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Lectures

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NEONATOLOGY: STEPS TOWARDS THE FUTURE IN THE COVID-19 ERA

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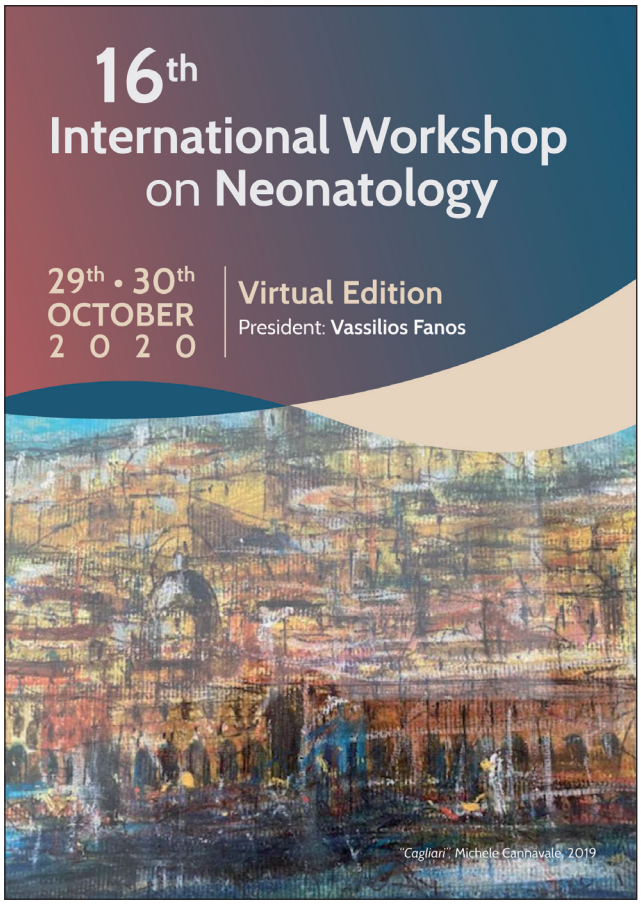

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LECT 1

NEONATAL VENTILATION IN THE THIRD MILLENNIUM

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Although life saving for the sickest infants, invasive mechanical ventilation (MV) has many undesirable side effects on the lung, brain and cardiovascular system. The process of lung damage from MV is multifactorial and cannot be linked to any single variable. Volutrauma and atelectrauma have been identified as the most important and potentially preventable elements of lung injury. Volutrauma is injury caused by over-distention and excessive stretch of tissues, which leads to disruption of alveolar epithelium, oedema, proteinaceous exudate and release of proteases, cytokines and chemokines causing in turn biotrauma. Atelectrauma is lung injury due to tidal ventilation in the presence of atelectasis. Shear forces at the boundary between aerated and atelectatic part of the lung cause tissue damage, while atelectatic areas determine an uneven distribution of ventilation. While using conventional MV, synchronization with infants' spontaneous breathing, volume-targeted ventilation, and the "open lung" concept (obtained by selecting proper PEEP levels) are the proven lung protective ventilatory strategies. Comparing elective conventional MV and elective high frequency oscillatory ventilation (HFOV), a recent *Cochrane* review [1] showed that elective HFOV results in a small reduction in the risk of CLD, but the evidence is weakened by the inconsistency of this effect across trials. Moreover, the benefit could be counteracted by an increased risk of acute air leak using HFOV. About long-term outcomes, most trials have not identified any difference between these two invasive modes. For the above mentioned reasons, avoidance of MV in favour of non- invasive modes of ventilation remains the most important step in preventing neonatal morbidity. Nasal continuous positive airway pressure (nCPAP), heated humidified high flow nasal cannula (HHHFNC), bilevel nCPAP (BIPAP) and nasal intermittent positive pressure ventilation (NIPPV) are the most common and currently available non-invasive modes. In recent years, also nasal HFOV has been introduced in Neonatology. All these modes, however, offer to infants a different degree of respiratory assistance. Non-invasive modes that apply to the airways a constant pressure, like nCPAP and HHHFNC, help infants to obtain and maintain an adequate functional residual capacity (FRC), thus reducing their work of breathing (WOB) through the improvement of the working condition of the respiratory system. These modes simply offer a non-invasive respiratory support. Contrariwise, a variable pressure mode like NIPPV, may actively influence the infant's ventilatory pattern by supporting spontaneous efforts with superimposed positive pressure breaths. This mode reduces infants' WOB and provides energy for ventilation, being a non-invasive ventilation mode. BIPAP uses small pressure differences between inspiratory and expiratory phases, but there is no evidence that confers any advantage over CPAP, and any clinical difference may only reflect a higher mean airway pressure applied to the respiratory system. Nasal interfaces have also been used with HFOV, but results are still uncertain [2]. Performance and effects of NIPPV can be optimized by synchronizing mechanical breaths to spontaneous ones; different methods of triggering have been developed: the Graseby capsule, the neurally adjusted ventilatory assist (NAVA), and the flow-sensor [3]. Non-invasive techniques are being increasingly used in preterm infants with respiratory failure and several trials seems to demonstrate that NIPPV and synchronized NIPPV (SNIPPV) are more effective than nCPAP in reducing extubation failure, as primary mode of ventilation and to treat apnoea of prematurity.

