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Lectures

Selected Lectures of the Course "Take care of children, 5th Edition. Inflammation between wellbeing and disease in Pediatrics" and the Meeting "Artificial intelligence in Medicine"

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The Course "Take care of children, 5th Edition. Inflammation between wellbeing and disease in Pediatrics" and the Meeting "Artificial intelligence in Medicine" are Satellite Meetings of the 19th International Workshop on Neonatology and Pediatrics, Cagliari (Italy), October 18th-21st, 2023.

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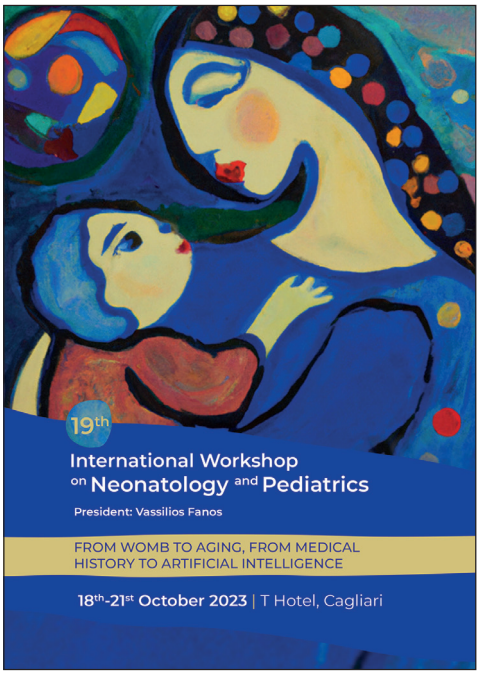

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LECT 1

INFLAMMATION AND THE GUT

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The gut is the largest interface between the human body and the outer environment. The intestinal homeostasis, which is defined as the maintenance of a healthy, balanced state, is determined by the dynamic interaction of the intestinal epithelium, the gut microbiome, and the host immune system. The gut barrier is a dynamical entity interacting with different and continuous stimuli. Under physiological conditions, the intestinal barrier is able to provide the right balance between the permeability of selective dietary nutrients from the intestinal lumen to the systemic circulation, and the protection from the penetration of pathogens and harmful components. Therefore, the maintenance of a stable intestinal barrier is crucial to prevent luminal substances and pathogens from entering the intestinal lumen. The impairment of the intestinal barrier caused by many possible factors, such as infectious and oxidative stresses, dysbiosis, etc., is mainly known as intestinal wall leakage syndrome and it may represent the first trigger of several pathologic conditions [1]. The other essential component of the gut wall is represented by the intestinal microbiome. The gut microbiome, also known as the "forgotten organ", comprises trillions of microbes, including bacteria, fungi and viruses, harbored in our intestinal mucosa. The relationship between the gut microbiome and the host is highly mutualistic, since the latter plays a crucial role in several essential pathways for the human being. The gut immune mucosal system represents the third essential player in order to keep the intestinal homeostasis. In physiological conditions, the gut microbiome exerts a symbiotic relationship with the immune system, helping to maintain a non-inflammatory homeostasis, through several mechanisms [2]. The alterations of one of these 3 essential players of the intestinal homeostasis may lead to chronic inflammation. To date, inflammatory bowel disease (IBD) embodies the most extreme and complicated disease, developing from a misbalance of the intestinal homeostasis. From an epidemiological point of view, IBD incidence is increasing at all ages, including pediatric, and at all latitudes [3]. IBD pathogenesis has not been completely elucidated, although the most recent evidence encompasses a complex interaction between host genetic, environmental, and microbial influences, resulting in a dysregulated mucosal immune response against the commensal intestinal microbiota. From a pathogenetic perspective, IBD represents the most fascinating model to elucidate all the sequential steps leading to the chronic inflammation of the human gut.

