

Selected Lectures of the 22nd International Workshop on Neonatology and Pediatrics

PRECISION NEONATOLOGY AND PEDIATRICS

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LECT 1

PLASTICS IN PERINATOLOGY

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Micro- and nanoplastics (MNPs) have entered the maternal-placental-fetal continuum, but their significance for perinatology may extend far beyond the simple question of whether particles cross the placenta. Human studies have documented MNPs in placental and other perinatal matrices, while experimental models show that maternal nanoplastic exposure can alter placental function and fetal metabolism [1, 2]. Yet the developing organism does not encounter an environmental exposure passively. Pregnancy is a dynamic information-processing system in which maternal physiology, placenta and fetus continuously sense, transform and respond to environmental signals.

We propose that plastics should therefore be considered not only as potential toxicants, but as evolutionarily novel perturbations interpreted through evolutionarily ancient biological systems. Membrane stress, lysosomal dysfunction, oxidative imbalance, mitochondrial changes, inflammation and altered metabolism may be read by conserved sensing pathways that were never selected to “recognize plastic” as such. The resulting response may range from adaptation and compensation to maladaptation and toxicity, depending on dose, persistence, developmental timing and biological context.

This perspective becomes particularly provocative in fetal life. The fetus may be affected even without receiving the original exposure in the same form. Maternal responses can modify inflammation, metabolism, endocrine signalling and vascular physiology; the placenta can further transform these signals through changes in transport, endocrine function and vascular resistance. Thus, the placenta should be viewed not only as a barrier or sensor, but as a biological translator: an external plastic

exposure may be serially transformed into maternal biological information, placental reinterpretation and, finally, fetal developmental signals. This concept is consistent with the broader DOHaD paradigm, in which the placenta is a central mediator between prenatal exposures and later health [3].

The central question for precision perinatology may therefore no longer be only: “How much plastic reaches the fetus?” It may be: “What biological information about a plastic-rich world reaches the fetus, and what phenotype is being constructed in response?”

The placenta is not merely a wall between two organisms. It is an interpreter between two worlds.

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LECT 2

ENVIRONMENT AND KIDNEY DAMAGE: WHAT ROLE DO MICRO- AND NANOPLASTICS AND ENDOCRINE-DISRUPTING CHEMICALS PLAY IN KIDNEY DAMAGE?

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The widespread presence of micro- and nanoplastics (MNPs) in the environment and in the human body, including the brain [1], poses a significant threat to human health [2]. Evidence from multiple studies in experimental models and in cultured cells suggests that MNP overexposure might induce nephrotoxicity. Multiple open questions

regarding MNP exposure and onset of kidney disease or progression remain. The possible toxic effects of MNPs on human cells include lysosomal dysfunction, oxidative stress, mitochondrial damage and DNA damage, ending with cell necrosis and apoptosis. Multiple methods have been developed for the identification of MNPs in cells and tissues, all characterized by advantages and challenges. The relationships between MNPs and kidney disease are complex and in part remain unclear. Podocytes and proximal tubular epithelial cells are generally indicated as the main targets of MNP-related nephrotoxicity. Furthermore, MNPs act as chemical sponges, absorbing multiple endocrine disrupting chemicals (EDCs) on their surfaces. The synergistic toxic interaction of MNPs and EDCs, referred to as “the cocktail effect”, might represent a crucial factor in MNP-related nephrotoxicity [3]. In this complex scenario, a crucial role could be played by AI-driven methods applied to MNP in research and in clinical practice. High-throughput analysis of large datasets, increased sensitivity and accuracy in the detection and characterization of MNPs, ability to reach certain quantitative data on MNPs-related kidney pollution, discovery of new patterns and biomarkers from histological kidney images are some of the multiple potential advantages of AI-driven models applied to research in the MNPs field. Although a direct causal link between MNP exposure and renal impairment has not been definitely demonstrated in humans, the irony lies in the semantic shift: while “plasticity” once symbolized the kidney’s capacity to change and adapt to environmental changes, “plastic” now threatens that very adaptability [1].

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LECT 3

PRESENT AND FUTURE OF NEONATOLOGY: FROM SURVIVAL TO LIFELONG HEALTH

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Over recent decades, neonatology has achieved remarkable improvements in survival, including for extremely preterm and critically ill newborns. However, the challenge is now changing because survival alone is no longer an adequate measure of success. The present and future of our discipline must be defined by survival without major morbidity, optimal neurodevelopment, quality of life and long-term health. This transition requires a shift from organ-centred intensive care towards individualized, developmental and family-integrated care. Less invasive respiratory support, human milk and precision nutrition, infection prevention, neuroprotection, pain and stress reduction, and active parental participation should no longer be considered separate interventions, but components of a single strategy aimed at protecting the developing brain and the infant’s developmental trajectory [1]. Precision medicine will increasingly reshape neonatal care. Rapid genome sequencing can provide an early diagnosis in critically ill newborns with suspected genetic disease and may directly modify clinical management, transforming the traditional diagnostic odyssey into real-time precision medicine [2]. At the same time, artificial intelligence and machine learning offer new opportunities to integrate the enormous amount of physiological and clinical data generated in neonatal intensive care. Predictive models may support earlier recognition of sepsis, respiratory deterioration, brain injury and other complications, but their introduction must be accompanied by rigorous validation, transparency, equity and human clinical oversight [3]. Technology, however, cannot define the future of neonatology by itself. The more sophisticated care becomes, the greater the need to preserve its human dimension. Parents must increasingly be recognized as partners in care, while communication, shared decision-making and ethical reflection remain central, particularly at the limits of viability and in situations of therapeutic uncertainty. Finally, the boundaries of neonatology are expanding. Care should be conceived as a continuum beginning before birth and extending beyond discharge through structured follow-up and the first 1,000 days, when biological, environmental and social determinants can influence lifelong health. The neonatologist of the future will therefore not only treat disease in the newborn period, but help shape the health trajectory of the child. The

future of neonatology is not simply about doing more. It is about doing better, earlier and more precisely: combining innovation with prevention, developmental care and humanity, and moving from the goal of survival to the ambition of lifelong health.

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LECT 4

THE LATEST NEWS ON RETINOPATHY OF PREMATURITY: WHAT TO KNOW, WHAT TO DO

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Retinopathy of prematurity (ROP) treatment is undergoing a paradigm shift. Laser photocoagulation has prevented blindness for decades, but it achieves disease control by ablating the avascular peripheral retina and is associated with structural changes and a substantial burden of high myopia. Intravitreal anti-vascular endothelial growth factor (anti-VEGF) therapy offers a less destructive approach, particularly for posterior and aggressive ROP. It induces rapid regression of plus disease and neovascular activity while preserving the peripheral retina and allowing physiological vascularization to continue. Comparative evidence now indicates favorable anatomical outcomes in selected cases and a consistently lower risk of high myopia than after laser treatment. Five-year randomized data also provide reassurance regarding visual,

ocular and systemic outcomes, although longer observation remains essential [1].

