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Lectures

Selected Lectures of the Balkan Meeting of Neonatology

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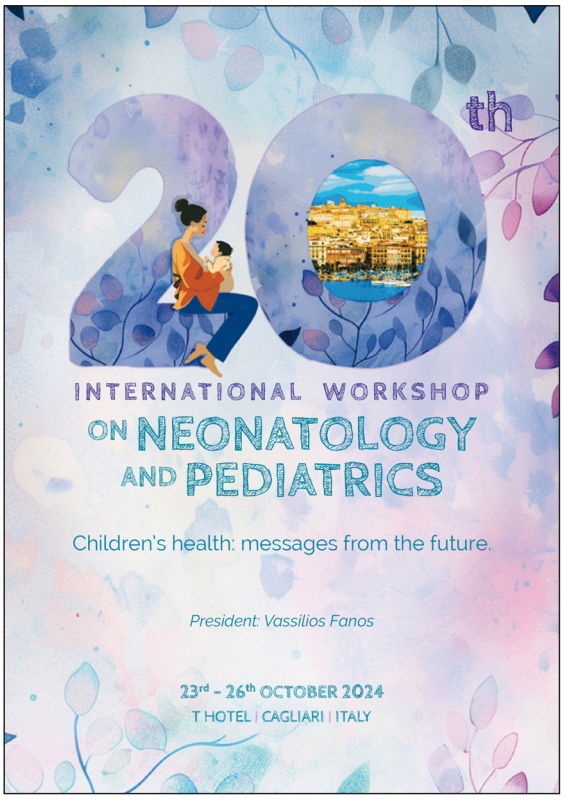

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LECT 1

MORTALITY RATE OF PRETERM BABIES BORN IN THE TERTIARY MEDICAL CENTER IN TIRANA AND THE IMPACT OF THE IMPROVEMENT OF THE KNOWLEDGE AND SKILLS OF THE HEALTH STAFF

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INTRODUCTION

Preterm infants are born at less than 37 weeks of gestational age and low birth weight, below 2.5 kg regardless of gestational age. High-quality universal newborn health care is the right of every newborn everywhere [1]. Preterm birth (< 37 weeks of gestation) is a global burden considered to be one of the main risk factors for neonatal mortality (under 5 years of age) and is associated with short-term and long-term effects, such as poor health and growth, intellectual and mental disabilities and early onset of chronic diseases, among others [2]. Complications from preterm births are the leading direct cause of neonatal deaths, accounting for 35% of all newborn deaths. Mortality rates increase proportionally with decreasing gestational age or birth weight. Moreover, these infants are also deemed to be a high-risk group for poor neurodevelopmental outcome [3].

Evidence-based knowledge in our Neonatal Care Unit has substantially increased during the last 5 years (2019-2023) due to the interventions that were done: 11 medical and nursing protocols have been created and 20 standard operating procedures (SOPs) were compiled, which help in the daily work of doctors and nurses. The final drafts of the protocols were submitted and approved by the National Center for Quality, Safety and Accreditation of Health Institutions and the Ministry of Health and Social Protection. The medical and nursing staff were trained and informed based on the protocols; moreover, the staff were trained on their application on infant care and on how to facilitate, improve and unify their work through the usage of the SOPs.

AIM

The aim of this study is to evaluate the impact of improvement the knowledge and the skills of the health staff in preventing neonatal mortality.