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LECT 2

UNDERSTANDING NEUROINFLAMMATION

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Neuroinflammation means the inflammatory reply of the nervous tissue to a broad range of injuries, like infection, toxins, ischemia and trauma. Characterized by the rise of several pro-inflammatory cytokines, the process recognizes microglia and astrocytes as the main actors, though even endothelial cells and the leukocytes that break through the brain-blood barrier play a key role. Despite a complex gear that prevents exaggerated responses, chronic insults – such as those occurring in neurodegenerative diseases – may keep the process alive, causing neuronal death and depletion [1]. The study of

neuroinflammation is relevant for the comprehension of the pathogenesis of different brain disorders. For instance, the neuropathology of Alzheimer's disease (AD), whose hallmarks are neuritic plaques, amyloid angiopathy, and neurofibrillary tangles, is caused by amyloid-β aggregates. After microglia recognition and phagocytosis, the activation of the inflammatory pathways, including cytokines, metal ions and oxidation, occurs, leading to the amyloid aggregation responsible for the pathology [1]. Another example is the intense neuroinflammation occurring during the acute phase of stroke, in which the brain-barrier breakdown leads to neuronal injury associated with worse neurological outcomes. Oxidative stress, metalloproteinase, microglial activation, and infiltration of peripheral immune cells into the ischemic tissue are the major players here [2]. In this scenario, the role of neuroinflammation and maternal immune activation in human neurodevelopmental disorders also turned up [3]. However, the idea that *in-utero* upsets can affect the offspring's health originated from the Barker hypothesis, which formally stated that maternal undernourishment during gestation and the susceptibility of the newborn to atherosclerosis and ischemic heart disease in adulthood are related. The further development of this hypothesis has found application in the pathogenesis of multiple other human diseases.

In conclusion, neuroinflammation is the sophisticated process that may explain the most frequent central nervous system diseases and the epigenetic factor that drives fetal programming toward neurological issues. This approach allows a better understanding of the process and leads to innovative treatment approaches. Since it is involved in the pathogenesis of these mentioned diseases, neuroinflammation become a leading target of research, particularly rocketing the number of papers published on this topic in the last 5 years. AD hallmarks, as well as the histopathological features of other neurodegenerative diseases, are now seen from a different point of view.

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LECT 3

GUT DYSBIOSIS AND INFLAMMATION IN AUTISTIC SPECTRUM DISORDERS

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The alteration of the gut microbial ecosystem has been associated with the development of autism spectrum disorders (ASDs) for a long time.

Almost all autistic children and adults exhibit loss of overall microbial diversity and beneficial microorganisms, associated with the excessive growth of various pathogens. However, results emerging from preclinical and clinical studies are highly heterogeneous, and data on gut dysbiosis in autism are inconclusive. Actually, the clinical heterogeneity of autism is reflected by the molecular and microbial heterogeneity.

Most studies report alterations in the abundance of *Firmicutes* and *Bacteroidetes* phyla in ASD subjects, with a higher *Bacteroidetes*/*Firmicutes* ratio compared to non-autistic individuals.

Regrettably, a number of studies reported a *Bacteroidetes*/*Firmicutes* ratio either closely comparable between autistic and non-autistic individuals or even lower in the former [1].

Further divergencies between studies about the gut microbial overgrowth and depletion in autism include bacterial taxa belonging to:

a. the *Firmicutes* phylum, such as *Clostridium*, *Dorea*, *Enterococcus*, *Faecalibacterium*, and *Ruminococcus*;
b. the *Bacteroidetes* phylum, such as *Bacteroides* and *Prevotella*;
c. the *Proteobacteria* phylum, such as *Desulfovibrio*, *Escherichia*, *Klebsiella*, *Shigella*, and *Parasutterella* [1].

Several factors affect discrepancies between studies. First, ASD is a highly heterogeneous disease; each autistic individual differs from any other one. Clinical differences between individuals with ASD consist of various factors, including:

a. the disease severity, assessed by clinical tools (e.g., ADOS 2-CSS);
b. the number and the specific amount of signs and symptoms building the clinical phenotype (e.g., stereotypic and compulsive behaviors, social relationships, irritability), assessed by standardized questionnaires (e.g., RBS, ABC, CARS);

c. co-morbidities, such as gastrointestinal diseases (e.g., colitis, chronic constipation/diarrhea, gastroesophageal reflux, nausea/vomiting, flatulence), epilepsy, seizures, sleep disorders, the genetic landscape (inborn errors of metabolism or inheritable and *de novo* mutations), food selectivity, and leaky gut;
d. patient's age;
e. social conditions and lifestyle;
f. geographical location;
g. medications (e.g., antibiotics, antidepressants);
h. type of biological sample (stools, biopsy of gut mucosa);
i. environmental risk factors (e.g., maternal diseases, birth complications);
j. microbiome analysis (e.g., terminal restriction fragment length polymorphism, 16S rDNA sequencing, whole genome sequence);
k. the statistical approach.

