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Lectures

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LECT 1

PULSE OXIMETRY IN CRITICAL AND SEVERE CONGENITAL HEART DISEASE

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Congenital Heart Diseases (CHD) are the most prevalent newborn malformation. Recently, prevalence showed an increase of 1.2/100 births in the general population [1]. CHD are responsible for high morbidity and mortality. When treated by a multidisciplinary, highly trained team of specialists, most patients became chronically ill with various other conditions besides the cardiovascular system for the rest of their life expectancy, explaining why caring for CHD is a very costly (expensive) task that not all countries can sustain [2].

CHD severity for early morbidity and mortality is classified in severe (s-CHD), critical (c-CHD) and ordinary risk cases. Furthermore, studies have shown up to a 25% misdiagnosed rate even in centers where fetal echocardiography is available.

We aim to draw attention to the use of pulse oximetry when combined with a "late as possible" medical history and physical examination, achieving the most of early detection of them.

In an ideal world, the population would be offering all the diagnostic methods we have for every pregnancy. These include a detailed medical history of the period just before consumption to rule out any hazards regarding the pregnancy, a thorough obstetrical follow-up of the pregnancy, a monthly scan of the fetus, development, a first-trimester nuchal translucency measurement and a 20-week anomaly scan. The fetal cardiac assessment will have been offered based on the indications from the obstetrical follow-up and the last two tests. Finally, if any significant suspicion or proof for any s-CHD or c-CHD, the delivery could occur in a hospital near a center that treats CHD. As this is only ideal, the use of pulse oximetry (POX) can bridge the lack of many of the previously mentioned diagnostic methods [3].

We have adopted a twice-simultaneously measurement of POX for term neonates. Firstly, after the first day of life, with a preductal (right hand) and postductal (any leg). The second measurement is done as "late as possible", depending on the policy regarding the duration of inpatient stay after delivery. Ideally, in many studies, this is a 72-hour period, postdelivery [2].

The normal cut of saturation of oxygen ($SatO_2$) would be in both measurements 95% and above, and a difference between the upper and lower measurements must be less than 3%. The test can be applied using an accurate pulse oximeter by anyone without special training in a time frame of 3 and a half to 9 minutes. Studies from the USA estimate the cost-effectiveness of this method from $5-14 per infant screened, estimating that $40,385 per life-year is potentially gained through screening [2].

POX screening offers an additional benefit in diagnosing acute respiratory distress syndrome, persistent pulmonary hypertension of the neonates, transient respiratory distress, and early-onset bacterial sepsis [2].

While we are still searching for the "Holy Grail" of CHD prevention, POX has proven to be an accurate and reliable postnatal tool. When integrated with clinical assessment (using accurate perfusion index in the future), POX constitutes the trustiest early detection screening test today [2].

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LECT 2

MACRONUTRIENTS AND MICRONUTRIENTS THROUGH GROWTH AND DEVELOPMENT

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Nutrition is essential for human growth, particularly among newborns, toddlers and adolescents when the body significantly changes, and diet can have a direct and visible impact on life. A correct growth has to be supported by correct nutrition, which has to ensure a proper amount of macronutrients and micronutrients. Macronutrients are commonly considered the compounds that humans consume in the largest quantities, and they are mainly classified in carbohydrates, proteins, fats, fibers and liquids. Instead, micronutrients are introduced in small quantities through the diet, but they are still necessary for adequate growth in the pediatric age. They include both organic and inorganic compounds and are principally represented by vitamins (both fat-soluble and water-soluble ones) and the great variety of trace minerals in foods, such as iron, zinc, iodine, selenium and fluoride. Effects and functions of each micronutrient are crucial for health, and the lack of even a single one of these elements can have important consequences on life, particularly in the long term, impairing growth, delaying body maturation or determining deficiency-related diseases.

Furthermore, each period of the pediatric age has its specific nutritional special needs. Growth is rapid during the first 6 months of life, and breast milk, despite relatively small amounts of some macro- or micronutrients, can fulfill growth and development optimally. Growth is very rapid at this stage: at 6 months, the birth weight is usually already doubled since the moment of birth, with an average length increase of 15 cm. A nutritional assessment in the first 6 months requires strict observation of feeding and growth: it is recommended to weigh the infant every week in this period to assess whether the feeding is sufficient to ensure proper growth.

Weaning, corresponding to the introduction of complementary feeding and which should begin between the age of 4 to 6 months, increases the risk of a possible unbalanced diet, and the pediatrician should support the family during this process. Further evidence suggests that this period not only could influence the initial stages of life but could also impact the pathogenesis of obesity and subsequent diseases even in adolescence and adult life.

In the first years of life, both growth and development are highly influenced by the nutritional balance in terms of macronutrients and micronutrients. Deficiencies of some micronutrients such as iron or folate may be the cause of anemias. On the other hand, the excess of nutrients such as proteins and milk-based products may be related to overweight and obesity during childhood and adolescence, with a high risk of tracking through adulthood.

With the puberty onset, indeed, a rapid increase in height and weight can be observed, and sexual maturation is performed: these changes need a proportional and balanced supply of specific macronutrients and micronutrients due to possible undernutrition, which could delay sexual maturation, or possible overfeeding, which could lead to obesity, diabetes and subsequent cardiovascular diseases in the long term. Adolescence then represents another fundamental period of growth, in which a significant and quick spurt and bone mass increase occur and where a proper macro- and micro-nutritional intake has to be achieved through a correct and balanced diet.

In order to support all the physiological processes of different ages, a deep knowledge of the specific nutritional needs of the young and how they change according to their age and health status is a fundamental tool of the clinical practice and should be possessed by the clinician.

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LECT 3

NEONATAL PERSISTENT PULMONARY HYPERTENSION: iNO FOR EVERYBODY?

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SIBEN – The Iberoamerican Society of Neonatology

Persistent pulmonary hypertension of the newborn (PPHN) occurs when the pulmonary vascular

resistance remains abnormally high and results in low pulmonary flow with or without right-to-left shunt through the ductus arteriosus or the foramen ovale. Extrapulmonary shunts (PDA and PFO) allow for right-to-left shunting and hypoxemia. It is characterized by refractory hypoxemia and is frequently associated with decreased systemic vascular resistance and low cardiac output because of increased afterload of the right ventricle, decreased pulmonary blood flow, decreased venous return to the left atrium, and severe myocardial dysfunction that compromises tissue oxygenation and threatens the life of the newborn. It can affect up to 10% of all newborns admitted to the NICU, and it is estimated that 7% to 20% of newborns who survive PPHN can develop short- or long-term problems. The literature reports an overall mortality rate between 10% and 20% – and between 10% and 50% in developing countries. We have previously described an abnormal gene expression causing vasoreactivity and vascular remodeling characteristic of PPHN [1]. This talk will summarize the recommendations of the 6th Clinical Consensus on PPHN of the Iberoamerican Society of Neonatology (SIBEN) [2]. It will describe the etiology, pathophysiology, and treatment (including maintaining the optimal oxygenation, alveolar ventilation, optimal perfusion, and use of pulmonary vasodilators, such as inhaled nitric oxide [iNO] and sildenafil). Other modalities, including the use of prostaglandins, milrinone, bosentan (as vasodilators), glucocorticoids (as anti-inflammatory), seem to have potential benefits. Newer drugs, including soluble guanylyl cyclase (sGC) activators, Rho-kinase inhibitors, recombinant human SOD (rhSOD), are being studied to understand their possible use in newborns [3]. Lately, the availability of functional echocardiography is allowing the evaluation of the effects of the treatments, not only making a quick diagnosis but perhaps guiding the therapies instituted. The future treatment of PPHN will probably include multiple pharmacological strategies – but without forgetting the basic pathophysiology. Most importantly, we need to remember what must NOT be done, like alkalosis, hyperoxygenation and hyperventilation [4].

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LECT 4

SLEEP DISTURBANCES IN THE NICU GRADUATE

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Prematurely born infants are inordinately susceptible to perturbations in their respiratory patterning. Such instability is multifactorial and can result in a variety of phenotypic manifestations that if recurrent, may lead to substantial morbidity and potentially mortality. As such, improved understanding of the mechanisms underlying respiratory pathology and the precipitating factors of such pathology are critical to address and prevent their morbid consequences. In this contextual setting, the emergence of apnea is a prominent and frequent event that requires a thorough assessment of its upstream etiology and familiarity with the clinical diagnostic evaluation and management. Since sleep states are vulnerable states in which apnea risk is markedly increased, improved knowledge on sleep regulation and homeostasis while infants are being treated in the NICU and after discharge to home is necessary to the process of clinical decision-making, and for precise recognition of the specific types of apnea and other autonomic consequences (e.g., arousal, tachycardia, bradycardia). Finally, disruptions in the maturation and phasing of the circadian clock system can further aggravate exiting propensities for apnea brought about by the prolonged dismaturity of the central and peripheral chemosensory pathways along with many of the neural reflexes mediating respiratory rhythm generation and neuromuscular reflexes of the upper airway. In this lecture, a review of the hierarchical constructs that enable a systematic assessment of the NICU graduate regarding sleep architecture and respiratory stability will be presented.