MATERIAL AND METHODS

In our country, there are only 2 tertiary-level Neonatal Intensive Care Units (NICUs), 11 regional maternity hospitals that offer secondary-level health services, and municipal maternity hospitals that offer first-level health services. This is a retrospective study that was conducted at UHOG "Koço Gliozheni" in Tirana and analyzed data in two time periods (January 1-December 31, 2019 and January 1-December 31, 2023). This maternity hospital has 16 level III NICU beds. In this maternity hospital, inborn babies, babies transferred from regional maternity hospitals, and babies transferred from private maternity hospitals are treated. However, in this study we included only inborn babies. Preterm birth is defined as a live birth with gestational age of < 37 weeks; in many studies the data are analyzed according to age groups, but in our study we divided them based on their weight groups (first group: 500-1,000 g; second group: 1,001-1,500 g; third group: 1,501-2,000 g; fourth group: 2,001-2,500 g; fifth group: > 2,500 g), in order to stay coherent with the classification of the Statistics Department of our maternity hospital. All neonatal deaths during this period, from birth to 28 days (or more), ≥ 500 g were included, but in detail we studied the mortality in preterm infants with a low birth weight (< 2,500 g), i.e., the fifth group was not considered.

RESULTS

About 7,538 babies were analyzed in total, of which 3,916 babies born in 2019 and 3,622 babies born in 2023. Premature babies, with a gestational age of 22-36^{+6} weeks were 768 infants (or 10.1%) in total (411 infants [or 10.4%], and 357 infants [or 9.8%], in 2019 and 2023, respectively). Despite a tendency for a decrease in the total number of births, the birth rates of the premature babies are roughly in the same percentages; however, what is noticed is that there is an increase in the number of babies born with fetal hypotrophy (92 infants [or 2.3%], and 106 infants [or 2.9%], in 2019 and 2023, respectively). From the comparison of the data of the two years (2019, when interventions began, and 2023), significant positive changes were observed in the reduction of infant mortality. In fact, according to the subgroups included in the study, we see that we have lowered mortality rate in the first group (98.5% versus 81%)

(however, in this group root interventions must be made); moreover, we see very significant changes in mortality in the other groups, i.e., in the second group (40.4% versus 12.5%), in the third group (7.8% versus 3.4%), and in the fourth group (5.8% versus 0 death). As we can see from the results, there is a statistically significant difference for the following groups: 1,001-1,500 g, 1,501-2,000 g, 2,001-2,500 g. This is a study that was carried out in a tertiary center in our country, and we will have to analyze and present the results from the whole country in another future activity.

CONCLUSIONS

These results suggest that, to decrease neonatal mortality, improved staff education and perinatal care quality is crucial.

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LECT 2

THE IMPACT OF EARLY CPAP IN THE DELIVERY ROOM IN PRETERM INFANTS WITH A GESTATIONAL AGE OF 31-36^{+6} WEEKS

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INTRODUCTION

Respiratory distress syndrome (RDS) is a primary pulmonary disorder associated with prematurity, particularly related to the immaturity of the lungs and, to a lesser extent, of the airways. It is a progressive atelectasis, which in the most severe form can lead to severe respiratory failure and death. The use of early continuous positive airway pressure (CPAP) in the Delivery Room for the management of RDS in preterm infants has shown very good results.

PURPOSE

This study aims to demonstrate the efficacy of the early use of CPAP immediately after birth for the management of RDS in preterm infants (our experience).

OBJECTIVES

To evaluate the efficacy and safety of early CPAP in the Delivery Room for reducing the severity of RDS in preterm infants (31-36^{+6} weeks of gestational age). To assess the impact of early CPAP on number of newborns transferred to a tertiar center.

METHODOLOGY

This is a retrospective study that analyzed data in two time periods (January 1-December 31, 2019 and January 1-December 31, 2023) at 5 maternity hospitals in Albania. The study included and compared newborns with a gestational age of 31-36^{+6} weeks, treated without early CPAP in Delivery Room in 2019 and with early CPAP in Delivery Room in 2023. Variables of interest include the severity of RDS, need for mechanical ventilation, and transfers to a tertiary center.

