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Lectures

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LECT 1

FEEDING INTOLERANCE IN PRETERM INFANTS

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The need to sustain an adequate growth through "aggressive" nutrition must come to terms in the neonatal intensive care unit with the intrinsic gastrointestinal immaturity of preterm infants, who often show signs and symptoms of feeding intolerance (FI), leading to feeding reductions or interruptions which interfere with a rapid achievement of full enteral feeding (FEF). FI leads to a discrepancy between the amount of milk, which is prescribed and the amount that the infant receives: this contributes to extra-uterine growth retardation, with potential negative consequences in neonatal long-term growth and neurodevelopment. In addition, neonates who achieve FEF slowly need to receive parenteral nutrition (PN) through a central venous catheter for longer periods, which increases the risk for late onset sepsis and complications related to prolonged PN. Despite the magnitude of the problem, a clear definition of FI is lacking, leading to significant variability in clinicians' attitude towards what is perceived as a sign or symptom of poor feeding. One definition of FI states that FI is "the inability to digest enteral feedings presented as gastric residual (GR) volume of more than 50%, abdominal distension or emesis or both, and the disruption of the patient's feeding plan" [1]. However, nowadays such a definition is highly controversial, as some clinicians tend to overvalue the clinical meaning of GRs, while others do not even check for GRs, in the hope that avoiding their routine evaluation might lead to an earlier achievement of FEF. A more precise and broadly shared definition of which warning signs are suspected or predictive of FI would be extremely helpful: in this perspective, some preliminary data suggest that continuous monitoring of splanchnic oxygenation through near-infrared spectroscopy in response to the first feed might predict further feeding tolerance in preterm infants [2]. In addition, a clear identification of neonatal populations at higher risk of FI, such as neonates with intrauterine growth retardation or absent/reversed end-diastolic flow in the umbilical arteries should help clinicians to tailor their nutritional intervention according to specific risk factors. Potential interventions aimed at preventing and treating FI in preterm infants are described hereunder.

- Mother's milk feeding is known to promote feeding tolerance compared to formula feeding, but the advantage of donor human milk (HM) over formula has been described with lower strength. For this reason, an exclusive mother's milk diet should be recommended for very preterm infants whenever possible, while further studies should clarify the role of donor milk, compared to formula, in reducing FI, and should highlight the potential advantage of HM-derived fortifiers, to better sustain the recommendation for an "exclusive-human milk" diet [3].
- When HM is not available, it is unclear which kind of formula could better limit FI. Recent studies compared extensively hydrolyzed protein formula (eHPF) vs. standard preterm formula in terms of reduction of FI, but on the whole they failed to document a clear advantage of eHPF and, at the same time, highlighted a slower weight gain in infants fed eHPF. Furthermore, none of these studies reported long-term outcomes such as neurodevelopment or allergy [4].
- Beyond nutrition, several non-pharmacological interventions have been suggested to prevent or limit the occurrence of FI in preterm infants: among these, probiotics appear one of the most promising, as they have the potential to restore gut microbiota disrupted by preterm birth and they act as symbiotic with HM. Several studies have documented a faster achievement of FEF in preterm infants receiving probiotics, especially in those fed exclusive HM [5]. Other clinical interventions, such as limitation of antibiotic use, implementation of neonatal care measures (i.e. kangaroo mother care and music therapy), and optimization of ventilation strategies have been suggested to improve feeding tolerance, but the extent of this improvement still needs to be assessed in detail for each intervention.

- Few pharmacological treatments have been proposed for FI in preterm infants. Among these, one of the most studied is erythromycin, which has been used at different dosages both for prevention and treatment of FI. The results of these studies were summarized by a *Cochrane* review in 2008, which concluded that there was not enough evidence to show any benefit in erythromycin use at any dose in preterm infants.

In conclusion, FI represents a daily issue in neonatal intensive care units, which should be addressed using a broadly shared definition with a special focus on high-risk populations. Several interventions appear promising for prevention and treatment of FI in preterm infants, but all of them still need to be assessed in further detail.

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LECT 2

PREBIOTICS ARE ALL THE SAME

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Intestinal microflora and the host present very close metabolic interactions. These interactions condition the health status of the host. Colonization itself is a very complex process. It begins immediately after birth, when the newborn comes into contact with the microorganisms present in the mother's genito-urinary tract, and continues with development and for the whole subsequent life in relation to many factors (nutritional, environmental, etc.). These factors condition the development of a determined intestinal microflora; consequently, numerous interactions between the various microbial groups and the host are established. Consequently each portion of the gastrointestinal tract is colonized by a specific microflora, whose composition is the result of adaptation to local environmental conditions and mutual commensalistic or parasitic interactions established between the components of the microbial community and the host organism. One of the most important functions of intestinal microbiota is the so-called "barrier effect" such that a micro-organism introduced by food in a normal host is eliminated, precluding the micro-organism from the possibility of proliferation; this competitive exclusion prevents many microorganisms introduced with food from settling in the digestive tract, proliferating and possibly exercising a pathogenic action. To "feed" this huge bacterial colony provides some nutritional substrates metabolized at the level of the microbiota that modify the intestinal immunological structure. Some carbohydrates that escape digestion in the upper digestive tract reach the colon without being absorbed during the passage through the small intestine. In the colon the set of metabolic activities performed by the entire microbiota has the effect of establishing interactions of synergy or nutritional interdependence, as well as competition, between different microbial groups. Because of the absorption in the small intestine, the colon is a poor environment of simple sugars, such as mono- and disaccharides, hence defined "prebiotics". Prebiotics are non-digestible or absorbable ingredients by the host that selectively stimulate the development or activity of a limited number of beneficial intestinal bacteria. Most prebiotics are carbohydrates, but the definition does not exclude other molecules that could exert the same effects. Prebiotics not only increase the number of *Bifidobacteria spp.* and lactic bacteria already present in the colon, but also their metabolic activities through the contribution of fermentable substrate: it increases metabolism that is central for the effect of prebiotics on the health of the guest. One consequence of this effect also involves the reduction of putrefactive or potentially pathogenic microorganisms such as *Clostridia spp.* and *Enterobacteriaceae*. These non-digestible carbohydrates reach the colon where they are depolymerized and fermented by the bacterial flora. The result of these processes determines the production of highly species-specific metabolites; the peculiarity of these processes lies in the need for an appropriate substrate binding, degradation and uptake system. The fermentation of these carbohydrates is fundamental for the micro-ecology

and physiology of the large intestine as it generates lactic acid and SCFA (short-chain fatty acids: acetic, propionic, butyric), which will be absorbed by the host or used by other microbial components. A good redistribution of lactic acid metabolism, as well as the production of organic acids, underlies the correct functioning of the whole intestine, from the higher portions to the colon, with effect not only on "barrier" or metabolic actions, but also on the anti-neoplastic function. The study of the effect of these probiotic nutrients on the human organism began not long ago starting from fruit-oligosaccharides and galacto-oligosaccharides (FOS and GOS) and from inulin, compounds that had first shown some of the effects listed above. Currently the field of so-called probiotics is constantly expanding, so much as to define new classes of probiotics, each with its own specificity and peculiarities in the effects on the human organism. In fact we talk about soy oligosaccharides (raffinose and stachyose), isomalto-oligosaccharides (IMOS, including isomaltose and panose), xylo-oligosaccharides (XOS) to name just a few. The main effects of prebiotics and their most relevant differences will be discussed here in the light of the most recent scientific acquisitions and their rational use in the neonatal and pediatric fields.