LECT 5

CAN WE BETTER TAILOR SURFACTANT THERAPY IN 2021?

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Despite the increased survival even at gestational ages at the limit of viability, the Respiratory Distress Syndrome (RDS) and the associated complications still represent a major problem in the Neonatal Intensive Care Unit. The current gold standard for management combines early CPAP with surfactant administration. Surfactant therapy effectively improves survival and reduces important morbidities such as air leaks and death or bronchopulmonary dysplasia. The research on surfactant therapy has progressed in the last few years, from creating synthetic preparation to new, "less invasive" methods for its administration, such as the Less Invasive Surfactant Administration (LISA) pharyngeal installation or nebulization. However, the decision about surfactant therapy administration according to international guidelines still relies only on oxygenation. However, different factors may influence the oxygen requirement at birth, such as hemodynamic impairment, thermoregulation, infections. Also, some infants may compensate for hypoxia by increasing their work of breathing and possibly delaying surfactant therapy. Metanalysis showed that surfactant therapy is more effective if given early during life.
Moreover, surfactant therapy is expensive and may be associated with complications secondary to administration (trauma, pain, need for sedation, hemodynamic instability). We will review new approaches to surfactant therapy in order to optimize its administration to preterm infants. Lung ultrasounds have become a widespread tool for assessing lung imaging at the bedside, and trials already evaluated its role for tailoring surfactant therapy. Biochemical tests such as the lamellar body counts, the stable microbubble tests and surfactant absorption tests also have been applied in clinical settings, but they still require further industrial development before becoming bedside diagnostic tools. The electrical impedance tomography evaluation of lung recruitment status is a promising tool but reported in single case reports. Finally, noninvasive oscillatory mechanics have become a bedside tool, and studies on its application for individualizing surfactant are ongoing.

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LECT 6

PRESEPSIN AND OTHER BIOMARKERS OF SEPSIS

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Sepsis has been recently defined as a "life-threatening organ dysfunction caused by a dysregulated host response to infection" [1]. This devasting syndrome is marked by the early activation of both pro- and anti-inflammatory responses leading to an inappropriate and excessively activated response of the complement system, and an imbalance of the homeostasis of coagulation and fibrinolysis causing an early hypercoagulability, followed by hypocoagulability, disseminated intravascular coagulopathy (DIC), microvascular thrombosis, multi-organ progressive failure, and ultimately death. In the neonatal age, sepsis remains the most frequent cause of death, especially in premature neonates. According to the Global Burden of Disease (GBD), the annual incident cases of neonatal sepsis are estimated at approximately 937 cases per 100,000 live births (1.3 million), and 203,000 neonatal deaths are sepsis-attributable [2]. In low-income and middle-income countries, the

prevalence of neonatal sepsis is higher, and every year over a million babies die within the first month of their lives in Sub-Saharan Africa and South Asia. A recent meta-analysis including 26 studies from 14 countries has reported a pooled neonatal sepsis incidence of 2.82%, with a mortality rate of 17.6% [3]. Neonatal sepsis is more than sepsis in adults; firstly, neonates are developmentally immature and thus more susceptible to systemic complications; secondly, neonatal sepsis is a highly dynamic and heterogeneous condition requiring an individualized approach. The most important factor reducing the risk of septic shock and death is the very early diagnosis of the disease; indeed, a prompt, targeted therapeutic intervention limits the progression and the severity of the disease. One-hour delay inappropriate antimicrobial therapy corresponds to an increase in the mortality rate of approximately 7-10%. Beyond the perinatal history and the recording of clinical signs, almost always nonspecific, laboratory medicine plays a crucial role in the early diagnosis of neonatal sepsis. Currently, multiple available molecular techniques enable accurate and rapid etiological diagnosis; however, they are expensive and require both innovative technology and professional expertise. Historically, biochemical markers have been widely used for the early diagnosis of neonatal sepsis; for example, C-reactive protein (CRP) and procalcitonin (PCT) remain basic laboratory tests for sepsis in Neonatal Intensive Care Units (NICUs). Unfortunately, most biomarkers show severe limitations in sensitivity or specificity, hampering the accurate and rapid diagnosis. An ideal biomarker should be near 100% sensitive and specific and discriminate infectious from inflammatory diseases. Over the past 10 years, the literature has proposed an endless list of candidate biomarkers for sepsis; most of them cannot be measured timely and by reliable methods in the routine clinical laboratory. Early studies observed that in patients with multiple organ failure, the 55 kDa soluble fraction of the membrane cluster of differentiation 14 (sCD14) significantly increases; later, it was found that a 13 kDa truncated form of sCD14, consisting of 64 amino acid residues, increases in the bloodstream during systemic infections and sepsis. This truncated form, named soluble CD14 subtype (sCD14-ST) or presepsin, is also directly synthesized and secreted by the liver during sepsis and inflammation; in particular, sCD14-ST demonstrates high sensitivity and the blood level increases at the very early stages of neonatal sepsis. In the blood of babies without sepsis or inflammation, sCD14-ST can vary approximately between 300-500 ng/L, depending on gestational age, neonatal hypoxia, and other perinatal variables. A commercially available chemiluminescent enzyme immunoassay (CLEIA), based on a non-competitive CLEIA combined with Magtration® technology, allows rapid and accurate measurement of sCD14-ST. The method requires whole blood as a biological matrix and is optimized on an automated immunoassay analyzer (PATHFAST™, Gepa Diagnostics, Milan, Italy). The method can be used in emergencies and even at the bedside since the turn-around time (TAT) is less than one hour. Various clinical studies have tested sCD14-ST in clinical practice, establishing reference ranges and cutoff levels [4]. In particular, sCD14-ST discriminates neonates with septic shock from those with sepsis at the onset of clinical signs of sepsis (median levels: 1,557 ng/L and 1,361 ng/L, respectively); by using a group of infected neonates without any evolution to sepsis, sCD14-ST sensitivity was 84% for sepsis and 83% for septic shock, while the specificity was 55% and 64%, respectively [5]. In that study, at the onset of symptoms, sCD14-ST blood levels correlated with the severity of the disease over the next 48 hours. These results are different from those published previously [4]; in that study, in neonatal bacterial sepsis, an sCD14-ST cutoff value of 548 ng/L showed a 100% sensitivity and 81.2% specificity, while a cutoff of 600 ng/L showed a 97.5% sensitivity and 100% specificity. However, differences in baby cohorts, criteria for sepsis diagnosis, and sampling time could significantly affect these discrepancies. In conclusion, sCD14-ST is a very sensitive and specific biomarker for diagnosing and monitoring neonatal sepsis.

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LECT 7

ENVIRONMENT, FETAL EPIGENETIC PROGRAMMING AND PREVENTION OF CHRONIC DISEASES

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In recent decades, the global epidemiological landscape has undergone an impressive change, consisting in a completely unexpected epidemiological transition, characterized by the rapid and continuous increase, at an ever-younger age, of all chronic-degenerative inflammatory and neoplastic diseases, which affect all organs, tissues and systems: endocrine and metabolic disorders (pandemics of obesity and diabetes); disorders of the immunocompetent system (allergies and autoimmune diseases); neurodevelopmental disorders (autism), neuropsychiatric and neurodegenerative diseases (Alzheimer's disease); cardiovascular diseases; neoplastic diseases.

This epidemiological transition represents an unprecedented public health problem and requires an urgent change in the biomedical approach. In fact, it cannot be interpreted simply with changes in lifestyles and even less with hypothetical genetic modifications (which have never been found, moreover).

The British epidemiologist David Barker was the first scientist to fully understand the importance of the fetal period in influencing human health and disease.

The growing attention on embryo-fetal events has redirected scientists' attention to epigenetics, a theory formulated by the British geneticist Waddington in the 1940s and underrated for decades. This entailed a radical change of perspective, according to which, if we wanted to intervene in time on the epidemiological transition underway, effective primary prevention strategies aimed at the preconception period, pregnancy and the first years of life would be necessary and urgent.

The fundamental change of perspective, in this context, mainly concerns a reconsideration of the genome as an open, fluid and complex system capable of processing information coming from the outside and transforming itself accordingly. The whole system should be considered open, in the sense that by continuously receiving chemical-physical information, it can process them and transform itself, at first the software, the epigenome, afterward even the hardware (the DNA sequence); fluid, because, by continuously changing, it can transmit ongoing changing information, both physical, in the form of endogenous electromagnetic fields, and biochemical, in the form of signal proteins and miRNAs, to correspond to the needs of the whole organism; complex, as it is made up of millions of molecules in continuous interaction and of complex circuits capable of activating or inactivating by means of positive and negative feedback mechanisms... within an organism composed of millions of integrated and communicating cells and in continuous transformation.