It is reasonable to assume that discrepancies between studies on gut microbiome in autism may be due to the enrolment of different subgroups of patients between studies [2].

A recent comprehensive omic analysis from the literature, performed by devising an innovative Bayesian differential ranking algorithm, demonstrated that, in autism, gut microbiome metabolism mirrors human brain metabolism [3]. Notably, this analysis evidenced a strong association among gut microbes, dietary patterns, host immunity, and brain expression.

Finally, the analysis of data obtained in an open-label fecal matter transplant study revealed a stable core microbiome in autistic children constituted by *Prevotella*, *Desulfovibrio*, *Bacteroides*, *Bifidobacteria*, and multiple butyrate producers.

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LECT 4

INFLAMMATION, NEUROINFLAMMATION AND IMMUNITY IN CHILDHOOD

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From the moment of conception, the development of the immune system and the nervous system are influenced by exposure to environmental factors. Food consumption, inhalation of contaminated air and particles and electromagnetic fields represent the main sources of exposure for humans. Various epidemiological research has highlighted the relationship between exposure to persistent organic pollutants and neurodevelopmental disorders and neurodegenerative diseases. Early exposure, especially in the first 1,000 days of life, a period of particular vulnerability, can interfere with the harmonious development of the child by influencing the acquisition of cognitive skills, movement, communication and social interaction. Consuming foods that contain chemicals such as additives, preservatives, flavorings, herbicides, fungicides and antibiotics causes alteration of the intestinal microbiota, with a reduction in the overall biodiversity of the intestine, an increase in *Firmicutes* and a reduction in *Bacteroidetes*. Persistent dysbiosis triggers a proinflammatory condition with increased Th17/Treg ratio and lipopolysaccharide, IL 1, 6 and 17, TNF-α production [1]. The permeability of the intestinal barrier is thus altered with the passage of microbes, endotoxins, immune cells, cytokines and undigested food molecules into the bloodstream, thus creating chronic systemic inflammation with the production of antibodies, which, in turn, due to cross-reactivity can, once the blood-brain barrier is overcome, activate microglia and astrocytes, thus leading to neuroinflammation in different brain areas. Daily exposure to high levels of fine particulate matter with an aerodynamic diameter equal to or less than 2.5 μm can affect neurological development and be associated with cognitive and behavioral disorders [2]. Recent studies have shown the possible negative effects of children's early exposure to digital content, with particular reference to screen time. In fact, excessive use of digital media can have important repercussions on

development, learning and the quality of family life. Internet-connected devices represent the key to accessing digital subculture, the content of which can have a negative impact on children's psychological and physical development [3]. In light of the evidence available to date, even if further studies and research are needed, it appears essential to develop a global strategy that protects the environment from pollution as a necessary action to protect the health of all individuals and especially children. Pediatricians must contribute to mothers' nutritional education from the beginning of pregnancy by encouraging a healthy and balanced diet rich in micronutrients, encourage and support breastfeeding, combat the use of drugs, alcohol and tobacco smoking and limit the use of medicines to actual needs, without forgetting the prevention of early exposure to environmental pollutants.

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LECT 5

INFANT ATOPIC DERMATITIS AND NUTRITION: CAN LIPIDOMICS AND METABOLOMICS EXPLAIN THIS RELATIONSHIP?

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Many aspects of atopic dermatitis have not yet been fully understood, despite the numerous studies and the high prevalence in infancy and childhood (20%). This disease can affect the individuals even in adulthood, worsening the quality of life of the patients, with high social and financial burdens for the community, as well. Nevertheless, recent literature highlighted the pivotal role of the environment and the habits of the individual, especially nutrition, in the early stages of atopic dermatitis. Indeed, elimination diets, with a few exceptions, seem to have detrimental effects. Moreover, chrono-insertion appears to be useless, together with some little benefit of breastfeeding in those at highest risk. In this context, metabolomics and lipidomics could provide a better understanding of the pathways underlying the etiology of this pathology. Indeed, the metabolic profile of children affected is different from that of healthy children. The differences are related to metabolites that are related to the gut microbiota. On the other hand, preliminary lipidomics studies can improve the knowledge concerning the alterations of the skin to ameliorate the formulation of skin care products for infants and children. Thus, the investigation of the different allergic phenotypes' responses should be considered, together with the investigation of the possible intestinal dysbiosis in these infants and children, in order to improve the diagnosis and the management of these little patients from the early stages of this pathology.