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LECT 3

NURSE AND PAIN MANAGEMENT IN NEWBORN: THEORETICAL AND PRACTICAL ASPECTS

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The NICU's environment is often chaotic and frantic and the model of care is not always based on the newborn's developmental needs; in addition, preterm infants, the most sensitive to pain, are exposed to painful multiple procedures (from 5 to 15 a day) including heel-stick, venipuncture, arterial and venous cannulation, endotracheal intubation and suctioning. Acquired knowledge showed how this experience, early in life may affect subsequent neuro-behavioral, emotional, psycho-social and pain system development [1]. NICU professionals face the challenge of offering an Early Developmental Care which aims to support the newborn's brain development through individualized developmental interventions, directed to the environment, the family, promoting positive sensorial stimulations, protecting sleep and reducing stress and pain [2]. Among them the Newborn Individualized Developmental Care and Assessment Program has been widespread [3]. On the basis of evidence it is clear that management of the newborn's pain and stress represents one of the principal objectives of perinatal care, since the timely recognition and treatment of newborn's pain are crucial to its immediate well-being and also to a better future outcome. In the approach to neonatal pain, inter- and multi-disciplinary collaboration is a relevant criterion for achieving effective actions and results, but the nurse has a key role and responsibility, because the prevention and treatment of pain are linked to nursing care and its personalization (Code of Ethics, art. 34). That means adopting in our everyday practice some simple attitudes, however simple, which add quality and value to the delivery of care. These attitudes are herein described.

a. Assessing how each newborn, including preterm newborn, responds to the nociceptive stimulus with a documentable physiological, hormonal and behavioral reaction. Thus, it is important to know these reactions, look for them with a watchful eye and consider pain the fifth vital sign.
b. Considering the environmental impact: pain is affected by many factors that can have positive or negative effects on the extent of the painful situation, some of which are controllable. The environment is one upon which we can and must act. It is important to promote behavioral and, if possible, structural changes to reduce light and sound levels in the macro and micro-environment.
c. Considering the relational aspect, premature birth impacts the whole family. There is a

basic requirement for the NICUs to be open 24 hours a day to the family and for its personnel to accept, support, educate and involve parents by promoting affective bonding, early touch and participation in the care of their newborn [4].

d. Measuring and documenting: it is essential to use appropriate pain scales, that allow an objective and homogeneous evaluation of pain. Choice of scale must be guided by some features: validity, inter-rater reliability, internal consistency, clinical applicability, preferably easy to apply. Responding to these criterion: PIPP (Premature Infant Pain Profile) and DAN (Douleur Aiguë du Nouveau-né) for assessing acute/procedural pain and EDIN (Échelle Douleur Inconfort Nouveau-Né) for prolonged pain. The effort put into implementing these pain scoring systems is dictated by an ethical commitment, but also by a legal obligation (L. 38/2010 art. 7).
e. Preventing and treating with non-pharmacological interventions:
   - minimizing the number of painful procedures;
   - using suitable devices;
   - making the environment comfortable, protecting newborns from high levels of light and noise;
   - when possible, choosing the best time for the infant, respecting the infant's sleep pattern;
   - involving parents; NICU staff should support parents as soon as possible in the observation of their infant's behavior and to help it, wherever practical with supportive holding, skin to skin, breastfeeding, grasping fingers, gently talking, offering a pacifier, giving mother's milk/oral sucrose to relieve procedural pain. Sucrose is most effective when used in combination with other non-pharmacological therapies as non-nutritive sucking and sensorial saturation (tactile, gustatory, auditory and visual stimulation) [5];
   - swaddling and supporting the newborn in comfortable positions which help its behavioral organization and stability and facilitate self calming behaviors such as hands to face and mouth, grasping and bracing feet;
   - even when analgesic therapy is required, it will be associated with the non-pharmacological interventions above mentioned, provided on an individual basis, separately or in combination before, during and after all caregiving interventions.
f. Reassessing: all the interventions should be documented, reliably reassessed (through pain scoring) and adapted in order to achieve the best outcome.
g. Staff training and support: nurses should receive continuous training and guidance on pain and stress management and also on building an effective relationship with both the NICU healthcare professionals and the parents.

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LECT 4

THE "THINKING" NURSE: A RESOURCE OR A TROUBLESOME FIGURE? HOW TO INTERACT WITHIN A MULTIDISCIPLINARY TEAM

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The progressive recognition of the figure of the nurse, by now free from her "ancillary" role, and the continuous change of working backgrounds, highlights the new position of the nurse within a multidisciplinary team. The nurse has always been the key figure in the critical patient's care but over the last few decades adequate preparation, specialized training and a critical mind-set have come to the fore as essential requirements for expert and independent workers. Good interaction and communication with other colleagues improves the patient's care and is rewarding to nurses, who provide assistance to patients every day. By displaying awareness of their

capacities, intelligence and critical sense, nurses are seen by the other professionals as a resource and a colleague worthy of respect. What happens when a "thinking" professional proposes something different that can interfere with the consolidated and reassuring routine within the unit? It is important to interact with the others without debates or arrogance. The objective always remains the patient and not our self affirmation: to debate within the team means to try to find together a solution to the common problems a professional faces every day.