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LECT 2

COVID-19 IN CHILDREN: WHAT DID WE LEARN?

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Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) is the causative pathogen of Coronavirus Disease 2019 (COVID-19) and has been identified as a novel enveloped RNA betacoronavirus. SARS-CoV-2 still infects millions of people globally, justifying the efforts to identify effective preventive strategies and optimal medical management.

Children at any age were mostly reported to have mild respiratory symptoms or were asymptomatic. Frequent clinical manifestations include fever, dry cough, and other upper respiratory symptoms, such as nasal congestion and runny nose [1]. Moreover, the main gastrointestinal symptoms were nausea, vomiting, and diarrhea [1]. In general, children and adolescents with COVID-19 had a good prognosis and recovered within 1 to 2 weeks after disease onset [1]. Published epidemiological data reported low mortality rates [1]. However, recent articles described cases of hyper-inflammatory states in children with COVID-19, that were currently defined Pediatric Inflammatory Multisystem Syndrome Temporally Associated with SARS-CoV-2 (PIMS-TS) and Multisystem Inflammatory Syndrome (MIS-C) [2]. The clinical presentation of the COVID-19 hyper-inflammatory phenotype varies significantly between patients and includes clinical and laboratory signs of systemic inflammation. The spectrum of symptoms is wide and ranges from fever and systemic inflammation to myocardial involvement resulting in tissue injury, shock, and the development of coronary artery dilatations and aneurysms (Kawasaki-like disease) [2]. The treatment of PIMS-TS/MIS-C is empiric and still not validated. Therapeutic interventions are usually chosen based on hospital experience and may include intravenous immunoglobulins, high-dose corticosteroids, and cytokine blocking agents. Anticoagulation should be considered especially in children with the pathologic activation of the coagulation system, and coronary dilatation [2].

Why some children and adolescents develop the hyperinflammatory phenotype in the context of SARS-CoV-2 infection remains unknown and probably related to the dysregulation of the host immune response against the virus [2]. PIMS-TS/MIS-C, fortunately, are rare complications of pediatric COVID-19 and generally respond to anti-inflammatory treatment. On the other hand, possible explanations for mild or asymptomatic presentations in most children include frequent contact to seasonal coronaviruses and co-clearance with other viral infections [2]. The higher levels of ACE2 in the airways of children may facilitate the SARS-CoV-2 infection but may reduce the risk of severe disease because of its involvement in anti-inflammatory signaling [2]. Other potential protective factors may concern recent vaccinations and a more diverse memory T cell repertoire when compared to adults [2].

In conclusion, further efforts are required to understand the pathogenetic mechanisms and the different phenotypes of COVID-19 in the pediatric population.