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LECT 6

PROBIOTICS AND PFAPA: RATIONALE FOR A PRECISION CHOICE

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PFAPA syndrome (periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis), first described in 1987 by Marshall, is the most common periodic fever syndrome occurring in childhood and can be classified among multifactorial diseases, non-hereditary, benign and autoinflammatory. There is no laboratory or genetic test to confirm the diagnosis, which remains based on clinical criteria. Children under the age of 5 years constitute the largest number of patients with PFAPA and, despite a favorable outcome, patients' quality of life is significantly compromised. In fact, flare-ups last on average 4-5 days and, although they resolve spontaneously, they reappear 2-4 weeks later with very precise and regular intervals during which the children are well. The exact mechanisms of PFAPA pathophysiology still remain unclear; a genetic basis is suggested with polygenic and multifactorial inheritance associated with environmental triggers,

such as latent infections capable of causing immune activation, dysregulation of innate and adaptive immunity, and significant inflammasome-mediated activation during febrile exacerbations. This immune imbalance, in PFAPA syndrome, is in favor of the expansion of inflammatory cytokines and the reduction of anti-inflammatory ones. Furthermore, it is known that the tonsils play a well-defined role in the pathophysiology of the syndrome, as demonstrated by the significant remission of symptoms after tonsillectomy. The tonsils likely represent the main focus of immune imbalance or contain the trigger of immune dysregulation in PFAPA-prone patients. There is no definitive cure for PFAPA; however, it is possible to reduce symptoms during fever attacks and it is possible to do prophylactic management aimed at reducing the frequency of acute episodes, improving the quality of life of children. Probiotics are currently used to prevent upper respiratory tract infections and disease flares associated with immune dysregulation. In this short report, we describe the rationale for a choice of precision bacterial therapy aimed at resolving the immune system imbalance and the dysregulated inflammatory state that characterize PFAPA through a non-invasive approach. In particular, we will describe the potential mechanistic role of *Streptococcus salivarius K12* in reducing acute symptoms and in PFAFA prophylaxis.

LECT 7

INFLAMMATION AND PREVENTION OF METABOLIC SYNDROME THROUGH NUTRACEUTICALS IN CHILDHOOD AND ADOLESCENCE

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Many parents are very concerned about their child's health. They take them for regular check-ups, vaccinate them, give them medication when they get sick, and undergo preventive treatments. However, they often overlook the aspect of their child's diet and weight. We know that individuals with abdominal obesity have a higher cardiovascular risk, regardless of the degree of overweight. In fact, it has been observed that in normal-weight or thin individuals, elevated abdominal circumference indicates an even greater risk of developing type 2 diabetes. The consumption of ultra-processed foods (UPF) leads to a deficiency in essential nutrients, including vitamins (especially vitamins C and E) and minerals. These foods are very palatable, inexpensive, and ready to eat. Increased UPF consumption has already been recognized as a risk factor for various chronic diseases because it promotes low-grade inflammation, thereby fostering the development of non-communicable diseases [1]. This is the obesity situation in Italy: 12.3% of children are obese, while 23.6% are overweight. More than 1 in 3 children, therefore, have a weight higher than what they should have for their age. In practice, throughout Italy, there are 1,100,000 children between the ages of 6 and 11 who are overweight or obese. There are significant differences among the various Italian regions, with the southern regions, particularly Molise, being the most affected areas. Obesity and associated metabolic diseases, such as type 2 diabetes and metabolic syndrome, are accompanied by a chronic low-grade (subacute) inflammatory response. In fact, adipocytes in adipose tissue and infiltrated macrophages produce numerous cytokines involved in inflammatory pathways (TNFα, MCP-1, IL-6, IL-8, leptin, resistin, adiponectin, etc.). The condition of subacute and chronic inflammation in overweight and obese individuals is due to the typical macrophage infiltration of adipose tissue and altered cytokine production, as well as a modest increase in C-reactive protein. Cytokines are recognized as an indicator of tissue inflammation [2]. There are numerous nutraceutical products of plant origin, vitamins, and trace elements that can help improve the subacute inflammation typical of overweight and obesity and regulate the metabolic parameters associated with these conditions. Among these, we can mention vitamins C and E, folic acid, zinc, selenium, chromium picolinate, alpha-lipoic acid (ALA), *Malus pumilia*, and *Coprinus comatus*.