RESULTS

About 15,532 babies were analyzed in total, of which 8,490 babies born in 2019 and 7,042 babies born in 2023, in UHOG "Koço Gliozheni" and regional maternity hospitals of Elbasan, Korça, Fier and Vlora. Despite the decrease in total number of births, the number of premature births is increasing. In all these maternity hospitals, early CPAP use in the Delivery Room was used for premature babies 31-36^{+6} weeks from January to December 2023. Early CPAP therapy (in the group of year 2023) was found to have advantages in all the variables. The rate of transfers to a tertiary hospital varied among the different regions, with Fier reporting the lowest rate and Korça the highest.

CONCLUSIONS

Early use of CPAP in the Delivery Room is a valuable intervention for managing RDS in preterm infants. It reduces the severity of RDS, minimizes the need for invasive interventions and transfers to a tertiary center.

LECT 3

IMPACT OF NEONATAL EARLY-ONSET SEPSIS CALCULATOR IN OUR CLINICAL PRACTICE

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BACKGROUND

Early-onset neonatal sepsis (EOS) is a life-threatening condition. Diagnostic tools in identifying

healthy from diseased infants remains a challenge. This often leads to overtreating and unnecessary antibiotic exposure. Recently, Kaiser Permanente EOS risk calculator, based on both maternal risk factors and infants clinical presentation, was used as a safe tool for management of late preterm and term newborns at risk of EOS, that has demonstrated potential to reduce antibiotic use.

OBJECTIVE

To evaluate the efficiency of the sepsis risk calculator in the management of late preterm and term newborns with infectious risk factors, compared with our practical clinic strategies based on recommendations of Centers for Disease Control and American Academy of Pediatrics.

METHODS

This was a single-center retrospective cohort study in tertiary medical center, Maternity Hospital of Tirana "Queen Geraldine". We included infants born at ≥ 35 weeks' gestation, without congenital anomalies or other comorbidities, who were screened and/or received antibiotics for EOS risk during two periods, before (July-December 2023) and after (January-June 2024) the implementation of the sepsis risk calculator.

RESULTS

100 out of 2,334 and 92 out of 2,105 total infants born during the study periods were included in the study in 2023 and 2024, respectively. Following the implementation of the calculator, antibiotic exposure was reduced significantly by 32% ($p < 0.01$) without reported negative outcomes. Laboratory tests were reduced by 42% ($p < 0.01$). Indications for antibiotic use shifted more towards clinical condition of the infant. There were one culture-proven cases of sepsis in the first period. There were no readmissions with EOS in either period.

CONCLUSION

EOS calculator could be considered a strategic and objective tool for managing EOS in our clinical practice. More data is needed for safe implementation.

LECT 4

MATERNAL DIET AND BREASTFEEDING

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The time frame commonly defined as "the first 1,000 days" refers to a child's life period from conception until they reach 2 years of age, and represents a critical window in determining future health outcomes. Human milk (HM) is considered the ideal nourishment for infants, and exclusive breastfeeding is recommended for the first 6 months of life for its established short- and long-term positive effects, both on mothers and offspring. HM is a dynamic complex fluid that contains both nutritive elements and non-nutritive bioactive substances, contributing to immune system's and organs' development, protection against infections, and microbiota colonization. Several factors, both maternal and child-related ones (such as gestational age, birth weight or number of feedings per day), influence HM's composition; among these, maternal diet has been attracting more and more attention, emerging as a factor that may be modulated to influence the trajectory of infants' development. While results and methodology are still heterogeneous among the available studies, and data are controversy especially regarding macronutrients such as carbohydrates and proteins, evidence on the association between maternal diet and milk fatty acids (FA) composition, minerals and vitamins' content, is rapidly increasing [1]. Maternal diet seems to especially affect the polyunsaturated FA (PUFA) content and, to a lesser extent, the saturated FA (SFA) and monounsaturated FA (MUFA); also, the total antioxidant capacity of HM as well as its concentrations of various vitamins (A, C, B6, D, thiamine, choline), minerals (iodine, selenium) and other substances (carotenoids) have been shown to reflect the maternal intake of these nutrients, even though this data need further confirmation. More specifically, Mediterranean diet has been associated with lower content of SFA and ω-6/ω-3 ratio, and with a higher content of MUFA, ω-3 FA and total antioxidant capacity in HM [2]. Recent evidence highlights that vegan and vegetarian diets, when well-balanced and supplemented, can be considered safe and do not impact the nutritional values of HM.

