do have an impact on the composition of sweat on the skin. They were initially described in 1826 and are associated with hair follicles, being present on an extensive skin surface, especially on the scalp, face, forehead and in the genital area, being absent on the soles and palms. The secretion is viscous, rich in lipids, with a rate of secretion that is under hormonal (androgen) control (12). The hydrolipidic film formed by sebum and sweat is the first line barrier of the skin and covers the skin surface, forming a protective layer. In addition, it favors the growth of normal microflora, and in dry environments it prevents excessive evaporation (17).

1.2.2 CONTROL OF ECCRINE SWEAT

Sweating is a physiological, vital response. The two types of sweating are: thermoregulatory, specific to humans and a few animals, such as horses and monkeys and emotional, which serves as a physical signal in cognitive and sensory-emotional processes and is mediated by the neocortical, prefrontal, and sublimbic center (20).

1.2.3 THE PHYSIOLOGICAL ROLES OF SWEAT

1. Thermoregulation
2. Skin health
3. Micronutrient balance
4. Comparison of sweat gland and kidney function (15).

1.2.4 ALTERATION OF SWEAT GLAND FUNCTION

Certain medications or medical pathologies can influence the composition and rate of sweating. A significant reduction of it occurs in multiple sclerosis, anhidrotic ectodermal dysplasia, spinal cord injuries and in diabetes mellitus, which leads to severe impairment of the ability to dissipate heat when increased thermal loads occur (12,21).

CHAPTER 2
HYPERHIDROSIS

2.1 DEFINITION

Sweating is a physiological process essential for survival in which the eccrine sweat glands release a watery secretion. Thanks to the rapid evaporation of sweat, body heat is also removed, protecting the body from overheating (22–24). The normal amount of sweat secretion is less than 1 mL/m2/min (10).

Hyperhidrosis is a chronic disease (25), relatively common, characterized by excessive, unexpected and uncontrollable sweating (26,27), appeared at rest (28), as a response to psychological or emotional stimuli (26,29), above the physiological need of the body to maintain thermohomeostasis (30,31).

2.2 PATHOPHYSIOLOGY

The cause of hyperhidrosis is not known. The possible etiology is hyperexcitability of reflex circuits of normal eccrine glands, which is associated with complex dysfunction of sympathetic and parasympathetic elements (32).

The pathophysiological mechanism is not clear. Patients have a normal density of sweat glands, but they have an increased production of secretion (25). This hypersecretion is thought to result from dysfunction of autonomic nervous system fibers (33). The histopathological findings demonstrate that at the level of hyperactive sweat glands, no changes occur either in their structure or in their number in the affected body area (9,34).

2.3 CLASSIFICATION

Hyperhidrosis can be classified as primary or secondary.

2.3.1 Primary hyperhidrosis (HP) is idiopathic and occurs in young people without comorbidities. It manifests focally and symmetrically, episodically and is triggered by stress or emotions, only during the day, never during the night. In 30-50% of cases there is a positive family history, which suggests a genetic component of disease transmission (35). Primary hyperhidrosis is the object of study of this thesis.

2.3.2 Secondary hyperhidrosis (HS) affects older patients and can occur in fever, in various physiological processes, such as pregnancy or menopause, in systemic diseases or as an adverse reaction after the administration of certain drugs (opioid analgesics, cyclooxygenase inhibitors, antibiotics, antivirals, antidepressants, anticholinergic or hypoglycaemic agents, antipyretics) or as a complication after medical procedures such as thoracic sympathectomy (36). Unlike the primary one, it is generalized, asymmetric, does not have genetic transmission and can also manifest during the night (9).

2.4 DIAGNOSIS

Both patients and doctors are not always aware that hyperhidrosis is a factor that can significantly alter the quality of life and that it is treatable (10,37). An early diagnosis allows the administration of appropriate treatment, necessary to minimize the physical, emotional and psychosocial effects. The first step is to rule out the diagnosis of secondary hyperhidrosis (10,25). The complete medical history and physical examination are important elements and provide all the information necessary to differentiate the two forms, HP having specific characteristics that allow the diagnosis (37). These features are:

• Young healthy patients with a possible positive family history

• Aggravating emotional, physical and/or thermal stimuli
• Focal, symmetrical and bilateral involvement of the palms, soles and/or axillae
• Symptoms relieved during sleep (25,38).

HP may affect one or more anatomical areas, including the armpit, palms, soles, face, or scalp (39). Palmar hyperhidrosis interferes with all activities that require dexterity (40). Avoiding contact leads to social, interpersonal exclusion and embarrassment. These symptoms provide an increased risk of disability, fear, avoidance, which will lead to anxiety (41). Plantar hyperhidrosis is easier to hide, but can cause infections, skin maceration and bromhidrosis = foul-smelling sweat (13,41). Axillary hyperhidrosis requires frequent changes of clothing and the use of numerous and expensive antiperspirants (41).

The following diagnostic criteria for primary hyperhidrosis have been proposed:

1. At least six months of focal excessive sweating with no apparent cause
2. Two or more of the following:
   a. Onset before 25 years
   b. Frequent occurrence, with at least one episode/week
   c. Bilateral, symmetrical distribution
   d. Positive family history
   e. Disappearance during sleep
   f. Interference with daily activities (35,38).

2.5 QUANTITATIVE TESTS

After establishing the diagnosis of primary hyperhidrosis, the rate and volume of sweat production can be determined (10).

Quantitative measurements of sweat production are not performed in routine clinical practice, but they may help establish the diagnosis or guide the therapeutic approach. As mentioned before, hyperhidrosis is not defined by the amount of sweat produced (25). Normal sweating is considered to be <1 mL/m2/minute, and axillary hyperhidrosis occurs at an amount >100 mg/5 minutes, while palmar HH can be diagnosed at more than 30-40 mg/minute (37). Several tests for measuring the amount of sweating are described in the specialized literature, but the most commonly used are the ***gravimetric test*** and the ***Minor test*** (25).

2.6 QUALITATIVE TESTS

Any amount of sweating that affects daily activities is considered abnormal. It is therefore imperative to qualitatively measure the effects of HH on quality of life. The scoring of the questionnaires is subjective because patients from different backgrounds and cultures may place different emphasis on certain aspects contained in them.

The impact on quality of life is the most valuable and essential assessment in primary hyperhidrosis. Quality of life involves the individual's environment, including occupation, family and friends, and this must be interpreted in the context of the patient's social and cultural environment, standards and values.

2.7 IMPACT ON QUALITY OF LIFE

In 1946 the World Health Organization (WHO) defined "health" as "complete social, mental and physical well-being and not the absence of infirmity or disease". From this definition it is possible to conclude that to be considered healthy, even in the absence of an organic change, one must live with quality. This concept no longer limits the

measurement of health to the absence of injury or disease, but it becomes important to take into account the repercussions or the different dimensions involved in everyday life and activities. Quality of life is defined as the general well-being of society and the individual, taking into account both negative and positive features (42).

2.8 COMPLICATIONS

Hyperhidrosis causes real discomfort to patients. In addition, due to the humidity, skin infections can develop (11). Patients have an increased risk of viral skin infections – warts, bacterial – punctate keratolysis, fungal – tinea pedis, onychomycosis, candida. Excess sweating creates a perfect environment for colonization and infection, which can cause pain, eczema and skin lesions (43,44). Intertriginous areas, such as the armpits, are more prone to infections and irritant dermatitis. Pompholix - dyshidrotic eczema appears on the palms, and punctate keratolysis, dyshidrotic eczema, maceration, onychomycosis, tinea pedis and unpleasant odor may occur on the plants.

Bad smell or bromhidrosis is a chronic condition, secondary to the excessive secretion of the sweat glands, which becomes foul-smelling due to bacterial decomposition. The frequently affected areas are the armpits. Odor can be controlled by frequent bathing, waxing, removing underwear, topical aluminum salts, antiperspirants, and antibacterial soaps (11).

2.9 TREATMENT

The objectives are:

- Complete improvement of symptoms
- Convenient and long-term application
- Elimination of adverse reactions

2.9.1 TOPICAL TREATMENT

a) *Topical antiperspirants based on aluminum salts*
b) *Topical anticholinergic agents – glycopyrrolate*
c) *Topical anticholinergic agents – oxybutynin*

2.9.2 ORAL TREATMENT

a) *Anticholinegics*
b) *Treatment of the elderly and pregnant women*

2.9.3 IONIZATION

Physiotherapy is a branch of general medicine that uses natural or artificial physical agents for therapeutic purposes. Electric current represents the movement of electric charges through a conductor (body through which continuous electric current can pass). Constant direct current represents the movement of electrons in the same direction at a constant intensity.

Ionogalvanization is the method by which pharmacologically active substances are introduced in ionized form with the help of galvanic current (45). Synonyms of this procedure, found in the medical literature, are: galvanoionotherapy, ionotherapy, iontophoresis, ionophoresis or ionization.

Two ways of application are also described:

1. tap water is poured into a tray connected to direct current, in which a spoonful of bicarbonate can be added to increase efficiency, after which plants and/or palms are inserted for 20-30 minutes (46,47)
2. apply surface electrodes covered with a hydrophilic protective layer soaked in tap water or water to which bicarbonate has been added (48).

2.9.4 BOTULINUM TOXIN

Botulinum toxin is a high molecular weight neurotoxin produced by Clostridium botulinum, an anaerobic, Gram-positive bacterium. Of its seven different serotypes, only two are used for therapeutic purposes – type A and type B (11,49). The mechanism of action of botulinum toxin is achieved by the reversible blocking of the release of acetylcholine in the neuroglandular junction, preventing the fusion of the vesicles that contain it on the surface of alpha motor neurons and sympathetic nerves, thus resulting in a decrease in the transmission of the impulse to the sweat gland (28,50). For this reason, in addition to inhibiting the stimulation of eccrine sweat glands, botulinum toxin also inhibits the contraction of striated muscles. Usually the anhidrotic effect appears after three days of administration and can be maintained from 3 to more than 12 months (50,51).