ALA has a well-defined antioxidant and immunomodulatory profile in various chronic immune-inflammatory conditions, such as diabetic neuropathy and metabolic syndrome, as well as antiviral action, including SARS-CoV-2 infection [3]. Florizine found in *Malus pumilia* extract has been shown to significantly contribute to cholesterol control in the bloodstream and reduce the incidence of cardiovascular diseases, both as a nutraceutical principle and as a component of the daily diet [4]. *Coprinus comatus*, an edible fungus with its components (flavonoids, coumarins, and chlorogenic acids), has antioxidant, hepatoprotective, anti-inflammatory, antidiabetic, anti-obesity, and antiviral properties [5]. The synergy between a

healthy lifestyle (Mediterranean diet and physical activity) and the use of suitable and high-quality nutraceuticals can improve the quality of life for young adolescents affected by metabolic syndrome, and beyond.

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LECT 8

REAL WORLD PRACTICE EXPERIENCES IN THE LOW DOSE APPROACH TO SPECIFIC LEARNING DISORDERS (ASDs). EVIDENCE FROM A RETROSPECTIVE OBSERVATIONAL STUDY

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Specific learning disabilities are conditions that present a discrepancy between the levels of academic performance and the potential deduced from the subject's actual intellectual abilities. Learning disorders involve difficulty in concentration or attention, in language development, or in processing visual and auditory information. Diagnosis includes intellectual, educational and language assessment as well as medical and psychological assessment. Treatment consists, first of all, in educational management and in medical, behavioral and psychological therapy. This presentation briefly examines the theoretical basis of low dose medicine [1] and subsequently neurological growth factors, such as brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF). The neurodevelopment of the child is then explored, identifying the critical periods for the various motor, linguistic, cognitive and socio-emotional skills, which coincide with maximum plasticity, as developmental age is a very vulnerable window whose alterations influence the entire development and life itself [2]. A study was reviewed in which low dose BDNF was administered to one group of children in comparison with another. At the check-up after 1 year at the child neuropsychiatry centers, it was found that the group that took BDNF recorded a statistically 50% higher performance than the control group in the various items.

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LECT 9

ANTI-MENINGOCOCCAL VACCINATION: THE IMPORTANCE OF THE BOOSTER IN ADOLESCENTS

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Meningococcal disease is sustained by more than 90% by 5 (A, B, C, W and Y) of the 13 known serogroups of *Meningococci*. Diseases may be non-invasive and invasive (IMD) (most frequently meningitis and sepsis). IMD, although infrequent, represent the most severe endemic infectious disease that can be prevented by vaccination, due to their epidemic potential, consequent disability and case fatality rate. For this reason, vaccination against *Meningococcus C* in childhood, the most prevalent serogroup among the 5, had already been introduced in practice some time ago by previous *National Immunization Prevention Plans* in Italy. This public health measure was based on the evidence that in those countries (the United Kingdom, the Netherlands) where childhood (the age group with the highest incidence rate of IMD) vaccination had been introduced first, in addition to a direct effect on the vaccinated, an important herd immunity effect had also been observed on the unvaccinated population. The flattering results obtained in controlling the disease in childhood,