Already from these brief hints, it is possible to deduce that the complexity and variety of human phenotypes are always infinitely greater than that of DNA and other biomolecules. Their variations, both in the physiological and pathological fields, are infinitely more complex than those of the genotype. In today's dominant bio-evolutionary and biomedical model, the phenotypic transformations of organisms ensure fortuitous, random, stochastic changes in the DNA sequence rewarded by natural selection. However, modern molecular biology and in particular the Genome Project (ENCODE) require changing this linear model to acquire a systemic one.

It should be evident that adopting such a systemic view in the context of molecular biology would mean completely changing the model: like every organism, so every biomolecule and in particular the whole genome should not be considered as linear sequences of information (essentially transcribable into mRNA and, ultimately, into proteins), but precisely as complex, open, plastic molecular systems, capable of processing information coming from the outside and consequently transforming themselves in an adaptive and even predictive way, especially in the early stages of life. In this sense, particularly, the adaptive-predictive modifications of the embryo-fetal epigenome (fetal programming) that pave the way for chronic diseases are of enormous interest and should be evaluated with great attention.

LECT 8

BRONCHIOLITIS: LONG-TERM CONSEQUENCES

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Bronchiolitis is a common respiratory tract infection in infants and children. The most frequent cause is Respiratory Syncytial Virus (RSV), constantly being the leading cause of hospitalization in previously healthy infants during the first year of life (0.5-2.0% of cases) [1]. It is well known that RSV lower respiratory tract infection in infants is linked to subsequent recurrent wheezing and asthma in childhood [2]. Piedimonte in 2013 showed how RSV could play an essential role in the inception of asthma, involving the persistence of the latent virus in extrapulmonary tissues [2]. More recently, Zhou et al. in a 425 patients series showed how RSV bronchiolitis might increase the incidence of recurrent wheezing and asthma; allergy, cesarean section and older onset age seem to be risk factors for developing asthma in childhood for these patients [3]. In this study of 425 patients, 266 cases completed the entire follow-up: 165 patients completely recovered, while 36 were in the recurrent wheezing group and 65 in the asthma group. The age of onset was higher in the asthma group than in the completely recovered group ($P < 0.05$), and the proportion of cesarean section was higher in the recurrent wheezing group than that in the completely recovered group ($P < 0.05$) [3]. Prevention of RSV infection is a crucial priority of the WHO, and the monoclonal antibody palivizumab is the only currently licensed for the prevention of severe RSV infection in high-risk infants [4]. When a cost-effectiveness analysis of RSV prophylaxis is done, long-term consequences of RSV bronchiolitis must be considered for the correct calculation of incremental cost-effectiveness ratios (ICERs) for each quality-adjusted life-year (QALY). If the time of follow-up for such analysis will be longer (at least 6 years), the cost-effectiveness of monoclonal prophylaxis will be much more effective when compared with a shorter time follow-up (1 year). Such a difference is due mainly to the long-term consequences such as recurrent wheezing and/or asthma. Blanken et al. in 2013 published the double-blind, placebo-controlled MAKI trial enrolling 429 preterm infants born at a gestational age of 33 to 35 weeks to receive either monthly palivizumab or placebo [5]. In this study, the authors concluded that in otherwise healthy preterm infants, palivizumab resulted in a significant reduction in wheezing days during the first year of life [5].

In conclusion, there are very strong pieces of evidence that RSV bronchiolitis causes long-term consequences not only in terms of respiratory symptoms such as recurrent wheezing and asthma but also hospitalization and costs for public health services. In this direction, prophylaxis continues to be the strongest way to improve long-term outcomes.

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LECT 9

INTRAUTERINE GROWTH RESTRICTION: CLINICAL CONSEQUENCES ON HEALTH AT ADULTHOOD

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As various other conditions of early life chronic stress, intrauterine growth restriction (IUGR) leads worldwide to significant perinatal morbidity and mortality and an increased propensity to chronic, non-communicable diseases in adulthood. Such diseases include metabolic, cardiovascular,

renal, neurologic and psychic disorders. Animal models help decipher the underlying mechanisms, which are surprisingly similar to those at work in opposite conditions of altered developmental programming, such as maternal overweight, obesity and hyperglycemia in pregnancy [1]. Altered vasculogenesis, with a risk for organ development and hypertension, altered vascular endothelium-dependent vasodilating capacity, arterial stiffness, nephron number reduction [2], insulin resistance of insufficiency have been found as key actors in both types of early malnutrition, either deficit or excess. Accelerated cell senescence due to oxidative stress appears as a common cause of altered developmental programming in many biologic systems, including the immune system [3], in various species. There is increasing evidence that epigenetic changes such as altered DNA methylation, histones posttranslational modifications, and non-coding RNAs intervene as a molecular basis to link altered nutritional exposures in early life and long-term disease. Moreover, such altered early imprinting is transgenerationally inheritable.

IUGR, as a major perinatal syndrome due to either maternal malnutrition or uteroplacental insufficiency, reveals as a model of the early conditioning of the allostatic risk encountered over the life course and increased risk for later disease in the general population.

Lessons learned from the long-term consequences of IUGR and their mechanisms open the field of early prevention of non-infectious diseases, which are currently the major cause of premature death, morbidity and economic burden in the world, including in low-income countries. Influencing positively lifestyles, optimizing maternal nutrition and limiting psycho-social vulnerability and stress can change the game in promoting global health as well as fighting IUGR. Efforts should be personalized and target early life, reproduction, mother and infant health by means of information, education, and continuing social support.

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LECT 10

NEONATOLOGY: A YOUNG SCIENCE

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In Biblical times, women were assisted by other women to stand on two bricks placed underneath their feet. The stones were dubbed "birthing bricks" and helped the midwife or assistant have extra room to catch the baby. Births in the Middle Ages were assisted exclusively by midwives since men generally considered it uncouth to set foot in the delivery room. Of course, this included the doctors since they were men. Physicians interested in the newborn were evident in the 19th century, but most were obstetricians. The idea that premature infants could be treated was probably introduced in the second half of the 19th century. Today it is hard to believe that only a century ago, most sickly and premature infants were sent home from the hospital without any special interventions; many of these children did not survive past their first birthday. The first Neonatal Intensive Care Units did not even appear in American hospitals until 1922; however, special care methods for infants began to be developed in the late 19th century. Pierre-Constant Budin, a French obstetrician, was a pioneer in the care of at-risk babies and in reducing infant mortality. He encouraged educating new mothers about proper nutrition and hygiene for their babies. Knowing the risks contaminated cow's milk could pose to newborns, urged the use of breast milk instead of cow's milk. He also brought gavage – the process of feeding through a tube that went directly to the stomach – into the spotlight, helping premature infants who were unable to feed normally receive the nutrition they needed. Martin Arthur Couney (1869-1950), a Polish advocate, first recognized the potential of incubators for helping premature babies. He was a pioneer of early neonatal technology. Couney, also known as "Doctor Incubator", offered this type of treatment for premature infants free of charge. Babies were shown for the public amusement in a park sideshow, "The Infantorium", where visitors paid 25 cents to see prematurely born babies exposed in incubators.

J.W. Ballantyne in 1923 was the first to recognize that "There is need for specialization in neonatal medicine. This applies to doctors and nurses as well as teaching and construction of hospitals. The specialist in neonatal diseases and the nurse intensively trained and expert in the management of delicate newborns will be commonplace here long". Neonatology is a young science. According to Mary Ellen Avery, "All neonatologists must be pioneers by definition because we are now looking after infants who would not have survived before". In the early 1950s, Virginia Apgar proposed a standardized assessment at birth. The Apgar score remains a valuable predictor of babies who will need ongoing support and those at higher risk of mortality. In the mid-1950s preterm infants who died after several days were found to have histologic evidence of hyaline membranes in the lungs at postmortem examination. They were considered to have hyaline membrane disease (HMD). Mary Ellen Avery and Jere Mead showed in 1959 that this disorder was linked to a deficiency of surfactant in lung fluid. In 1960 the term "neonatology" was coined and was attributed to Alexander Schaffer, who used the term in the introduction to the first edition of his book. Modern neonatology had a large impulse after Patrick Bouvier Kennedy, born premature, died after 39 hours of life on August 7, 1963; Patrick was born about 37 weeks, weighing 4 pounds, 10 ½ ounces (2,100 g). One of the doctors to receive a call from Patrick Kennedy's doctors was a young pediatrician from Toronto Children's Hospital, Dr. Maria Delivoria-Papadopoulos, who is today considered the "Mother of Neonatology".

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LECT 11

WHAT IS NEXT FOR PEDIATRICS AFTER COVID-19?

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The COVID-19 pandemic highlighted several critical issues related to the pediatric age, both in terms of social inequalities and the need to reorganize pediatric care and training pediatricians. Data relating to social inequalities in Italy are worrying, especially referring to the post-pandemic period. The territorial disparity between the North and the South of the country is significant and regards access to healthcare, education, and adequate living conditions. Most of the children in disadvantaged conditions live in the South of Italy, where the risk of social exclusion is extremely high in one of the most important periods of emotional and psychological development, with deleterious long-term consequences. As pediatricians, we are obliged to act and submit concrete proposals to the Institutions to guarantee every child the same right to health and education, regardless of the family and the region of origin.