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LECT 3

COVID-19, MICROBIOTA AND LUNG-GUT AXIS

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Until 2010, it was thought that healthy lungs were sterile. But in the last decade it has been demonstrated that normal lungs have their own microbiota. It is much smaller, in numerical terms, than that of the gut but it is able to affect the health status of an individual.

There are evidences that the gut microbiota and the lung microbiota develop together right after birth. Moreover, the composition of the lung microbiota

depends on several factors including micro-aspiration and inhalation, known as microbial migration. Thus, there it has been hypothesized a cross-talk between these two districts: gut and lung. Some species of bacteria appear in the gut before being detected in the respiratory tract: the so-called "more gut in the lung" [1]. Indeed, patients with respiratory diseases generally have gut dysfunctions indicating a more severe clinical course. The status of the lung microbiota may be related to the admission of the patient in intensive care. The microbiota could also be responsible for the different inter-individual activations of the receptors used by the SARS-CoV-2 to exert the pulmonary and systemic damages in COVID-19. Thus, there may be a close relationship between COVID-19 and the lung microbiota even in Pediatrics [2, 3]. In this scenario, metabolomics could be used as very useful tools in order to have an early diagnosis, predict mortality and the response to the treatment of each patients. In fact, one of the most recent articles concerning the application of the metabolomics in the investigation of COVID-19 showed a different activation of the IL-6 among patients with different degrees of severity of the disease. Never forget that metabolomics with its ability to detect in real time the metabolic status of an individual is the Rosetta Stone of the microbiomics. Thus, it could provide us a dictionary to interpret the status of the microbiota in case of COVID-19 and save as many patients as possible.

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LECT 4

ENTERAL NUTRITION FOR VERY PRETERM INFANTS: THE FACTS, THE ASSUMPTIONS AND THE UNKNOWNS

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Very preterm babies are born for many different reasons ranging from infection/inflammation of the fetus to maternal diseases and placental dysfunction. Very preterm babies are at high risks for subsequent complications after preterm birth. We have learned in recent years that enteral feeding is highly important for a good outcome with respect to growth and avoidance of adverse events. In this presentation, I will discuss the evidence for the time of onset of enteral feeding, the most appropriate enteral nutrition, the rate of increasing the enteral feeds, the fortification of enteral feeds, the measurement of gastric residues and the spontaneous stool passages. Nowadays pediatricians know the primary need to provide sufficient calories to enable appropriate growth [1]. I will discuss the basic lack of systematic assessments of the effects of cow milk protein fortifiers to minimize risks for adverse outcomes like necrotizing enterocolitis [2]. The biological basics of gut development, gut microbiota and the role of gut microbiota are discussed for the risk for sepsis and brain development [3]. In summary, this talk highlights the concepts and skills needed by pediatricians/neonatologists/nurses to optimize enteral nutrition for very preterm babies.

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LECT 5

LACTOFERRIN IN THE PREVENTION OF VIRAL INFECTIONS: FROM MOLECULAR MECHANISMS TO CLINICAL IMPLICATIONS

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The glycoprotein lactoferrin (LF), a physiological component of mammalian milk, is an important effector of the innate immunity in newborns, having broad-spectrum antimicrobial, anti-inflammatory and immunomodulatory activity.

