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Lectures

# Selected Lectures of the Course "Take care of children", 4th Edition

## FROM THE ENVIRONMENT TO HEALTH BEYOND COVID-19 TAKE CARE OF CHILDREN AS THEY GROW UP

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## LECT 1

## THE PEDIATRICIAN AND MATERNAL BREASTFEEDING: A KEY ROLE IN THE FUTURE HEALTH OF THE CHILD AND THE ENVIRONMENT

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The decline in breastfeeding rates began in the 20th century, especially in high-income countries. During this period, the advent of breast milk substitutes was seen as an innovation, a prestige, while breastfeeding was associated with the poorer social classes. In response to this dynamic, policymakers and international agencies in 1990 formulated the Innocenti Declaration, supporting exclusive breastfeeding from birth to 4-6 months of age for all children. In 2001, the World Health Organization modified these recommendations by extending the period of exclusive breastfeeding for the first 6 months of life [1]. However, even today, the world is not a favorable environment for most women who want to breastfeed: adequate legal and policy guidelines are lacking, and women's working and employment conditions are not favorable. In addition, there is the need for more support from health services and the nurturing of social values that are less hostile toward breastfeeding women [1]. In this context, the benefits of breastfeeding for mothers and their children have been widely documented for several years, but data from the most recent scientific evidence over the past decade, have expanded the already known benefits of breastfeeding, overcoming the known lower consensus on its importance in high-income countries. In fact, to date, it has been shown that extending breastfeeding to a near-universal level could be a preventive measure against 823,000 annual deaths of children under age 5 and 20,000 annual deaths from breast cancer. Also, positively affecting intelligence, reduction of overweight and diabetes [2]. Furthermore, policies, programs, and investments to promote maternal breastfeeding are actions that contribute not only to optimizing diet quality and population health but also to improving the sustainability of the global food system. In fact, data from selected countries in the Asia-Pacific region, specifically Australia, South Korea, China, Malaysia, India and the Philippines, reveal an estimated emission of at least 3.95 kg $CO_2$ eq. per kg for infant formula products and 4.04 kg $CO_2$ eq. per kg for "follow-up" and "growing up" milk [3]. The recent COVID-19 outbreak has strained the health care system with major impacts on support for new mothers. Indeed, hospitals have decreased the length of stay for mothers and their infants, limiting the time available for families to receive adequate care and proper support, bringing out strongly the importance of equal access to adequate support for all families to ensure the maintenance and growth of breastfeeding education [4].

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## LECT 2

## NEW PATHS IN IMMUNOMODULATING TREATMENTS IN PEDIATRICS: LOW-DOSE MEDICINE

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Low-dose medicine (LDM) comes from the combination of molecular biology and psycho-neuro-endocrine-immunology (PNEI) and is in continuous development, supported by the results of research in the field of low-dose pharmacology.

LDM introduces an innovative point of view in the medical field: to restore the physiological conditions in a diseased organism through the administration of biological molecules (signaling molecules) that, in physiological health conditions, guide and manage

cellular, tissue and organ or system functions. In a pathological condition, the signaling molecules often result altered in their qualitative-quantitative expression.

The oral administration of signaling molecules at low physiological doses (sub-nanomolars, in the order of nanograms-femtograms) is possible by sequential kinetic activation (SKA) technology, an innovative drug delivery system that allows sub-nanomolar concentrations to be active even below the minimum effective dose considered effective, with therapeutic results comparable to those induced by high concentrations.

The mechanism of action of low-dose cytokines SKA is based on response modulation of the corresponding cellular and plasma receptors, comparable to the physiological action range of signaling molecules.

Since 2009, scientific literature suggests persevering in this direction, based in particular on the high safety and effectiveness of low-dose drugs in maintaining a low level of disease activity in patients with chronic and complex diseases, due to the absence of adverse effects or overload.

In these pathological conditions, LDM is one of the most interesting innovations even in pediatrics, allowing to reduce the harmful effects of excessive use of antibiotics or corticosteroids.

It was possible to collect a relevant set of basic and clinical data that can demonstrate the possibility of an overlapping approach and of use in long-term treatments to keep disease activity low (for example in rheumatoid arthritis), the possibility of combined use of cytokines in an animal model of allergic asthma or intestinal infection, as well as the need for SKA activation in the preparation of low-dose signaling molecules, in studies that have shown any biological activity and therapeutic effect of the low-dose signaling molecules not activated.