In addition, the progressive reduction of funds for healthcare that characterized the last few decades determined the profound suffering of the National Health System (NHS), which became particularly clear during the COVID-19 pandemic. In fact, general practitioners and pediatricians have been overwhelmed by the care burden. It is, therefore, necessary to rethink the structure of our NHS, defining new models of care-networks that will replace those currently existing, no longer suited to the needs of our population. The reorganization of our healthcare system needs to be associated with a reorganization of the training of pediatricians due to the collapse in the number of specialists that will further worsen in the future.

It is mandatory to guarantee the right of all subjects of developmental age to be assisted by a pediatrician. In fact, it is frequent that children are evaluated by specialists in the care of adults due to the lack of pediatricians. It is, therefore, crucial to reshaping university and specialist training programs, enhancing the most deficient areas based on territorial needs.

LECT 12

CLINICAL FEATURES OF CHILDREN AND ADOLESCENTS WITH COVID-19: THE EXPERIENCE OF A TERTIARY PEDIATRIC HOSPITAL

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) affects people of any age with the highest mortality and morbidity in adult patients older than 65 years [1]. Reports on pediatric COVID-19 highlighted that children generally are asymptomatic or develop milder symptoms compared to adults [2, 3]. To date, a few pediatric Italian case series have been reported [4]. We aimed to assess the epidemiological and clinical features of children and adolescents hospitalized at our Pediatric Clinic for SARS-CoV-2 infection.

METHODS

We conducted a retrospective observational study enrolling pediatric patients with COVID-19 hospitalized at the Pediatric Hospital of Pavia, Italy, between February 1, 2020, and April 30, 2021. We mostly collected clinical and epidemiological data.

RESULTS

Seventy-one patients aged 0-16 years were included in the study. Thirty-three (46%) were females and 38 (54%) males. Thirty-three (46%) patients had other coexisting chronic diseases, such as obesity and onco-hematological diseases. Thirty-one (44%) children were exposed to COVID-19-positive household members and acquired the disease at home. Nine (12.7%) patients were asymptomatic, whereas 57 (80.3%) had a mild-moderate disease. Only five (7%) patients showed a severe or critical disease, and two patients required ICU admission. The most frequent symptoms were pyrexia (76%), loss of appetite (26%), gastrointestinal symptoms (19%), and cough (19%). Chest X-ray was performed in 42 patients and showed abnormal findings in more than half of symptomatic patients. The most common laboratory features were lymphopenia and eosinopenia associated with high levels of inflammation markers.

CONCLUSIONS

This study confirmed that pediatric COVID-19 has a mild-moderate course compared to adults, as reported in the literature about COVID-19 in pediatric age [2, 3].

This study also confirms how it is important analyzing every clinical information to determine the categories of disease severity and assess the risk of severe evolution. Coexisting chronic diseases, age and laboratory findings, such as lymphopenia, eosinopenia, and RCP elevation, are considered the main predictive factors of severe COVID-19. This evaluation of patients allows a prudent and personalized therapeutic strategy to offer each patient the optimal target management. Finally, the study offers a wide panoramic of COVID-19 clinics and management in pediatric age, starting from the experience gained by a Northern Italian reference center for the disease, contributing to improve clinical practice.

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LECT 13

WEANING: FROM RESPONSIVE FEEDING TO MODULATION OF CHILDREN'S FOOD PREFERENCES

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"Feeding times are period of learning and love", reads the Global strategy for infant and young child feeding made by the World Health Organization (WHO) [1]. These are the assumptions that, combining the principles of psycho-social care with the most recent discoveries in the nutritional field, have placed responsive feeding as an indispensable condition for a good approach to complementary nutrition. Therefore, in trying to provide every child with the best possible nutrition, what is fed is certainly important, but it is not possible to overlook how, when, where and by whom is fed [2]. In this context, the family plays a decisive role, not only in creating a positive environment during the meal. This means that the unique times of each child are respected; they are encouraged to eat without ever forcing them and possible distractions are minimized. Furthermore, during the meals their

food preferences are forged [1]. In fact, scientific evidence regarding the modulation of children's taste preferences provides a possible guideline on the correct strategies to adopt. In this regard, four possible food-related developmental learning processes emerged from a recent systematic review of the literature [3]. One of the most important is familiarization, meaning the early and repeated exposure to a wide variety of foods, especially in the early stages of weaning. In later stages, there is the imitation and the example provided by the members of their families and other important people in their lives. Associative learning, to the state of current knowledge, does not seem to be an advantageous conditioning. Categorization, given the age of interest, is difficult to apply and requires further investigation. Some considerations about the innate taste preferences of children should be added to these purely methodological evaluations. Therefore, in the past, the need for survival has made the human beings more prone to the consumption of sweet foods to ensure a good energy supply leading to an innate repulsion for the bitter taste in order to prevent the consumption of possible poisonous substances. To date, the circumstances are very different, and the high availability of highly energetic and low-cost food does not make the innate taste preferences of the species more advantageous. However, human beings, with their adaptation ability, can modulate these preferences through exposure as effectively as earlier and repeated [4]. It therefore seems clear that the propensity towards the consumption of a certain food by children is strongly influenced by the ability to recognize that food as familiar, underlining the delicate role of weaning in establishing correct eating habits and in the formation of taste preferences. In this perspective the initial expressions of disgust towards some foods, especially vegetables, must not compromise the offer as part of a path of acceptance [4].

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LECT 14

MICROBIOME, METABOLOMICS AND WEANING DIET: WHAT IS THE CORRELATION?

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It is now well known the remarkable pervasive capacity of the molecules deriving from the metabolic activity of the intestinal bacterial flora, which seems to affect most of the organs of the human species [1]. In addition, the metabolic response to the diet itself seems to be influenced by the interaction of the host with the microbiome [2]. In this context, the high plasticity of the early stages of development is of particular interest. In fact, the weaning period represents a critical moment for the nascent intestinal microbiota due to the decrease in the contribution of breastfeeding to its development and physiology, which is now partially replaced by food-related stimulation. Moreover, in this period there is the simultaneous completion of the maturation of the adaptive immune response thanks to the antigenic load of the food itself [1]. The contribution of omics sciences, such as metabolomics, in this field can be important. A recent study [3] evaluated the metabolic impact of a probiotic, *Lactobacillus paracasei ssp. Paracasei*, during weaning. They showed both an increase in putrescine, potentially associated with the correct growth and maturation of the intestinal barrier, and a decrease in palmitoleic acid, recently related to visceral obesity in younger people. However, the dietary contribution was not evaluated in this research despite the fact that, as already demonstrated, it has an important metabolic impact especially on weight-related problems in children [2]. In fact, again thanks to the use of omics sciences, the important etiological contribution of intestinal dysbiosis in both simple childhood obesity and that with a genetic component, has been highlighted. It has also emerged the usefulness of dietary interventions, responsible for the transition from a dysbiotic microbiota to a eubiotic flora. In fact, a well-balanced diet appropriate to the age, sufficiently rich in complex carbohydrates and high in non-digestible carbohydrates seemed to favor the bacterial species producing beneficial substances from the fermentation of carbohydrates and to reduce the components producing toxic metabolites from fats and proteins [2]. It would

therefore be desirable to investigate the possible use of metabolomics during weaning in order to provide the best possible nutrition for each child, especially in critical periods of development such as the first thousand days of life.

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LECT 15

THORACIC ULTRASOUND IN NEWBORNS

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Lung ultrasound (LUS) has rapidly grown in the last few years in Neonatology. Evidence has recently been published on the use of LUS for differential diagnosis of neonatal respiratory distress, growing evidences show the role of LUS as a bedside tool.

LUNG ULTRASOUND AND DIAGNOSIS OF NEONATAL RESPIRATORY DISTRESS

Studies have used LUS to document the rapid liquid clearance from the lungs of a cohort of mostly term infants. The potential of LUS as a non-invasive technique to monitor the liquid clearance and anticipate the need of respiratory support after birth was assessed by our group in 2012 [1] in a cohort of 154 late preterm and term babies. Images were classified as type 1 (white lung image), type 2 (prevalence of comet-tail artifacts or B-lines) or type 3 profiles (prevalence of horizontal or A-lines). Shortly after birth, 14 neonates were assigned to the type 1, 46 to the type 2 and 94 to the type 3 profile. Within 36 hours there was a gradual shift from types 1 and 2 to type 3. LUS had a high accuracy in predicting NICU admission with a sensitivity of 77.7%, specificity of 100%, positive predictive value of 100% and negative predictive value of 97%. Since 2007, Copetti and Cattarossi showed that neonates with transient tachypnea had a white lung image and a regular pleural image at LUS whilst the classical LUS imaging of hyaline membrane disease (HMD) shows a white lung image with no spared areas and an irregular pleural surface. Also, small subpleural consolidations can be detected in HMD. LUS is also useful in detecting complications of HMD (hemorrhage, pneumothorax, pneumonia and atelectasis).