Interestingly, there is also increasing evidence that suggest how modulation of maternal gut microbiota, via diet or probiotic intake, might modify HM microbiota (either by bacterial transfer via the entero-mammary pathway or by modifying short-chain FA or HM oligosaccharides profiles), which in turn may shape infant gut microbiota and its function [3].

Finally, maternal body composition may be associated with the nutritional value of HM: undernutrition with lack of vitamin B12, D, calcium and DHA during lactation may lead to low vitamin content in HM, while maternal overweight and obesity have been shown to alter HM composition with higher fat and protein content, elevation in HM hormones, pro-inflammatory cytokines and oligosaccharides, that are positively associated with child adiposity and growth; many studies have demonstrated that dietary interventions can mitigate the effect of obesity on HM composition.

This presentation aims to portray the current knowledge regarding the influence of maternal diet on HM composition, examining how diet interventions during lactation may promote both maternal and infant's health.

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LECT 5

NUTRITION AND GROWTH OF PRETERM BABIES IN NICUs

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Preterm birth is a worldwide health concern, affecting approximately 1 in 10 newborn infants. Optimizing the nutrition of preterm infants during their hospitalization in the Neonatal Intensive Care Unit (NICU) is crucial for their growth and long-term outcomes. Insufficient nutrition leads to inadequate growth and a delay in brain development. On the other hand, rapid weight gain is associated with an increased risk of obesity, diabetes, and heart disease. Human milk is considered the optimal nutrition for neonates. For very low gestational age infants, it is recommended to provide either their mother's milk or, if unavailable, donor milk from a milk bank. When breast milk is not an option, preterm formula can be used. In cases where full enteral feedings are not feasible due to the infant's medical conditions, partial or total parenteral nutrition is necessary. Breast milk needs fortification in order to meet the growth and developmental needs of low birth weight infants. It is critical to start feeding as soon as possible, as well as to minimize the use of parenteral nutrition. However, recommendations for nutrient intakes, types of feed, breast milk fortification and monitoring of nutrient adequacy vary considerably.

Challenges persist in establishing a consensus on the ideal extrauterine growth pattern for preterm infants, as well as for the optimal monitoring practices in the NICU. There is significant variability in the definitions of "postnatal growth faltering", also known as "extrauterine growth restriction", that has continued to be a significant concern startlingly evident since 25 years ago. It is defined as cross-sectional (with weight less than the 3rd or 10th percentile) or longitudinal (as loss of 1 or 2 SD from birth, at a time point, discharge, or 36/40 weeks postmenstrual), assessed using different growth charts such as Fenton 2013 and INTERGROWTH-21st.

In conclusion, early nutritional interventions are crucial for preterm infants' growth, development, and overall health outcomes. Addressing the challenge of inadequate growth and nutritional support tailored to the specific needs of different gestational ages requires standardizing guidelines for feeding and growth monitoring practices, in order to improve outcomes and reduce variability between countries and NICUs.