LECT 5

COMPARISON OF PAIN MEASUREMENT PERFORMED BY NURSES AND PARENTS

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Pain relief represents a need, and a fundamental right, of the infants assisted in the NICU (Neonatal Intensive Care Unit). In pre-verbal patients, pain relief depends on the ability of caregivers to recognize signs of discomfort. The presence in the NICU of skilled professionals, able to capture these signals and to encode them in algometric scores, reduces neonatal pain/stress and improves the neuro-developmental outcome. In recent years, individualized development-centered care, in collaboration with the family, has been established as the gold standard in the management of the newborn in NICU. Supporting parents in understanding their child's communicative cues represents a fundamental investment for the future of the whole family and improves the experience associated with the hospitalization. Parents of infants referred to the NICU worry that their infant may experience pain, and this concern may contribute to increased parental stress; moreover, parents ask for greater involvement in preventing and managing their babies' suffering [1-5]. Nurses, doctors, therapists and parents can work together to facilitate the child's stability, relaxation and comfort through:

- Reducing environmental stressors;
- Kangaroo care;
- Swaddling/facilitated tucking;
- Grasping and bracing;
- Non-nutritive sucking;
- Oral solution e.g. breast milk, colostrum, sucrose;
- Touch/massage;
- Soothing voice;
- Analgesic drugs.

The effectiveness of these strategies must be evaluated through the use of algometric scales. Data from literature have documented parental satisfaction when involved in pain assessment and management of their children. Involvement in their infant's pain care in the NICU setting is therefore feasible and improves parent-infant attachment and parenting competence or confidence after discharge from the NICU [3]. The role of parents in the management of the infant's pain is a relatively new area of research. We are conducting a single center prospective study, in a III level NICU where the Newborn Individualized Developmental Care and Assessment Program (NIDCAP, www.nidcap.org) is applied. The main purpose of this study is to compare the measurement of prolonged pain, using the EDIN scale [6], performed by mothers and nurses. The secondary end-point is represented by assessment of the level of maternal stress detected through the administration of the NICU scale at the time of discharge from NICU. Newborns are included in the study and monitored using the EDIN scale according to the specific NICU protocol. Parents, especially mothers, receive specific training on the signs of well-being and distress of their child and learn how to manage them. For this purpose, a brochure was written entitled *How to help our children to prevent stress and pain in the neonatal intensive care*; this brochure and videos are used during training meetings with families by a dedicated nursing group; during these sessions the EDIN scale is illustrated in detail. The EDIN scale was proposed by Debillon [6] and is useful for the evaluation of prolonged pain, even in preterm newborns and even if they are intubated. It includes the evaluation of 5 behavioral items (facial expressions, body movements, quality of sleep, comfort, quality of the contact with the caregiver). Its application does not require specific training as the EDIN scores are determined while performing the usual care of the child. Preliminary results show that the EDIN scores detected by the parents are higher than those detected by the nurses and that the scores attributed by parents, but not those attributed by nurses, correlate with the presence or absence of painful maneuvers or respiratory assistance. The ultimate goal of this study is to include parents as

primary caregivers of their children in NICU, by also promoting the management of pain/stress along their learning trajectory.

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LECT 6

RED REFLEX AT BIRTH: AIM, EXECUTION AND IMPLEMENTATION

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A screening eye examination is an essential item of the newborn's assessment. Its aim is to identify treatable visual abnormalities and to refer those patients who need a comprehensive evaluation to an ophthalmologist skilled in examining children. The Red Reflex allows detection of diseases such as coloboma, cataract, glaucoma, retinoblastoma, retinal and vitreous abnormalities, systemic diseases with ocular manifestation and serious refractive disorders. In 2008 the American Academy of Pediatrics revised their previous policy statement published in 2002 and recommended the routine research of Red Reflex in infancy and childhood, before discharge from the neonatal nursery and during all subsequent routine visits to the pediatrician or other primary care physician. These recommendations are still valid. The test is performed using a direct ophthalmoscope with a non-invasive technique, of simple and rapid execution and well tolerated by the newborn. The Red Reflex is more prominent in a darkened room, by the use of a bright light source. Clinicians with a refractive error can examine without wearing their spectacles (holding the instrument more closely to their eye) by setting their spectacle corrective power into the ophthalmoscope. It is suggested that the Red Reflex be examined in both eyes simultaneously for a symmetrical reflex and then in each eye at a time. If the pupils are small and the reflex diminished, it is possible to recheck 10 minutes after dilating the pupils with 1% tropicamide. If a mobile opacity is observed, it could be due to the presence of mucus in the tear film and be resolved with blinking. In neonates with increased pigmentation of the eye a less bright reflex is common and it can be helpful to examine the child's parents to establish a normal reference. An asymmetrical Red Reflex (colour, size, shape or position) can indicate the need for urgent ophthalmology referral. Some pathological findings are: white pupil (leukocoria) when the light is obstructed by a white intraocular abnormality (in the cornea or lens or vitreous body or retina); black reflex when the light is obstructed without reflection as in cataract, corneal scar or intraocular hemorrhage; large reflex due to albinism (the reflex transmits through the iris as well as the pupil) or to a coloboma of the iris (key-hole shaped pupil). In all cases of abnormal Red Reflex (after having retested to confirm the finding) an urgent referral to a pediatric ophthalmologist is mandatory, especially to rule out retinoblastoma (life threatening) or congenital cataract (need for surgery at 6 weeks of age, to avoid amblyopia). It is prudent for the pediatrician to contact the ophthalmologist personally to communicate the suspicion and to express the urgency of the appointment to the parent. All infants with a positive family history of retinoblastoma, congenital cataract, congenital glaucoma or retinal abnormalities should be referred to a pediatric ophthalmologist for a complete eye examination regardless of the status of the Red Reflex because these children are at high risk of vision, and potentially life-threatening eye abnormalities. However, it is still valuable for the pediatrician to perform the Red Reflex on these patients to help determine if it is necessary to promote a prompt referral. The Red Reflex

screening tool can be easily learnt and is not a skill reserved solely for ophthalmologists. It should be performed in all birth centers on all newborns before discharge by the neonatologist or pediatrician of the department, after training by a pediatric ophthalmologist, as suggested by the AAP. In Italy the standard healthcare provision (LEA) program was revised in 2017, focusing on early diagnosis of neurosensory organ diseases. The National Plan of Prevention 2014-2018 aims to carry out visual screening on all newborns from 1 January 2018 and recommends that protocols be developed to obtain a universal screening with coverage of 100% of births. For correct implementation of the screening it is essential that there is good integration between hospital and territory.

CONCLUSIONS

Diseases identifiable by the Red Reflex test can lead to serious and irreversible effects on the visual function and global health of the infant, if not detected early. Diagnosis and therapy of congenital cataract are priorities because it is the most common treatable cause of visual impairment in childhood. Untreated congenital cataract is responsible for about 10% of all childhood blindness in the world. Every birth center should implement Red Reflex testing based on a well-structured plan as recommended by the scientific and governmental societies.