The carry-over effect, that is, from the low-dose signaling molecules to induce immunomodulation also in the periods of non-assumption of the treatment, has emerged in a clinical study conducted on pediatric patients suffering from atopic dermatitis.

Finally, the clinical studies showed the safety of LDM, supported also by the evidences of the basic studies.

More than 13 years of LDM research have passed and we can say now that it is not just a scientific theory anymore, but could be the basis for a new treatment paradigm, especially in pediatrics.

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## LECT 3

## SLEEP DISORDERS AND PEDIATRIC ACUTE-ONSET NEUROPSYCHIATRIC SYNDROME SYMPTOMS

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Pediatric acute-onset neuropsychiatric syndrome (PANS) is a recently described disorder presenting with: abrupt onset of obsessive, compulsive symptoms and/or severe eating restriction, with at least two concomitant cognitive, motor, behavioral, or affective symptoms such as anxiety and/or irritability/depression [1]. PANS is currently conceptualized as a complex syndrome with a number of etiologies and disease mechanisms rising from an immune reaction triggered by various agents. A growing scientific evidence demonstrated the association between different microbial infections and the abrupt emergence of both psychiatric symptoms and sleep disorders. Sleep disorders are one of the most frequent manifestations of PANS. Around 80% of patients show wide range of sleep disorders, frequently emerging at the onset of the psychiatric symptoms and regressing later, during the following course of the disease. The most frequently mentioned sleep disorders are parasomnias (nightmares, nocturnal pavor, sleepwalking or somnambulism), difficulties in falling asleep or maintaining sleep (early or mediate insomnia), early awakenings (terminal insomnia), REM sleep disorders such as REM sleep without atonia (RSWA), and sleep movement disorders such as periodic limb movement disorder (PLMD) [2].

Since a panel of specific biomarkers, available for the clinical practice, is still lacking, the formulation of the diagnosis of PANS must be currently based on the identification of the specific symptomatic constellation [3]. However, numerous research groups are trying to find clear objective signs and biomarkers in order to validate the PANS as a clinical specific phenotype, matching the diagnostic criteria described by Swedo and colleagues in 2012 [1]. Therefore, it is needed to provide an objective characterization of sleep alterations associated to PANS phenotype in order to better understand the biological basis of the syndrome. Starting from the consideration that basal ganglia play a crucial role in sleep physiology and pathophysiology, a hypothetical dysfunctional model, explaining the co-occurrence of sleep, motor, obsessive-compulsive and cognitive symptoms in PANS, has been recently proposed [3]. In particular, the midbrain dopamine system, via the dorsal and ventral striatum, could alter the cortical inputs, modulating a wide range of functions including cognition, motor behavior, and sleep-wake states. Moreover, disrupted sleep patterns have been related to alterations of basal ganglia structure during the course of immune-mediate and neuroinflammatory diseases. In particular, a symptomatic overlap between PANS and other sleep disorders, of well-established immune-mediated pathogenesis (e.g. narcolepsy and Kleine-Levin syndrome), has been observed [4]. Therefore, it is not surprising that sleep disturbances are so frequently observed in PANS cohorts. For all these reasons, we have recently proposed [3] to consider sleep disruption as a cardinal symptom of PANS phenotype, because of its prevalence and impact on quality of life. Currently, sleep abnormality is not a major criterion for the diagnosis of PANS. A revision of the diagnostic criteria, including the objective evaluation of sleep quality, should be taken in consideration. From a clinical point of view, an accurate evaluation of sleep patterns is suggested for all PANS patients at the onset of the disorder, and a polysomnographic investigation should be recommended in more severe PANS cases.

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## LECT 4

## REASONED APPROACH TO FEVER

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Fever is an increase in body temperature occurring as a result of a systemic response mediated by the central nervous system and it is the most common reason children present to the Emergency Department. Although most febrile children have self-limited viral infections, a small proportion have an invasive bacterial infection. The goal for clinicians remains to identify those infants with an invasive bacterial infection without the overuse of diagnostic testing and antibiotics in low-risk infants. Despite the dissemination of guidelines, recent studies have found low adherence to guidelines [1-3].

In children, fever is generally attributable to an infectious disease. Although the majority are viral and benign infectious processes, it is the clinician's job to detect children with bacterial infections that need to be treated.