2.9.5 SURGICAL TREATMENT

Surgical treatment is reserved as a last resort after less invasive procedures have failed.

a) *Local surgical treatment*

The principle consists in injuring or removing the sweat glands, but it carries the risk of developing hypertrophic or atrophic scars and dispersion of the glands. This is done by liposuction, curettage, excision or a combination of these. It is only recommended for the axillary area, the other areas possibly affected by hyperhidrosis being contraindicated (11).

b) *Endoscopic thoracic sympathectomy*

It is reserved for carefully selected patients as a last step in severe refractory cases. This procedure performed by neurosurgeons consists of video-guided thoracoscopy with interruption of the bilateral sympathetic chain by ablation, cauterization or clamping of the T3 or T4 thoracic ganglion (11,47).

c) Endoscopic lumbar sympathectomy

It is performed following a standardized, minimally invasive surgical technique with minimal traumatic tissue damage and minimal perioperative morbidity (52).

2.9.5 OTHER TREATMENTS

a) *Laser therapy* is used to destroy glandular tissue by subdermal coagulation (11).

b) *Microwave devices* that destroy the glands by increasing the temperature, reaching thermolysis. It is applied after local anesthesia.

c) *Fractional microneedle radiofrequency* is used for HHA and consists of positioning the needles 2-3 mm under the skin and applying the radiofrequency (47).

2.9.6 RECOMMENDATIONS ACCORDING TO THE HYPERHIDROSIS SEVERITY SCALE

For all patients with primary hyperhidrosis, assessment by measuring the severity of the disease using the HDSS - Hyperhidrosis Severity Scale is crucial, in order to determine the appropriate treatment and to monitor its results. To define therapeutic success for the patient with HP using the HDSS, an improvement in the score from 4 to 2

or 1, from 3 to 2 or 1, or from 2 to 1 is considered. To define therapeutic failure, the lack of tolerability of the therapy is considered or an unchanged severity scale score after one month of treatment (53).

2.10 SPECIAL ASPECTS REGARDING PRIMARY HYPERHIDROSIS IN CHILDREN

For many years, hyperhidrosis was thought to be a condition of no medical importance. Instead it is debilitating, significantly affecting interaction and social activities. Children may be too embarrassed to play sports or hold other children's hands. Teenagers tend to believe that they are the only ones with this problem and have to face it alone, leading to insecurity, self-blame and isolation (10,54).

The problem of body image is more important in teenagers than in adults. This visible skin condition endangers acceptance and restricts social activities, being a barrier to acceptance (24).

The impact of hyperhidrosis on quality of life is comparable to that of other dermatological diseases such as scleroderma (55), acne vulgaris (56) or psoriasis (57).

2.11 DISCUSSIONS

Skin diseases have serious consequences on daily life, social, professional activities or psychological well-being. Negative emotions are a reason for avoiding certain activities that may aggravate their symptoms. Patients with skin pathology, including hyperhidrosis, can benefit from help to cope more easily with the effects of the disease, such as psychotherapy, counseling or medical education, including in the online environment, where availability is increased (58).

Compared to other skin pathologies, acne, psoriasis or eczema, where the lesions are visible, well defined, familiar to the patient, in HH the symptoms are intermittent, and can be omitted during a medical consultation. Patients also omit reporting due to embarrassment or the belief that there is no treatment (43).

Individual possibilities and choices are limited by hyperhidrosis, starting from adolescence to adulthood. Career choices and future plans are affected by the negative influence on social interactions that this disease has. Excessive sweating discourages interaction and creates routines, which do not allow spontaneity (59).

Although the prevalence of hyperhidrosis among the population is relatively high, it remains an insufficiently studied disease, with a very low addressability to medical services. Access to treatment is limited by a lack of awareness of the severity of the disease, with many patients not receiving any treatment. Early treatment can prevent the development or exacerbation of the disease (43).

CHAPTER 3

3.1 MOTIVATION AND REFLECTION ON SPECIALTY LITERATURE

The World Health Organization (WHO) defines quality of life as the individual's own perception compared to his expectations. There are many factors that can influence this perception, such as objectives, own goals, social values, the culture of the area where they live and, of course, the standards imposed by society.

Hyperhidrosis has a significant impact on mental health, self-esteem, relationships, social interactions or occupational concerns and deserves equal attention with other well-known dermatological diseases. In the specialized literature, studies show that 48% of patients have poor and very poor quality of life. There is a lack of awareness of this disease and its therapeutic options, both from patients and doctors (43). In one study it was found that 47% of patients thought nothing could be done and 51% of patients had spoken to a medical professional and 60% of them did not know it was a medical condition (39).

For medical research, questionnaires are needed to measure the quality of life, in order to evaluate the effectiveness of the proposed therapies. The decrease in the quality of life in patients with hyperhidrosis is due to the influence that excessive sweating has on the daily routine (43).

Rating scales were applied before and after treatment to establish the effect of ionization on improving the quality of life.

The aim of this study is to analyze the severity of hyperhidrosis and the impairment of quality of life before treatment and to compare them with those after treatment. Studies including children are few, but those conducted only on children are even fewer. Therefore, this work is intended to contain useful information to better understand this disease, to improve diagnosis, treatment and quality of life.

The present study includes a total of 76 tables and 105 figures.

3.2 INTRODUCTION

The study of epidemiological data such as incidence, prevalence, demographic factors (age, gender, environment) has an important role in establishing the etiopathogenesis of diseases, being necessary in any type of disease, especially in those whose mechanisms are not yet known. There are no studies on primary hyperhidrosis in Romania, and even less so in limited geographical areas, such as Galați county. Searching the international specialized literature, there are very few studies conducted on children. That is why this work can be useful both regionally and nationally.

The purpose of this study is to obtain information about the epidemiological data and the correlation of place with the period when the treatment was performed, about the affected areas, the genetic factor involved and about the addressability to the treatment.

The disease produced by the newly discovered virus - SAR-CoV-2 (COVID-19) is highly contagious, with the World Health Organization declaring the pandemic as of March 11, 2020 (60).

The COVID-19 pandemic has produced significant changes in the lives of many people. Due to the countless deaths and infections worldwide, massive prevention measures have been implemented. Although the impact was at the level of the entire population, children and adolescents had to face the changes imposed on their lives, school closures, social distancing, isolation at home, which led to them adding to pre-existing problems and increasing the deterioration of the quality of life. In addition, access to

medical centers was also limited, resulting in the lack of treatment for certain diseases, considered by them or their relatives, less important (61–63).

This trend can also be observed in our retrospective studies, 1 and 2 respectively, in which we can see the decrease in children's addressability to ionization therapy and to the dermatologist, respectively.

3.3 ETHICAL RULES IN MEDICAL RESEARCH

This study was initiated after the approval of the Ethics Commission of the "Sf. Ioan" Emergency Clinical Hospital for Children, Galati, with number 31117/4.12.2023, prior to accessing the database (27). The study follows the fundamental principles of ethics in medical research applied to human subjects. These principles are contained in the Declaration of Helsinki (WMA DECLARATION OF HELSINKI – ETHICAL PRINCIPLES FOR MEDICAL RESEARCH INVOLVING HUMAN SUBJECTS) from 1964, revised in 2008, through the guide to good clinical practice (GCP – Good Clinical Practice) (64).

Confidentiality principles were respected, the results being in the form of anonymized statistical data.

3.4 STUDY LOCATION AND RESOURCES INVOLVED

The study is carried out in the Neuropsychomotor Recovery clinic within the "Sf. Ioan" Emergency Clinical Hospital for Children, Galați, a hospital that serves the population of the eastern region of Romania.

3.5 STATISTICAL DATA PROCESSING

Patient data were entered into an initial database using Microsoft EXCEL, necessary to centralize and systematize patient data. To perform the statistical analysis of the data we used the XLSTAT 2024 software. The descriptive analytical methods we used are:

- mean ± SD (standard deviation)
- the median
- first quartile – Q1 (1st quartile)
- the third quartile – Q3 (3rd quartile)
- the interquartile range – IQR

STUDY 1
Epidemiological characteristics of children with primary hyperhidrosis who presented to the Neuropsychomotor Rehabilitation Department
CHAPTER 4

4.1 OBJECTIVES

1. Establishing the number of patients who came to our service for ionization over the 10-year period
2. Distribution of primary hyperhidrosis according to gender, age, environment
3. Establishing age groups with higher attendance
4. Establishing the presence of each gender in the age groups
5. Establishing the predominant localization: palmar, plantar or the palmo-plantar association
6. Making a curve of the cases presented each year
7. Observing the trend of addressability of patients
8. Establishing genetic involvement

4.2 MATERIALS AND METHODS

4.2.1 PARTICIPANTS IN THE STUDY

Study batch 1 includes 111 patients who presented themselves in the Integrated Outpatient Department of the Neuropsychomotor Recovery Department between January 1, 2014 and December 31, 2023, a batch considered to be statistically adequate to achieve the statistical objectives. The electronic databases, consultation and treatment records of all patients who presented themselves during the indicated period were analyzed.

4.2.2 INSTRUMENTS USED

All patients were integrated into an electrotherapy program for 10 days, using galvanic current.

4.3 RESULTS

4.3.1 STUDY OF DEMOGRAPHIC FACTORS

The studied group includes a number of 111 patients diagnosed with primary hyperhidrosis who presented at the Neuropsychomotor Recovery clinic for ionization between January 1, 2014 and December 31, 2023(27).

A. AGE

The ages of the patients included in the study vary between 6 and 17 years, the average age being 10.59±2.87 years. We decided to segment the patients by age groups, starting with the 6-8 years segment. This classification into four categories allowed us to form a clear picture of the ages and identify trends in each interval.

Distribution by age groups:

• 6-8 years – 27 (90%) girls and 3 (10%) boys, out of a total of 30 (27.03%) children
• 9-11 years – 25 (58.14%) girls and 18 (41.86%) boys, out of a total of 43 (38.73%) children
• 12-14 years – 15 (50%) girls and 15 (50%) boys, out of a total of 30 (27.03%) children

• 15-17 years – 0 (0%) girls and 8 (100%) boys, out of a total of 8 (7.21%) children (27).

We observe an increased addressability at younger ages, as they get older the addressability decreases, probably due to getting used to the symptomatology, occupying time with more extracurricular and school activities, such as studying for important exams, or because at a younger age they are more easily convinced to undergo treatment. The maximum incidence in this study is in the age group 9-11 years, with a number of 43 children, which represents 38.73% of the total number of cases.