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LECT 7

ERRORS IN THERAPY ADMINISTRATION IN THE NEONATAL INTENSIVE CARE UNIT: WHICH IS THE BEST STRATEGY TO PREVENT THEM?

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INTRODUCTION

Medication administration errors (MAes) are some of the worst problems for all health systems both in terms of patient wellness and economic implications. Considering the pediatric population, the potential adverse drug events rate is suggested to be three times higher than that of the adult population and even higher in neonatal intensive care units (NICUs). According to several authors, nursing interruptions during medication administration are among the main causes of medication errors [1-3].

METHODS

The aim is to assess the effectiveness of an improvement program to reduce the number of interruptions during the medication administration process. Pre-post study design was used to monitor nursing interruptions during medication cycles in the NICU of Sant'Anna Hospital in Turin. The intervention included the use of a bright band worn by nurses during medication cycles, education sessions for healthcare providers and families, and distribution of patient and parent educational material. Interruptions were reported on an observation sheet (MADOS-P) adapted to the pediatric context [3, 4].

RESULTS

31 nurses were observed both before and after the intervention; 96 drug administrations were observed before the intervention and 118 after the intervention. The median of interruptions occurring in each cycle decreased from baseline to post intervention but not significantly with the Mann-Whitney test (4 vs 3, $p > 0.05$). Categories' analysis showed that interruptions caused by physicians, nursing staff, parents and conversation decreased while the interruptions linked with technical causes (e.g. monitor alarms, medication shortages, external noises, etc.) increased.

CONCLUSION

Use of a bright band worn by nurses was effective in decreasing nurse distractions due to human interruptions. However, the reduction in total interruptions was not satisfactory due to the increase in interruptions due to care requirements after the intervention. This is likely due to the high number of newborns hospitalized and the advanced treatment complexity of the post intervention observation period.

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LECT 8

KANGAROO MOTHER CARE AT THE HEART OF INDIVIDUALIZED FAMILY-CENTERED CARE: IMPLICATIONS FOR THE DEVELOPMENT OF PRETERM INFANTS

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The individualized family-centered care (IFCC) approach is a model of early intervention with high-risk neonates in which the role of the family in the Neonatal Intensive Care Unit (NICU) is strongly emphasized. The IFCC is one of the consequences of the increased knowledge of the complex interplay between biological, psychological and socio-cultural factors in determining the long-term developmental outcome and quality of life of the child. The focus of intervention includes not only the infant but also the parents and the NICU environment: the vulnerability and sensitivity of the developing brain of the neonate hospitalized in a stressful NICU are always at the center of attention. The rationale for this model is that the development of a high-risk infant can be improved through care strategies whose target is not only the wellbeing of the neonate and the implementation of the mother-father-infant interaction but also the wellness of the family. According to this model, the developmental outcome is a result of the interplay over time of individual child factors (e.g., the severity of prematurity and of the related clinical patterns) and the continuous dynamic interaction of the infant with the family and social physical and emotional environment. In the IFCC model the empowering of the parents as "primary caregivers" – even in a high-technology environment – is the main target: parents are supported in the understanding of their infant's behavior and needs, are involved in the reduction of stress and pain experiences and in the implementation of behavioral self-regulation in order to minimize the effect on the child's development of the frequent stressful events of the NICU and of mother-infant separation. Moreover, the collaboration between the family and the operators of the NICU is promoted by IFCC. Over the past few years stressful experiences – related at first to inadequate multi-sensorial experiences and the mother/child separation – has come to be considered increasingly recognized as a potential risk factor for the brain development, especially if maternal deprivation and sensorial over-stimulation or deprivation happen in the postnatal sensitive period [1]. In the traditional NICUs the fragile infant receives various stressful stimuli as painful procedures, excessive noise and light, negative touch experiences, sleep disruption; moreover in the incubators preterm and small infants are separated and deprived of the skin-to-skin contact with their mother and of the "natural" positive sensorial experiences as maternal cuddling, smell, gentle touch, vocalization, visual contact. It's important to remember that the mother-child separation worsens the stress experiences that – in the absence of the buffering role of the mother – assume the feature of "toxic stress" [2] that is characterized by a prolonged activation of the physiological stress management system with consequences on neuroendocrine axis. Kangaroo mother care (KMC) method is a relevant part of the IFCC: many studies [3, 4] highlight that KMC reduce the "toxic stress", improve the mother-child bonding and promote a better quality of development. Through the skin-to-skin prolonged contact during the KMC mother become the main provider of the biological and emotional needs: the KMC corner stone is the kangaroo position whereby the infant is placed and held in direct STS contact on the mother's chest in up-right position under her clothes. The KMC position gives to the babies the possibility to perceive the scent of their mother, the breast smell, the taste of the breast milk drops from the nipple, the warmth of maternal skin, the vocalization and furthermore to experience the mother's body cuddling: these multi-sensorial stimuli may influence positively the brain organization (at first the limbic system) with consequences on emotional pattern, memory

and cognitive potential of the infant. Moreover the KMC reduces the sleep disruptions and improves the sleep-awake rhythm of preterm infants, and enhance the brain plasticity – that is the brain capacity to adapt his function to environmental stimuli – by supporting thereby the self-regulatory system [2]. Since 2005 the European network EDC (Early Developmental Care for Extremely Premature Babies in NICU) whose purpose is the implementation of survey about the development of NICUs infants has identified eight basic procedures for the assistance of these fragile babies): skin-to-skin contact is one of eight principles for family-centered care. More recently, Roué et al. [5] confirmed the value of the eight procedures, including KMC. KMC has been recommended since 2015 by the WHO [6] for the routine care of newborns weighing 2,000 g or less at birth in all health care facilities (even in low income countries) as soon as the newborns are clinically stable: infants should be provided as close to continuous KMC as possible, even if intermittent KMC – where continuous KMC is not possible – is recommended too. Finally, KMC – by promoting positive interactions with preterm infants – reduces the maternal psychological stress caused by separation and by the global NICU experiences, ameliorates the negative maternal mood, improves her mental wellbeing and even promotes "the breastfeeding wheel" with relevant consequences on the lactation process. The consistency of these findings provides support for widespread implementation of KMC as standard of care for newborns but – at the moment – the diffusion of KMC is not homogeneous. In a survey of 2017 [7], whose target was to investigate the adoption by Italian NICUs of the KMC method, it was found that KMC was a part of the routine care in 94% of the NICUs, with various differences between center and center: in 62% of the centers KMC is offered with time restrictions, in 43% KMC is proposed only in the most intensive care area, in 35% it is offered just once a day. Moreover, fathers are engaged in KMC only in 13% of cases. The same study highlighted the relation between the number of opening hours to the parents and KMC duration: this was longer in the neonatal units open 24 hours a day. In conclusion, the survey showed that the adoption of KMC by Italian NICUs is still a long way from the WHO requirements.