Piastra et al. in 2014 described 6 neonates with meconium aspiration syndrome. All patients showed interstitial involvement and coalescent or sparse consolidations, atelectasis and bronchograms. Findings changed overtime, maybe related to displacement of meconium in the lungs. Similar findings were also published by Liu et al. in 2016 in a larger cohort of 117 neonates with meconium aspiration syndrome.

In 2016 our group led the first international, prospective study on LUS diagnosis of tension pneumothorax in the neonate [2]. In 42 infants presenting with significant sudden decompensation, we showed that LUS has diagnostic accuracy for tension pneumothorax outperforming the clinical diagnosis; furthermore, LUS was performed earlier compared to chest radiography (5.3 ± 5.6 minutes versus 19 ± 11.7) and the drainage tube was positioned after the LUS scan but before chest X-ray for 9 neonates.

LUS findings related to pneumonia show areas of large lung consolidation with irregular margins and air bronchograms, pleural line abnormalities, and interstitial syndrome.

Chen et al. in 2017 showed that the routine application of LUS in NICU discovered 32 cases with clinical and ultrasound evidence of pneumonia not diagnosed by chest X-ray. LUS outperforming chest X-ray for diagnosis of pneumonia is well established in adult medicine.

Predicting those infants which will develop chronic lung disease (CLD) is an useful clinical information. In 1996, Avni showed that diffuse retrodiaphragmatic hyperechogenicity at LUS scan present in all the patients with HMD resolved except in those who were later diagnosed with CLD (oxygen dependency at day of life 28). In such neonates the day 18 was the earliest day where the persistence of the abnormal hyperechogenicity was observed in 100% of the patients presenting CLD at day 28.

FUNCTIONAL LUNG ULTRASOUND

Nowadays in NICU a functional approach may be used to link a specific LUS profile to a clinical decision. For the first time, in 2014 our group [3] in a cohort of 54 preterm neonates admitted to the NICU showed that bilateral type 1 LUS imaging predicts intubation and surfactant administration within 24 hours from scanning. Type 1 lung profile showed a high diagnostic accuracy compared to chest X-ray (sensitivity 88.9%, specificity 100%, positive predictive value 100%, and negative predictive value 94.7%). The LUS functional approach as a tool to individualize the level of respiratory support and the need for surfactant replacement has been confirmed subsequently by other research groups.

Brat et al. in 2015 correlated a LUS score to several indices of oxygenation and to the administration of surfactant. In neonates with gestational age < 34 weeks, a LUS score cutoff of 4 predicted surfactant administration with 100% sensitivity and 61% specificity. Similar conclusion with a similar LUS scoring system has been confirmed more recently by different research groups. In 2021 a multicenter study led by our group [4] showed that among FiO_2 level, $SatO_2/FiO_2$ ratio, LUS and Silverman scores as criteria for surfactant administration, the combination of $SatO_2/FiO_2$ and LUS had the highest predictive power (AUC 0.93) regardless of the gestational age. Finally, very recently in 2021, our group [5] in a multicenter study demonstrated that in preterm neonates affected by RDS, the LUS trajectory is gestational age dependent, significantly correlates with the oxygenation status, and predicts development of CLD.

CONCLUSION

In recent years LUS is engaging as a bed side tool for neonatologist not only for a descriptive approach to diagnose lung neonatal diseases but also as a tool allowing clinical decisions to tailor the therapeutic approach to each single neonate. The near future opens a scenario in which LUS may play a role not only for individualized surfactant administration but also for follow-up of respiratory failure and early prediction of bronchopulmonary dysplasia.

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LECT 16

PERINATAL ASPHYXIA: NEW EVIDENCE, WHAT WE KNOW, WHAT WE DO NOT KNOW

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After the meta-analysis conducted by Jacobs et al. in 2013 [1] of 11 RCTs comparing outcome in infants affected by moderate-severe hypoxic ischemic encephalopathy (HIE) treated or not treated with therapeutic hypothermia, no other RCTs have been published on the subject.

Unanswered questions, after this meta-analysis, include the role of cooling in infants with mild HIE, after 6 hours of life, in critically ill infants, in premature infants with HIE or in combination with other therapies.

Studies conducted over the past 10 years have addressed these issues. Here, I will focus on the long-term outcome of infants with mild HIE and the possible protective role of hypothermia in these cases.

Several studies report the risk of brain damage in infants with mild HIE [2-9]; however, their level of evidence tends to be low or very low due to the difficulty of accurately identifying the neurological characteristics of the study population. Indeed, many of the children classified as having mild HIE in these studies showed hypotonia, seizures, or neurophysiological abnormalities, which do not closely fit the definition of mild HIE provided by Sarnat and Sarnat [10]. To better understand this aspect, it should be remembered that the original study [10] classified the HIE in Sarnat I, with an invariably favorable prognosis, Sarnat II, with a poor prognosis in 50% of cases, and

Sarnat III, with an invariably poor prognosis, based on repeated neurological evaluations, performed at 12-24 hour intervals, up to 6 days of life, and then on a daily basis until discharge; all supported by EEG data and neuroimaging. At present, however, there is a need to carry out an early and rapid neurological examination, aimed at a timely recruitment to hypothermic treatment. In this context, and with this timing, it is not possible to make an accurate classification of the HIE. In fact, it is known that the severity of the clinical signs of HIE can evolve in the first 2-3 days after birth, with the concrete possibility of obtaining less accuracy when the classification is carried out early. This was confirmed by a study comparing clinical neurological examination with aEEG for prognostic purposes. The authors suggested that classifying an HIE as mild within 6 hours of life, using only a clinical neurological classification, risks underestimating the degree of HIE instead confirmed by the aEEG [11]. It may therefore happen that some forms of HIE, classified as mild within 6 hours of life, may subsequently evolve into moderate forms: in pre-hypothermia, when the classification was carried out in the days following birth it was more likely that these forms had been classified according to the right degree of severity.

It is therefore necessary, in order to implement a timely and effective neuroprotection, to identify the early and sensitive neurological signs of developmental brain damage, rather than setting the goal of making a complete classification.

A study [12] that evaluated sensitivity, specificity, positive predictive value and negative predictive value of the individual neurological signs that make up the modified Sarnat score, performed within 6 hours of life, reported that, among all categories examined, hypotonia was the only one to predict, with a 100% sensitivity, a disability at 18-22 months of life, albeit with a specificity of only 30%. The negative predictive value of a normal tone was also 100%, while the positive predictive value of an altered tone was only 25%. Given the high benefit/risk ratio of using hypothermia in infants with HIE at risk of long-term neurological sequelae, it will be necessary to privilege clinical signs with greater sensitivity in recruiting infants to therapeutic hypothermia, regardless of specificity. This approach will help better define the long-term risks of mild HIE, helping to recruit all children who might benefit from therapeutic hypothermia.

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LECT 17

IUGR AND NEUROLOGICAL OUTCOME

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Intrauterine growth restriction (IUGR) is an abnormal fetal growth pattern that occurs in approximately 8% to 10% of pregnancies. It is associated with neonatal morbidity and mortality. IUGR refers to an impoverished fetal growth with fetal, maternal, or placental causes (i.e., congenital or chromosomal abnormalities, infections, and vascular disorders) and nutritional deficiencies that lead to cardiovascular deterioration, extreme blood flow resistance, and decreased fetal growth rate. In pregnancies in which IUGR occurs, the fetus attempts to prevent damage by slowing its growth and shortening its gestation. However, the adaptive responses to face up to *in-utero* malnutrition have long-lasting consequences related to adverse developmental and health-related outcomes throughout life. IUGR children can develop a range of poorer developmental outcomes in cognitive, socio-emotional, and behavioral domains as compared to children who were born appropriate for gestational age (AGA).

Moreover, IUGR fetuses are delivered small for gestational age (SGA). SGA is a neonatal classification that describes newborns with birth weight below the 10th percentile for gestational age. Despite the high comorbidity between SGA and IUGR, it is important to differentiate between the two conditions. IUGR reflects fetal distress, whereas SGA only provides a measure of birth size and not a direct measure of antenatal growth quality. SGA infants are usually described as constitutionally small fetuses and postnatal differentiation between IUGR and SGA can be hard. However, several antenatal factors (e.g., umbilical artery Doppler assessment) have been proposed to increase accuracy in antenatal diagnosis. Despite this, SGA could represent a delayed or attenuated subtype of IUGR, therefore, a pathological origin of SGA cannot be excluded.