therefore, led to vaccination also being offered to other age groups where the incidence was high, and in particular among adolescents, as well as to the categories at greater risk for the disease (immunocompromised, splenectomized, etc.). However, studies were beginning to show that the immunity conferred by vaccination was not permanent, but lapsed significantly when 5 years had passed since priming. This led to both childhood and adolescence being identified as dual targets for vaccination age. Even in the USA, given the peculiar characteristics of the spread of the disease among young people attending college, the ACIP introduced not only vaccination in early adolescence but also a booster at 16 years before entering college. Thanks to the control of meningococcal C disease exerted by universal childhood vaccination and extensive adolescent vaccination, the provision by research of multi-valent conjugate vaccines (MenACWY) and also against meningococcal B disease (MenB) was the driver for thinking about a vaccination offer towards all 5 meningococcal serogroups. This is why the previous *National Immunization Prevention Plan* already introduced vaccination against *Meningococcus B* in childhood and led to a switch from the monovalent MenC vaccine to the tetravalent MenACWY vaccine. Moreover, although prevention in childhood was consolidated, little was indicated at national level for adolescence. This is why most of the Regions, following indications from the scientific societies, have autonomously introduced vaccination also in adolescence [1-3]. The recent *National Immunization Prevention Plan 2023-2025* (*PNPV-2023-25*) [2], approved by the State-Regions Conference at the beginning of August 2023, standardizes the vaccination offer against these pathologies in our Country, giving clear indications also for adolescents. In particular, it indicates:

a. tetravalent vaccination against *Meningococcus ACWY*: one dose, starting from the age of 12, both for adolescents never previously vaccinated and those already immunized in childhood with MenC or MenACWY;
b. vaccination against *Meningococcus B*: depending on the epidemiological situation of the individual Region/Autonomous province, the offer may be supplemented by age, with a cycle according to the type of vaccine used.

These indications contribute to placing our Vaccination Schedule among the most comprehensive in the world. However, there are still aspects to be filled, in particular with regard to *Meningococcus B*, for which the possibility of recall vaccination in adolescence for those who received priming against this serogroup during childhood or school age with one of the two vaccines currently on the market (4CMenB) has not been considered. At the international level, recommendations in this regard are extremely heterogeneous. In fact, despite the fact that the two MenB vaccines (4CMenB and FHbpMenB) are authorised in 58 countries, at present, only the USA and Brazil provide the MenB vaccination for adolescents who have not previously been vaccinated, while in Australia and the Czech Republic [3] a booster vaccination is also proposed to those who were vaccinated for MenB at birth. For this reason, the scientific societies united in the *Vaccine for Life Calendar* [1] – in view of the fact that immunity given by antibodies is subject to waining, and consequently it is important to maintain high antibody titres against all *Meningococci* in order to guarantee effective protection – have also begun to analyze this aspect.

There may be different options for offering it to adolescents and co-administering it with other vaccines offered at these ages. In any case, there is a consensus towards an offer to all adolescents, starting preferably not earlier than the age of 13 so as to ensure the greatest efficacy in the years at greatest risk during adolescence (16 years or older). This offer may be made in co-administration with the other vaccines offered at these ages, including booster or MenACWY priming, and should be diversified according to the vaccinee's vaccination experience:

- basic cycle to naive subjects with two doses using either the 4CMenB vaccine or the FHbpMenB vaccine without mixing the two vaccines;
- single booster dose to those who received priming with 4CMenB;
- completion of vaccination with the same vaccine to those who started and did not complete the baseline course with either vaccine.

In conclusion, pending the availability of a single new vaccine capable of covering most of the pathogenic serogroups (MenABCWY), it is currently recommended that, in the short term, the possibility of an extensive introduction of both the MenACWY vaccine and the MenB vaccine in adolescents be evaluated – also through the results of Health Technology Assessment (HTA) studies. In this sense, it is also appropriate that the Regions that organisationally can introduce this vaccination more extensively than the indications of the *PNPV-2023-25* put in place all

the surveillance tools for a timely evaluation of such pilot projects.