The biological advantage of retinal preservation introduces a new clinical responsibility. After anti-VEGF treatment, vascularization may remain incomplete and persistent avascular retina (PAR) may coexist with apparently stable posterior findings. Reactivation can occur later than after laser, occasionally beyond the conventional screening period. Consequently, initial regression must not be considered the end of treatment. Follow-up should continue until vascular maturation is clearly documented, using wide-field imaging and fluorescein angiography when clinically indicated. Eyes with PAR require individualized, very long-term surveillance because the lifelong implications of persistent nonperfusion, vascular abnormalities and late vitreoretinal complications remain incompletely defined [2, 3].

The goal of ROP therapy must therefore extend beyond retinal attachment and short-term sight saving. By controlling pathological angiogenesis while preserving the conditions for neurovascular and ocular development, treatment should aim to reduce refractive morbidity, optimize visual function and support the child's development, participation and quality of life. Success should be measured across the life course: not simply by whether sight was saved, but by how well the child is able to see, develop and live.

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LECT 5

VIABILITY OF EXTREMELY PREMATURE NEONATES: CLINICAL APPROACHES AND OUTCOME

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Periviability, the earliest gestational stage at which survival becomes possible, remains one of the most difficult areas in neonatal medicine. Infants born in this window carry a high risk of death or survival with long-term morbidity, and decisions about resuscitation raise unresolved clinical, ethical, and legal questions.

Historically, the lower limit of viability has moved steadily downward, from around 28 weeks in the 1970s to 22-24 weeks today, reflecting advances in perinatal and neonatal intensive care rather than a fixed biological threshold. Current guidelines describe a “gray zone”, generally between 22 and 25 weeks, in which the decision to resuscitate is individualized and family-centered, bounded by a lower limit below which resuscitation is not recommended and an upper limit above which it is considered obligatory. Gestational age alone is an imprecise predictor of outcome; birth weight, sex, singleton status, antenatal corticosteroid exposure, and the presence of severe anomalies or growth restriction all modify prognosis and should be considered together.

Outcomes vary considerably between countries because of differences in obstetric and neonatal practice, gestational age assignment, and national policy. Survival rates of infants born at 22 and 23 weeks’ gestation remained low in many countries or regions (< 50% for 22 weeks’ gestation and < 60% for 23 weeks’ gestation) aside from a few exceptions, such as in Japan, Sweden, and Germany. Sweden reports survival at 22 weeks approaching 50%, while in the United States about 29% of actively treated infants born at 22 weeks survived to discharge in 2019. These differences mean that no single international threshold for viability is appropriate; each country must interpret the evidence within its own resources and outcome data.

In Türkiye, births before 20 weeks of gestation are legally defined as miscarriage, while any infant born beyond 20 weeks showing signs of life is entitled to resuscitation under the right to life, and physicians may later be required to demonstrate that all essential interventions were performed.

Ethically, the management of extremely preterm infants is governed by the tension between beneficence, which drives efforts to save the infant, and non-maleficence, which requires avoiding unnecessary harm to the infant and family. Parental

decision-making is further shaped by the physician’s counseling, family input, and religious and cultural attitudes, all of which carry particular weight in societies such as Türkiye.

In summary, survival and outcomes for infants born at 22-25 weeks have improved worldwide, but a universal definition of viability is not achievable. Management decisions should rely on national data and guidelines and must integrate clinical, legal, and ethical considerations rather than gestational age alone.

LECT 6

PREMATURITY AND MORE: CLINICAL CHALLENGES AND LESSONS LEARNED FROM COMPLEX CASES

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Overlap of prematurity with complex multi-organ disorders challenges neonatal intensive care, requiring a multidisciplinary approach and close cooperation between second-level and third-level centres. We report four clinical cases managed through this network with Neonatal Intensive Care Units from Sardinia, highlighting lessons learned about prompt referral, integrated expertise and shared follow-up.

CASE REPORTS

Case 1

A preterm male, born at 27 weeks, was diagnosed with cystic fibrosis complicated by meconium ileus, severe bronchopulmonary dysplasia and chronic respiratory failure requiring invasive ventilation. He underwent placement of a tracheostomy, gastrostomy, and ileostomy, and was started on compassionate-use CFTR modulator therapy (ivacaftor/elextacftor, tezacaftor, and ivacaftor), which led to clear clinical improvement. Close teamwork between neonatal surgeons and cystic fibrosis specialists made intestinal re-anastomosis possible and progressive respiratory weaning, with

a tailored home-care plan organized between the hospital team and local community health services.

Case 2

A preterm male, born at 23 weeks, developed severe acute kidney injury with anuria and diffuse edema. He required hemodynamic and antimicrobial support. A hemodynamically significant patent ductus arteriosus (PDA), unresponsive to pharmacological closure, was surgically closed with clinical benefit. Renal function progressively normalized, while severe cystic periventricular leukomalacia emerged on cerebral ultrasound. This prompted the team to set up a dedicated long-term developmental follow-up plan alongside his local healthcare team.

Case 3

A neonate with prenatal diagnosis of interrupted aortic arch, hypoplastic aorta and large ventricular septal defect was transferred from a second-level center at three days of life for hybrid cardiac intervention. Stenting of the PDA and pulmonary artery banding stabilized systemic perfusion, followed by anticoagulation and staged medical therapy including diuretics and captopril. Transient intestinal pneumatosis and post-contrast renal impairment resolved with supportive care, illustrating the need for integrated cardiac-neonatal-surgical expertise for very-low-birth-weight infants.

Case 4

A late-preterm female was referred at one month of age for suspected congenital arthrogryposis. Tracheostomy and gastrostomy were required for severe spastic hypertonia and feeding difficulties, and baclofen was started. Next-generation sequencing identified compound heterozygous *TOR1A* variants. Orthopedic casting, neurological and genetic counseling were coordinated to plan long-term rehabilitation and family support.

CONCLUSIONS

In complex neonates, prematurity often coexists with or mimics genetic malformative disorders. These cases confirm that structured collaboration between second- and third-level centers, through timely transfer, shared governance and coordinated follow-up, is essential for managing complex neonates and ensuring continuity of care.