The concentration of LF is higher in colostrum, and progressively decreases in mature milk [1]. The antibacterial action of LF is well known and derives from the iron sequestration, which inhibits bacterial growth and replication. On the other hand, the evidences on its antiviral properties are more recent and progressively increasing. *In-vitro* studies performed on several RNA and DNA virus, including influenza A, parainfluenza virus, SARS-CoV, respiratory syncytial virus, herpesvirus and adenovirus, demonstrated that LF is able to inhibit viral replication and to impair the viral anchoring on the cellular surface. At a molecular level, the action on viral anchoring depends on the blockade of the interaction between the virus and the heparin sulfate glycosaminoglycan expressed on target cells, which inhibits the recognition of the specific cellular receptors by the virus [1]. LF facilitates the clearance of the infectious agent also by promoting the innate and adaptive immune response against the pathogens. Indeed, it acts as a stimulator of neutrophil chemotaxis and its function increases cytotoxic activity of natural killer cells and enhances T helper 1 cell response [2]. The molecular effects of LF are not limited to the direct and immune-mediated antimicrobial activity, as LF has a role in the modulation of the inflammatory response, through the reduction of the secretion of different pro-inflammatory cytokines (IL-1, IL-6, TNF-α and others), potentially minimizing the inflammatory tissue damage in patients with microbial infections. This latter effect could be particularly relevant in viral infections associated with a significant immune and inflammatory tissue damage, as severe SARS-CoV-2 infection [3]. LF is strongly implicated in the beneficial effects of breastfeeding in the prevention of infections, and its clinical impact could be higher in preterm infants, which receive the higher concentrations of LF [3]. Moreover, different works investigated the effect of the *in-vivo* supplementation with bovine lactoferrin (bLF), which has a high aminoacidic homology with human LF. In these studies, supplementation with bLF was able to reduce the incidence of late-onset sepsis in preterm infants, the incidence of necrotizing enterocolitis, the duration and severity of symptoms in viral gastroenteritis and the incidence and symptoms of common cold, without evidence of significant adverse effects [2]. Although clinical data on other specific infections, including influenza, are lacking, early breastfeeding and supplementation with bLF can help in preventing viral infections and influencing the clinical course in infected patients, through the facilitation of viral clearance and limitation of the secondary tissue damage.

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LECT 6

NEONATAL SEPSIS: PRESENT AND FUTURE

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Neonatal sepsis still remains a devastating medical condition associated with high morbidity and mortality, especially in more immature infants, with significant long-term consequences in survivors. Developmental deficiencies in neonatal host defense, underlying medical conditions as well as pre- and postnatal exposure to microbes are major factors predisposing to sepsis. Nevertheless, despite significant improvement in the understanding of neonatal sepsis, there are important gaps in knowledge.

Most diagnostic criteria used so far are based on clinical manifestations and laboratory parameters associated with the systemic inflammatory response to the invading microbes. Nevertheless, given that their performance is far from optimal, sepsis diagnosis as well as definition in infants is a challenging task [1]. Recently, a number of "biophysical markers" have also been evaluated for the diagnosis of early and late neonatal sepsis (EOS-risk calculator and Heart Rate Characteristics, respectively) that could help neonatologists in the evaluation of neonates at risk. Similarly, scoring systems such as the neonatal Sequential Organ Failure Assessment (nSOFA) were reported to predict mortality based on objective evidence of organ dysfunction.

Blood cultures remain the gold standard for the definition of neonatal sepsis. Still, cases of clinical (blood culture negative) sepsis are commonly seen. To this end, molecular assays have been applied to

detect involving microbes, but currently they only seem to have an adjunctive role as diagnostic tests. The -omics technology (genomics, proteomics, metabolomics) is increasingly being used in septic infants as a means to explore underlying pathophysiology and potentially identify novel sepsis biomarkers with promising results [2]. Integration of clinical signs, laboratory and molecular tests including multi-omics technologies may enable timely and accurate diagnosis of neonatal sepsis in the future.

From a therapeutic point of view, antibiotics are crucial in the management of septic neonates. The increasing number of multi-resistant strains and relatively slow development of novel antimicrobial agents, however, are a major concern associated with increased morbidity and mortality. Moreover, the high susceptibility of preterm infants to invasive infections has prompted the exploration of a number of adjunctive or preventive interventions. Although some of these were found to improve certain immunologic deficits, no intervention has proved its utility in confidently reducing mortality of neonatal sepsis [3].

Overall, significant progress has been made in the diagnosis and management of sepsis in neonates. Still, there are considerable obstacles that need be overcome in order to eliminate the burden of sepsis and improve outcome in this age group, while technological advances may allow for the application of "precision medicine" in septic infants.