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LECT 10

MICROBIOMICS IN CLINICAL PRACTICE

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The term "microbiome" refers to the collection of genomes of all the microorganisms inhabiting and interacting with a given environment (human body, biological fluid, organ, tissue, animal body, plant organism, ground, air, water). On the other hand, the term "microbiota" refers to the community of microorganisms themselves, namely the microbial taxa. Microbiome colonizes almost all the human body sites, especially the gut, mouth, skin, lung, urogenital tract, mammary gland, and many other sites. Interactions between microbiome and human body sites may be commensalistic, mutualistic, or pathogenic. Although the number of microbial cells that colonize the human body is similar to the number of human cells, with a ratio of 1.3 bacterial cells for every 1 human cell [1], phages could outnumber microbial estimates by at least an order of magnitude [2]. In addition, viruses, fungi and archaea significantly contribute to the total number of microorganism cells constituting the human microbiome [3, 4]. Interestingly, while human genome consists of about 23,000 genes, microbiome encodes approximately 2.5-3 million genes, which in turn encode thousands of proteins and enzymes. Consequently, thousands of metabolites, produced by microbial metabolic pathways, are recognizable in human body fluids and tissues. During the life course, age, nutrition, lifestyle, hormonal changes, inherited genes, and underlying diseases are major determinants of the human microbiome. *Firmicutes*, *Bacteroidetes*, *Actinobacteria*, *Proteobacteria*, *Fusobacteria*, and *Verrucomicrobia* are the dominant gut microbial phyla; in particular, *Firmicutes* and *Bacteroidetes* represent almost 90% of gut microbiota. More than 200 different genera belong to the *Firmicutes*, including *Lactobacillus*, *Bacillus*, *Clostridium* (95% of the *Firmicutes* phyla), *Enterococcus*, and *Ruminicoccus*. *Bacteroides* and *Prevotella* are the predominant genera of *Bacteroidetes*. Perturbations of the gut microbial ecosystem, intended as alterations in composition and function of microbiome, are associated with human diseases, with local and distal injuries and cell dysfunction. The recognition of changes in gut microbiome composition and diversity is strategic, not only for deciphering the pathogenetic mechanisms promoting the development of many diseases, such as neurodevelopmental and neurodegenerative disorders, autoimmune diseases, infectious diseases, and many other chronic diseases, but also for improving the care of these patients by restoring the microbial homeostasis. Indeed, gut dysbiosis is deleterious because it promotes inflammation, reduction in beneficial bacterial metabolites, such as short-chain fatty acids, alterations of the gut-brain axis, and incomplete digestion of food. In our clinical laboratory, gut microbiota is usually investigated both by metagenomics and microbial culture; the report contains a graphical representation of the microbial composition, the quantitative determination of the most important bacterial strains, and a narrative comment facilitating the interpretation of the results by the general practitioner and the patient.

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LECT 11

ARTIFICIAL INTELLIGENCE IN MEDICINE

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"The use of artificial intelligence in medicine has the potential to make significant improvements in the diagnosis, treatment and management of disease. Artificial intelligence technologies such as machine learning can analyze large amounts of medical data, including test results, diagnostic images and patients' medical histories. This can enable physicians to gain a more complete and accurate view of a patient's situation, helping them in the early detection of diseases and selection of the most appropriate treatments". This text was produced by GCP (Gougle Cloud Platform) and is sure to cause discussion. To walk the bumpy path between techno-enthusiasts and techno-skeptics is to ask the question of how to govern the transformation, that is, how to ensure that the human remains at the center of the digital revolution. On the other hand, it is inevitable that the future of medicine will be based on the use of artificial intelligence, because biology is too complex for humans to understand. Today, artificial intelligence in medicine accounts for only 3 percent of its use in human activities, a negligible percentage, although one that is clearly on the rise. Many physicians fear confrontation with artificial intelligence, but as Bertalan Mesko states, "physicians will not be replaced by artificial intelligence, but those who use it will take the place of those who do not". We can say that machine learning often makes more consistent decisions than humans, so much so that on the board of a Hong Kong biotechnology investment company sits VITAL, which stands for Validating Investment Tool for Advancing Life science. He is an algorithm and his opinion carries the same weight as that of the other five (human) members of the board. It might be interesting to consider a similar perspective in medicine as well. Paradoxically, the centrality of machines will put humans back at the center, called to imagine a future in which machines and progress are at the service of the person's happiness, relationships, and freedom. What if, before asking ourselves what ethics machines should respond to, we went back to questioning our own ethics? About our values? Because, in the end, it does not matter how powerful this technology is, but what matters is that human relationships remain at the center of society, pushing us to do good toward others, as Fei-Fei Li says. I conclude with a quote from Antony Gervin Oettinger: "The issues surrounding artificial intelligence are too scientific in nature to be left to philosophers alone. But, on the other hand, they are also too philosophical in nature to leave them to scientists alone".