LECT 7

NEONATAL ARRHYTHMIAS

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Neonatal electrocardiography (ECG) remains a cornerstone in the early diagnosis and management of cardiovascular disorders in newborns. Its interpretation is particularly challenging because of the unique physiology, ongoing postnatal adaptation, and transitional circulation that distinguishes the neonatal heart from that of older children and adults. Typical neonatal ECG findings include higher heart rates, age-dependent variability in QRS and repolarization patterns related to myocardial immaturity and autonomic development, as well as transient changes associated with ductus arteriosus closure. These factors necessitate age-specific interpretive criteria and careful clinical correlation.

NEONATAL ARRHYTHMIAS

The spectrum of neonatal arrhythmias extends from benign rhythm variants to critical disturbances.

Premature atrial and ventricular contractions are frequent and often self-limited but may sometimes reflect structural or metabolic abnormalities.

Supraventricular tachycardia is the most common clinically significant arrhythmia in neonates; early detection is essential to avoid hemodynamic compromise.

Bradycardia is frequently observed, especially in preterm infants, and may be associated with hypoxia, acidosis, or sinus node dysfunction. Severe bradycardia requires prompt evaluation.

Conduction disorders, including first- and second-degree atrioventricular (AV) block, may occur in newborns born to mothers with autoimmune diseases or in neonates with congenital heart defects such as atrial septal defect. These conditions can progress to complete heart block.

Abnormal P waves and PR intervals may also indicate atrial disease, pre-excitation syndromes (e.g., Wolff-Parkinson-White), or emerging AV nodal dysfunction, highlighting the importance of careful interpretation.

ECG IN CONGENITAL HEART DISEASE

Although echocardiography remains the gold standard for congenital heart disease, ECG offers valuable complementary insights.

Conduction abnormalities such as prolonged PR intervals, bundle branch block, or altered P-wave patterns can provide early diagnostic clues.

ST-segment and T-wave abnormalities may indicate repolarization disturbances linked to structural defects or altered ventricular loading.

Signs of chamber hypertrophy or strain can suggest pressure or volume overload and guide further imaging.

Postoperative monitoring relies on serial ECGs to assess recovery, detect arrhythmogenic substrates,

and promptly identify complications such as junctional ectopic tachycardia or conduction blocks.

CONCLUSION

Despite advances in echocardiography and imaging, the neonatal ECG remains essential in Neonatal Intensive Care Units. Accessible and non-invasive, it helps detect arrhythmia, identify subtle signs of congenital heart disease, and guide both acute and long-term management. By combining expert interpretation with innovative analytic methods, ECG continues to enhance diagnostic accuracy, support therapeutic decisions, and improve neonatal cardiovascular outcomes.

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LECT 8

UREA CYCLE DEFECTS

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The pathway of ammonia metabolism in mammals was discovered in 1932 as a metabolic cycle present in the liver in different compartments and in 1958 was described the first human disorder of the urea cycle. Since then, defects affecting all urea cycle steps have been described as primary urea cycle disorders (UCDs) [1]. Patients with a complete enzyme deficiency in the majority of cases present in the first days of life with hyperammonemic coma and most survivors with a neonatal presentation are at a high risk of recurrent crises and suffer from a severe neurological disease with developmental delay, as brain damage correlates with duration and severity of hyperammonemia. Patients with a milder enzymatic defect and less severe mutations may present at any age with a chronic presentation and a wide variety of clinical signs. Therefore, at all ages patients must be identified as soon as possible to reduce

the risk of brain damage and improve prognosis. Accordingly, ammonia must be assessed in all acutely sick neonates and in children, adolescents and adults with unexplained neurological symptoms. Hyperammonemia is the hallmark of UCDs but is a nonspecific disease biomarker. To establish a precise diagnosis determination of plasma ammonia must be run in parallel with the analysis of plasma amino acids and of urine orotic acid combined with the genetic analysis [2]. Recently, to reduce diagnostic delay some UCDs have been included in neonatal screening. Treatment of UCDs relies on the management of acute hyperammonemia – consisting in stopping protein intake, start of i.v. glucose, initiation of first line medications and, in unresponsive cases, in extracorporeal depuration – while the long-term treatment is based on a low protein diet combined with essential amino acids supplementation, arginine and/or citrulline therapy and the ammonia scavengers drugs benzoate and phenylbutyrate [2].

Overall, the UCDs comprise defects of any of the six enzymes (NAGS, CPS1, OTC, ASS, ASL, Arginase) or of two aminoacid transporters (Ornt1 and Citrin) which are primarily involved in the process of ureagenesis from the priming molecules, ammonia, ATP, and bicarbonate. With exception of OTC deficiency which is inherited as an X-linked disorder, all UCDs are autosomal recessive diseases. Regardless of presentation modalities (i.e. acute or chronic), diagnosis of the specific defect and the initial medical treatment must proceed simultaneously since other conditions may affect biochemical pathways connected with the urea cycle, as seen in other “intoxication type” inborn errors of metabolism (e.g. organic acidurias) or in conditions not genetically determined (e.g. infections, drugs, neoplasia, vascular malformations). Despite progress in conventional patient management, including modalities for extracorporeal depuration, the development of nitrogen scavengers in novel formulations, the improvements of dietary interventions, the overall prognosis of UCDs still remains poor for many of the patients [2]. To fill this gap, severe cases with frequent metabolic crises, high disease burden and poor quality of life are increasingly treated by liver transplantation with the objective of providing an *in vivo* enzyme replacement therapy [3]. This approach, especially in early treated patients, allowed a significant improvement of long-term prognosis, of cognitive skills and of quality of life, by reducing disease burden and risk of hyperammonemic crises [3].

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LECT 9

NEONATAL-ONSET GENETIC ENCEPHALOPATHIES: DIAGNOSTIC APPROACH, TIMELY INTERVENTION, AND PRECISION THERAPIES

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Neonatal epilepsies constitute a group of epilepsies that can result from various genetic, structural, and metabolic etiologies within the first 28 days of life [1]. Although the majority of seizures are secondary to acute insults, approximately 15% of cases represent the onset of a neonatal epilepsy, where the seizure is a symptom of an underlying condition that can be defined by specific electro-clinical phenotypes [2]. Continuous video-EEG (cEEG) monitoring remains the indispensable gold standard for diagnosing both electrographic and subclinical seizures, as well as for identifying the phenomenon of electro-clinical uncoupling induced by antiseizure medications [1]. The integration of clinical semiology and EEG background helps clinicians identify the etiology: tonic or sequential seizures suggest channelopathies (e.g., *KCNQ2*, *SCN2A* genes), whereas myoclonic seizures are suggestive of inborn errors of metabolism. In this scenario, next-generation sequencing (NGS) techniques and rapid exome sequencing constitute a first-line tool for obtaining a timely molecular diagnosis in critically ill neonates [3]. Differentiating acute provoked seizures from neonatal-onset epilepsies, which are typically genetic and demand longer-term treatment, is a new cornerstone for the management of seizures in neonates.