In addition, prematurity is an important variable to consider when studying IUGR and SGA development as approximately 5-7% of preterm neonates are born with IUGR. Recently, Sacchi et al. issued a meta-analysis that investigated the association between IUGR or SGA birth and childhood cognitive outcomes in both preterm and at term children. They found poorer cognitive function during the first 12 years of life in children who had IUGR and were SGA as compared to AGA-matched control group [1]. Moreover, prematurity resulted to be an incremental risk factor for neurodevelopmental delays in IUGR infants. Furthermore, school-aged children who experienced IUGR presented difficulties in different areas related to executive functioning, language and creativity, short-term and working memory deficits, learning disabilities and lower academic achievements (verbal knowledge, reading decoding and comprehension, and arithmetic). However, some studies found that language scores were not significantly lower in the IUGR very preterm (VPT) group, highlighting the importance of post-natal environmental factors (socio-economic status) for linguistic functions.

Advanced magnetic resonance imaging studies have shown that IUGR is associated with structural differences that can be identified very early in life. The biological mechanisms that could explain those findings are not fully understood but are likely to involve antenatal brain developmental processes.

However, it is still unclear whether the intrauterine environment offers a better long-term outcome for the growth-restricted infant than an early exposure to the extrauterine environment. Recent long-term postnatal studies in preterm newborns with IUGR evaluated at term-corrected age have found reductions in the cerebral cortical grey matter, hippocampal volume and sulcation index, which were accompanied by less mature behavioral scores. These macrostructural alterations have been associated with microstructural and metabolic changes assessed by diffusion tensor imaging and spectroscopy, which could underlie the increased risk of neurodevelopmental deficits.

In addition, correlations between growth patterns and neurocognitive development in IUGR infants have been demonstrated. Recent studies show that there are no significant neurological and developmental outcomes in severe IUGR infants as compared to preterm AGA infants at 12 months. However, delays in perceptual, memory and executive function domains may be subtle and difficult to be early captured by traditional developmental tests. Most developmental capacities and cognitive processes begin to be established and become prominent later in childhood when their assessment allows probable differences to be identified. Improvements on nutritional management after discharge may have some effects on the postnatal growth in IUGR infants. Both preterm and at-term IUGR infants had adverse influences at a critical period of brain growth that can be seen at 12 months when microcephaly appears in a large proportion of IUGR infants, suggesting greater vulnerability in brain growth compared with AGA infants. As mental outcome in the first years appears to be closely related to growth and brain volume,

Tan et al. suggest that improving nutrition in VPT infants may improve brain growth and maturation. Specifically, in IUGR children, head circumference and somatic growth indices are positively associated with outcome at 10 years of life.

IUGR is frequently accompanied by placental insufficiency and a response to reduced placental blood flow, hypoxemia and undernutrition. Such adverse environmental conditions may result in neural changes with consequences for the developing brain. IUGR fetuses display altered patterns of brain volumetric growth, including smaller temporal lobes and cerebellum [2]. Some authors [3] identified a distinct neuroanatomical pattern in IUGR VPT infants at term-equivalent age which was characterized by global brain growth failure, alterations in the cerebellum and brainstem as compared to AGA preterm infants. Other studies show significant reduction in intracranial volume and in cerebral cortical grey matter, smaller thalamic, basal ganglia and hippocampal volumes, and altered cortical gyrification and cortical thickness in preterm IUGR newborns as compared to AGA preterm peers [4, 5]. Structural brain changes have further been documented at 12 months, with findings including reduced grey matter volumes in temporal, parietal, frontal and insular regions. A longitudinal study, in a large sample of VPT newborns, showed that IUGR (compared with AGA) was associated with extensive relative volumetric brain differences at term-equivalent age and with poorer cognitive and motor outcomes and a higher positive autism screening risk at 22 months. The absence of severe focal brain lesions and of significant differences in postnatal courses (days of ventilation and parenteral nutrition, days of CPAP) between IUGR and AGA newborns suggests that the developmental alterations may be triggered by prenatal events. At term-equivalent age, differences in the relative volume of grey matter were observed between IUGR and AGA VPT infants: frontal and temporal cortices exhibit increased maturational priority over the sensory-motor regions and become key areas for the regulation of neural activity and neurocognitive development. Between 37 and 44 weeks of postmenstrual age, sensory and limbic areas and posterior parietal regions display more pronounced maturational changes compared with areas related to higher order functions (like prefrontal cortex). Previous studies have also reported increased cortical sulcation in proportion to surface and reduced cortical thickness, reduced cortical and hippocampal volume in VPT neonates with IUGR compared with those without IUGR. Potential causal pathways leading to IUGR-related brain alterations include hypoglycemia, neuroinflammation, like the microglia activation, and maternal nutrient restriction. Animal models elucidated the microstructural, functional and biochemical mechanisms that may contribute to such brain alterations like neuronal cell loss, altered developmental progression of oligodendrocytes and myelination, decreased dendritic outgrowth, reduced cellular connectivity and reduced structural integrity of the neurovascular unit. The most pronounced relative volumetric differences between IUGR and AGA VPT infants concern the limbic areas, that may be particularly vulnerable to poor intrauterine growth in terms of volumetric reductions and altered regional brain network topology. This could be due to the susceptibility of the limbic system, and especially amygdala and hippocampus, to hypoxic-ischemic injury and maternal preconception health, as well as fetal exposure to glucocorticoid levels that are heightened under conditions of maternal stress and/or placental dysfunction.

The spectrum of brain alterations associated with IUGR is heterogenous, possibly reflecting both antenatal *in-utero* events as placental dysfunction and other complications associated with VPT birth. Some authors interpreted the relative larger grey matter volumes in the IUGR group in the context of adaptive brain sparing processes, which refer to the fetus' cardiac output redistribution to favor vital organs and support development of critical brain regions. Fetal brain sparing includes a hierarchical prioritization of oxygen supply to the frontal lobes, as a response to chronic hypoxia/placental insufficiency, followed by a decrease in supply if the fetal condition worsens to favor the basal ganglia. Thus preservation of selective brain areas depends on the stage of fetal hemodynamic compromise. Increases in volume of temporal-parietal cortices could reflect the effects of *ex-utero* experience that may be enhanced in IUGR compared to AGA VPT infants. In particular, these areas are involved in hearing (primary auditory cortex) and sensory processing (primary and secondary somatosensory cortex). Previous research has shown larger white matter volume in the occipital cortex and increased functional connectivity in the visual network in 12-months old IUGR infants, as well as accelerated neurophysiologic maturation.

IUGR VPT toddlers are more likely to score positively on autism screening questionnaire (M-CHAT) as compared to AGA VPT peers (43% vs 27%). Rates of positive M-CHAT screening have

ranged between 21% and 41% in preterm children, with higher prevalence in those with younger gestational age. Positive M-CHAT screening has been also reported in 25% of very low birth weight children (less than 1,500 g) aged 2 years and in 31% of IUGR VPT (< 34 GA) 12-months old toddlers. Mechanisms potentially explaining the association between IUGR and autism outcomes might involve shared genes that predispose to both IUGR and autism risk. Further IUGR may represent a prenatal factor that may be associated with autism risk such as metabolic alterations, reduced insulin-like growth factor, fetal hypoxia and perinatal inflammation.

We interpret the brain volumetric alterations in limbic component in the context of age-dependent relationships between brain and cognitive maturation and speculate that limbic alterations might affect the development of IUGR infants' emotional skills that will emerge only later in childhood. Studies in IUGR infant and toddlers have highlighted poor social interactions and adaptive behaviours and higher levels of negative affectivity and temperament difficulties. As the limbic circuitry has been implicated in such functions, the limbic volumetric changes observed in IUGR VPT infants may increase their vulnerability to develop emotion and behaviour regulation problems later in life. IUGR in VPT children might confer a neurodevelopmental risk that is greater than that posed by VPT birth alone, where environmental stress experienced antenatally alters brain growth and global development early in life. These findings might help identifying time-dependent prenatal factors impacting brain development of IUGR VPT infants that are associated with both cognitive and psychiatric risk.

Current studies highlight the importance to disentangle IUGR and SGA diagnosis in both preterm and at-term infants in order to improve prediction of their neurodevelopmental outcomes through regular clinical follow-up visits.

The effect of IUGR on neurodevelopment has been particularly documented from infancy to school-age period demonstrating that several functions, including adjustment to school, language and memory continue to be compromised in IUGR children.

Large follow-up studies describing developmental and functional brain patterns from infancy to later-childhood and adolescence are needed as deficits could be more evident as soon as more demanding tasks arise. Moreover, we recommend to take into account the effects of environmental factors (such as socio-economic status and parental education) on developmental patterns of IUGR children.

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LECT 18

RETINOPATHY OF PREMATURITY

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Retinopathy of prematurity (ROP) is a vasoproliferative retinal disorder, which is the main cause of visual impairment and blindness in preterm infants. It has been reported that some stages of ROP occur in 40-50% of infants born < 30 weeks of gestational age, while severe ROP occurs in 7-8%, and treatment is needed in 5-6%.

ROP is a two-phase disease with a first phase of reduced retinal vascular growth and loss of blood vessels due to a lack of growth factors and abnormal oxygenation. During this phase, the retina is incompletely vascularized with the development of a peripheral avascular zone which becomes increasingly hypoxic. This hypoxia induces the second phase of ROP characterized by an increase in the expression of the vascular endothelial growth factor (VEGF) which can promote uncontrolled neovascularization and retinal detachment.