It is useful to guide the pediatric clinician to correctly frame a febrile child, asking the right questions and performing the right tests on the right patients to find, among the many children who rush to the Emergency Department with fever from common and harmless viral infections, those who are suffering from a bacterial disease that is disseminating and potentially could be an alarm situation. Like a detective, the clinician will have to follow a diagnostic pathway that is aimed first at framing the patient. Based on specific characteristics, it is possible to classify into a risk class and assess the appropriateness of additional testing and possible antibiotic treatment. At first approach, very important is the age criterion of the patient we are facing. In all infants < 1 month the age is the determining factor; all other clinical parameters take a backseat. A feverish infant < 28 days has to be treated as a septic infant (so even lumbar puncture sometimes has to be performed) and to be hospitalized at least for observation. In

this class of patients with poor communication, the "general look", defined as the first visual impact of the child, takes on greater importance; if the child appears impatient, particularly irritable, with poor general clinical condition, it is likely that we are dealing with a child with potentially more severe bacterial infection.

The anamnesis is the clinician's fundamental tool. Useful information to have is the exact course of events, the occurrence of accessory symptoms preceding or following the onset of fever, the presence of contact with other sick children, the presence of other affected family members. To better investigate, at first, we should understand the timing of the fever, that is, how long ago it appeared; sometimes it can also be helpful to recognize the fever pattern (intermittent, remitting, sustained, relapsing, recurrent) we are facing, because it might point us to the right diagnostic direction. Always keep in mind to investigate any comorbidities predisposing to major infections, for instance children carrying devices or genetic disorders predisposing to infections. A common example is the child with sickle cell anemia, who is by nature of the underlying pathology predisposed to infection by capsular bacteria.

Once the useful information has been collected, the clinician will examine the child for signs to corroborate the hypotheses generated. Firstly, essential to collect are the vital parameters:

- oxygen saturation and respiratory rate, to find out whether there is a respiratory commitment;
- blood pressure and heart rate, physiologically increased during fever;
- capillary refill, essential especially in younger patients to assess peripheral perfusion and possible dehydration.

Then the clinician will continue with the physical examination: the symptoms that can accompany fever are varied, and can lead us back to the aetiology; in particular, he/she will look for signs in the external auditory canal and mouth to visualize otitis and pharyngitis, skin, cardiopulmonary, abdominal, neurological areas, and even simple irritability for infants. Furthermore, it should be remembered that urinary tract infections are not always accompanied by overt symptomatology of the district, especially in the youngest patient.

If there are no red marks, an active child with a good general look, with a low refill time, well hydrated, with a normal neurological evaluation appropriate for the age is reassuring and does not cause worry: it is with high probability a benign febrile state.

On the basis of the aforementioned information, the initial approach to the febrile child makes it possible to classify them as more or less at risk of a bacterial infectious disease, meriting further diagnostic tests and possible antibiotic treatment.

Investigations to perform in feverish infants between 1 and 3 months are: urine test, urineculture, full blood count, blood culture, and C-reactive protein. If respiratory signs are present, a chest X-ray should be performed; if diarrhea is present, a stool culture should be performed. In infants < 28 days with high risk signs, perform lumbar puncture (unless contraindicated) and then give parenteral antibiotics.

In infants, perform full blood count, blood culture, C-reactive protein, urine testing if one or more risk signs are present.

In feverish children without apparent source and who have no features of serious illness, urine test and urineculture should be mandatory; also, any signs of pneumonia should be checked. In this group, it is not useful to routinely perform blood tests and chest X-rays.

In conclusion, the febrile child is a common challenge for the clinician. For a correct approach to a febrile child, it is necessary to take a complete history and perform a thorough physical examination in order to unearth possible clues pointing towards a bacterial infection, although in the vast majority of cases, the clinician will be faced with a viral infection. Fundamental is the age criterion: febrile newborns aged < 28 days should always be hospitalized due to elevate risk of severe disease and paracetamol is the only antipyretic indicated for use in newborns. A conservative approach, with some laboratory tests, is also recommended in infants with one or more signs. In the end, the specific case is left to the common sense of the clinician, who will judge the management according to the child's condition and family and social background. Often, in an older child with no discernible clinical signs, it may be appropriate to adopt a wait-and-see strategy without carrying out examinations or antibiotic therapy.