The timeliness of treatment is the most critical factor: initiating antiseizure therapy within 1 hour of the first electrographic seizure significantly reduces the total seizure burden and the number of seizures in the subsequent 24 hours compared to delayed treatments. Early control of the seizure burden is essential in mitigating the risk of secondary epilepsy and protecting neurodevelopment [1]. Etiological diagnosis guides precision medicine interventions:

- channelopathies (*KCNQ2*, *SCN2A* GoF, *PRRT2*) – these conditions show a rapid and targeted response to sodium channel blockers (e.g., carbamazepine, oxcarbazepine, phenytoin) [2];
- metabolic epilepsies – disorders such as pyridoxine-dependent epilepsy benefit from an early therapeutic trial with pyridoxine to stop seizures and prevent severe neurological outcomes [2];
- molecular pathogenetic cause – drug repurposing (e.g., fenfluramine, ganaxolone, mTOR inhibitors) and advanced gene therapies (antisense oligonucleotides – ASOs, adeno-associated viral vectors – AAV) open new therapeutic possibilities aimed at the molecular pathogenetic cause [3].

In conclusion, integrating translational research into patient care is essential to fully leverage the potential of repurposed drugs and new gene-based therapies. Diagnostic and therapeutic timeliness, and the adoption of etiology-specific precision therapies represent an essential component of current care to mitigate seizure burden and support neurodevelopment [1].

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LECT 10

IMPORTANCE OF CRANIAL ULTRASOUND IN EXTREMELY PRETERM INFANTS

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BACKGROUND

Cranial ultrasound (cUS) is a routine imaging technique in Neonatal Intensive Care Units (NICUs), owing to its accessibility, safety, low cost, and feasibility at the bedside. In the neonatal period, it provides good anatomical resolution and allows serial assessment of brain development and injury. The anterior fontanelle approach can be complemented by posterior, mastoid, or occipital fontanelle views.

OBJECTIVE

To highlight the role of cUS in the early diagnosis, monitoring, and follow-up of major brain lesions in extremely preterm infants.

DISCUSSION

The first cUS examination should be performed shortly after birth to detect congenital malformations and prenatal or perinatal brain injury, providing a baseline for subsequent examinations. Intracranial hemorrhage is a major cause of neonatal mortality and long-term neurological disability. In preterm infants, more than 90% of hemorrhages occur within the first 3 days of life, with progression during the first week. cUS is essential for initial diagnosis, monitoring of lesion evolution, and assessment of sequelae.

Periventricular leukomalacia represents a major ischemic lesion of the preterm brain and an important cause of permanent neurological injury, occurring in approximately 25-40% of infants weighing < 1,000 g. The most commonly affected white matter is located in arterial watershed regions, particularly around the trigones of the lateral ventricles and in the frontal regions. cUS may be normal during the first week, whereas cystic lesions can develop and become evident within the first month. These lesions may subsequently regress, leaving *ex vacuo* ventricular dilatation.

Cerebellar injury is increasingly recognized as an important complication of extreme prematurity. Cerebellar hemorrhage may be underestimated when assessed only through the anterior fontanelle: it has been reported in approximately 3% of infants < 30 weeks of gestation using anterior fontanelle ultrasound, compared with 9% using the mastoid fontanelle and 19% with magnetic resonance imaging (MRI).

In infants weighing < 1,500 g and with a gestational age < 32 weeks, cUS at term-equivalent age is particularly important for detecting residual or late-onset white matter injury, cystic leukomalacia, *ex vacuo* or post-hemorrhagic ventricular dilatation, porencephalic evolution of periventricular hemor-

rhagic infarction, and cystic changes of arterial infarction, usually involving the middle cerebral artery territory.

CONCLUSIONS

cUS is a fundamental first-line imaging modality for preterm infants in the NICU. It enables serial bedside assessment of germinal matrix/intraventricular hemorrhage, white matter injury, and cerebellar lesions, supporting early recognition of brain injury and its evolution. However, its sensitivity is limited for mild or diffuse white matter abnormalities; therefore, MRI remains complementary when more detailed assessment is required.

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LECT 11**NEONATAL BIOETHICS IN 2026: PROGNOSTIC UNCERTAINTY, PROPORTIONATE CARE, AND RESEARCH WITHOUT PRIOR CONSENT**

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Neonatal bioethics is increasingly concerned not simply with whether life can be sustained, but with how morally defensible decisions can be reached when prognosis is uncertain, parental authority is constrained, and intervention cannot await complete deliberation. This critical narrative analysis examines three interconnected controversies through empirical studies, normative scholarship, and consensus recommendations recently published: decision-making at the limits of viability, proportionality in neonatal end-of-life care, and research without prior parental consent. The central argument is that uncertainty should intensify procedural safeguards rather than justify either therapeutic automatism or the transfer of responsibility to distressed families [1-5].

First, perivable decision-making requires distinguishing biological limitations from outcomes partly shaped by treatment policies. Survival estimates depend on which infants receive active care, available expertise, and previous obstetric decisions; presenting these estimates as immutable individual predictions risks reinforcing institutional practices through self-fulfilling prognoses. Counselling should therefore disclose relevant denominators, contextual variability, and the limits of developmental prediction, while separating empirical probabilities from value judgements about disability. Antenatal deliberation must also respect maternal bodily autonomy rather than subsuming maternal interests within neonatal benefit. Where several options remain ethically defensible, parental participation should be negotiated, not assumed to require exclusive responsibility for the final decision [1].

A 2026 multicentre study illustrates the gap between endorsed and experienced participation: among 71 parents, 89% wanted substantial involvement, whereas 63% felt included. Some described coercion despite the language of shared decision-making. These findings support explicit exploration of family values, transparent clinical recommendations, and opportunities to express disagreement; however, the predominance of bereaved respondents limits generalisability. Meaningful partnership requires attention to relational vulnerability, not merely disclosure followed by a signature [2].