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LECT 12

ARTIFICIAL INTELLIGENCE IN MEDICINE: APPLICATION EXAMPLES

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Artificial intelligence (AI) represents a novel technical discipline employing computer technology to explore and develop theories, methods, techniques, and application systems aimed at simulating, extending, and amplifying human intelligence. A significant part of artificial intelligence is machine learning, of which there are 3 main types – supervised learning, unsupervised learning, and reinforcement learning [1]. The advent of new AI technologies has ushered in profound changes within the conventional medical landscape. For instance, the process of diagnosing patients through radiological, pathological and biochemical examinations has been markedly improved, leading to heightened diagnostic accuracy and reduced human workload. Recently, AI has garnered significant attention, primarily within the healthcare and medical domains. Its applications span disease detection, coordination of referrals, service provision, pharmaceutical innovation, predictive analytics, and decision augmentation, resulting in substantial transformations in certain facets of patient care. Research in AI has showcased a more promising output-input ratio in the realm of medicine compared to other fields. The synergy between AI and medicine is reshaping the conventional health-

care model, heralding a revolutionary advancement [2].

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LECT 13

THE IMPERFECT BEAUTY

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Physical appearance and beauty act as pervasive and powerful agents, energetically orienting the evaluation of the surrounding world, the perception of ourselves and the others. The recent emphasis on platform communications and image sharing produced an increasing interest in idealized physical looks. Automated analysis and machine-learning algorithms have been developed to digitally enhance human physical attractiveness in platform image sharing, computer-assisted online search of partners, etc. In the contemporary social context, the struggle for "beauty", rather than being just a joyful entertainment, turned to be an obsessive task, a challenge for an unattainable beauty, as the ongoing tremendous demand for cosmetic surgery stands for. In present times, social media developed as to become one of the most important factors contributing to the mental, emotional, physical and spiritual health of individuals. Constantly portraying ideal beauty and body image comparisons, beauty choices are globally affected. More interactive than traditional media, they trigger more compelling effects in the definition of "universal beauty standards". They contribute to the development of body dissatisfaction and body image disturbances, linked to depression, body image anxieties and long-standing mental health dysfunctions [1]. As a general outcome, people using the retouching filters on their social threads surrender, preferring to look like their retouched self. Cosmetic industries have immensely benefited from the increasing popularity of social media, determining the development of beauty apps, based on augmented reality and artificial intelligence. Cases of teenagers discussing the idea of getting plastic/cosmetic surgery to look more like the beautified filtered version of themselves increased enormously, confirming the pervasive nature of filtered self-taken images and their attitude to trigger a "body dysmorphic disorder" [2]. The quality of life of the young generation would probably prosper once the struggle for an unattainable flawless beauty would be driven toward a universally appreciated, flawed and imperfect humanity [3].

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LECT 14

ARTIFICIAL INTELLIGENCE: FROM POST-PARTUM DEPRESSION TO EXPOSOMICS

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The human voice is a complex and fascinating phenomenon, the result of an intricate biological and physiological process. It can be defined through several characteristics.

1. Fundamental frequency: this is the number of cycles of vocal cord vibration per second (Hertz). In adult men, it typically ranges from 80 to 180 Hz, while in adult women, it ranges from 165 to 255 Hz. (This difference may have an evolutionary role?) It is even higher in children.
2. Harmonics: these are whole-number multiples of the fundamental frequency and contribute to the timbral complexity of the voice.
3. Rhythm: this refers to the temporal pattern of speech, including the duration of pauses and the rhythm of spoken syllables. It can vary significantly between languages and can influence how speech is interpreted.
4. Intonation: this refers to the melodic variation in speech; intonation can change the meaning of a sentence, indicating whether it is a question or a statement.
5. Volume.
6. Expressive dynamics.
7. Articulation.
8. Pronunciation.
9. Timbre: this is a distinctive characteristic of each person's voice and represents a unique footprint.

10. Emotional expression: the voice can convey emotions, often unconsciously, making it a vehicle for expressing feelings.

We have just demonstrated that it is possible to teach an algorithm to recognize emotional states from the voice. The question is, what other knowledge can we discover within the human voice? Can we identify early markers for neurodegenerative diseases, mental health conditions, respiratory disorders, acid reflux, or even aging? This vast field of research is made possible through AI. The human voice also serves as a sentinel for the continuous interaction of the human body with its surrounding environment (Exposomics).

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