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LECT 9

KANGAROO MOTHER CARE IN ITALY: 2017 SURVEY

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The NICU environment exposes the preterm baby to excessive sensory and motor stresses. The family plays a fundamental role in enhancing therapeutic and care processes. The kangaroo mother care (KMC) is a simple and effective method to promote the health and well-being of the preterm baby; it is increasingly used to promote contact, outside the incubator, between the newborn and its parents. A large number of KMC studies have highlighted the positive effects of KMC. First, it reduces mortality and the hospital stay of preterm infants in both low and high-income countries.

KMC is considered an optimal therapy for the premature infant and its parents: it promotes a macro and micro environment adequate to the fragility of the newborn, supports physiological neuromotor stability, reduces stress, induces periods of rest, regulates the sleep-wake rhythm, promotes self-regulation and the maturation of neuro-behavioral development. Previously published articles showed that although KMC appears to be a well-known practice within Italian NICUs, its application and the time spent on it were limited and strongly

influenced by the restrictive access to the Units. One of the main objectives of the Italian Society of Neonatology (SIN) Neonatal Care Group is to support national interventions to allow the active parents' involvement and to promote policies for the NICU 24 hour a day opening. The World Health Organization (WHO) considers KMC and breastfeeding the most effective practices for implementing developmental care, together with staff training and the implementation of written protocols and recommendations concerning the role of parents in their child's development support programs. The primary objective of the study is to verify if KMC is routinely proposed in the Italian NICUs, to investigate whether the time and the implementation of KMC are in line with the recommendations of WHO and whether there are significant differences from region to region. A secondary objective is to analyze access modality to the unit and the attitude towards the parents according to the "developmental care" approach. We prepared a structured questionnaire to collect information on policies on parental engagement in NICUs. Areas of interest of the survey were: NICU general characteristics, access and attitude towards the parents, KMC, breastfeeding support. General characteristics included staff information, number and types of cots, presence of consultants. We recruited second and third level NICU (according to Italian definitions) admitting infants ≤ 32 weeks of gestation in all Italian regions. We excluded from the study first level centers. No patients were involved in the study and no intervention was planned. We identified a regional referent for the distribution and the collection of questionnaires. The survey included: a) a presentation of the study by phone contact and then by e-mail, sending an informative letter; b) a formal adhesion to the study by the NICU director participating in the survey; c) illustration of the questionnaire and explanation of the objectives of the study, finally the identification of a referring operator. The distribution and subsequent collection of the questionnaires took place between June and November 2017. We mailed 107 questionnaires to the directors of NICUs admitting preterm newborns of less than 32 weeks. We collected 86/107 complete questionnaires in the recruiting period. The national response rate was 80.3%, but it was very different in the various areas of the country, ranging from 100% to 50%. The proportion of Units allowing parental visits at any time over the 24 h period is around 60%, without significant difference between the entry time of mothers and fathers. Parental access at any time over 24 h is significantly different in the three macro-regions of Italy, ranging from 84% to 25% ($p < 0.01$). Among NICUs declaring limited time parental access, the average daily opening time is 7 ± 4 hours, but only 27% have a daily opening time higher than 10 hours. Only some parents' facilities, such as reclining chairs and milk room are widespread in Italian NICUs. Almost all NICUs state they recommend KMC, only 1/3 without time restrictions. The average duration of a single KMC session is 1 h 45', while the total daily duration is 2 h 45'. KMC is proposed more than once a day in 2/3 of the centers. The absence of written protocols and the lack of training activities are common features in Italian NICUs. KMC is a routine practice in almost all NICUs interviewed. Breastfeeding is often proposed during intensive care and the presence of parents next to the child is increasingly seen as fundamental. There is still a great cultural gap with other European countries on policies to support the promotion of parenting skills and there are large differences even within our nation. The SIN can help to fill this gap, as quickly as possible, through identifying, planning and sustaining targeted training intervention in the field.

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LECT 10

NEWBORN OF MOTHERS AFFECTED BY THYROID DISEASE

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Thyroid dysfunction is one of the major endocrine disorders occurring during pregnancy. Physiological changes in the thyroid gland occur during the gestational period, and pathologic processes may interfere with normal hormone production. Accurate assessment of maternal thyroid function is essential because adequate thyroid hormone levels are required for proper fetal development. Maternal hypothyroidism, auto-immune thyroiditis, and hyperthyroidism could impact on the outcome of a pregnancy.

Hypothyroidism occurs in 2-3% of pregnancies. Maternal auto-immune thyroiditis is the most common cause of hypothyroidism during the gestational period; however, it may sometimes be present with normal TSH and FT4 values. In fact, thyroid peroxidase antibodies (AbTPO) and thyroglobulin antibodies (AbTG) are described in 2-17% of pregnant women. This condition is associated with a greater prevalence of neonatal transient hypothyroidism in the first months of life. In addition to the initial neonatal screening performed at day 3, there are currently no clear indications to repeat thyroid function exams in newborns of mothers affected by auto-immune thyroiditis during the first month of life. An Italian study has demonstrated that 28% of their cohort of infants, born to mothers with autoimmune thyroiditis, were diagnosed with neonatal hyperthyrotropinemia. Therefore, the authors suggest performing blood tests between day 15 and day 30 to check TSH and FT4 levels. Nevertheless, all the subjects presented with a transient form of hypothyroidism; the majority of them (93.3%) did not need replacement therapy. Other recent studies suggest that all cases of hyperthyrotropinemia might be detected by neonatal screening, making further thyroid function exams unnecessary. Currently, in our region, the first neonatal screening and the second confirmation at day 15 are mandatory for all newborns of mothers affected by gestational, idiopathic, or autoimmune hypothyroidism, as well as autoimmune thyroiditis in euthyroidism.

Hyperthyroidism occurs in 0.1-0.5% of pregnancies and high levels of thyroid stimulating antibodies may cause fetal and neonatal hyperthyroidism in 1:25,000 newborns. Fetal surveillance is needed in hyperthyroid pregnant women with high/not known TRAB levels since this condition is associated with increased fetal and neonatal complications and mortality if not recognized and treated. As in pregnant women with active Graves disease, the dosage of anti TSH receptor antibodies (TRAB) is recommended during the second half of pregnancy (from the 20th week of gestation) in mothers affected by hypothyroidism with a previous history of Graves disease, treated with either radioiodine or thyroidectomy. TRAB can persist long after definitive treatment and may interfere with the fetal thyroid function after crossing the placenta.