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## LECT 5

## MEDICINAL PLANTS USE FOR RESPIRATORY DISORDERS

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Infectious diseases represent a challenge and a health emergency that must be tackled with a global approach. The history of epidemics can only remind us that these diseases emerge suddenly, they can eventually disappear and then re-emerge. The recent SARS-CoV-2 pandemic is a prime example of how this challenge must lead us to be timely in taking all necessary measures to contain the spread of infectious agents and effective for the protection of public health and mainly the supply of vaccines [1].
The role of vaccination in global health, the progress made on the diagnostic, therapeutic and prevention planning, the improvement of hygiene and behavioral conditions have contributed to the reduction of the incidence of infectious diseases. Some infectious diseases such as acute respiratory infections (ARI), including upper respiratory tract infections (URI) and lower respiratory tract infections (LRI), continue to be a frequent cause of consultation in primary pediatric care and represent over 25% of medical consultations in developed countries; they also represent a leading cause of morbidity and a high-risk factor for infant mortality worldwide [2].
Over the past three decades, the use of herbal medicines and phytonutrients for primary health care has increased exponentially. Complementary and alternative medicine (CAM) has become more popular and accepted also in Europe. In Italy, many herbal medicines are available as food supplements that must comply with all the provisions of food law applicable to safety, labeling and claims; for placing on the market they must be notified to the Ministry of Health.
The outbreak of the Coronavirus SARS-CoV-2 pandemic, with the lack of specific therapy, has further pushed patients to resort to greater use of food supplements, herbal remedies, probiotics, vitamins, minerals and trace elements, in order to improve their well-being, promote the immune response and manage the typical symptoms of colds, flu and other conditions related to respiratory pathology also in the context of COVID-19 disease [3].
Several studies have been conducted on some herbal medicines, listed in the WHO and EMA monographs, others studied for their widespread traditional use, to evaluate the therapeutic efficacy in respiratory system disorder. It has been shown that the incidence of infections and the duration of the disease were favorably influenced by the intake of some phytotherapeutic drugs; a significant improvement in the symptoms was also observed; an adequate and superior safety profile was also found of drugs proven of reference [4].

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## LECT 6

## INTEGRATED MEDICINE IN ALLERGIC DISEASES

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Allergies are among the most common chronic diseases seen in children. If we consider atopic dermatitis, allergic rhinitis and bronchial asthma together, their incidence reaches double figures, and if we also include sensitisation on skin tests, it rises to 20-25%, albeit with some age-related differences. Both genetic and environmental factors combine to determine these diseases and there has been a sharp rise in their incidence in recent decades. Historically, this has been interpreted on the basis of the hygiene hypothesis, but more recently the role of the intestinal microbiota has been highlighted.
Diagnosis is based on *in-vivo* or *in-vitro* tests. *In-vivo* diagnosis is based on skin prick tests,

while *in-vitro* diagnosis is based on measurement of the level of allergen-specific IgE antibodies (RAST test) or characterization of the molecular components of each allergen (component resolved diagnosis [CRD]). The therapeutic approach is laid down in both national and international guidelines drawn up by the leading scientific societies in the field: American Academy of Allergy, Asthma & Immunology (AAAAI), European Academy of Allergy and Clinical Immunology (EAACI), Società Italiana di Allergologia, Asma ed Immunologia Clinica [Italian Society of Allergology, Asthma and Immunology] (SIAAIC), Associazione Allergologi Immunologi Italiani Territoriali e Ospedalieri [Association of Local and Hospital Allergologists and Immunologists] (AAIITO), Società Italiana di Allergologia e Immunologia Pediatrica [Italian Society of Paediatric Allergology and Immunology] (SIAIP), etc.

Complementary medicine – or, as it is more recently known, traditional and complementary medicine (T&CM) – has always paid considerable attention to the management of allergies. While this has undoubtedly been unsuccessful in terms of diagnosis – given the unreliability of the various tests suggested over the years (electroacupuncture according to Voll [EAV], the DRIA test, cytotoxic test, and so on) – it offers some interesting pointers in relation to treatment. A surprising number of patients with signs of allergy turn to T&CM. Kłak and colleagues, in their 2016 survey of a vast number of subjects with allergic diseases, found that 20.6% had used homeopathy, 14.7% acupuncture and 11.9% herbal medicine at least once in the previous 12 months [1].