Second, decisions to continue, withhold, or withdraw intensive treatment should be grounded in proportionality, understood as an individualised appraisal of achievable benefits, treatment burdens, suffering, and the infant's interests. Disability alone cannot establish that continued treatment is contrary to those interests. Conversely, physiological survival does not automatically justify every technically available intervention. The 2026 Society of Critical Care Medicine guideline supports advance care planning, specialist palliative involvement, systematic symptom management, and bereavement support, while acknowledging very low certainty of evidence underlying its conditional recommendations. This evidential limitation warrants careful implementation and evaluation, not the postponement of compassionate care. Palliative care should accompany appropriate intensive treatment rather than become available only after its withdrawal. Time-limited trials require agreed clinical goals, review points, and explicit discussion of possible treatment limitation;

otherwise, provisional intervention may become indefinite escalation. The distinction between abandoning disproportionate treatment and abandoning the patient must remain unequivocal, with continuing commitments to comfort, parental presence, and respectful care after death [3].

Third, urgent neonatal research exposes tensions between protection from unauthorised participation and protection from exclusion from knowledge-generating studies. Deferred permission, opt-out procedures, and consent waivers are not interchangeable, and recruitment efficiency alone cannot justify departing from prospective parental authorisation. In a 2026 mixed-methods study involving 38 parents across six centres, research without prior consent received lower acceptability ratings than prospective consent, particularly concerning perceived control, alignment with family values, and respect. Because participants evaluated hypothetical scenarios, these findings identify ethical vulnerabilities without establishing how families will respond during actual emergencies [4]. A contemporaneous modified Delphi process produced 21 recommendations addressing justification, information before allocation, opportunities to decline participation, and communication after allocation. Their relevance lies in making departures from conventional consent accountable rather than routine. Appropriate safeguards include independent ethical review, a defensible risk assessment, clear communication of equipoise, timely parental engagement, and genuine choice about continued participation. Additional justification is required when interventions are strongly preference-sensitive. Subsequent permission cannot retroactively authorise an intervention already delivered; it must instead govern ongoing participation and applicable decisions about data use within the relevant regulatory framework [5].

Across these controversies, ethically robust neonatal care requires a revisable, documented process linking evidence, values, professional accountability, and independent scrutiny. The proposed approach preserves parental involvement without making families bear unsupported decisional burdens, recognises uncertainty without converting it into therapeutic fatalism, and enables research without reducing consent to an administrative obstacle. Its success should be prospectively assessed through family-reported inclusion, symptom relief, fairness, and the quality of deliberation, alongside clinical outcomes. Protecting the newborn means protecting both the

substance of decisions and the conditions under which they are made.

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LECT 12

PDA SCORING: ENHANCING CLINICAL DECISION-MAKING AND MANAGEMENT STRATEGIES

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Patent ductus arteriosus (PDA) remains one of the most controversial clinical challenges in the care of extremely preterm infants. The presence of a PDA has been associated with important neonatal morbidities, but interventions aimed primarily at achieving ductal closure have not consistently improved clinical outcomes. The 2025 American Academy of Pediatrics clinical report recommends against routine very early or early treatment to induce closure and emphasizes that evidence remains insufficient to guide management of

hemodynamically significant PDA beyond two weeks of age [1]. This uncertainty raises an important question: should treatment decisions be based on the presence of a PDA, or on the physiologic burden that the ductal shunt creates in an individual infant? Recent findings support greater attention to hemodynamic assessment. In a multicenter cohort of infants born at 23-29 weeks, PDA-related hemodynamic burden assessed during the first 14 days using the PLASE score was associated with adverse neurodevelopmental outcomes at 3 years, with the association most apparent among infants born at 25-26 weeks [2]. Adverse neurodevelopmental outcomes included developmental delay, cerebral palsy, visual impairment, or hearing impairment. The relationship was not uniform across gestational ages, suggesting that the significance of PDA-related hemodynamic findings may differ according to infant maturity. At the same time, the 24-month follow-up of the BeNeDuctus randomized trial found no difference in survival without neurodevelopmental impairment between expectant management and early ibuprofen treatment in extremely preterm infants with echocardiographically confirmed PDA [3].

These findings highlight an important distinction between risk prediction and treatment benefit. Greater PDA-related hemodynamic burden may help identify infants at increased risk for adverse neurodevelopmental outcomes; however, identification of increased risk does not establish that interventions aimed at ductal closure will improve those outcomes. PDA scoring systems may therefore be useful as clinical decision-support tools rather than automatic treatment thresholds. Integration of gestational age, serial echocardiographic findings, clinical trajectory, and evidence of pulmonary overcirculation or systemic hypoperfusion may support a more individualized assessment of PDA significance. Prospective studies are needed to determine whether physiology-guided selection can identify infants who benefit from intervention.

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LECT 13

ENGAGING HEALTHCARE PROVIDERS, PATIENTS AND CAREGIVERS AS PARTNERS IN PERINATAL CARE: WHOLE-PERSON APPROACHES FOR HEALTH ACROSS THE LIFESPAN

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Health care and outcomes during the perinatal period form the foundation for a healthy lifespan. Multiple stakeholders including the parents, family members, health care providers, community members, advocates, researchers, health care organizations and policy makers play key roles in ensuring not only maternal and newborn health during the perinatal period but also shape the quality of life across the lifespan of the mother and child and, consequently, the family [1]. Meaningful and timely engagement of stakeholders from multiple sectors in perinatal care is essential particularly in communities with low healthcare access globally. Women in low health care access communities such as those in Texas Public Health Regions 9/10, USA located in the binational (United States-Mexico border) are twice as likely to receive late or no prenatal care compared to women residing in communities located away from the United States-Mexico Border [2]. Consequently, low birthweight, pre-term and early-term birth are prevalent birth outcomes in such communities located on the United States-Mexico Border [2] – many of which are also designated as Health Professional Shortage Areas (HPSAs) and Medically Underserved Areas (MUAs). Living in rural communities further exacerbates perinatal health disparities [3]. Hence customizing care for the mother, newborn and child during the prenatal and post-partum period to specific individuals and populations is vital to optimizing birth outcomes and healthspan. The inner and outer settings shaping perinatal health outcomes and stakeholder engagement must be examined to design effective strategies for timely interventions.

Stakeholder identification, relationship-building, shared priority-setting and decision-making, resulting intervention design and implementation, outcomes evaluation, and sustainability will be discussed as key components of enhancing health outcomes for the mother and child(ren) during the perinatal period and beyond. Examples of globally adaptable and scalable community engagement strategies for needs assessment, treatment planning and linkage to services during the perinatal period from rural and urban HPSAs and MUAs in Texas Public Health Region 9/10 will be referred to in relation to the social determinants of perinatal health outcomes. In addition, implications of stakeholder empowerment for systems level changes in perinatal care for underserved communities will be discussed.