The age groups 6-8 years and 12-14 years have a lower ratio, of 27.03% of cases, while the 15-17 group has the lowest percentage, of 7.21%.

If we analyze the presence of patients for each year taken into account, we observe a relatively constant trajectory in the first years analyzed, with a sudden drop to 0 in the period 2020-2022, a period that coincides with the restrictions due to the COVID-19 pandemic. It is important to mention that the two patients registered in 2021 presented themselves for another pathology that required recovery treatment, a lumbar pain syndrome and a post humerus fracture status, pathologies for which the immediate start of specific procedures was required. During the clinical examination of these two patients, profuse sweating was also observed, for which the treatment was supplemented with ionization, after the diagnosis of primary hyperhidrosis was confirmed by the dermatologist (27).

These findings support data from the literature, which states that patients and their families consider hyperhidrosis to be a less serious disease for which treatment can be delayed.

B. GENDER

The gender ratio is in favor of the females, with 67 (60.36%) cases compared to 44 (39.64%) male patients. This proportion respects the data from the literature, which describes the predominance of the female gender. However, this does not reflect the actual incidence of the disease among the two genders, which is relatively equal, but the addressability and desire to receive treatment, which is more common in girls. The average number of patients presenting for treatment per year was 6.7 female and 4.4 male (27).

A more detailed analysis reveals an average age of girls of 10.71±2.95 years, and of boys of 10.40±2.76 years.

C. ENVIRONMENT

The analysis of the distribution of HP cases according to the area of origin reveals an increased prevalence of patients from the urban environment. So that a number of 89 (80.18%) come from the urban environment and 22 (19.82%) come from the rural environment. Taking into account the total number of inhabitants approximately equal between the urban and rural areas of Galati county, the region where the study was carried out, we can conclude that the marked difference in the two values is due to increased addressability, easier access to medical services and a more medical culture of those in the urban environment. The average number of patients who presented themselves for treatment per year was 8.9 from the urban environment and 2.2 from the rural environment (27).

The average age of patients from urban areas is 10.78±2.94, and those from rural areas is 9.81±2.50.

4.3.2 STUDY OF THE CHARACTERISTICS OF THE DISEASE

The limit of the study of the affected regions is given by the inclusion of only patients who performed ionization in the Recovery clinic, implicitly only those with palmar, plantar or palmo-plantar hyperhidrosis, because these are the areas where the electrodes needed for the treatment can be applied.

A. LOCATION

Next we analyzed the body distribution of sweat only on the areas mentioned above. The palmo-plantar association is the most common, with 90 (81.08%) of the cases, followed by the palmar region with 15 (13.51%) cases and the plantar region with 6 (5.41%) patients. The obtained data are consistent with the specialized literature, which describes the palmo-plantar association as the most common (27).

The average age of patients with HHP is 11.53±3.42, that of patients with HHPl is 9.33±3.83, and that of patients with palmo-plantar association is 10.52±2.69.

B. FAMILY HISTORY

A positive family history for primary hyperhidrosis, with a parent, brother or sister with excessive sweating, diagnosed or not, occurs in 60 (54.10%) of the children, the difference of 51 (45.90%), having no cases in the family (27).

The average age of patients with a positive family history is 10.26±2.71, and of those without a family history is 10.98±3.03.

C. TREATMENT EFFECT

All patients underwent ionization, without completing a severity scale before or after. The patients had noted in the consultation sheet the evolution of the symptoms after the 10 days of treatment. 82 (73.87%) of the patients stated that they sweat less, and 29 (26.13%) that the amount of sweat did not change at all. No local adverse effects of the current were reported in any consultation record and no discontinuation of treatment was reported in any treatment record (27).

The average age of the patients for whom the treatment has an effect is 10.32±2.75, and of those without an effect of the treatment 11.34±3.10

D. ASSOCIATED PATHOLOGIES

In the clinic, patients with various pathologies are treated: cerebral palsy, vertebral static disorders, genetic syndromes, etc. Of the 111 patients included in the study, 63 (56.76%) patients were diagnosed before presentation and came targeted to perform ionizations, and the difference of 48 children presented for other pathologies: scoliosis (18), kyphosis (15), post trauma status or pain (9), genu valgum (3) and flat foot (3) and ionization was added to their treatment plan (27).

4.4 DISCUSSIONS

1. The result of the gender distribution is consistent with the studies carried out, which state that the female gender predominates. It also states only a higher false incidence due to increased addressability and a greater desire to receive treatment of the girls.

2. Although the studies carried out indicate an average age of onset of 15 years, our study describes a group of children aged between 6 and 17 years, with the predominance of the 9-11 year age group, with a total of 43 patients.

3. The average age of the group included in the study is 10.59, significantly lower than the data supported in the specialized literature.

4. The COVID-19 pandemic also left its mark on the adressability to treatment of patients with primary hyperhidrosis, which was low anyway due to other factors. The drop to 0 of treatment presentation in years with pandemic restrictions demonstrates this fact.

5. Although the group is limited to patients diagnosed with palmar, plantar hyperhidrosis and their combination, the predominance of the palmo-plantar association is also supported by other studies.

6. Also the presence of the involvement of the genetic component is supported by the predominant number of children, 60 compared to 51, who have a brother, sister or parent who shows excessive sweating.

7. Ionization is a treatment with immediate beneficial results, with a cumulative effect every day of treatment, even in the days following its completion. In our study only 29 out of 111 patients mentioned that it had no effect on the amount of sweating, and the difference of 82 patients noticed improvement of symptoms.

8. It is not painful, expensive, but it is time-consuming and with limited effect, the symptoms reappear or intensify relatively quickly, after about 3 months, a period mentioned in specialized studies.

STUDY 2
Epidemiological characteristics of children with primary hyperhidrosis who presented to the Dermatology Department
CHAPTER 5

5.1 OBJECTIVES

1. Determining the number of patients who visited the dermatology clinic for diagnosis and treatment over the 10-year period
2. Distribution of primary hyperhidrosis according to age, gender, environment
3. Establishing age groups with higher attendance
4. Establishing the presence of each gender in the age groups
5. Making a curve of the cases presented each year
6. Observing the trend of addressability of patients

5.2 MATERIALS AND METHODS

5.2.1 PARTICIPANTS IN THE STUDY

Study group 2 includes 210 patients who presented themselves in the Dermatology Outpatient Clinic between January 1, 2014 and December 31, 2023, a group considered to be statistically adequate to achieve the statistical objectives. Electronic databases were analyzed to identify all patients who presented during the indicated period.

5.2.2 INSTRUMENTS USED

After analyzing the cases and applying the inclusion and exclusion criteria, the final group comprised 180 patients. Patient data required for this study have been entered in Study Sheet 2 for easier access. Data such as age, gender, background were used.

5.3 RESULTS

5.3.1 STUDY OF DEMOGRAPHIC FACTORS

The studied group includes a number of 180 patients diagnosed with primary hyperhidrosis who presented themselves at the Dermatology outpatient clinic between January 1, 2014 and December 31, 2023.

A. AGE

The ages of the patients included in the study vary between 6 and 17 years, the average age being 11.54±3.06 years.

We decided to segment the patients by age groups, starting with the 6-8 years segment. This classification into four categories allowed us to form a clear picture of the ages and identify trends in each interval.

Distribution by age groups:

• 6-8 years – 18 (50%) girls and 18 (50%) boys, out of a total of 36 (20%) children

• 9-11 years – 28 (49.12%) girls and 29 (50.88%) boys, out of a total of 57 (31.67%) children

• 12-14 years – 27 (60%) girls and 18 (40%) boys, out of a total of 45 (25%) children

• 15-17 years – 26 (61.90%) girls and 16 (38.10%) boys, out of a total of 42 (23.33%) children

We observe a somewhat equal addressability between age groups, but an increase is observed from the first interval, 6-8 years to the second, then a slight decrease in addressability as age advances. The maximum incidence in this study is in the age group 9-11 years, with a number of 57 children, which represents 31.67% of the total number of cases.

A smaller ratio, of 23.33% (n=42) and 25% (n=45) of the cases, has the age groups 15-17 years and 12-14 years, respectively, remaining for the 6-8 years group the lowest percentage, 20% (n=36).

If we analyze the presence of patients for each year taken into account, we observe a relatively constant trajectory in the first years analyzed, with a sudden drop to 0 in 2020, the year that coincides with the beginning of the COVID-19 pandemic, then a slow increase in the next 2 years with restrictions, 2 and 6 patients per year, respectively. In 2023, it returned to the initial value, the one before COVID-19.

These findings support data from the specialty literature, which states that patients and their families consider hyperhidrosis to be a less serious disease for which treatment can be delayed.

B. GENDER

The gender ratio is in favor of the females, with 99 (55%) cases compared to 81 (45%) male patients. This proportion respects the data from the literature, which describes the predominance of the female gender. However, this does not reflect the actual incidence of the disease among the two genders, which is relatively equal, but the addressability and desire to receive treatment, which is more common in girls. The average number of patients presenting for treatment per year was 9.9 female and 8.1 male.

A more detailed analysis reveals an average age of girls of 11.84±3.13 years, and of boys of 11.17±2.95 years.

C. ENVIRONEMENT

The analysis of the distribution of HP cases according to the area of origin reveals an increased prevalence of patients from the urban environment. So that a number of 137 (76.11%) come from the urban environment and 43 (23.89%) come from the rural environment. Taking into account the total number of inhabitants approximately equal between the urban and rural areas of Galati county, the region where the study was carried out, we can conclude that the marked difference in the two values is due to increased addressability, easier access to medical services and a more medical culture of those in the urban environment. The average number of patients who came to receive treatment per year was 13.7 from the urban environment and 4.3 from the rural environment.

The average age of patients from the urban environment is 11.39±3.00, and of those from the rural environment is 11.59±3.09.

5.3.2 STUDY OF THE CHARACTERISTICS OF THE DISEASE

Next we analyzed the body distribution of sweat on the areas mentioned in the diagnosis. The palmo-plantar association is the most common, with 120 (66.67%) cases, followed by the palmar region with 25 (13.88%) cases and the plantar region with 12 (6.67%) patients. 23 (12.78%) patients have a diagnosis of axillary hyperhidrosis or a combination with the other regions.