The idea that T&CM is based on obsolete concepts does not reflect reality. Let us consider its three mainstays: herbal medicine, acupuncture and homeopathy. It is now clear that herbal medicines, whether used as phyto-complexes or as extracts, have various anti-inflammatory effects on specific aspects of allergic inflammation [2]. Acupuncture, through the traction obtained by rotating the needle in the subcutis, is able to interfere with the production of inflammatory cytokines [3]. Finally, the favourable effects of homeopathy in the treatment of various allergies, documented instrumentally with rhinomanometry and the bronchial challenge test, were demonstrated some years ago, in studies performed by Reilly's group that used homeopathic dilutions of allergens. In addition, Sainte-Laudy and Belon have shown that homeopathic dilutions of histamine interfere with basophil degranulation, one of the mechanisms underlying the reactions triggered on contact with allergens [4].

Obviously, research must not only describe the mechanisms of action, but must also offer data on the efficacy of the approach. In relation to herbal medicine, recent studies showed that a product containing perilla, quercetin and vitamin D has significant positive effects in the treatment of allergic rhinitis [5]. Other studies have documented the effects of acupuncture on the same condition.

In relation to homeopathy, it is worth noting the studies by Ferreri and colleagues in Pitigliano and Rossi and colleagues in the outpatient's clinic at the Lucca Local Health Unit. Ferreri administered a questionnaire assessing clinical score to 430 patients of different ages with signs of respiratory allergy (asthma, rhinitis), reporting a significant improvement in 75% of patients after a first cycle of 2 months of treatment [6]. Rossi, from a sample of 165 paediatric patients with various allergies (asthma, rhinitis, atopic dermatitis), traced 107 of them 7 years after discharge and found that 75 (70.1%) reported a complete remission of symptoms [7].

In conclusion, therefore, T&CM offers interesting treatment possibilities in the field of allergology.

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## LECT 7

## LONG COVID-19 IN PEDIATRIC AGE: HOW IS IT GOING IN ITALY?

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Long COVID-19 syndrome represents a complex clinical entity, defined by clinical manifestations that occur or continue after acute SARS-CoV-2 infection, with no other probable diagnoses. It is estimated that around 25% of patients with acute COVID-19 infection may develop long COVID-19 syndrome, which signifies a significant health burden [1]. Like adults, also children and adolescents can be affected by long COVID-19. The most common symptoms detected in pediatric age are mood symptoms, fatigue, sleep disorders, headache, respiratory disturbs, sputum production or nasal congestion, cognitive deficit, loss of appetite, and altered smell [2, 3].

Currently, studies on long COVID-19 in pediatric population are heterogeneous in design, inclusion criteria, outcomes, and follow-up time, and the definition of long COVID-19 or "post-COVID-19 condition" itself remains not univocally established: in this sense, the potential range of severity of sign and symptoms and the real frequency of this disease is still unclear. Moreover, since much of the studies in literature focused on hospitalized cohorts of children, the incidence of post-COVID-19 condition in primary care setting and in non-hospitalized pediatric population is actually not known.

For these reasons, a study has been conducted in Italy between October 2020 and June 2021 to assess the prevalence of post-COVID-19 condition in a cohort of 629 pediatric primary care patients based in 8 Italian regions, and in a cohort of 60 pediatric patients hospitalized during acute infection. Observation period went from 8 to 36 weeks from the first negative swab, and long COVID-19 syndrome was diagnosed if at least 1 of the above symptoms had increased in frequency during the observation time, compared with the previous year.

As for primary care setting, post-COVID-19 symptoms were found in 153 children, that corresponds to a cumulative incidence of 24.3%. Cumulative incidence was more than doubled in hospitalized children (58.3%), with respect to the primary care setting.

The most frequently reported manifestations were asthenia (7%), neurological disorders (6.8%), and respiratory problems (6%) for the primary care children. Hospitalized children had more frequently psychological manifestations (36.7%), cardiac symptoms (23.3%), and respiratory disorders (18.3%). Cumulative incidence between females and males showed no differences in both cohorts.

Pre-existing illnesses (even respiratory or allergic ones) did not influence the probability to develop long COVID-19. On the other hand, in primary care setting, post-COVID-19 condition appears to be strongly associated with the existence of a symptomatic acute phase: incidence of long COVID-19 went from 11.5% in children who had had an asymptomatic COVID-19 to 46.5% in those who had presented symptoms when tested positive.