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LECT 7

THE NEONATOLOGY AFTER COVID-19

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During the last decades the number of live births in Europe has declined at a relatively steady pace, with Italy showing the lowest birth rates with less than half a million births per year.

The possible impact of SARS-CoV-2 pandemic on global birth rate is unknown but a further decline is expected in Italy and different scenarios have been hypothesized according to theoretical increasing unemployment rates, used as proxy of social and economic disadvantage, and subsequent recovery time.

The effects of COVID-19 restrictions on preterm birth rates have been also investigated but evidence is still controversial. Denmark and Ireland reported a decrease in the admission rate to Neonatal Intensive Care Units of extremely preterm and extremely low birth weight infants during lockdown, while a Nepalese study reported the contrary. These observational studies are based on small numbers and therefore caution is needed when interpreting these data.

SARS-CoV-2 pandemic has induced important changes in the hospital management of mother-infant pairs, posing important challenges. Maternity wards had to face the re-organization of the clinical activity of obstetricians and neonatologists in order to provide appropriate care to SARS-CoV-2 positive mothers and their neonates and to newborn infants with suspected or confirmed SARS-CoV-2 infection, while minimizing the risk of spreading of the infection through the perinatal wards. Hub and spoke hospitals have been identified and *in-utero*, neonatal emergency transportation has been implemented in order to centralize infected pregnant women and neonates, and dedicated spaces and routes have been created in hub maternity hospitals.

The available evidence, although limited, demonstrates very low rates of testing-based vertical or perinatal transmission of SARS-CoV-2 infection and mild clinical manifestations of neonatal infection. The safety of delayed cord clamping, mother-infant skin-to-skin contact and rooming-in approach for the mother-infant dyad has been recently supported, provided that the mother is instructed to wear a surgical mask and to perform hand and breast hygiene before assisting the neonate, to mitigate the risk of postnatal transmission. Similarly, breastfeeding should be supported as breast milk does not seem to be a transmission vehicle. However, if maternal conditions do not allow the mother to take care of her infants, a temporary separation may be appropriate and feeding with expressed milk should be encouraged.

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LECT 8

THE DEVELOPMENT OF IMMUNITY, FROM FETAL LIFE TO NEWBORN: WHERE HEALTH BEGINS

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The immune system is a complex network of cells, tissues, organs, humoral factors, and cytokines. Immunity is divided into two parts, named the innate and the adaptive responses. Innate immune responses play a main role in host defence, they are activated by the identification of different microbial pathogens. Innate immune cells express various pattern-recognition receptors (PRRs), which are involved in recognising non-self molecules and signals of changes in homeostasis. There are many different classes of PRRs, Toll like receptors (TLRs) are an example. TLRs are expressed in various immune and non-immune human cells, each of the TLRs recognizes various molecular patterns, they play a crucial role in defending against infection through the induction and shaping of the host defence reactions [1]. Numerous studies on TLRs highlighted their main role to establish the right therapeutic strategies for various diseases including sepsis, allergy, even cancer. Maturation of the immune system starts early in fetal life. Pregnancy is a unique situation in which the mother and the fetus peacefully coexist. Several fetal and maternal regulatory mechanisms are necessary to promote the immunological tolerance, which avoids the rejection of the fetus by the mother's immune system. During pregnancy, in physiological conditions, immunological changes help to prevent immunological associated disease such as preterm labour, infections and sepsis. Preterm infants are at higher risk of fatal infection compared to all other age group, because of their deficient immune system. The newborns and young infants are more vulnerable to infections because of the severe differences between their immune responses and immune responses at later ages; this characteristic is known as "neonatal immune immaturity". Transplacental transfer of immunity mediators from mother to fetus during pregnancy, infant breastfeeding and immunisation by vaccine can attenuate this neonatal immune immaturity. Breastfeeding has many positive aspects for the newborn, it helps to generate the intestinal microbiota, modulate and positively influence the infant's immune system. However, the immune system is also regulated by genetic factors; numerous types of gene mutations can cause severe diseases, from recurrent infections [2], immunodeficiencies to immune dysregulation and autoimmunity.

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