The most common treatment of severe ROP is retinal ablation using laser photocoagulation to reduce VEGF production of the hypoxic peripheral retina, but this treatment destroys approximately two-thirds of the retina. Over the last few years, intravitreal injections of anti-VEGF have emerged as an effective first-line treatment for severe ROP, and many authors have reported favourable outcomes using these drugs.

Recently, many studies have investigated risk factors and co-morbidities associated with ROP, but it is worth noting that large differences in ROP frequency are reported between different Neonatal Intensive Care Units (NICUs). Moreover, it is important to observe that risk factors have a significant etiopathogenetic effect in some units or countries while in other settings they do not.

Therefore, we evaluated the incidence of ROP and investigated risk factors for its development in a large cohort of Italian very preterm infants. We studied a total of 178 infants of whom 67 (38%) developed ROP. Regression analysis demonstrated that maternal milk decreased the risk of developing ROP, while intraventricular hemorrhage (IVH) increased it. Moreover, RBC transfusion increased the risk of ROP at discharge.

These results confirm previous studies demonstrating that feeding with mother's own milk can decrease the risk of ROP in very preterm infants. Physiological mechanisms through which human milk may prevent the development of ROP include the antioxidant and immune-protective properties of breastmilk. Moreover, human milk encompasses higher concentrations of insulin-like growth factor 1 (IGF-1) which is known to have a crucial role for physiological retinal vascularization. We found that the occurrence of any grade IVH increased the risk of ROP. This correlation can be explained by similar aspects of ROP and IVH pathogenesis, such as the vascular immaturity of retina and germinal matrix, and the role of oxidative stress. RBC transfusions was found to be a risk factors for ROP at discharge but not at the screening visit. This is consistent with the fact that the majority of transfusions for anemia of prematurity are performed after the first weeks of life and, therefore, it can be speculated that they affect the progression of ROP rather than its onset. This correlation between RBC transfusions and ROP confirms previous findings which have been explained by the pro-oxidant effect of transfusions due to the increase in oxygen delivery to the retina secondary to increased packed cell volume and lower oxygen affinity of adult haemoglobin in packed red cells (PRCs), and secondary iron overload.

In conclusion, ROP remains a severe complication in very preterm infants although the progress in their assistance and the recent effective contribution of anti-VEGF drugs to its therapy. Therefore, the prevention is essential and the knowledge of ROP pathogenesis and clinical risk factors can give a fundamental support to its achievement.

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LECT 19

PEDIATRIC ASTHMA MANAGEMENT DURING COVID-19 TIMES

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Severe acute respiratory syndrome Coronavirus-2 (SARS-CoV-2), first reported from the Wuhan city of China in December 2019, swept the world in a few months and became a global health emergency of primary international concern and continues to be a priority health problem.

During the COVID-19 pandemic there was a consistent reduction of asthma exacerbations [1, 2]. The cause of this reduction could be multifactorial but public health measures such as masking, hand washing, and physical distancing surely had an important role in reduce viral transmission [2].

For this reason, we questioned if it could be possible tapering asthma medications in children during COVID-19 pandemic without facing the risk of asthma exacerbations.

Before COVID-19 pandemic, scientific evidence strongly supported a step-down therapy in children with good asthma control, in particular according to GINA strategy a step-down therapy could be considered in children with a good asthma control for at least 3 months [3, 4]. This was different during the COVID-19 pandemic because without asthma maintenance therapy both the risk of asthma exacerbations and the access to Emergency Department could increase. Moreover, during pandemic, follow-up visits were less frequent than before pandemic. Furthermore, it is known that inhaled corticosteroids used for asthma maintenance therapy are useful against COVID-19 infection too [4].

To evaluate the risk and benefits of a step-down therapeutic approach, it could be useful to weigh some key factors, in particular atopic status, baseline risk and others. The atopic status (eczema, food allergy, eosinophilia) is one of the most important because it predicts asthma persistence and exacerbations, and it plays an important role in the decision of tapering therapy or not [4].

The second factor is the baseline risk of poor asthma outcomes. It includes low pulmonary function, smoke exposure, and previous exacerbations. According to GINA strategy, it is not recommended to taper therapy in children with atopic status and/or high baseline risk [5].

There are also other circumstances that influence decision making, in fact it would not be recommended to consider a step-down approach during autumn or when children return to school, in fact in these circumstances there is a higher risk of viral infection transmission.

In all patients with asthma who are eligible (aged > 12 years with no medical comorbidities) both COVID-19 vaccination and annual influenza vaccination are recommended [5].

In conclusion, in children affected by asthma, it is advised to maintain usual asthma medications during the pandemic. It could be useful the stratification of the risk especially according to atopic status and baseline risk, in association with public health measures.

Further research will help to establish whether a more nuanced approach could be considered in pandemic guidance in the future.

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LECT 20

CHARACTERISTICS OF SARS-COV-2 INFECTION IN CHILDREN

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Originally called the New Coronavirus, the SARS-CoV-2 virus has rapidly spread, being difficult to manage globally and quickly, becoming a global public health problem, leading to an international mobilization, probably, unprecedented in the recent human history [1-3].

Current knowledge about SARS-CoV-2 infection is still in its infancy and many questions have been awaiting an answer, but what is apparently obvious, at least so far, is the low incidence of the disease among the pediatric population.

Analyzing the international as well as the national epidemiological data, there is a reduced impact on the pediatric population compared to adults. Globally, the incidence of the new Coronavirus infection among children has increased from less than 3% at the beginning of the 2020 year, to more than 15% today [1-3]. However, the deaths in pediatric age are extremely low compared to what happens in adults.

The low incidence of the disease among the pediatric population is a topic of high interest for current and future research. The literature mentions so far several theories, but three hypotheses regarding the low incidence of the new Coronavirus infection in the pediatric population are most important [3-5].

It has been shown that angiotensin convertase 2 (ACE 2) receptors would be the gateway into human cells for some Coronaviruses, including the SARS-

CoV-2 virus; also, the low expression of these receptors in the respiratory tract of children could be the explanation for which they are less vulnerable to SARS-CoV-2 virus [4, 5]. More recent studies, however, question this theory because the category of patients under the age of one year, in which ACE 2 expression is lowest, is still an extremely vulnerable group for the new Coronavirus. Another hypothesis that has attracted the attention of researchers is the endothelial damage that occurred before the infection, which facilitates the spread of the inflammatory process.

Because there is a low incidence of diseases recognized as causing endothelial destruction (cardiovascular disease, diabetes) in the pediatric population, it is estimated that the spread of the inflammatory process is limited in the conditions of unhealthy epithelium.

Driven by the many viruses that children overcome in the first years of life, as well as the administration of vaccines, the innate immune system of children apparently plays an important role in the protection against SARS-CoV-2. This hypothesis seems to be increasingly exploited and requires special attention in the future, especially that the researchers increasingly mention some possible correlations between influenza immunization and protection against Coronavirus.

Romania faced the first confirmed positive case of SARS-CoV-2 virus infection on February 26, 2020, and about a month after that, the first secondary deaths of this infection appeared. The epidemiological situation imposed, starting with March 16, 2020, the establishment of the state of emergency on the Romanian territory, involving special measures both from a sanitary and socio-economic point of view. Subsequently, from May 14, 2020, the state of emergency was replaced by a series of other measures, and 1 year after the first case confirmed in the country, there is still a struggle to try to limit the spread and especially the impact of the COVID-19 pandemic in the population. At the time of writing, 1,165,886 cases and 35,851 deaths secondary to SARS-CoV-2 infection were confirmed in Romania [2].

From the analysis of international and national epidemiological data, since the first months of the pandemic, there is a significant difference between the pediatric population and the adult population, in terms of infection rate, methods of transmission, clinical manifestations. In the first months of the pandemic, the incidence of the new Coronavirus infection among children was reported at about 3%, so that now, it reaches 6.52% of a total number of 74,474 infected children (September 19, 2021) [2]. Reports from the US Centers for Disease Control (CDC) on the rate of SARS-CoV-2 infection in children have shown an upward trend. Thus, if at the beginning of April 2020, the incidence of infection with the new Coronavirus in children was only 2.6%, one year later (September 19, 2021) the percentage increased to 15.7%, given that about 5,518,815 infected children were reported [1, 3].

Following the evolution of the pandemic, there is a change in the pattern of involvement of the pediatric population, which, although it remains less affected compared to adults, faces new facets of infection with the evolution of the second and third wave.

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LECT 21

WHICH FUTURE FOR CHILDREN AND ADOLESCENTS AFTER COVID-19

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The contribution, from a psychosocial perspective, addresses the task that Communities have to hypothesize guidelines aimed to facilitate the development of a future for children and adolescents, without prejudice to all individual "profiles", gender, ethnicity, disability etc., allowing to deconstruct the collusion between COVID-19 and social retirement. Today, in what we hope will be the post-pandemic, in fact, health professionals (pediatricians, psychologists, childhood and ado-

lescence neuropsychiatrists, etc.) ask themselves some questions when they must hypothesize the future for children and adolescents who have lived and are living an evolutionary emergency [1], such as the one that characterizes a dysfunctional life condition during times of social emergency.