Age was a risk factor for most post-COVID-19 symptoms, particularly fatigue, neurological, or psychological symptoms. However, these data should be looked at bearing in mind that it is more difficult to assess such symptoms in young children. Respiratory symptoms, on the contrary, seem to be more frequent in toddler and infants: this fragile age range should be carefully monitored because babies could be more predisposed to severe respiratory complications.

This study emphases the importance of monitoring all pediatric patients after acute COVID-19 infection, even if it has been mild or non-symptomatic.

Moreover, the present results highlight the importance of vaccination in pediatric population, also to prevent the consequences of long COVID-19 syndrome.

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## LECT 8

## MOOD DISORDERS OF ADOLESCENTS IN THE SARS-CoV-2 PANDEMIC: ROLE OF PHYTOTHERAPY

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The SARS-CoV-2 infection caused health problems. These did not stop at the infection itself: an important percentage of children and adolescents continued to present physical and mental health problems over time.

An extremely fruitful period for children's brain development is recognized in the first 1,000 days of life, in which the brain cells synapse blooming and pruning reach very high levels of activity and concentration. During adolescence we can observe the same situation.

In this particular period of life, the cerebral areas development of the limbic cortical system, that is responsible for the control of sensations, does not mature in a symmetrical way respect to the areas of the prefrontal cortex, where the processing of feelings takes place. Therefore, we are faced with a difficulty of control of emotions and their impact on relationship life.

For this reason, adolescents tend to sensation seeking and to act impulsively. Early developing behaviors may be in contrast with the common behaviors of everyday life. Failure to regulate these attitudes increases the risk of maladaptive outcomes, including substance abuse, such as alcohol and drugs.

Individual differences in the tendency to seek stimulation, act on impulse, and engage in substance use are correlated with the anatomical structure of cognitive control circuitry.

Therefore, the delay in the maturation of the anatomical structures in the brain of the cognitive control circuits is the main cause of the so-called "adolescent crisis", a source of discomfort in relationships and within the family, at school and in relationships between adolescents.

The SARS-CoV-2 pandemic has exacerbated all these situations; lockdown at home, intra-family violence, excessive use of the Web and social media, fear of the disease for oneself and for family members, symptoms linked to the COVID-19 disease have caused a state of anxiety and, in some cases, even depression. Indeed, depressive and anxious episodes and symptoms are now present more frequently in the pediatric population than pre-pandemic estimates. Recently collected data shows that children and adolescents who have fallen ill, who have faced lockdown, remote schooling and quarantines, are 5 times more likely to request intervention from services of mental health. The interventions can be multiple from the point of view of psycho-behavioral therapy: support for families and for young people themselves in their relationships with each other and with educational institutions. When this support network is not enough, and serious events such as the crisis triggered by the SARS-CoV-2 pandemic cause a great worsening of life conditions of young people, pharmacological intervention is also necessary. Unfortunately, psychiatric drugs often have non-negligible secondary effects, therefore families often resort to Integrated Medicine and herbal medicines called phytotherapies. The most prescribed and most used phytotherapeutic drugs are part of traditional medicine in use in both Western and Eastern civilizations.

Those most in use are *Crocus sativus*, *Hypericum perforatum*, *Melissa officinalis*, *Passiflora incarnata*, *Zyziphus jujuba*, *Tilia tomentosa*, *Tea sinensis*, *Scutelalria galericulata* and *Rodiola rosea*. Some of these have scientific publications to support their action, such as *Crocus sativus* and *Rodiola rosea*, while others are used thanks to their traditional use and the clinical responses they provide in daily practice. *Crocus sativus L.* reduces the symptoms of depression and strengthens the antidepressant effects of current drugs (fluoxetine), reducing the adverse events of these therapies [1]. Some saffron compounds have, on the central nervous system, biological properties and strong antioxidant and anti-inflammatory properties. Crocin appeared to be able to inhibit the absorption of dopamine and noradrenaline. Safranal inhibits the reuptake of serotonin. Crocin has also shown neuroprotective abilities, increasing the intracellular levels of neurotrophic factors such as brain-derived neurotrophic factor (BDNF) in *in-vitro* and animal

models. Therefore, *Crocus sativus* proves to be an interesting drug for the treatment of the secondary effects caused by stress, in particular in young people who have recovered from COVID-19 [2]. There are also studies that evaluate the effect of *Rodiola rosea* in terms of cognitive and mental functions in subjects subjected to stress from illness (COVID-19) and adverse situations. A recent review demonstrates how the *Rodiola rosea* can be used in the management of various aspects of stress-induced conditions; it is demonstrated how the repeated administration of the *Rodiola rosea* extract exerts an anti-fatigue effect that increases mental performance, in particular the ability to concentrate, and decreases the cortisol response to stress from awakening in burnout patients with fatigue syndrome [3].