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LECT 14

PULMONARY HYPERTENSION IN NEWBORNS: FROM PATHOPHYSIOLOGY TO CONTEMPORARY MANAGEMENT

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BACKGROUND

Pulmonary hypertension (PH) in the neonatal period represents a heterogeneous group of disorders characterized by abnormally elevated pulmonary vascular resistance and impaired transition from fetal to postnatal pulmonary circulation. The most clinically recognized phenotype is persistent pulmonary hypertension of the newborn (PPHN), in which pulmonary vascular resistance remains inappropriately high after birth, resulting in right-to-left shunting through the patent ductus

arteriosus and/or foramen ovale, severe hypoxemia, and potentially life-threatening cardiovascular instability [1].

CLINICAL PRESENTATION AND DIAGNOSIS

The clinical manifestations of neonatal PH are variable and largely reflect the severity of pulmonary vascular dysfunction and associated disease. Persistent or worsening cyanosis, respiratory distress, oxygen requirement, preductal-postductal oxygen saturation differences, and evidence of right ventricular dysfunction should raise suspicion. Echocardiography remains the principal diagnostic and monitoring modality.

MANAGEMENT

Treatment should be directed toward both the pulmonary vascular disorder and its underlying cause. General supportive measures remain essential. Inhaled nitric oxide (iNO) is the best-established selective pulmonary vasodilator for infants with significant PPHN. Its effectiveness is influenced by the underlying cause of PH, and it is less consistently beneficial when pulmonary hypoplasia or severe parenchymal disease predominates [2].

Other pulmonary vasodilators may be considered in selected infants with persistent or refractory PH. Phosphodiesterase-5 inhibition, particularly with sildenafil, may enhance nitric oxide-cyclic guanosine monophosphate signaling and has been used when iNO is unavailable or insufficiently effective. Prostacyclin analogues and endothelin-receptor antagonists have also been explored [3].

Optimization of respiratory support is another central component of treatment. When hypoxemia remains refractory despite maximal conventional treatment, extracorporeal membrane oxygenation (ECMO) may provide life-saving cardiopulmonary support in appropriately selected patients.

Right ventricular function and hemodynamic considerations

Although PH is primarily a disorder of the pulmonary circulation, right ventricular performance is a major determinant of clinical outcome. Management should therefore aim to restore adequate right ventricular-pulmonary artery coupling and preserve systemic perfusion. In some infants, vasoactive support may be required to maintain systemic arterial pressure and coronary perfusion.

LONG-TERM IMPLICATIONS

Neonatal PH should not necessarily be regarded as a transient disorder without future consequences. Survivors of severe PPHN may experience persistent respiratory symptoms, neurodevelopmental impairment, hearing abnormalities, or exercise intolerance.

CONCLUSIONS

PH in newborns is a complex and heterogeneous clinical syndrome resulting from abnormal pulmonary vascular transition, developmental abnormalities, pulmonary disease, cardiac pathology, or combinations of these mechanisms. PPHN remains the most prominent clinical phenotype. Greater understanding of the transition from fetal to postnatal pulmonary circulation may ultimately allow earlier intervention and improve both short- and long-term outcomes for affected newborns.

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LECT 15

NUTRITIONAL BEST PRACTICES FOR THE VERY LOW BIRTH WEIGHT INFANT

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Very low birth weight infants are at high risk for malnutrition, postnatal growth failure, morbidity, and suboptimal neurodevelopment because birth interrupts the rapid nutrient accretion of the third trimester, when substantial protein, fat, minerals, and micronutrients are transferred for brain, bone, and tissue development. These patients, therefore, enter the world with minimal energy and nutrient reserves and must achieve continued growth outside the womb. Their immature gastrointestinal, renal and metabolic systems, and increased demands from illness further increase energy and protein demands [1].

As enteral intake initially cannot meet nutritional needs, parenteral nutrition must be started promptly with minimal enteral feeds introduced as soon as feasible. Human milk is the preferred feeding, ideally mother's own milk, with donor milk used when unavailable. As feeding volumes increase, caloric fortification and supplementation with

iron, calcium, phosphorus, vitamin D and other micronutrients become necessary [2].

The goal is not simply to maximize growth, but to achieve the appropriate balance of energy, protein, and micronutrients to support neurodevelopment, lean tissue accretion, and healthy body composition while avoiding excessive nutrient delivery. Inadequate nutrition may impair neurodevelopment and growth, while excessive or imbalanced nutrition may contribute to later metabolic and cardiovascular risk [3].

Feeding plans should be standardized across the Neonatal Intensive Care Unit (NICU), with clear guidelines for initiating and advancing feeds, indications for holding feeds, defining feeding intolerance, and introducing fortification. Nutritional assessment should include serial weight, length, and head circumference measurements, along with appropriate laboratory monitoring. Reviewing these measures at both the individual and NICU levels helps identify nutritional gaps, assess the effectiveness of feeding practices, and guide timely adjustments to improve outcomes.

Nutritional management does not end when the infant reaches full feeds or leaves the NICU. The discharge plan needs to consider the infant's growth, feeding history and remaining nutritional needs. Follow-up can then be adjusted as those needs change.

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LECT 16

EMERGENCY POINT OF CARE ULTRASOUND IN THE NICU

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Neonates admitted to the Neonatal Intensive Care Unit (NICU) are exceptionally vulnerable to sudden, life-threatening decompensations, such as severe bradycardia, profound oxygen desaturation,

and refractory shock. In these highly time-sensitive scenarios, relying solely on traditional clinical evaluation and conventional radiography can critically delay life-saving interventions and expose the infant to repeated ionizing radiation. Point-of-care ultrasound (POCUS) has revolutionized the approach to the “crashing neonate,” shifting the diagnostic paradigm from delayed anatomical imaging to a rapid, functional, and real-time bedside assessment [1].

This lecture provides a comprehensive overview of POCUS applications in the NICU, focusing on the rapid identification of reversible causes of acute deterioration. Utilizing a simplified, rule-in/rule-out sonographic methodology, clinicians can systematically evaluate the most critical intra-thoracic and extra-thoracic emergencies within minutes. We will detail the sonographic signatures of life-threatening pulmonary emergencies, emphasizing the high diagnostic accuracy of lung ultrasound (LUS) in detecting tension pneumothorax – characterized by the absence of lung sliding, the “stratosphere sign,” and the “lung point.” This immediate detection allows for prompt, ultrasound-guided needle aspiration or chest tube placement. Furthermore, we will explore targeted cardiac POCUS to rapidly exclude cardiac tamponade, detect massive pleural effusions, and perform a qualitative evaluation of myocardial contractility and volume status during shock.