5.4 DISCUSSIONS

1. The result of the gender distribution is consistent with the studies conducted, which state that the female gender predominates, but it is only a falsely higher incidence due to increased addressability and a greater willingness to receive treatment.

2. Although the studies carried out indicate an average age of onset of 15 years, our study describes a group of children aged between 6 and 17 years, with the predominance of the 9-11 year age group, with a total of 57 patients. And this statement supports the observation that many patients and their families do not know essential information about this disease and that it can be treated.

3. The average age of the group included in the study is 11.54, significantly lower than the data supported in the specialized literature, because only children are included in this study, compared to studies abroad where studies with adult or mixed groups dominate.

4. Although the most frequent location described in specialized studies is the axillary, in our study it is not the most frequent. The explanation of this low ratio of cases with HHA is that our study includes patients between 6 and 17 years of age, and the presence of profuse axillary sweating begins after puberty.

5. The COVID-19 pandemic also left its mark on the addressability of patients with primary hyperhidrosis to the doctor, which was low anyway due to other factors. The drop to 0 of treatment presentation in years with pandemic restrictions demonstrates this fac

STUDY 3
Evaluation of the quality of life of children with primary hyperhidrosis who underwent bicarbonate ionization treatment
CHAPTER 6

6.1 INTRODUCTION

In 1995, in a study conducted on a group of children between the ages of 3 and 16, it was desired to create and validate a questionnaire as simple as possible to measure the quality of life of children with skin diseases. They received 169 responses, with 111 different issues that were sorted into various categories. Thus, 10 questions were composed with reference to the previous week, similar to the 10 questions of the DLQI for adults. The CDLQI score sums the answers to the questions, with a maximum of 30 and a minimum of 0 points. The higher the score, the greater the influence on quality of life is (65).

Children can be deeply affected by dermatological diseases, the quality of life being influenced, also the relationship with family and friends, school, practicing a sport and playing. Thus their development is influenced, both physically and especially psychologically (66).

In this study we did not objectively measure sweating, as objective tests only provide measurements at a given time, not data for the entire day. That's why we chose to use subjective scales, to measure the child's perception of the effects of hyperhidrosis.

6.2 OBJECTIVES

The main objective of this study is to determine the severity of hyperhidrosis, by completing the Hyperhidrosis Severity Scale and its impact on the quality of life of children aged between 6 and 17 years, using as an evaluation methods the Hyperhidrosis Disease Severity Scale and the Dermatological Index of the Quality of Life in Children, applied before and after performing 10 ionization sessions, thus helping to understand this very complex disease and to raise awareness of the significant effects it has on the child and its development.

Secondary objectives are:

- determining the age of the patients and determining the incidence for each age
- segmentation by age groups, for easier tracking of results
- determining the gender of patients and its ratio in age groups
- determining the environment of origin and its ratio in age groups
- the study of the characteristics of the disease, by analyzing the localization of excessive sweating, the family history through the presence of hyperhidrosis in 1st degree relatives, the aggravating factors, the treatments followed in the antecedents and their effects
- application of 10 ionization sessions and follow-up of the patient during the 10 days
- determining the frequency of occurrence of adverse effects
- determining the severity of hyperhidrosis, before and after treatment
- determining the impact on quality of life, before and after treatment
- determining the effect of ionizations on improving the quality of life
- the analysis of all the results obtained and the creation of a diagnostic and treatment protocol for primary hyperhidrosis

6.3 MATERIALS AND METHODS

6.3.1 ETHICAL RULES IN MEDICAL RESEARCH

This study was initiated after the approval of the Ethics Commission of the "Sf. Ioan" Emergency Clinical Hospital for Children, Galati, with number 31117/4.12.2023, prior to the initiation of patient evaluation. The parents or legal owners of the children included in this study gave their written consent before the start of their assessment. The consent is elaborated in simple terms, being explained to them throughout the research, the purpose, the rhythm and the way in which the data will be used. Confidentiality principles were respected, the results being in the form of anonymized statistical data.

6.3.2 STUDY LOCATION AND RESOURCES INVOLVED

The study is carried out in the Neuropsychomotor Recovery clinic within the "Sf. Ioan" Emergency Clinical Hospital for Children, Galați, a hospital that serves the population of the eastern region of Romania.

6.3.3 PARTICIPANTS IN THE STUDY

Study batch 3 includes 103 patients who presented themselves in the Integrated Outpatient Department of the Neuropsychomotor Recovery Department between March 1 and May 1, 2024 for ionization. An attempt was made to form a group as homogeneous as possible, in order to avoid the impact of other factors on the treatment results, epidemiological data and on the patients' quality of life.

6.3.4 INSTRUMENTS USED

A. QUESTIONNAIRE

After the analysis of the cases and the application of the inclusion and exclusion criteria, the patients were given a map containing 2 sets of questionnaires, on each set indicating the date of its completion, the first day of treatment, completing the data before its initiation, respectively 7 days after the last day of treatment.

The questionnaires used to assess the severity of patients' symptoms and their quality of life were:

I. HYPERHIDROSIS DISEASE SEVERITY SCALE - HDSS

II. CHILDREN'S DERMATOLOGY LIFE QUALITY INDEX - CDLQI

B. ELECTRIC CURRENT AND APPARATUS

I. GALVANIC CURRENT

II. APPARATUS

The devices used for the treatment were:

1) COMBINE THERAPY COMBI 400V

2) COMBINE BTL 5625

These were used randomly, depending on availability at the time of the patient's arrival at the treatment base.

6.3.5 STATISTICAL DATA PROCESSING

We used XLSTAT 2024 as a program for statistical data processing, from which we used descriptive analytical methods, univariate and multivariate analytical methods.

6.4 RESULTS

6.4.1 STUDY OF DEMOGRAPHIC FACTORS

The studied group includes a number of 103 patients diagnosed with primary hyperhidrosis who presented themselves between March 1, 2024 and May 31, 2024 in the integrated outpatient department of the Neuropsychomotor Recovery Department for bicarbonate ionization.

A. AGE

The ages of the patients included in the study vary between 6 and 17 years, the average age being 11.84±2.89 years.

In this third study we also decided to segment patients by age groups too, starting with the 6-8 years segment. This classification into four categories allowed us to form a clear picture of the ages and identify trends in each interval. The difference between the two studied groups, girls and boys, can be observed within each segment, thus highlighting the demographic complexity and diversity of the studied group.

The following data emerge from the analysis of age groups:

• 6-8 years – 9 (64.29%) girls and 5 (35.71%) boys, out of a total of 14 (13.59%) children

• 9-11 years – 22 (61.11%) girls and 14 (38.89%) boys, out of a total of 36 (34.95%) children

• 12-14 years – 15 (55.56%) girls and 12 (44.44%) boys, out of a total of 27 (26.22%) children

• 15-17 years – 12 (46.15%) girls and 14 (53.85%) boys, out of a total of 26 (25.24%) children

The predominant group is the one between the ages of 9 and 11, with 34.95%, followed by the 12-14-year-old group and the 15-17-year-old group, with 26.22% and 25.24%, respectively. The lowest percentage is represented by the 6-8 year group, with 13.59%.

B. GENDER

The proportion between genders is in favor of the females, with 58 cases compared to 45 male patients, 56.31% and 43.69%, respectively.

We cannot compare the obtained data with those in the specialized literature because the patients were selected from previous retrospective studies and called for inclusion in this study. Therefore, the data on the distribution of patients during the 3 months of the study are not relevant.

A more detailed analysis reveals an average age of girls of 11.53±2.85 years, and of boys of 12.24±2.93 years.

C. ENVIRONEMENT

The analysis of the distribution of cases with primary hyperhidrosis according to the environment of origin reveals an increased prevalence of patients from the urban environment. So that a number of 81 patients come from the urban environment and 22 from the rural environment. Their percentage distribution is 78.64% urban patients compared to 21.36% rural patients.

6.4.2 STUDY OF THE CHARACTERISTICS OF THE DISEASE

The limit of the study of the affected regions is given by the inclusion of only patients who performed ionization in the Recovery clinic, implicitly only those with palmar, plantar or palmo-plantar hypohidrosis, because these are the areas where the electrodes necessary for the treatment can be applied.

A. LOCATION

Next we analyzed the body distribution of sweat only on the areas mentioned above. The palmo-plantar association is the most common, with 62 (60.19%) of the cases, followed by the palmar region with 28 (27.18%) cases and the plantar region with 13 (12.63%) patients. The plantar area is affected in 13 children, 7 girls and 6 boys, the palmar area in 28 children, 17 girls and 11 boys, and the palmo-plantar association occurs in 62 children, 34 girls and 28 boys.

The average age of patients with HHP is 11.32±3.04, that of patients with HHPl is 11.69±2.65, and that of patients with palmo-plantar association is 12.11±2.88.

B. FAMILY HISTORY

A positive family history for primary hyperhidrosis, with a parent, brother or sister with excessive sweating, diagnosed or not, occurs in 63 (61.17%) children, the difference of 40 (38.83%) children, having no cases in the family.

Of the total number of children who have relatives with excessive sweating, 35 (55.55%) are girls and 28 (44.45%) are boys, and among those who have no relatives, 23 (57.50%) are girls and 17 (42.50) are boys.

The average age of patients with a positive family history is 11.93±2.81, and of those without a family history is 11.70±3.04.

C. FAVORATING FACTORS

Analyzing the favorating factors that accentuate profuse sweating, the 4 mentioned by the children are: stress, emotions, heat and physical exertion.

D. PREVIOUS TREATMENT

From the total of 103 patients included in the study, 40 (38.83%) children did not undergo any treatment, and the difference of 63 (61.17%) children underwent topical treatment, ionization or both.

The distribution of those who have undergone treatment in the past is:

• Ionizations – 16 (57.14%) girls and 12 (42.86%) boys, out of a total of 28 (44.44%) children

• Topical treatment – 14 (50%) girls and 14 (50%) boys, out of a total of 28 (44.44%) children

• Ionizations and topical treatment – 4 (57.14%) girls and 3 (42.86%) boys, out of a total of 7 (11.12%) children.