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## LECT 9

## BIFIDOBACTERIAL DYSBIOSIS

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It has been known for years that our intestine hosts a specific microbiota which is a complex microbial ecosystem characterized by bacteria, viruses, fungi and other microorganisms. This ecosystem is capable of living in mutualistic symbiosis with the host organism.

The human gut microbiota is able to perform important biological functions such as the synthesis of essential vitamins, the development of the immunity system, the protection against infectious pathogens, and the modulation of brain development.

In the last decade, scientific literature showed the existence of a "critical time frame of vulnerability", which coincides with the first 1,000 days of the new-born and is extremely important for establishing an adequate and biodiversified "microbiotic core". This type of microbiota is capable to contribute to the health of the infant and the child.

In fact, the initial colonization of the neonatal intestinal tract is influenced by maternal microbiota, type of birth, type of feeding, intake of drugs and environmental factors to which it is exposed.

The state of intestinal dysbiosis (i.e., reduced biodiversity of the microbiota) in the early stages of life can significantly affect the health of the child, as well as contribute to the disease sensitiveness in later stages of life. In particular, recent studies indicate that a reduced presence of *Bifidobacteria* (i.e., bifidobacterial dysbiosis) is involved during the neonatal and postnatal phase in the onset of allergic diseases, celiac disease, chronic inflammatory bowel diseases, necrotizing enterocolitis, obesity.

Several studies show that *Bifidobacteria* are among the "pioneer colonizers" of human gastrointestinal tract and make up to 90% of the neonatal intestinal microbiota during the first 12 months of life for infants born at term, by vaginal delivery and breast-fed.

Researchers sustain that these bacterial genera represent the keystone of infant microbiota. "Without these bacterial genera, the ecosystem collapses like the keystone of an arch".

*Bifidobacteria* are important "engines" of the structure and the integrity of intestinal microbial community. They play a unique key role in the microbial community. A reduction or absence can cause a radical change in the structure and function of the microbiome.

A relative abundance of these bacterial genera has certainly undergone a significant reduction over the years of human evolution, to the point that researchers agree that they are in a potential state of "relative extinction". This drastic *Bifidobacteria* "impoverishment" is probably linked to host factors and environmental factors. Factors such as industrialization process, change of diet during pregnancy (especially in terms of reduced fiber intake), an increased number of C-sections, a major use of formula rather than breast milk, an increase in hygiene practices and excessive use of drugs (especially antibiotics), have certainly contributed to a significant reduction of *Bifidobacteria* over the time.

A recent study, performed on fecal samples from 227 children under 6 months of age, showed that 9 out of 10 children do not have *Bifidobacterium longum* in the intestine and that the vast majority of them are deficient in this key intestinal bacterium from the first few weeks of life.

Recent evidences also show that fecal pH in breast-fed infants has undergone a considerable increase in the last 100 years, passing from a pH 5 to a pH 6.5. That change is capable of influencing the progressive "generational loss" of *Bifidobacteria* by exposing the microbiota to an increased presence of potential pathogenic microorganisms.
In relation to the data illustrated so far, it is evident how an adequate bifidobacterial integration can be important, both during neonatal and postnatal phase, and it can be capable of increasing the biodiversity of neonatal microbiotic core, in order to help the microbiota to be more performing during the pediatric age.

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## LECT 10

## EFFICACY OF PROBIOTICS IN THE PREVENTION OF UPPER RESPIRATORY INFECTIONS IN CHILDREN


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Upper respiratory infections (URI), rhinosinusitis, pharyngotonsillitis and otitis, are a group of frequent pathologies in childhood, representing one of the main reasons for accessing pediatric evaluation with the use of pharmacological therapy (cortisone, mucolytics, antibiotics) and sometimes surgical therapy (adenotonsillectomy). They are also a significant cause of reduction in the quality of life of children and families as well as important risk factors for acute complications and even severe chronic outcomes.