Poor control of the maternal disease may cause: goiter, IUGR, oligohydramnios, prematurity, and fetal death. At birth a careful physical examination must be performed, paying close attention to the non-specific signs/symptoms that may be caused by this disease: tachycardia, hyperexcitability, poor weight gain in presence of large appetite, goiter, small anterior fontanel, hepatosplenomegaly, periorbital edema, retraction of the eyelids, cardiac insufficiency, craniosynostosis, and microcephaly. Blood tests and TRAB measurements should be taken between 3-5 days of life; treatment should be promptly started in case of abnormal thyroid levels. Neonatal hyperthyroidism is a severe but usually transient condition as TRAB are cleared from the neonatal circulation in 3-4 months. There is no indication for further follow-up in children with negative TRAB levels.

However, newborns of mothers affected by Graves disease and treated with an anti-thyroid drug can also develop a transient form of hyperthyrotropinemia, since thionamides are able to cross the placenta.

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LECT 11

NURSING RECOMMENDATIONS ON THE SKIN MANAGEMENT OF TERM AND PRETERM INFANT

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The Italian Society of Neonatology (SIN) Nursing Working Group and the SIN Nursing Committee organized in February 2018 a task force for the development of recommendations for the skin management of the term and preterm infant. This project is the result of the motivational drive generated by the great success of the nursing course on the prevention of skin injuries in the Naples 2016 Conference, where nurses felt involved and responsible to contain the risk of skin-breakdown. A group that had already started to study the problem decided to work together in a multi-center nursing project in order to face at a disciplinary level the iatrogenic damage of the treatment, considered an indicator of the quality of care at international level. The choice of the Working Group was therefore to address "the subject of study" with the common language and the tools of the nursing profession in order to promote and disseminate "good clinical practice". The task force was organized by identifying the following people who have always been dealing with this problem: Elena Bernabei – Pediatric Nurse RUO Neonatology P.O. Moscati, Aversa (CE), Paola Coscia – Coordinator SC of Neonatology and NICU ASST Great Metropolitan Hospital Niguarda, Milan; Michela Di Giuseppe – Nurse NICU AOU Polyclinic of Modena; Luisa Guarinoni – Nurse NICU P.O. Children's Hospital – ASST Spedali Civili of Brescia; Simona Tuccio – Nurse NICU P.O. Children's Hospital – ASST Spedali Civili of Brescia; Valentina Vanzi – Pediatric Nurse DPUO-PGS IRCCS Bambino Gesù Children's Hospital, Rome.

The skin care of the newborn has been little studied to date, and clinical trials and efficacy tests are also limited. Cutaneous lesions affect 19-23% of the premature babies admitted to neonatal intensive care, and such injuries are always related to pain and infections. Skin integrity is a priority for nursing research and it is an indicator of quality of care. Newborns, especially if preterm, have significant risk factors for the development of lesions. The purpose of this work is to provide to NICU operators and to neonatology departments recommendations based on scientific evidence in literature on the prevention and treatment of skin injuries, in order to improve the effectiveness of our interventions. We hope to provide standard and basic knowledge to all professionals who use this document, in order to allow them to choose autonomously and knowledgeably the most appropriate interventions and to act as reference for department procedures. All the problems related to neonatal skin have been addressed for term and preterm infants. Recommendations must involve all professionals involved in the care of the newborn, directing professionals in the choice of preventive strategies aimed at limiting the risk of pressure injuries and in the evaluation of the most appropriate treatment in the presence of injuries. The methodology used for this document was based on systematic methods for the research of scientific evidences. The following databases were accessed: Medline, Embase, CINHAL and Cochrane library, based mostly on reviews of the literature of the last 10 years and prospective studies. The studies that emerged from the literature review were shared, discussed and compared during the meetings for a more appropriate development of recommendations. The difficulty of finding studies aimed at the neonatal population, and the desire to create a document drawn up autonomously in line with the mission of the nursing Working Group inevitably delayed the time of development. Other sources were the NPUAP 2014 guidelines with 2016 update. The document is structured into chapters, depending on the type of injury to be treated, starting from the physiology of the skin of the newborn, both term and preterm, and then moving on to the different types of injuries and related procedures for prevention and treatment. We hope, in the near future, to be "forced" to develop new editions, based on the suggestions of those who continually test new procedures in the field and those who aim to continuously improve the quality of care based on continuous scientific research. The components of the Task Force and the nursing Working Group are not in conflict of interest and the printing of recommendations will be carried out directly by the SIN without affecting the content of the information included. The document must be approved before publication by the SIN Board.