• Out of the total of 28 (44.44%) children who underwent ionization in the antecedents, for 20 (71.43%) children the effect was favorable, and for the difference of 8 (28.57%) children it had no effect

• From the total of 28 (44.44%) children who underwent topical treatment in the antecedents, for 13 (46.43%) children the effect was favorable, and for the difference of 15 (53.57%) children it had no effect

• Out of the total of 7 (11.12.%) children who underwent combined treatment, topical and ionization, for 6 (85.71%) children the effect was favorable, and for the difference of 1 (14.29%) child it had no effect.

6.4.3 DISEASE SEVERITY STUDY

The 103 children included in the study were given a set of questionnaires consisting of the Hyperhidrosis Severity Scale and the Children's Dermatological Quality of Life Index, both before the start of treatment – T0 and one week after its completion – T1. We chose this time variant because the CDLQI measures the effects of dermatological diseases on the quality of life in the last week, thus the effect was analyzed after the completion of the 10 therapeutic sessions.

I. HDSS – T0

The hyperhidrosis disease severity scale consists of a single question with 4 possible answers, with a final score ranging from 1 to 4 (67). Patients with scale values between 2 and 4, which correspond to a moderate or severe form of hyperhidrosis, are included in our study. The average value of the score is 2.95±0.70.

Principal components analysis between age and HDSS values at T0 revealed no correlation, $r=-0.085$; $p<0.392$.

The girls who participated in this study have an average value of 2.96±0.74, and the boys have an average value of 2.93±0.65.

- ✓ **HDSS T0– 2 points**

A score of 2 points corresponds to a moderate form of the disease and was recorded in 28 (27.18%) children, 17 (60.71%) girls and 11 (39.29%) boys.
The distribution of value 2 on the hyperhidrosis severity scale depending on the patients' environment of origin is:

- 6 (27.27%) rural patients – 2 girls and 4 boys
- 22 (27.16%) urban patients – 15 girls and 7 boys

- ✓ **HDSS T0– 3 points**

A score of 3 points corresponds to a severe form of the disease and was recorded in 52 (50.49%) children, 26 (50%) girls and 26 (50%) boys.
The distribution of value 3 on the hyperhidrosis severity scale according to the patients' environment of origin is:

- 11 (50%) rural patients – 7 girls and 4 boys
- 41 (50.62%) urban patients – 19 girls and 22 boys

- ✓ **HDSS T0– 4 points**

Un scor de 4 puncte corespunde cu o formă severă a bolii și a fost înregistrat la 23 (22.33%) de copii, 15 (65.22%) fete și 8 (34.78%) băieți.
Distribuția valorilor HDSS în grupele de vârstă este următoarea:

- 6-8 ani – din cei 14 copii din această grupă:

- 2 (14.29%) copii au valoarea 2 – 1 (50%) fată și 1 (50%) băiat
- 10 (71.42%) copii au valoarea 3 –7 (70%) fete și 3 (30%) băieți
- 2 (14.29%) copii au valoarea 4 - 1 (50%) fată și 1 (50%) băiat
    - 9-11 ani – din cei 36 de copii din această grupă:
- 12 (33.33%) copii au valoarea 2 – 9 (75%) fete și 3 (25%) băieți
- 12 (33.33%) copii au valoarea 3 – 6 (50%) fete și 6 (50%) băieți
- 12 (33.34%) copii au valoarea 4 – 7 (58.33%) fete și 5 (41.67%) băieți
    - 12-14 ani – din cei 27 de copii din această grupă:
- 8 (29.63%) copii au valoarea 2 – 5(62.5%) fete și 3(37.5%) băieți
- 14 (51.85%) copii care au valoare 3 – 6 (42.86%) fete și 8 (57.14%) băieți
- 5 (18.52%) copii care au valoarea 4 – 4 (80%) fete și 1(20%) băiat
    - 15-17 ani – din cei 26 de copii din această grupă:
- 6 (23.08%) copii au valoarea 2 – 2 (33.33) fete și 4(66.67%) băieți
- 16 (61.54%) copii au valoarea 3 – 7 (43.75%) fete și 9 (56.25%) băieți
- 4 (15.38%) copii au valoarea 4 – 3 (75%) fete și 1 (25%) băiat

The distribution of value 4 on the hyperhidrosis severity scale according to the patients' environment of origin is:

- 5 (22.73%) rural patients – 3 girls and 2 boys
- 18 (22.22%) urban patients – 12 girls and 6 boys

II. HDSS – T1

All children started treatment on a Monday, completed 5 consecutive days, then Saturday and Sunday off, and continued the following week with another 5 consecutive days, completing all 10 days on a Friday. On Friday, 7 days after the completion of treatment, the children completed another set of questionnaires, consisting of a Hyperhidrosis Severity Scale and a Dermatological Quality of Life Index in Children. The mean value of the HDSS score at T1 is 1.92±0.80.

Principal components analysis between age and HDSS values at T1 revealed a weak correlation, $r=-0.125$; $p<0.208$.

The girls who participated in this study have an average value of 1.89±0.89, and the boys have an average value of 1.95±0.82.

✓ HDSS T1 – 1 point

At the time of T1, the results of the Hyperhidrosis Severity Scale add up to 37 (35.92%) responses with a value of 1, as follows:

• 17 (45.94%) responses decreased from the value of 2, 10 girls – 9 from the urban environment and 1 from the rural environment, and 7 boys – 4 from the urban environment and 3 from the rural environment

• 17 (45.94%) responses decreased from the value of 3, 11 girls – 7 from the urban environment and 4 from the rural environment, and 6 boys – 5 from the urban environment and 1 from the rural environment

• 3 (8.12 %) responses decreased from the value of 4, 2 girls from the urban environment, aged 9 and 11 respectively, with palmo-plantar hyperhidrosis and 1 boy from the rural environment, aged 9, with plantar hyperhidrosis

Of the 37 answers with the value 1, 23 (62.16%) were recorded for girls and 14 (37.84%) for boys.

The distribution of HDSS value 1 at T1 in age groups is as follows:

• 6-8 years – of the 14 children in this group, 5 (35.71%) children have the value 1 – 3 (60%) girls and 2 (40%) boys
• 9-11 years – of the 36 children in this group, 12 (33.33%) children have the value 1 – 9 (75%) girls and 3 (25%) boys
• 12-14 years – of the 27 children in this group, 10 (37.04%) children have the value 1 – 6 (60%) girls and 4 (40%) boys
• 15-17 years – of the 26 children in this group, 10 (38.46%) children have the value 1 – 5 (50%) girls and 5 (50%) boys
The distribution of value 1 on the hyperhidrosis severity scale depending on the patients' environment of origin is:

- 10 (45.45%) rural patients – 5 girls and 5 boys
- 27 (33.33%) urban patients – 18 girls and 9 boys

✓ **HDSS T1 – 2 points**

At the time of T1, the results of the Hyperhidrosis Severity Scale add up to 42 (40.78%) responses with a value of 2, as follows:
• 11 (26.19%) answers stayed at the value of 2, 7 girls – 6 from the urban environment and 1 from the rural environment, and 4 boys – 3 from the urban environment and 1 from the rural environment
• 22 (52.38%) responses decreased from the value of 3, 8 girls – 7 from the urban environment and 1 from the rural environment, and 14 boys – 12 from the urban environment and 2 from the rural environment
• 9 (21.43%) responses decreased from the value of 4, 6 girls – 6 from the urban environment and 0 from the rural environment, and 3 boys – 3 from the urban environment and 0 from the rural environment.
Of the 42 responses with a value of 2 at the time of T1, 21 (50%) were recorded in girls and 21 (50%) in boys.
The distribution of the HDSS value 2 at T1 in the age groups is as follows:
• 6-8 years – of the 14 children in this group, 7 (50%) children have the value 2 – 5 (71.43%) girls and 2 (28.57%) boys
• 9-11 years – of the 36 children in this group, 17 (47.22%) children have the value 2 – 11 (64.71%) girls and 6 (35.29%) boys
• 12-14 years old – of the 27 children in this group, 11 (40.74%) children have the value 2 – 4 (36.36%) girls and 7 (63.64%) boys
• 15-17 years – of the 26 children in this group, 7 (26.92%) children have the value 2 – 1 (14.28%) girls and 6 (85.72%) boys

✓ **HDSS T1– 3 points**

At the time of T1, the results of the Hyperhidrosis Severity Scale add up to 19 (18.45%) responses with a value of 3, as follows:
• 13 (68.42%) answers stayed at the value of 3, 7 girls – 5 from the urban environment and 2 from the rural environment, and 6 boys – 5 from the urban environment and 1 from the rural environment
• 6 (31.57%) responses decreased from the value of 4, 4 girls – 4 from the urban environment and 1 from the rural environment, and 2 boys – 2 from the urban environment and 0 from the rural environment.
Of the 19 responses with a value of 3 at T1, 11 (57.89%) were recorded for girls and 8 (42.11%) for boys.
The distribution of HDSS value 3 at T1 in age groups is as follows:

• 6-8 years – of the 14 children in this group, 2 (7.14%) children have the value 3 – 1 (50%) girl and 1 (50%) boy
• 9-11 years – of the 36 children in this group, 6 (16.66%) children have the value 3 – 2 (33.33%) girls and 4 (66.67%) boys
• 12-14 years – of the 27 children in this group, 4 (40.74%) children have the value 3 – 4 (36.36%) girls and 0 (63.64%) boys
• 15-17 years old – of the 26 children in this group, 7 (26.92%) children have the value 3 – 4 (57.14%) girls and 3 (42.86%) boys

The distribution of the value 3 on the hyperhidrosis severity scale at the time of T1 according to the environment of origin of the patients is:

- (18.18%) rural patients – 3 girls and 1 boy
- 15 (18.52%) urban patients – 8 girls and 7 boys

✓ **HDSS T1– 4 points**

At the time of T1, the results of the Hyperhidrosis Severity Scale add up to 5 (4.85%) responses with a value of 4 who stayed after the treatment, 3 (60%) girls, 1 from the urban environment and 2 from the rural environment and 2 (40%) boys, 1 from the urban environment and 1 from the rural environment.
The distribution of HDSS value 4 at T1 in age groups is as follows:
• 6-8 years – of the 14 children in this group, 0 (0%) children have the value 4
• 9-11 years – of the 36 children in this group, 1 (2.78%) child has the value 4 – 0 (0%) girls and 1 (100%) boy
• 12-14 years – of the 27 children in this group, 2 (7.41%) children have the value 4 – 1 (50%) girl and 1 (50%) boy
• 15-17 years – of the 26 children in this group, 2 (7.69%) children have the value 4 – 2 (100%) girls and 0 (0%) boys

The distribution of value 4 on the hyperhidrosis severity scale at the time of T1 according to the environment of origin of the patients is:

- 3 (13.63%) rural patients – 2 girls and 1 boy
- 2 (2.47%) urban patients – 1 girl and 1 boy

Principal components analysis between HDSS values at T0 and T1 revealed a statistically significant correlation, $r=0.479$; $p<0.0001$.