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LECT 6

NEONATAL SKIN AND RARE DISEASES

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It is common to find skin spots in newborn, which can take on a completely different meaning depending on their characteristics and sometimes allow us to recognize some rare diseases. The clinical approach to skin spots considers some aspects such as the color, shape and the size of the margins. It is essential to identify the simultaneous presence of other cutaneous anomalies, in order to identify any syndromic conditions. The time of onset, distribution pattern and evolution of these lesions are helpful in differentiating rare disorders. Detailed family history can be decisive in order to direct the diagnosis. There can be different causes that lead to the formation of skin spots. First of all genetic alterations, endocrine, metabolic and inflammatory causes, nutritional deficiencies (rare in the first days of life but which can appear later) and alteration in cell proliferation. We can distinguish three types of skin alterations: hyper-, hypomelanosis and vascular malformations. All these conditions can hide genetic diseases. Among the pathologies with hypomelanotic spots, the most frequent pathology is neurofibromatosis and tuberous sclerosis is another neurocutaneous disease; both have multisystem involvement. Clinical presentation of vascular anomalies is extremely variable and linked to hyperproliferation or hyperdistribution, and anomalous communication between the various vascular structures (capillaries, veins, and arteries) are typical of some syndromic conditions. It is important to know how to recognize conditions due to the characteristic skin lesions, as they are typical of complex rare disorders, and a multidisciplinary approach is necessary for the follow-up and management of these patients, to evaluate the evolution and identify associated signs or symptoms.

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LECT 7

PREVENTION AND EARLY CARE OF PRESSURE ULCERS IN THE NICU SETTING: A QUALITY IMPROVEMENT PROJECT

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The prevention of hospital-acquired pressure injuries (HAPIs) in neonates admitted to high and medium intensity settings is of paramount importance for both the pediatric patient and his family. Long-term stays in the Neonatal Intensive Care Unit (NICU) can potentially result in high rates of HAPIs due to physiological factors and the difficulty or inability to reposition these small and fragile patients.

It becomes necessary to develop a multimodal and multidisciplinary translational HAPI prevention program, creating and training multidisciplinary and multi-specialty personnel so as to have wound prevention teams, have HAPI risk assessment tools, and provide specific training regarding the use of dressings (5-layer foam silicon coated) and prophylactic surfaces (fluidized positioners).

The protocol that uses these coupled technologies is called "double protection strategy protocol" (DPS).

Numerous studies have evaluated the intraoperative efficacy of different prophylactic dressings on the areas of adults at greatest risk (sacrum, heels), among which foams and 5-layer edged foam dressings appeared to be the most protective against the development of pressure sores. Very few studies have focused on the prevention of pediatric HAPIs during surgery and are limited to testing only the effectiveness of prophylactic foam dressings during placement in the operating room. As noted by Schlüer et al., most of the preventive interventions used so far in pediatrics concern the evaluation of the skin and the redistribution of pressure surfaces.

As part of the evaluation of the project's effectiveness in reducing HAPIs, we conducted a prospective cohort study on two groups of patients: in the intervention group, 200 newborn undergoing long-duration NICU stays and submitted to a DPS were considered, and their results were compared with an historical cohort of 200 children (the control group) who had undergone similar NICU stays the previous year without experiencing DPS.

Results demonstrated an 80% reduction in HAPIs in the intervention group ($p < 0.01$) compared to the control group when controlling for age and weight, pathology, comorbidities, and duration of intervention. We believe that the results demonstrate that it is possible to significantly reduce the incidence of HAPIs in these highly vulnerable patients by using a multimodal, multidisciplinary evidence-based HAPI prevention strategy.