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LECT 12

INTRAUTERINE GROWTH RESTRICTION: SHORT AND LONG TERM OUTCOME

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Intrauterine (or fetal) growth restriction (IUGR, FGR) is defined as a condition in which the fetus does not reach its biological growth potential as a consequence of a variety of factors. The etiology of FGR can be categorized as maternal (e.g. chronic conditions associated with vascular disease), fetal (e.g. chromosomal abnormalities), and placental (e.g. abnormal placentation). Although the underlying pathophysiological mechanisms may be very different, they often lead to the same endpoint: suboptimal utero-placental perfusion and fetal nutrition [1]. Placental insufficiency arises when the vasculature of the placenta develops abnormally, resulting in vascular occlusion, infarction and permanent structural damage. One of the early vascular signs of FGR is reduced blood flow in the umbilical artery, particularly during end-diastole. The afterload in the right ventricle becomes elevated, and cardiac output is shifted in favor of the left ventricle. This, along with a decreased resistance in the cerebral arteries, results in an increased blood flow towards the brain, at the expense of lower body weight. This phenomenon is known as "brain sparing" [2] and its consequence is the so-called "asymmetrical" IUGR. Being born SGA is associated with long term unfavorable outcomes such as growth deficit learning difficulties, behavior problems, and the development of metabolic syndrome. However, an appropriate diagnosis is mandatory for appropriate clinical management and for the definition of the prognosis of these subjects [3]. The acronyms IUGR and SGA (small-for-gestational age) are often used as synonymous, but a distinction between the two terms must be made. The definition of SGA is usually referred to an infant with a birthweight (but also length or cranial circumference) < 10th centile of a given neonatal chart [3]. By this definition, based on a cross-sectional evaluation, it is not possible to distinguish healthy fetuses with a physiological small size (known as "constitutionally small") from those that are truly growth restricted because of abnormalities in the mother, the placenta, or the fetus itself [1]. This definition also fails to identify fetuses with a birthweight > 10th centile that have not achieved their growth potential. Falling above the threshold for SGA, these infants may remain undiagnosed, despite being at risk for adverse outcome [2]. Several parameters have been suggested to distinguish IUGR from SGA. They may improve the detection of FGR and its complications compared to the use of biometric measurements alone. These include longitudinal fetal ultrasound biometry focusing on centiles downward crossing, functional parameters such as Doppler waveform analysis (umbilical artery, uterine artery, fetal middle cerebral artery and ductus venosus) and serum biomarkers. Biomarkers and Doppler velocimetry reflection are "functional parameters" that reflect placental function at the time of assessment. Because of the latency between the onset of placental dysfunction and its effect on biometric measurements, functional parameters could be useful in anticipating diagnosis. Ultrasound assessment of fetal anatomy and amniotic fluid volume is complementary to the Doppler investigation of feto-placental circulation to distinguish FGR from constitutionally small fetuses [4]. Multiple definitions of IUGR have been suggested over the decades by National and International Societies and experts. Nevertheless, currently no gold standard for this diagnosis is available [4]. Over the last few years, several authors have attempted to estimate the possible relationship between fetal and maternal Doppler velocimetry, and neonatal outcomes in preterm babies. As a matter of fact, most studies simply compared AGA (appropriate for gestational age) versus SGA infants. In other cases, outcomes were reported based on cross sectional evaluation of birth weight centile, without information on longitudinal fetal growth [5]. In a current study we demonstrated that infants who have experienced intrauterine growth restriction (IUGR) face considerable hurdles, not

just in the "*in utero*" period but also immediately after birth, especially with respect to feeding intolerance. Our results suggest the need for a close and careful monitoring of infants with antenatal suspicion of fetal growth, according to biometry and Doppler velocimetry. A strong collaboration between obstetrics and neonatologists is essential to provide optimal auxological evaluation of the newborn and to better define intervention strategies.

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LECT 13

INTERSOCIETY POLICY STATEMENT ON THE USE OF WHOLE-EXOME SEQUENCING IN THE CRITICALLY ILL NEWBORN INFANT

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The decreasing costs of next-generation sequencing (NGS) technology for whole-exome sequencing (WES) and whole-genome sequencing (WGS) have permitted its wide use both for research purposes and for the clinical diagnosis of suspected single-gene disorders. Genetic disorders, which include individually rare monogenic disorders, copy number variations (CNVs) and chromosomal abnormalities, overall affect a substantial proportion of the general population [1]. The Online Mendelian Inheritance in Man (OMIM) Gene Map Statistics reports that 5,170 single-gene disorders have been described so far, that can be explained by genetic variations in 3,541 genes [2]. A genetic disease may already be overtly expressed during the neonatal stage [3]. However, in many cases, the clinical presentation can be initially nonspecific, especially in infants in critical conditions receiving intensive care. In such situations, the diagnostic process may be time-consuming, uncomfortable for the patient, and not always effective in the molecular characterization of a condition during the stay in the neonatal intensive care unit (NICU). Specifically, serial gene sequencing (Sanger sequencing) can be successful in the study of conditions where a diagnostic hypothesis is strongly suspected based on the clinical phenotype and laboratory results; newborn screenings on Guthrie cards only test for a limited number of genetic diseases; and microarray technology fails to detect single-nucleotide variations and small insertions-deletions. The use of WES in selected cases is an essential diagnostic tool to obtain the molecular characterization of clinically aspecific and/or genetically heterogeneous conditions presenting in the NICU. Indications or position statements of genetic societies for the use of NGS in the setting of suspected genetic disorders have been proposed [4], but specific indications for suspected genetic conditions occurring in critically ill newborn infants are lacking, with the resulting risk of over- or under-using NGS in the NICU and consequently increasing costs for the healthcare system or reducing the diagnostic success rate, respectively. Four Italian scientific societies (the Italian Society of Pediatrics, SIP, the Italian Society of Neonatology, SIN, the Italian Society of Pediatric Genetic Diseases and Congenital Disabilities, SIMGePed, and the Italian Society of

Human Genetics, SIGU) have addressed this issue by publishing an intersociety policy statement that aims to define the best indications for the use of WES in the NICU [5]. An algorithm showing the most suitable genetic testing for each possible scenario is provided (**Fig. 1**). The policy statement proposes that WES be used in the NICU for critically ill newborn infants when an early diagnosis is desirable to guide clinical management during their NICU stay, when a strong hypothesis cannot be formulated based on the clinical phenotype or the disease is genetically heterogeneous, and when specific non-genetic laboratory tests are not available. The use of WES may reduce the time for diagnosis in infants during their NICU stay and may eventually result in cost-effectiveness. Given the rapid advancements in the field, the policy statement will need periodic revision by the issuing scientific societies. Open questions still remain, and include: use of WGS versus WES; integration of WES/WGS with other technologies to improve the diagnostic yield (RNAseq or metabolomics); use of NGS for the study of CNVs; and ethical aspects (identification of genetic defects unrelated to the clinical phenotype; identification of variants of unknown significance; privacy and data security issues, particularly sensitive for individuals in the pediatric age).