6.4.4. QUALITY OF LIFE STUDY

I. CDLQI – T0

The Dermatological Quality of Life Index in Children is a simple questionnaire with 10 questions and 4 answer options, from 0 to 3 and with a maximum score of 30 points.

The interpretation of the results is:
- 0-1 = no effect on quality of life
- 2-6 = low effect on quality of life
- 7-12 = moderate effect on quality of life
- 13-18 = important effect on quality of life
- 19-30 = very important effect on quality of life (68).

The average value of the CDLQI results recorded in this study is 7.09±3.59, with the minimum value of 2 points and the maximum value of 18 points, which correspond to a low, moderate or important impact.

The girls who participated in this study have an average value of 6.65±3.4, and the boys have an average value of 7.66±3.78.

✓ 2-6 = LOW EFFECT ON QUALITY OF LIFE

A score between 2 and 6 was recorded in 51 (49.51%) children, 34 girls and 17 boys.

• value 2 – 4 cases:
o 2 girls, with an average age of 12.57±2.12, a minimum of 11 and a maximum of 14 years
o 2 boys, aged 12 years.

• value 3 – 11 cases:
o 7 girls, with an average age of 12.17±1.67, a minimum of 10 and a maximum of 15
o 4 boys, with an average age of 11.75±2.98, a minimum of 9 and a maximum of 16 years

• value 4 – 13 cases:
o 9 girls, with an average age of 11.88±3.65, a minimum of 7 and a maximum of 17 years
o 4 boys, with an average age of 13.50±3.87, a minimum of 8 and a maximum of 17 years

• value 5 – 10 cases:
o 7 girls, with an average age of 11.14±3.62, a minimum of 6 and a maximum of 16 years
o 3 boys, with an average age of 15.66±1.15, a minimum of 15 and a maximum of 17 years

• value 6 – 13 cases:
o 9 girls, with an average age of 10.88±3.44, a minimum of 7 and a maximum of 17 years
o 4 boys, with an average age of 11.5±2.95, a minimum of 7 and a maximum of 15 years

✓ 7-12 = MODERATE EFFECT ON QUALITY OF LIFE

A score between 7 and 12 was recorded in 41 (39.81%) children, 19 girls and 22 boys.
• value 7 – 15 cases:
o 6 girls, with an average age of 12.33±2.42, a minimum of 8 and a maximum of 15 years
o 9 boys, with an average age of 12.55±2.18, a minimum of 10 and a maximum of 15 years

• value 8 – 6 cases:
o 4 girls, with an average age of 12±3.53, a minimum of 8 and a maximum of 16 years
o 2 boys, with an average age of 10±2.82, a minimum of 8 and a maximum of 12 years

• value 9 – 10 cases:
o 4 girls, with an average age of 11.5±3.10, a minimum of 9 and a maximum of 16 years
o 6 boys, with an average age of 11.33±3.72, a minimum of 6 and a maximum of 17 years

• value 10 – 7 cases:
o 3 girls, with an average age of 11±1.73, a minimum of 9 and a maximum of 12 years
o 4 boys, with an average age of 11±3.55, a minimum of 8 and a maximum of 16 years

• value 11 – 2 cases:
o 1 girl, aged 11 years
o 1 boy, aged 16

• value 12 – 1 case:
o 1 girl, aged 13 years

✓ **13-18 = IMPORTANT EFFECT ON QUALITY OF LIFE**

A score between 13 and 18 was recorded in 11 (10.68%) children, 5 girls and 6 boys.
• value 13 – 4 cases:
o 2 girls, with an average age of 11.5±0.70, a minimum of 11 and a maximum of 12 years
o 2 boys, with an average age of 10±1.41, a minimum of 9 and a maximum of 11 years

• value 14 – 1 case:
o 1 boy, aged 10 years

• Value 15 – 3 cases:
o 2 girls, with an average age of 9±2.82, a minimum of 7 and a maximum of 11 years
o 1 boy, aged 12

• value 17 – 2 cases:
o 1 girl, aged 9 years
o 1 boy, aged 16

• value 18 – 1 case:
o 1 boy, aged 14

We can conclude that hyperhidrosis most frequently interferes with the choice of clothes or shoes, in our study 100% of children gave 1, 2 or 3 points to this question. 102 (99.03%) of the 103 children believe that hyperhidrosis influences their relationship with friends.

II. CDLQI – T1

The average value of the CDLQI score at T1 is 3.57±2.93, with a minimum value of 0 and a maximum of 16.
The girls who participated in this study have an average value of 3.05±2.42, and the boys have an average value of 4.24±3.40.

0-1 = NO EFFECT ON QUALITY OF LIFE
A score between 0 and 1 was recorded in 25 (24.27%) children, 16 girls and 9 boys.
2-6 = LOW EFFECT ON QUALITY OF LIFE
A score between 2 and 6 was recorded in 60 (58.25%) children, 35 girls and 25 boys.
7-12 = MODERATE EFFECT ON QUALITY OF LIFE
A score between 7 and 12 was recorded in 16 (15.54%) children, 7 girls and 9 boys.
13-18 = IMPORTANT EFFECT ON QUALITY OF LIFE
A score between 11 and 20 was recorded in 2 (1.94%) children, boys.

6.5 DISCUSSIONS

1. 103 children aged between 6 and 17 years were included in this study between March 1, 2024 and May 31, 2024, after applying the inclusion and exclusion criteria. Before starting treatment, each child received a set consisting of one copy of the Hyperhidrosis Severity Scale and one copy of the Children's Dermatological Quality of Life Index, time called T0. After 7 days from the end of the treatment they received the same set again, time called T1.

2. The treatment performed for each child consisted of 10 bicarbonate ionization sessions, performed consecutively, from Monday to Friday, for two weeks. The chosen application technique was that of surface electrodes covered with a hydrophilic protective layer soaked in tap water mixed with bicarbonate. In the specialized literature, I did not find any study conducted using this technique or this rhythmicity of the treatment. The only specified details were that you can add bicarbonate to the tap water to increase the favorable effect.

3. The average age of the patients included in this study is 11.84±2.89 years, with a minimum of 6 years and a maximum of 17 years. We segmented the ages of the patients into 4 groups, starting with the 6-8 years segment. The 9-11-year-old group predominates with 36 (34.95%) children, followed by the 12-14-year-old and 15-17-year-old groups, with 27 (26.22%) children, respectively 26 (25.24%) children. The least represented group is the one formed by children aged 6-8 with 14 (13.59%) children.

4. The predominant group is that of girls, 58 compared to 45 boys. Although in all the studies carried out and published in the studied articles the female gender predominates, the incidence is not increased in them, only the addressability to a medical service to receive treatment. The same trend was observed in the three studies carried out in this thesis.

5. The average value of the HDSS score at the time of T0 is 2.95, and at the time of T1 it is 1.92, a significant decrease is observed. The decrease is statistically significant, demonstrated by the value t obs > t crit and the test parameter belonging to the critical region, so the null hypothesis is rejected.

6. Analyzing the definition of the success of a treatment related to the HDSS value - improvement of the score from 4 to 2 or 1, from 3 to 2 or 1 or from 2 to 1 - we can argue that a decrease from 4 to 2 or 1 occurs in 12 (11.65%) children, from 3 to 2 or 1 occurs in 39 (37.86%) children and from 2 to 1 occurs in 17 (16.50%) children. We can conclude that the treatment was successful in 68 (66.01%) children.

7. The average value of the CDLQI score at time T0 is 7.09±3.59, and at time T1 it is 3.57±2.93, observing a statistically significant decrease, demonstrated by the value t obs > t crit and the test parameter belonging to the critical region, thus the hypothesis the null is rejected.

8. The difference between pre- and post-treatment CDLQI values represents the effect of therapy on quality of life – T0-T1=7.09±3.59–3.57±2.93

9. Bicarbonate ionization is an effective and safe method for treating palmar and plantar hyperhidrosis in children.

STUDY 4
A series of 5 particular cases treated by ionization with bicarbonate
CHAPTER 7

7.1 INTRODUCTION

This last part of the doctoral thesis is a therapeutic study, in which we compare the patient's condition before treatment with that after treatment, using the contralateral limb as a control.The purpose of this study is to obtain information about the effectiveness of the treatment used and to compare the effects on the treated limb with the control limb.

In a study conducted in 1987 on a group of 18 patients to whom ionization was applied to one hand, the other being used as a control. The result of the study was a marked reduction in sweating on the treated hand in 15 of the 18 participants (69).

7.2 OBJECTIVES

1. Establishing a sample of patients with profuse palmar/plantar sweating.
2. Completing the hyperhidrosis severity scale.
3. Selection of a number of 5 patients with the maximum value of 4 of the HDSS.
4. Treating the target area.
5. Comparison with the contralateral side after performing 10 iontophoresis sessions.
6. Establishing the effectiveness of the treatment based on the comparison of the photos before and after the treatmentt

7.3 MATERIALS AND METHODS

7.3.1 ETHICAL RULES IN MEDICAL RESEARCH

This study was initiated after the approval of the Ethics Commission of the "Sf. Ioan" Emergency Clinical Hospital for Children, Galati, with number 31117/4.12.2023.

7.3.2 STUDY LOCATION AND RESOURCES INVOLVED

The study is carried out in the Neuropsychomotor Recovery clinic within the "Sf. Ioan" Emergency Clinical Hospital for Children, Galați, a hospital that serves the population of the eastern region of Romania.

A number of 5 patients with value 4 on the Hyperhidrosis Severity Scale were selected from the group of the third study.

7.3.3 PARTICIPANTS IN THE STUDY

Study batch 4 includes 5 patients who presented themselves in the integrated outpatient department of the Neuropsychomotor Recovery Department between March 1, 2024 and May 31, 2024.