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LECT 8

SEPSIS AND ITS TREATMENT FROM NEWBORNS TO ADULTS

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Neonatal sepsis is a serious systemic infection that can occur in infants, especially premature infants or those with other vulnerable conditions. Pediatric sepsis refers to the same condition but occurs in older children. Both conditions carry a high risk of mortality if not treated quickly and adequately.
Sepsis leads to a systemic inflammatory response that can damage multiple organs and activate disseminated intravascular coagulation (DIC). DIC is a condition in which blood clots abnormally in blood vessels, consuming clotting factors and causing bleeding and organ damage. In patients with severe sepsis, a reduction in functional protein C may occur, which could contribute to the development of blood clots and DIC, leading to a worse prognosis [1].
Because protein C is an essential component of the blood coagulation system and serves as a natural anticoagulant, in neonatal or pediatric sepsis the possible use of protein C obtained from purified human plasma by murine monoclonal antibodies has recently been evaluated to restore protein C levels in children with sepsis who have DIC or a thromboembolic tendency. Some studies and clinical reports suggest that administration of exogenous protein C could improve microcirculation and reduce tissue damage, helping to improve prognosis in pediatric patients with severe sepsis.
However, the use of exogenous protein C in infants or children with sepsis is experimental and not yet officially approved for this purpose. There have been reports of improvements in patients with sepsis and DIC treated with protein C, but the results are not yet sufficient to make general recommendations. It is not a routine treatment for neonatal or pediatric sepsis, but may have a role in clinical situations complicated by coagulation defects or DIC.
The use of exogenous protein C in adults is not a treatment envisaged in any sepsis guideline.
However, it seems to have a rationale for its use in sepsis [2]. In the first decade of the 21st century, activated recombinant protein C was introduced into the treatment of sepsis in order to reduce the hypercoagulative problems of sepsis. The studies conducted at the beginning presented striking results, but these data were soon undermined by the increase in mortality due to lethal hemorrhagic events for adult patients. This led to its withdrawal from the market and from clinical use. Subsequently, some research centers have started to test exogenous non-activated protein C, but the results present in the very limited literature have not yet fully confirmed its usefulness. Probably, assessment of the individual hemostatic phenotype could thus be a solid background to identify those patients that may benefit from certain treatment modalities like administration of protein C [3]. Meningitic sepsis represents the pathology in which the best results have been achieved. The timing of administration seems to be a decisive factor in obtaining a clinical result.

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LECT 9

ARTIFICIAL INTELLIGENCE IN NEONATOLOGY

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Artificial Intelligence (AI) and Machine Learning (ML) are rapidly transforming the landscape of neonatal care, offering innovative solutions to address the unique and complex challenges encountered in this field. AI technologies have demonstrated significant potential in enhancing diagnostic accuracy, predicting clinical outcomes, and personalizing treatment strategies in Neonatal Intensive Care Units (NICUs). Specifically, AI models are being increasingly utilized for the early detection of life-threatening conditions such as neonatal sepsis, necrotizing enterocolitis, and bronchopulmonary dysplasia. These models leverage large datasets derived from electronic health records, physiological monitoring systems, and advanced imaging techniques, enabling more timely and accurate interventions [1].

Despite the promising applications, the integration of AI in neonatology faces several challenges. These include concerns related to data privacy and security, and the need for robust and diverse multicenter datasets. Moreover, the successful deployment of AI technologies in clinical settings requires a multidisciplinary approach that fosters collaboration between neonatologists, data scientists, engineers, and healthcare administrators [2].

As AI continues to evolve, its role in neonatology is expected to expand further, offering new avenues for research, innovation, and clinical care. Future developments may include more sophisticated predictive models, enhanced decision support systems, and AI-driven precision medicine approaches tailored to the individual needs of neonates. These advancements hold the promise of improving survival rates, reducing complications, and optimizing long-term developmental outcomes for the most vulnerable patient population [3].

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LECT 10

AUTISTIC SPECTRUM DISORDERS IN NICU CANDIDATES

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Prevalence of autistic spectrum disorders (ASD) has increased steadily over the years, reaching the astonishing number of 1/39 children in the USA, according to WHO data. Despite this ASD pandemic, little is known about the true origin of the disease, resulting in the absence of targeted etiological treatment apart from symptomatic interventions. Theories regarding etiological factors involve genetic predisposition co-occurring with environmental conditions. Neonatal Intensive Care Unit (NICU) candidates (such as preterm neonates, infants with hypoxic ischemic injury and congenital heart disease) are at increased risk for ASDs compared to the general population, without a clear etiology.

Studies from different geographic areas show increased ASD prevalence amongst preterm adults compared to full-term. A large population study in Sweden, with over 4,000,000 single births from 1973-2013, showed a 3-fold increased risk of ASD in extremely preterm cases, compared to term, and about 2-fold increase in moderately preterm, compared to term.