In addition to the anatomical predisposition that naturally makes children more susceptible to this type of pathology, another very important predisposing factor is the bacterial biofilm of the oral cavity and, in particular, the presence at this level of an imbalance with a prevalence of pathogenic bacterial species belonging to the so-called "infernal trio" (*Streptococcus pneumoniae*, *Moraxella catarrhalis* and *Haemophilus influenza*).
It has been seen that the prevalence in the microbial flora of the oral cavity of a particular species of *Streptococcus* (*Streptococcus salivarius K12*) is a protective factor against URI, with lower frequency of infectious recurrence and lower proliferation of the "infernal" bacteria in the oral cavity, thanks to the receptor antagonism, occupation of the living spaces and competition for nutrients; it has also a direct bactericidal action through the "salivaricine A2 and B" which generate pores in the pathogen bacterial membrane. Finally, it favors a local increase in the production of interferon-gamma by limiting the entry of viruses.
Studies conducted with polymerase chain reaction (PCR) demonstrated that the administration of *Streptococcus salivarius K12* is able to lead to a colonization of the oral cavity by the strain; other studies showed its safety and efficacy as a probiotic therapy of URI in the pediatric age [1]. The continuous administration of *Streptococcus salivarius K12* reduces the number of recurrent pharyngotonsillitis (-92%) with a reduction in SBEGA pharyngotonsillitis (-84%) and viral pharyngitis (-76%) [2]; a reduction (-40%) in the number of acute otitis media (AOM) exacerbations in children with effusive otitis media (EOM) and a reduction (-80%) in the frequency of EOM [3]. In children with chronic adenoiditis, it determines a significant reduction of infections (-67%) and the need of surgical treatments in recurrent patients (28% in the treated group vs 100% in the untreated group) [4]. Finally, recent and relevant data emerged in the context of the COVID-19 pandemic where *Streptococcus salivarius K12* drastically reduces the infections in children [5].
*Streptococcus salivarius K12* is today a new safe and effective weapon in the prevention of URI in children, allowing a reduction of pharmacological and surgical therapies and significant improvement in the health and quality of life for children.

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## LECT 11

## SOCIAL MEDIA PEDIATRICS AND DR. GOOGLE

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There is now extensive family access to technology due to the enormous availability of Internet and the decreasing cost of multimedia devices. The available data are unequivocal: an increase from 55% to 86% in the use of digital information in the past 11 years has been documented. However, the repercussions of this trend are not always positive, there is indeed a significant increase in misinformation and misleading advertising [1, 2]. In addition, there is the phenomenon of child influencers, who generate millions of impressions and can help promote the consumption of unhealthy food and beverage brands. In fact, it is now well known that exposure to unhealthy food advertising is associated with poor diet, especially in young children, but data regarding the impact of unhealthy products through social media influencers is still understudied as most research on food advertising has focused on television commercials or online advertisements produced by companies [2]. This was also recently addressed by the World Health Organization (WHO), which reported that breastmilk substitutes are strategically promoted in an integrated way through multiple digital channels, especially through social media, with direct-to-consumer advertising in real time and collaboration with influencers. Even in this specific context, studies about the impact of digital marketing are scarce; however, the negative impact on breastfeeding intention and initiation has been documented [3]. WHO statements to protect and promote breastfeeding are clear: there is a need for a "coordinated global action and strengthened national measures ... to implement, monitor and enforce the International Code [of Marketing of Breast-milk Substitutes 1981] in a digital context" and possible restrictive measures directed toward marketing of breastmilk substitutes by social media platforms [3]. In this regard, the importance and usefulness of the presence of health influencers for the proper dissemination of health information to the public has emerged [1, 4]. Data from China point out that the greatest impact of health influencers involves women's health, with particular reference to obstetric-gynecological issues, pregnancy-related risks, and childcare. The Italian Society of Pediatrics has also recently expressed its views on this, not only recognizing the importance of the development of this new form of communication, but also stating the need for the scientific community to be actively involved in social media communication. In fact, through a pilot study, the role of pediatric influencers in communicating health information to children and adolescents was evaluated and its effectiveness in promoting proper health communication emerged [1].

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