7.3.4 RESEARCH PLAN

The protocol applied to all 5 patients was as follows:

1. Before the initiation of the treatment, the purpose, duration, particularity and rhythmicity of the treatment were explained to the patient and his parents or legal guardians.

2. After entering the clinic, the patient rested for 10 minutes sitting on a chair, at a constant, measured temperature of 21oC±0.5 oC, with the palms and soles free in the ambient environment thus created.
3. After 10 minutes the palms/plants were placed on a white absorbent paper for 10 seconds
4. A photo was taken and after 10 seconds the limbs were removed from the paper and a new photo was taken
5. Daily, from Monday to Friday, for two weeks, the therapeutic session was carried out, for 10 minutes, at the level of the right, upper or lower limb
6. After the tenth session, the patient was left for 10 minutes in a cabinet with a constant, measured temperature of 21oC±0.5 oC
7. After 10 minutes the palms/plants were placed on a white absorbent paper for 10 seconds
8. A photo was taken and after 10 seconds the limbs were removed from the paper and a new photo was taken

7.3.5 INSTRUMENTS USED

After analyzing the cases and applying the inclusion and exclusion criteria, the steps of the previously presented protocol were followed. Simple white absorbent paper, a phone for photography, a medical office equipped with air conditioning, a simple thermometer to measure the ambient temperature were used as necessary materials. All patients were integrated into an electrotherapy program using galvanic current. The hyperhidrosis severity scale was applied to the patients to select only patients with a scale value of 4. At the end of the 10 sessions, the protocol from the first day was repeated.

7.4 RESULTS

The studied group includes a number of 5 patients diagnosed with primary hyperhidrosis, 2 boys and 3 girls, who have a value of 4 on the Hyperhidrosis Severity Scale.

7.5 DISCUSSIONS

1. A series of 5 cases, 2 boys and 3 girls, aged 7 to 16 years, who met the inclusion criteria and did not meet any of the exclusion criteria, were selected.

2. The patients came both from the urban environment, 4 cases, and from the rural environment, 1 case.

3. Based on the hyperhidrosis severity scale score, all patients stated that: “4. My sweating is unbearable and always interferes with my daily activities.”

4. All patients had favorable effects after the 10 treatment sessions, demonstrated by the pictures taken of each one.

5. The area did not become euhydrotic, but the amount of transpiration decreased significantly.

6. Iontophoresis is a first-line treatment for palmo-plantar hyperhidrosis, with visible effects after 10 sessions.

7. No patient presented adverse effects cited in the specialized literature.

CHAPTER 8
CONCLUSIONS

This paper comprises a total of 4 independent studies. Study 1 is a retrospective study carried out over a period of 10 years, on a group of 111 children who presented themselves for ionization in the ambulatory integrated Neuropsychomotor Recovery section of the "Sf. Ioan" Emergency Clinical Hospital for Children, Galati, in which the demographic factors and the characteristics of the disease were analyzed. Because this study also spanned the period of the COVID-19 pandemic, and findings regarding children's responsiveness to treatment showed a drop to 0 in those years, we supplemented it with Study 2. This is also a retrospective study conducted over the same time period like the first, on a batch of 180 children who addressed the Dermatology outpatient clinic of the same hospital. The findings regarding the addressability during the three pandemic years coincide with those of the first study, but also with the studies published in specialized journals.

Study 3 represents a prospective analysis of 103 patients who were invited to participate in it between March and May 2024. We chose to combine the presentation of children during this period to eliminate as much as possible external factors that can influence sweating, in this case the presentation of all during the spring period, eliminating the increased ambient temperature during the summer as the favoring factor of excessive sweating.

The number of studies on hyperhidrosis published to date demonstrate an interest in this disease, but most of them include cohorts of adults or mixed cohorts of children and adults. Studies only on groups of children are limited in number, therefore this thesis is intended to help those who want to understand and deepen the physical and emotional impact that hyperhidrosis has on the child and its subsequent development. We also found no studies conducted exclusively in children that looked at the effects of treatment on symptom relief or quality of life.

Study 4 aimed to objectively demonstrate the effect of ionizations on palmar and plantar hyperhidrosis. This was done by treating only one limb, and thus the amount secreted under the same conditions, under the effect of the same emotions or stress after the treatment was finished, could be compared. From all the data collected from the specialized literature, I have not found a similar study conducted for the direct observation of the effects of ionization, neither in adults nor in children.

CHAPTER 9
ORIGINALITY OF THE STUDY AND PERSPECTIVES

We chose to conduct a study that included a group of children between the ages of 6 and 17 because there are very few published articles that analyze only children. Also and rarer are the studies that describe the effect of bicarbonate ionizations, analyzing both the severity measured using the Hyperhidrosis Severity Scale, and the effect on the improvement of the quality of life, by applying the Dermatological Index of the Quality of Life in Children, recorded both before and 7 days after completion of treatment. We chose these time points for the analysis because the CDLQI measures the impact of the dermatological disease in the last week, so real results of the effect of the treatment after its completion could be recorded.

Since there is no treatment protocol for primary hyperhidrosis, we chose as a technique the possible application with the existing equipment in our clinic, namely surface electrodes covered by a hydrophilic protective layer soaked in tap water to which bicarbonate has been added. The rhythmicity chosen for the application was 5 days a week for two weeks, with a total of 10 days. This technique is unique in Romania, not being described in any published study to date.

The limitations of this study are the relatively small number of participants, but sufficient to determine statistically significant results regarding the effect of the treatment used and the use of tap water with added bicarbonate.

I believe that this study will open new perspectives for the future through new studies that can compare the effect achieved by plain tap water and that achieved by the addition of bicarbonate, but also by using the elaborated protocol. Study 4 can also be continued by creating a larger batch.

BIBLIOGRAPHY

1. Lotfollahi Z. The anatomy, physiology and function of all skin layers and the impact of ageing on the skin. Wound Pract Res. 2024;32(1):6–10.
2. Di Meglio P, Perera GK, Nestle FO. The Multitasking Organ: Recent Insights into Skin Immune Function. Immunity [Internet]. 2011;35(6):857–69. Available from: http://dx.doi.org/10.1016/j.immuni.2011.12.003
3. Nestle FO, Di Meglio P, Qin JZ, Nickoloff BJ. Skin immune sentinels in health and disease. Nat Rev Immunol [Internet]. 2009;9(10):679–91. Available from: http://dx.doi.org/10.1038/nri2622
4. Abdo JM, Sopko NA, Milner SM. The applied anatomy of human skin: A model for regeneration. Wound Med [Internet]. 2020;28(January):100179. Available from: https://doi.org/10.1016/j.wndm.2020.100179
5. Thappa DM. Essential in Dermatology. Vol. 53, Journal of Chemical Information and Modeling. 2009.
6. Cosgarea R, Tătaru A, Baican A, Daniela P-V. Dermato-venerologie clinică curs pentru studenți. 2011. 5, 113 p.
7. Caius Solovan EC. Manual de Dermatologie și Venerologie. 2013. 216 p.
8. Lawlor KT, Kaur P. Dermal contributions to human interfollicular epidermal architecture and self-renewal. Int J Mol Sci. 2015 Nov 25;16(12):28098–107.
9. Kisielnicka A, Szczerkowska-Dobosz A, Purzycka-Bohdan D, Nowicki RJ. Hyperhidrosis: Disease aetiology, classification and management in the light of modern treatment modalities. Postep Dermatologii i Alergol. 2022;39(2):251–7.
10. Solish N, Wang R, Murray CA. Evaluating the Patient Presenting with Hyperhidrosis. Thorac Surg Clin. 2008;18(2):133–40.
11. Nocivin I, Þiplica G. General Reports Synopsis of Therapeutic Options in Hyperhidrosis. 2018;35–45.
12. Baker LB. Physiology of sweat gland function: The roles of sweating and sweat composition in human health. Temperature [Internet]. 2019;6(3):211–59. Available from: https://doi.org/10.1080/23328940.2019.1632145
13. Cohen JL, Cohen G, Solish N, Murray CA. Diagnosis, Impact, and Management of Focal Hyperhidrosis: Treatment Review Including Botulinum Toxin Therapy. Facial Plast Surg Clin North Am. 2007;15(1):17–30.
14. Semkova K, Gergovska M, Kazandjieva J, Tsankov N. Hyperhidrosis, bromhidrosis, and chromhidrosis: Fold (intertriginous) dermatoses. Clin Dermatol [Internet]. 2015;33(4):483–91. Available from: http://dx.doi.org/10.1016/j.clindermatol.2015.04.013
15. Baker LB, Wolfe AS. Physiological mechanisms determining eccrine sweat composition [Internet]. Vol. 120, European Journal of Applied Physiology. Springer Berlin Heidelberg; 2020. 719–752 p. Available from: https://doi.org/10.1007/s00421-020-04323-7
16. Atkins JL, Butler PEM. Hyperhidrosis: A review of current management. Plast Reconstr Surg. 2002;110(1):222–8.
17. Murota H, Matsui S, Ono E, Kijima A, Kikuta J, Ishii M, et al. Sweat, the driving force behind normal skin: An emerging perspective on functional biology and regulatory mechanisms. J Dermatol Sci [Internet]. 2015;77(1):3–10. Available from: http://dx.doi.org/10.1016/j.jdermsci.2014.08.011
18. Cui CY, Schlessinger D. Eccrine sweat gland development and sweat secretion. Exp Dermatol. 2015;24(9):644–50.
19. Jabłonowska O, Woźniacka A, Dziankowska-Bartkowiak B. Hyperhidrosis: causes and treatment options. Przegl Dermatol. 2020;107(3):246–56.