Theories about increased ASD prevalence in NICU candidates, and especially in preterm neonates, are related to two pathways.

The first pathway possibly leading to ASD is related to environmental factors and mechanisms that led to prematurity. Advanced paternal and maternal age, maternal autoimmune disease such as diabetes, smoking, heavy metals in mother's diet, maternal depression and the use of anti-depressant medication, maternal bacterial or viral infection, chorioamnionitis, fetal inflammation, oxidative stress are all possible etiologic associations acting alone or as modifiers to genetically predisposed cases. Studies in humans and experimental models explore the role of cytokines and inflammation cascade in altering brain construction. Many sophisticated connectivity and brain growth studies in humans and animal models show various structural abnormalities early in life related to inflammatory or bacterial products such as over-connectivity, disturbances in axonal, cell maturation and migration, reduced cortical volume, impaired pruning, synaptic plasticity, neurogenesis and neurotransmission. Subsequent behavioral and developmental measurements in humans and animal models connect these early structural findings with later difficulties to cognition, executive functioning

and social behavior. Thus, prematurity is either a concurrent event or a modifying factor to genetic predisposition and to environmental risk exposure.
The second pathway possibly leading to ASD is extrauterine brain development at this very early stage. Womb is a low sensory environment for the fetal developing brain, providing all necessary stimuli for normal brain construction. In intrauterine life, there are minimal light and tactile stimuli, dull noises, absence of intense smells, no sleep disturbances. All these are forcefully and dramatically altered after preterm birth, although most NICU nursing policies are protecting premature neonates from exposure to increased noise, light, pain, sleep disturbances to some extent.
Finally, studies investigating possible association of congenital heart diseases and ASD focus on shared gene pathways playing a theoretical common role in the development of both heart and brain.
To conclude, NICU candidates are at increased risk of ASD, but etiology remains obscure. Many environmental factors are being targeted, with no clear evidence. Prospective, large, well-designed studies are required to clarify etiology and take appropriate action to diminish the risk.

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LECT 11

RESPIRATORY SYNCYTIAL VIRUS (RSV) INFECTION: NOT ONLY PRETERM INFANTS

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Respiratory syncytial virus (RSV) is a leading cause of morbidity and mortality in children under 5, particularly affecting infants under 1 year old. RSV is responsible for over 80% of lower respiratory tract infections in infants and remains the most common cause of pneumonia and bronchiolitis, with up to 90% of cases attributed to RSV. Children who suffer from RSV infections during infancy have an increased likelihood of developing chronic respiratory conditions, such as asthma and wheezing, later in life. RSV also has significant associations with the development of chronic obstructive pulmonary disease in adulthood, suggesting long-term impacts of early childhood infections. Certain high-risk groups (such as premature infants and infants with underlying medical conditions, such as chronic lung disease of the premature, bronchopulmonary dysplasia, hemodynamically significant congenital heart disease, immunocompromised conditions, severe neuromuscular disease) are prone to severe RSV-related illness, with higher morbidity and mortality rates. RSV diagnosis is generally based on physical examination, especially during peak seasons. While laboratory tests are often unnecessary for mild cases, they may be employed to confirm severe infections. Early identification of high-risk patients is critical. Recent research into the transcriptomic signatures of RSV-infected individuals has led to advancements in identifying predictive biomarkers. These biomarkers can help classify disease severity, predict responses to treatment, and improve clinical outcomes. The development of monoclonal antibodies, particularly those targeting the RSV fusion (F) protein, represents a significant step forward in preventing severe RSV infections. Although there are no recommended treatments or approved vaccines for RSV, passive immunization with the monoclonal antibodies have been shown to reduce RSV-related hospitalizations and is currently indicated to prevent severe lower respiratory tract disease caused by RSV in certain categories of high-risk children aged < 2 years.

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