The scope of emergency POCUS extends beyond the thorax. We will discuss its crucial role in the rapid bedside diagnosis of severe intraventricular hemorrhage during sudden neurological or hemodynamic deterioration, as well as the detection of ascites and free abdominal fluid in acute intestinal emergencies. Additionally, the lecture will address iatrogenic emergencies; given the high rate of secondary migration of neonatal central venous catheters, real-time ultrasound assessment is paramount to detect malpositions that can lead to arrhythmias, thrombosis, or pericardial effusion [2]. Beyond strictly emergent scenarios, we will also highlight the well-established role of LUS in the early management of neonatal respiratory distress syndrome. A targeted LUS score has proven highly accurate in predicting the need for surfactant replacement therapy, allowing for personalized, physiology-driven respiratory care [3].

Ultimately, emergency POCUS is no longer merely an adjunctive imaging modality, but an essential extension of the neonatologist's clinical examination. Its integration into daily practice

standardizes care, accelerates targeted resuscitation, and improves outcomes in our most fragile patients.

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LECT 17

EPOCAL CHANGES IN HUMAN MILK BANKS

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It is well known that Human Milk Banks (HMBs) thrive in countries where they are protected, promoted, and supported as a vital component of national breastfeeding policies and newborn care. The government has an especially important role in successfully integrating human milk banking with newborn care.

In Europe (EU) we currently have almost 300 active HMBs operating throughout Europe. A study observed that national medical guidelines for the use of donor human milk (DHM) have been issued in 11 countries, and that specific national legislative regulation is in place in only two of them. Moreover, a huge variation in practices was observed, not only between but also within countries [1, 2].

Until 2024 in the EU there were specific Directives on Blood, Tissues and Cells, that however did not include regulation regarding DHM and HMBs.

This uncertainty regarding the status and handling of DHM worked as a disincentive to adopt evidence-based practices and led to concerns

about safety, representing a hindrance for its use in feeding preterm and critically ill newborns.

From this context, among all the stakeholders, emerged a pressing need for legislative intervention to regulate and standardise the use of DHM to ensure that its procurement, storage, processing and distribution meet high quality and safety standard in a harmonized manner.

In July 2024, a new *Regulation on Quality and Safety for SoHO Intended for Human Application* was adopted by the Council of the EU and approved by the European Parliament. The SoHO Regulation will enter into force in 2027.

To implement the standards provided for in this Regulation, two important documents – *Imagine* and *EDQM*, developed on the basis of scientific knowledge – are going to be available by 2026 to be used as technical guidelines on quality and safety of DHM as SoHO.

This new regulation constitutes an “epocal change” in HMB procedures and in the use DHM, which has to be considered no more as a food but as a tissue.

These new high standards on safety and quality, while granting Member States the flexibility to adopt specific measures to align with their national regulations, aim:

1. to improve uniform distribution of HMB, strengthen their networking and facilitate digitalization and monitoring of their activities;
2. to ensure equitable access to safe human milk for preterm and critical newborns;
3. to promote a culture of use of human milk in NICUs;
4. to assure protection against commercialization of human milk and its derivatives.

Nevertheless, several challenges must be acknowledged. Compliance with the more stringent SoHO standards will require investment in physical infrastructure, equipment, and personnel training, and the implementation of robust quality management and risk management procedures. A fundamental question of adequate resourcing underlies all of these requirements, particularly for smaller or less well-established HMBs, for which the transition may prove especially demanding without dedicated funding and institutional support at both European and national level.

In conclusion, the new SoHO Regulation represents a landmark opportunity to harmonise and elevate the standards of human milk banking across Europe, provided that its implementation is accompanied by the political commitment, institutional support, and adequate resources that this paradigm shift demands.

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LECT 18

NEUROCUTANEOUS SYNDROMES: HISTORY AND FUTURE PERSPECTIVES

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The term “neurocutaneous syndromes” refers to a heterogeneous group of hereditary and nonhereditary disorders involving the skin and nervous system. Their clinical spectrum is, however, considerably broader, as several other organs may also be affected, including the eyes, kidneys, lungs, cardiovascular system, and, in some cases, the endocrine system. These disorders are caused by alterations in genes, proteins, or receptors involved in the activation or inhibition of intracellular and extracellular signaling pathways and metabolic cascades implicated in cell proliferation, tumorigenesis, and angiogenesis. The RAS and mTOR pathways are of particular relevance in this context.

In 1923, van der Hoeve was the first to group these disorders together, coining the term “phakomatoses” from the ancient Greek word *phakos*, meaning “spot” or “birthmark.” This category initially included the two most commonly recognized conditions at the time: neurofibromatosis and tuberous sclerosis. In 1930, Paul Ivan Yakovlev introduced the term “neurocutaneous syndromes”. Today, this designation encompasses all conditions characterized by congenital lesions, such as hamartomas, or by a predisposition to the development of tumors involving multiple organs.

Their classification has undergone numerous revisions over the past several decades following the identification of new disease entities. One currently proposed classification divides neurocutaneous syndromes into conditions characterized by: tumor

predisposition; vascular malformations and tumors; epidermal or connective-tissue cutaneous mosaicism; and “twin-spotting” phenomena, including paired hyperpigmented and hypopigmented lesions and malformations associated with vascular hyperplasia or hypoplasia.

Neurofibromatosis type 1 (NF1), with an incidence of approximately 1 in 2,500 live births, is one of the most common rare genetic disorders. It is inherited in an autosomal dominant pattern and is characterized by variable expressivity. NF1 results from abnormal differentiation and migration of neural crest cells during the early stages of embryogenesis and is caused by inactivating variants in the “*NF1*” gene, located on chromosome 17q11.2. This gene encodes neurofibromin, a tumor-suppressor protein involved in regulating cell differentiation and proliferation. Loss of functional neurofibromin disrupts normal cell-cycle regulation, leading to uncontrolled proliferation and abnormal cellular differentiation.

NF1 represents an important model for investigating the molecular mechanisms underlying oncogenesis. Research in this field has led to the development of novel therapies that interfere with or modulate specific proteins within intracellular signaling cascades, thereby altering the course and natural history of neurocutaneous disorders.

The various signaling pathways involving these proteins help explain the marked clinical heterogeneity of these conditions and now represent potential therapeutic targets. Allosteric inhibitors targeting components of these pathways have proven effective in slowing disease progression. A more comprehensive understanding of the additional molecular mechanisms underlying neurocutaneous syndromes may further improve prognosis and quality of life through targeted therapies supported by long-term studies assessing their efficacy and safety.