20. Schlereth T, Dieterich M, Birklein F. Hyperhidrose - Ursachen und therapie von übermäßigem schwitzen. Dtsch Arztebl. 2009;106(3):32–7.
21. Notley SR, Poirier MP, Yardley JE, Sigal RJ, Kenny GP. Impaired whole-body heat loss in type 1 diabetes during exercise in the heat: a cause for concern? Vol. 62, Diabetologia. Germany; 2019. p. 1087–9.
22. Wörle B, Rapprich S, Heckmann M. Definition und therapie der primären hyperhidrose. JDDG - J Ger Soc Dermatology. 2007;5(7):625–8.
23. Rzany B, Bechara FG, Feise K, Heckmann M, Rapprich S, Wörle B. Update of the S1 guidelines on the definition and treatment of primary hyperhidrosis. JDDG - J Ger Soc Dermatology. 2018;16(7):945–53.
24. Wheeler T. Sweat and tears: Treating the patient with primary hyperhidrosis. Br J Nurs. 2012;21(7):408–12.
25. Nawrocki S. Diagnosis and qualitative identification of hyperhidrosis. Shanghai Chest. 2019;4(10):1–11.
26. Ho Y Le, Jamaluddin MF, Krishinan S, Kareem BAA. Diagnosis, impact and management of hyperhidrosis including endoscopic thoracic sympathectomy. Med J Malaysia. 2020;75(5):555–60.
27. Nastase F, Verenca MC, Niculet E, Radaschin DS, Busila C, Vasile CI, et al. Primary Hyperhidrosis in Children—A Retrospective Study and a Short Review. Life. 2024;14(5):1–12.
28. Romero FR, Haddad GR, Miot HA, Cataneo DC. Palmar hyperhidrosis: Clinical, pathophysiological, diagnostic and therapeutic aspects. An Bras Dermatol. 2016;91(6):716–25.
29. Lai FC, Tu YR, Li YP, Li X, Lin M, Chen JF, et al. Nation wide epidemiological survey of primary palmar hyperhidrosis in the People's Republic of China. Clin Auton Res. 2015;25(2):105–8.
30. Pariser DM, Ballard A. Topical Therapies in Hyperhidrosis Care. Dermatol Clin [Internet]. 2014;32(4):485–90. Available from: http://dx.doi.org/10.1016/j.det.2014.06.008
31. Morard MRS, Martins RB, Ribeiro ACL, Lima PGR, Carvalho BDS, Junior JCBS. Primary hyperhidrosis prevalence and characteristics among medical students in Rio de Janeiro. PLoS One. 2019;14(9):1–10.
32. Hornberger J, Grimes K, Naumann M, Glaser DA, Lowe NJ, Naver H, et al. Recognition, diagnosis, and treatment of primary focal hyperhidrosis. J Am Acad Dermatol. 2004;51(2):274–86.
33. Ro KM, Cantor RM, Lange KL, Ahn SS. Palmar hyperhidrosis: Evidence of genetic transmission. J Vasc Surg. 2002;35(2):382–6.
34. Shayesteh A, Boman J, Janlert U, Brulin C, Nylander E. Primary hyperhidrosis: Implications on symptoms, daily life, health and alcohol consumption when treated with botulinum toxin. J Dermatol. 2016;43(8):928–33.
35. Del Sorbo F, Brancati F, De Joanna G, Valente EM, Lauria G, Albanese A. Primary focal hyperhidrosis in a new family not linked to known loci. Dermatology. 2012;223(4):335–42.
36. Shayesteh A, Janlert U, Brulin C, Boman J, Nylander E. Prevalence and Characteristics of Hyperhidrosis in Sweden: A Cross-Sectional Study in the General Population. Dermatology. 2017;232(5):586–91.
37. Callejas MA, Grimalt R, Cladellas E. Hyperhidrosis Update. Actas Dermosifiliogr [Internet]. 2010;101(2):110–8. Available from: http://dx.doi.org/10.1016/S1578-2190(10)70597-7
38. Walling HW. Clinical differentiation of primary from secondary hyperhidrosis. J

Am Acad Dermatol [Internet]. 2011;64(4):690–5. Available from: http://dx.doi.org/10.1016/j.jaad.2010.03.013
39. Doolittle J, Walker P, Mills T, Thurston J. Hyperhidrosis: an update on prevalence and severity in the United States. Arch Dermatol Res. 2016;308(10):743–9.
40. Fujimoto T, Kawahara K, Yokozeki H. Epidemiological study and considerations of primary focal hyperhidrosis in Japan: From questionnaire analysis. J Dermatol. 2013;40(11):886–90.
41. Eisenach JH, Atkinson JLD, Fealey RD. Hyperhidrosis: Evolving therapies for a well-established phenomenon. Mayo Clin Proc. 2005;80(5):657–66.
42. de Campos JRM, de Paula Loureiro M, Kauffman P, Wolosker N. Hyperhidrosis: A Complete Guide to Diagnosis and Management. Hyperhidrosis A Complet Guid to Diagnosis Manag. 2018;1–284.
43. Parashar K, Adlam T, Potts G. The Impact of Hyperhidrosis on Quality of Life: A Review of the Literature. Am J Clin Dermatol [Internet]. 2023;24(2):187–98. Available from: https://doi.org/10.1007/s40257-022-00743-7
44. Henning MAS, Ibler KS, Ostrowski SR, Erikstrup C, Nielsen KR, Bruun MT, et al. Hyperhidrosis and the risk of being treated for skin infections. J Dermatolog Treat [Internet]. 2022;33(4):2263–9. Available from: https://doi.org/10.1080/09546634.2021.1944971
45. WALIA N, RATHORE B, JAISWAL A. Treatment of Palmoplanter Hyperhidrosis By Iontophoresis. Med J Armed Forces India [Internet]. 2000;56(1):27–8. Available from: http://dx.doi.org/10.1016/S0377-1237(17)30085-0
46. Jacob CI. Examining hyperhidrosis: an update on new treatments. Am J Manag Care. 2018;24(23):S496–501.
47. McConaghy JR, Fosselman D. Hyperhidrosis: Management options. Am Fam Physician. 2018;97(11):729–34.
48. Davidson JRT, Foa EB, Connor KM, Churchill LE. Hyperhidrosis in social anxiety disorder. Prog Neuro-Psychopharmacology Biol Psychiatry. 2002;26(7–8):1327–31.
49. Naik PP. Utilities of botulinum toxins in dermatology and cosmetology. Clin Cosmet Investig Dermatol. 2021;14:1319–30.
50. Hosp C, Hamm H. Safety of available and emerging drug therapies for hyperhidrosis. Expert Opin Drug Saf [Internet]. 2017;16(9):1039–49. Available from: http://dx.doi.org/10.1080/14740338.2017.1354983
51. Glogau RG. Treatment of palmar hyperhidrosis with botulinum toxin. Semin Cutan Med Surg. 2001;20(2):101–8.
52. Rieger R, Pedevilla S, Lausecker J. Quality of life after endoscopic lumbar sympathectomy for primary plantar hyperhidrosis. World J Surg. 2015;39(4):905–11.
53. Kamudoni P, Mueller B, Salek MS. The development and validation of a disease-specific quality of life measure in hyperhidrosis: the Hyperhidrosis Quality of Life Index (HidroQOL©). Qual Life Res. 2015;24(4):1017–27.
54. Kouris A, Armyra K, Stefanaki C, Christodoulou C, Karimali P, Kontochristopoulos G. Quality of life and social isolation in Greek adolescents with primary focal hyperhidrosis treated with botulinum toxin type A: A case series. Pediatr Dermatol. 2015;32(2):226–30.
55. Ardalan K, Switzer GE, Zigler CK, Hershey NM, Torok KS. Psychometric properties of the children's dermatology life quality index in pediatric localized scleroderma. J Scleroderma Relat Disord. 2018;3(2):175–81.
56. Öztekin C, Öztekin A. The association of depression, loneliness and internet addiction levels in patients with acne vulgaris. Biopsychosoc Med. 2020;14(1):1–7.

57. Salman A, Yucelten AD, Sarac E, Saricam MH, Perdahli-fis N. Families : a Cross-Sectional Study *. 2018;93(6):819–23.
58. Kamudoni P, Mueller B, Halford J, Schouveller A, Stacey B, Salek MS. The impact of hyperhidrosis on patients' daily life and quality of life: A qualitative investigation. Health Qual Life Outcomes. 2017;15(1):1–10.
59. Shayesteh A, Brulin C, Nylander E. The Meaning of Living for Men Suffering From Primary Hyperhidrosis. Am J Mens Health. 2019;13(6).
60. Poudel AN, Zhu S, Cooper N, Roderick P, Alwan N, Tarrant C, et al. Impact of Covid-19 on health-related quality of life of patients: A structured review. PLoS One [Internet]. 2021;16(10 October):1–20. Available from: http://dx.doi.org/10.1371/journal.pone.0259164
61. Ravens-Sieberer U, Kaman A, Erhart M, Devine J, Schlack R, Otto C. Impact of the COVID-19 pandemic on quality of life and mental health in children and adolescents in Germany. Eur Child Adolesc Psychiatry [Internet]. 2022;31(6):879–89. Available from: https://doi.org/10.1007/s00787-021-01726-5
62. Nobari H, Fashi M, Eskandari A, Villafaina S, Murillo-Garcia Á, Pérez-Gómez J, et al. Adolescents and Children: A Systematic Review. Int J Environ Res Public Heal [Internet]. 2021;18:4563. Available from: https://doi.org/10.3390/ijerph
63. Ahn SN. The Potential Impact of COVID-19 on Health-Related Quality of Life in Children and Adolescents: A Systematic Review. Int J Environ Res Public Health. 2022;19(22).
64. BRUCE-CHWATT LJ. Declaration of Helsinki. Recommendations Guiding Doctors in Clinical Research. WHO Chron. 1965;19(June):31–2.
65. Lewis-Jones MS, Finlay AY. The Children's Dermatology Life Quality Index (CDLQI): Initial validation and practical use. Br J Dermatol. 1995;132(6):942–9.
66. Park H, Hospital N. Holme_et_al-2003-British_Journal_of_Dermatology (1). 2003;285–90.
67. Hamm H. Impact of Hyperhidrosis on Quality of Life and its Assessment. Dermatol Clin [Internet]. 2014;32(4):467–76. Available from: http://dx.doi.org/10.1016/j.det.2014.06.004
68. Olsen JR, Gallacher J, Finlay AY, Piguet V, Francis NA. Quality of life impact of childhood skin conditions measured using the Children's Dermatology Life Quality Index (CDLQI): A meta-analysis. Br J Dermatol. 2016;174(4):853–61.
69. Stolman LP. Treatment of excess sweating of the palms by iontophoresis. Arch Dermatol. 1987 Jul;123(7):893–6.