The first question concerns the complexity of the "field" condition which gave life to dysfunctional relationships of children and adolescents with the systems of reference (Family, School, Services) during the pandemic. These are subjects often characterized by a fragility of the "domains" [2] that define the functioning of the mind. Among these domains, identity, emotions and relationships present in a particular way some impairments. Also, the mentalization of the pandemic experience seems to be oriented in the sense of an internalization and of the cellular memory [3] in the sense of danger, loneliness, etc.

A further question concerns the identification of possible risks, between adjustment disorder [4] and developmental traumatic disorder [5]. Finally, it must be asked towards which type of child, adolescent and young man do we want to direct the development of the future?

After having tried to answer to these questions, the contribution focuses on some specific directions, according to an ecological and systemic approach, hypothesizing some specific actions directly addressed to children and adolescents, to families, and to other systems. Among the directions that can help to outline and build the future for these children/adolescents, in a strengthening perspective, they must be identified: processing times and spaces in which a cognitive and emotional integration and elaboration of the individual and social emergency can be promoted, directing in them a transformation of the mentalization of the pandemic lived experience. A further direction must be identified in promoting contact times and spaces, facilitating situations in which close relationships can be activated. These allow children/adolescents to feel safe, to experience cognitive and emotional "nourishment" relationships, to contact their own spiritual dimension, to preserve knowledge, certainties, bonds. At the same time, these close relationships permit to identify the possibility of going further, as well as being aware of one's own resources. Other directions for the promotion of the future must be identified in the development of both internal protection factors and life skills, and of the motivational profile. Last but not least, the directions relating to the promotion of a new, conscious approach to the social networks must be considered, as well as the development of democratic skills to promote a new way of being in social relations.

At the end of the reflection, the contribution poses a final question: will we, as health professionals, know how to promote a new ethics of the future for our children and adolescents?

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LECT 22

THE FIRST THOUSAND DAYS OF LIFE: THE ROLE OF THE MICROBIOTA

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Pregnancy, birth, breastfeeding and growth are the pillars of the foundation of the individual. And certainly not mistaken were those who said that it is much better to build a healthy child than to fix a sick adult.

Human bacterial colonization starts during fetal life, in opposition to the previous paradigm of the "sterile womb". Placenta, amniotic fluid, cord blood and fetal tissues have each their own specific microbiota, influenced by maternal health and habits and having a decisive influence on pregnancy outcome and offspring outcome.

The first thousand days from conception ("a thousand days of you and me", the mother and her child, to remind it through the verse of a splendid Italian song) are strategically decisive for all future health, which is equivalent to all future life. Today, even this concept of the first thousand days is already superseded by the formula 6 + 9 + 6, which means 6 months before pregnancy, 9 months of pregnancy, 6 months after birth (those of breastfeeding). Using the language of medicine, these are the concepts of Perinatal Programming and Developmental Origins of Health and Disease.

In this puzzle, the real protagonists are the pioneer bacteria, the ones that arrive first and colonize the body districts first, control the territory and never want to leave. It becomes difficult to replace them, for better or for worse. If we could play "back to the future" and choose our future, we would choose skinny grandparents, a healthy mother who has a normal pregnancy that comes to an end, a spontaneous birth, breastfeeding for 6 months. In this case we would receive the microbes of the good beginning of life (*Lactobacilli* and *Bifidobacteria*), the old friend of the human beings. For example, in the case of a C-section, breast milk is a lifeline because it supplies the good bacteria, the same ones that the baby should have received from the maternal vagina in case of spontaneous birth.

In fact, during the perinatal period, neonatal microbiota seems to be influenced by delivery mode, drug administration and many other conditions.

Special attention must be reserved for early neonatal nutrition, because breastfeeding allows the transmission of a specific and unique lactobiome able to modulate and positively affect the neonatal gut microbiota.

Basically, we are understanding, slowly but we are getting there, that the microbiota is not just an additional organ that we still forget about, but it is an essential component of what it means to be human and for this reason it must be increasingly investigated and known by physicians and health professionals in general.

The physicians of the future will become actual microbiota engineers, manipulating in our favor the communities of bacteria we harbor. Already in the near future, it will be possible to integrate and modulate our microbiota artificially, obtaining an individualized super-microbiota: we will become not super-humans, but "augmented" humans. Thus, the newborn of the future, the "augmented" newborn, can also be strengthened through a treatment of good bacteria administered to the future mother before conception, or to the pregnant mother or to the newborns themselves after birth, with positive effects for the whole life in terms of health. Pioneer bacteria are real pillars of health, that influence the whole life of each subject.

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LECT 23

THE FIRST THOUSAND DAYS OF LIFE: FROM THE PLACENTA TO NEURODEVELOPMENT

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Increasing attention has been paid to the main pollutants and epigenotoxic factors to which pregnant women and therefore mother-fetus dyads are exposed. But there are still few results concerning the possible biomarkers of exposure and damage that can be used by neonatologists, pediatricians, pediatric neuropsychiatrists and epidemiologists for a concrete and effective follow-up of these children.

The main objective of our research will be to discriminate between these two essential sources of pollution and therefore of potential disturbance of embryo-fetal epigenetic programming (fetal programming). A key objective, given that for at least thirty years, it has been increasingly evident that the rapid and continuous increase of all chronic diseases (inflammatory, neurodegenerative, neoplastic...) cannot be explained with the usual causes concerning the lifestyles of populations and their genetic makeup. But an increasingly clear and irrefutable explanation has been found in the disorders of epigenetic programming in developing individuals and especially in the first 1,000 days of life.

If so far, the idea has prevailed that lifestyles, pollution in a general sense, especially food chains represent the main factor behind the increase in chronic diseases ("non communicable diseases"), we believe that it is important to introduce the evaluation of these parameters, especially the epigenetic ones, since they are very sensitive to environmental factors (meaning they represent the mechanism through which environmental factors interact with our genome, modifying their expression).
We believe that studying the local environmental situation is very important and that certain exposures can be effectively correlated with specific biomarkers, increasingly linked to what is the real exposure of the individual child, with the potential to be in the future used by the pediatrician in a preventive and prognostic sense.

LECT 24

BIFIDOBACTERIA AS BIOMARKERS OF THE BABY'S GUT HEALTH

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The human body is a complex ecosystem inhabited and influenced by an abundance of microorganisms including bacteria, viruses, fungi, archaea and protozoa that collectively make up the commensal microbiota. The microbiota offers many benefits to the host, through a range of physiological functions such as strengthening gut integrity or shaping the intestinal epithelium, harvesting energy, protecting against pathogens and regulating host immunity [1]. A more complex, stable, and adult-like microbiota is established between 1 and 3 years after birth. Although it is commonly accepted that the intrauterine environment and newborn infant are sterile until delivery, some evidence shows the presence of bacteria in the intrauterine environment and suggests that these bacteria may influence the microbiota of the infant before birth [2]. During gut microbiota establishment, the first microbial actors that render the gastrointestinal environment fully anaerobic are facultative anaerobes, which include several members of the *Enterobacteriaceae* family. After the removal of oxygen, the infant gut undergoes extensive colonization driven by strictly anaerobic bacteria taxa, such as those belonging to the genera *Bifidobacterium*, *Clostridium*, *Bacteroides* and *Ruminococcus*. Although the composition of intestinal microbiota is subject to continuous and dynamic changes, it seems that the perinatal period is critical for the emergence of its proper pattern, which may guarantee health or otherwise illness in adult life. Several studies have shown that various environmental and host-related factors such as maternal microbiota composition, delivery patterns, breastfeeding, drug exposure, hospitalization after birth, diet, and genetic factors can alter the microbial ecosystem to an extent such as to succeed its resistance and resilience with consequences on the immune and anti-inflammatory responses responsible for autoimmune, neurodegenerative, chronic inflammatory bowel diseases and metabolic diseases. *Bifidobacteria* represent one of the earliest and most abundant bacterial colonizers of the neonatal gut [3]. Colonization with *Bifidobacterium* is believed to be essential for infants because it promotes their intestine maturation and metabolic, immune and brain development [4]. Maternal gut and milk dysbiosis induced by maternal conditions, such as maternal western diet, obesity, alcohol, and tobacco use, can be vertically transmitted to offspring. Cesarean section, preterm delivery, infant formula and early life antibiotic exposure are other factors for imbalanced infant gut bacterial community, especially *Bifidobacterium*. *Bifidobacteria* are resident microbiota members throughout our lifetime and have been shown to modulate specific immune cells and pathways but several diseases are linked to *Bifidobacterium* dysbiosis that often occurred in the early step of gut colonization including obesity, diabetes, necrotizing enterocolitis, allergic diseases, inflammatory bowel diseases [5].

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