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LECT 19**LUNG MICROBIOTA: WHAT WE KNOW**

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The prevalence of allergic diseases is steadily increasing in Western countries. The composition of the intestinal flora, known as the microbiome, appears to play a central role in the postnatal development of the immune system. This regulates the development of the microbiome even at the organ level. Thus, other organs are rapidly colonized shortly after birth. This also occurs in the respiratory system, where the upper airways are colonized within the first few hours of life, influenced by microbial influences transmitted by the mother and the environment. The microbiome of newborns born by cesarean section or prematurely is also different in this area. Subsequently, colonization also progresses to the lower airways through ingestion or inhalation.

A complex structure thus forms throughout the airways, acting as guardians of the airways and the individual's respiratory health. Colonization primarily by *Streptococci* in the upper airways can lead to an increased risk of developing wheezing.

The structure is affected by antibiotic therapy cycles, but also by the state of illness. The microbiome of a child who gets sick frequently, for example, will be different. The lower airways are therefore certainly not sterile; indeed, the "healthy" microbiome represents a defense mechanism that must be preserved. Some speak of a veritable airway guard dog.

The first studies characterizing the lung microbiome were conducted in patients with cystic fibrosis, where the microbiome is very different in children than in sick adults, due to the duration and therefore the progression of the underlying disease. It is naturally very different from that of healthy subjects.

In asthma, the airway microbiome appears to influence the therapeutic response to conventional drugs, contributing to the failure to control the underlying disease. Patients who respond well to inhaled corticosteroid therapy have a wealth of microbial agents that those who respond poorly lack. Furthermore, the presence of eosinophilic bronchial inflammation is once again correlated with a particular microbiome.

All of this data is currently difficult to investigate for clinical application in individual patients. However, what is emerging from studies and research encourages us to consider the role of the airway and lung microbiome as central to defense mechanisms. It is therefore essential to care for it from early in life, continuing in healthy children or those with chronic respiratory diseases.

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LECT 20**BLADDER, KIDNEY AND BRAIN: UNRAVELLING THE HIDDEN COMPLEXITY OF PEDIATRIC FUNCTIONAL DISORDERS**

G. Masnata

*Department of Pediatrics, ARNAS G. Brotzu, Cagliari, Italy***BACKGROUND**

Bladder-bowel dysfunction (BBD) is a useful clinical concept that has changed the approach to functional lower urinary tract disorders (LUTD) in children. However, it mainly describes a local bladder-bowel interaction and does not fully account for connections with the central nervous system, individual behavior, higher brain functions, or intestinal and urinary microbial ecosystems. Children with similar urinary symptoms may differ in bowel dysfunction, behavior, treatment response and risk of recurrent infection, suggesting different underlying mechanisms.

CURRENT EVIDENCE

Continence is more than bladder maturation. A child must perceive bladder filling, postpone voiding when appropriate, and coordinate detrusor and pelvic floor activity. These abilities develop alongside attention, inhibitory control and awareness of internal bodily signals. Bladder sensation, storage and voiding depend on communication among cortical and subcortical regions, the periaqueductal gray and the pontine micturition center [1].

Bowel dysfunction remains central to BBD. Constipation and stool withholding may interfere with bladder emptying and pelvic floor relaxation, promote residual urine and complicate urinary tract infection and vesicoureteral reflux [2]. Yet a basic question remains: to what extent does BBD reflect learned behavior, neurodevelopmental differences, or biological susceptibility, including differences in visceral sensory mechanisms? Functional LUTD alone are unlikely to determine renal injury; concern increases when recurrent infection, reflux or congenital urinary tract abnormalities coexist.

The gut microbiome, immune signaling and microbial metabolites participate in gut-brain communication, while metabolomic studies have identified distinct urinary biochemical profiles in children with neurodevelopmental disorders [3]. Their relevance to pediatric LUTD remains unknown, but these findings are difficult to accommodate within an exclusively bladder-centered model.

NEW PERSPECTIVE

We propose the “Brain-Bladder-Kidney Neurodevelopmental Network” as a working framework for research, not a new diagnosis. Continence is viewed as the result of interaction among brain control, visceral perception, bladder function, bowel-pelvic floor activity and renal vulnerability.

CLINICAL IMPLICATIONS AND CONCLUSIONS

Early recognition of BBD and standardized urotherapy can achieve good outcomes and may limit unnecessary antibiotics and invasive investigations. Our model does not replace BBD; it places it within a broader developmental context and may help explain why similar symptoms do not necessarily identify the same underlying phenotype or predict the same outcome. Prospective studies integrating clinical phenotyping, neurodevelopmental assessment and neuroimaging, microbiome and metabolomic analyses are needed to test this hypothesis.

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LECT 21

CHILDHOOD MASLD AND EARLY CARDIOVASCULAR DAMAGE: A CALL FOR ACTION

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Metabolic dysfunction-associated steatotic liver disease (MASLD) in childhood is increasingly recognized as a multisystem condition rather than an isolated liver disorder. Its association with insulin resistance, dyslipidemia, hypertension, chronic inflammation, and vascular dysfunction raises a critical question: do the processes leading to cardiovascular disease begin much earlier than overt disease becomes clinically apparent?

The metabolic-cardiovascular connection is not new. Reaven identified insulin resistance and compensatory hyperinsulinemia as part of a cluster of abnormalities associated with increased coronary artery disease risk, demonstrating that metabolic dysfunction may exist while glucose homeostasis is still maintained [1]. This concept has important implications for children with MASLD, in whom metabolic abnormalities may precede diabetes and cardiovascular disease by many years.

Long-term evidence now strengthens this concern. Children and young adults with fatty liver disease have demonstrated increased rates of major adverse cardiovascular events, including ischemic heart disease and congestive heart failure [2]. Longitudinal evidence further indicates that liver steatosis and associated metabolic abnormalities beginning in childhood may persist into adulthood, with cardiovascular and metabolic consequences [3]. MASLD may therefore represent an early clinically recognizable signal of a broader cardiometabolic trajectory rather than solely evidence of hepatic disease.

A critical vulnerability may occur during the transition from adolescence to adulthood. MASLD can progress silently, while fragmented medical records and limited follow-up can interrupt continuity of care during a period when metabolic abnormalities may persist or progress [3]. Children identified with MASLD may therefore enter adulthood with evolving cardiometabolic risk that is no longer consistently assessed.

Pediatric MASLD should prompt attention beyond the liver. Earlier recognition of the interconnected hepatic, metabolic, and cardiovascular trajectory,

together with sustained follow-up into adulthood, may provide an important opportunity for prevention.

Prospective studies should determine which markers best identify children at greatest cardiovascular risk and whether earlier intervention alters long-term outcomes.

The cardiovascular consequences of metabolic disease may begin in childhood; our opportunity to prevent them may begin there as well.

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