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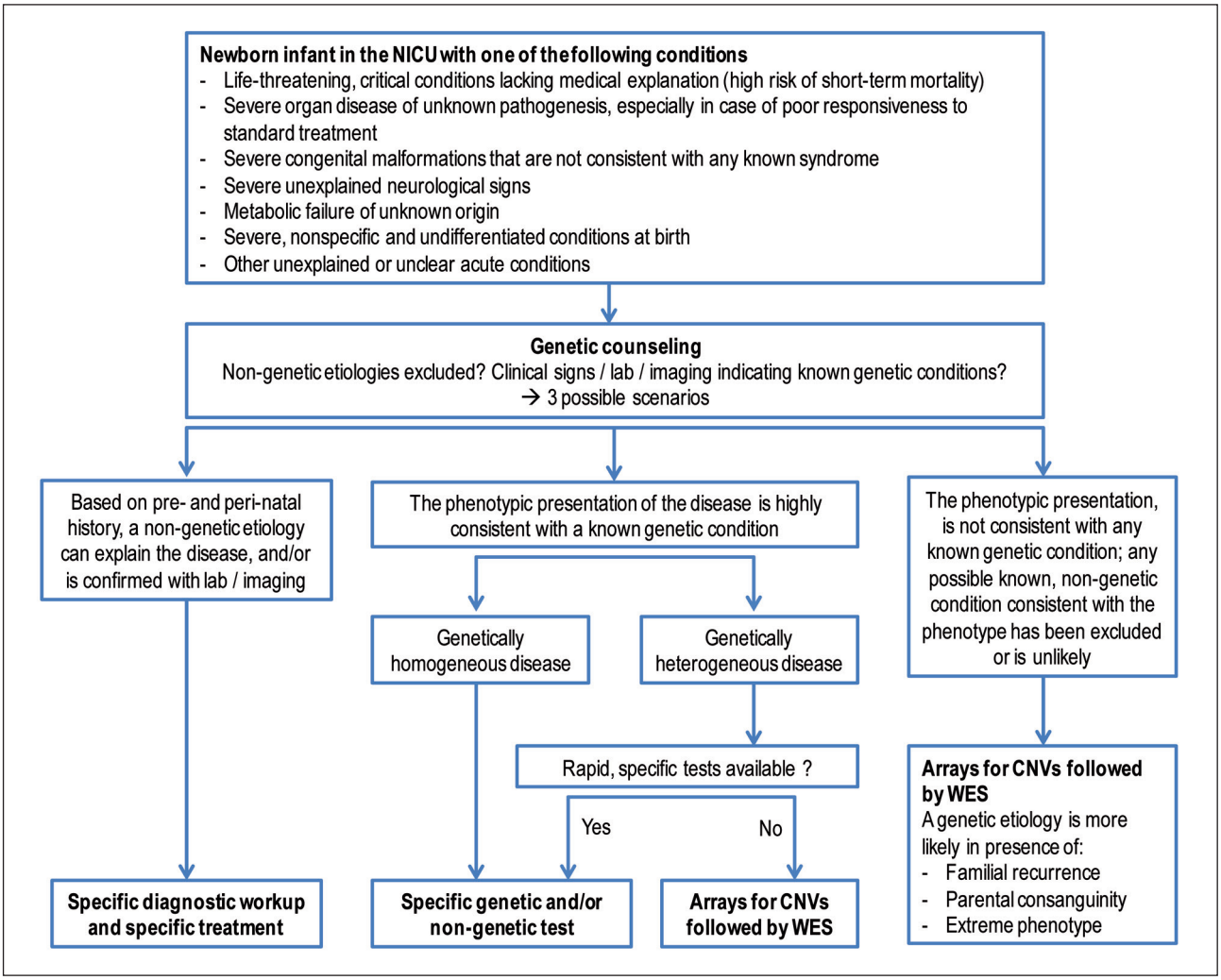

Figure 1 (LECT 13). Diagnostic algorithm for genetic testing in the critically ill newborn infant.
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LECT 14

LET'S SHED SOME LIGHT ON DISCHARGE INSTRUCTIONS FOR NEWBORNS

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Discharge of a newborn may give rise to many doubts and questions for the new parents even though it represents a special moment for the baby's family. Therefore, discharge can be the right time to give parents the right advice about breastfeeding, medications, screening programs, umbilical cord care, genital care and the most common safety instructions. Hence, if well performed, newborn discharge can represent the first important act of preventive medicine of our life. In most of the neonatal units, discharge occurs at about 48 hours of life when breast milk production is often not yet adequate. Parents sometimes can be tempted to feed their babies with formula even when it is not strictly necessary. For these reasons it is important to remind them that human milk leads to better growth and neurodevelopment and it will help to prevent acute and chronic disease. On the other hand, it is not right to demonize formula, which may be necessary to guarantee baby safety while awaiting an adequate breast milk supply. It would be a good practice to re-evaluate the infants at 48-72 hours after discharge whenever possible and to refer baby and parents to the local lactation consultants or to their pediatricians. It is also important to explain the importance of vitamin D and vitamin K supplementation. The American Academy of Pediatrics guidelines recommend supplementation of vitamin D 200 IU/day, whereas in Europe 400 IU/day for the first year. Supplementation for preterm infants should reach 800-1,000 IU/day. Vitamin K is recommended in a single intramuscular dose (0.5 mg for birthweight < 1,500 g or 1 mg for birthweight > 1,500 g) administered to all newborns within the first 6 hours of life. Iron supplementation 2 mg/kg/die after the first month of life if gestational age < 37 week. Fluorine supplementation 0.25 mg/die after 6 months (Ministry of Health Guidelines); however, odontogenesis begins in uterus and continues after birth, so many pediatricians also recommend fluorine supplementation in the first six months of life. No guidelines are available for supplementation with lutein, that can be important to protect baby's eyes from oxidative stress damage. Parents should be informed about the significance of neonatal screenings performed before discharge (metabolic screenings, red reflex, hearing test, oximetry) and other recommended screening (ECG and hip ultrasound scan at 4-6 weeks of life). Finally, give parents advice about baby care, to prevent SIDS and remind them of the importance of vaccinations both for the health of their child and for the entire community.

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LECT 15

STOP-IVH PROTOCOL IN VERY LOW BIRTH WEIGHT INFANTS: A QUALITY IMPROVEMENT APPROACH

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BACKGROUND

Intraventricular hemorrhage (IVH) is one of the most dramatic events that may occur in the early days after preterm birth. Its occurrence is associated with a range of neurological sequelae such as neuro-developmental delay, cerebral palsy, convulsions. Strategies aimed to prevent IVH in preterm neonates are based on minimizing hemodynamic instability and stressors that may play a major role in this event. However, we still lack clear evidence as to the effectiveness of systematic interventions aimed to prevent IVH during the first week of life.

AIM

To compare the prevalence of IVH before and after the introduction of a dedicated protocol (STOP-IVH) to manage very low birth weight infants (VLBWI) both in the delivery room and during the first postnatal days in a III level NICU.

MATERIALS AND METHODS

At the NICU of the Hospital of Padua since July 2016 the STOP-IVH Protocol has been introduced for all those between 23^{+0}-31^{+6} weeks gestation and birth weight < 1,500 g. The protocol targeted two settings: the delivery room and the NICU and consisted of the following interventions: a) placental blood drawings in the delivery room to minimize neonatal blood losses; b) prevention of heat loss in DR and NICU; c) prevention, monitoring and treatment of pain and stress; d) early positioning of IV lines; e) postponed recording of auxological parameters at the second day of life; f) minimal handling. Data were collected before and after the introduction of the protocol and the various aspects of application of the protocol were examined.

RESULTS

99, 110 and 103 VLBWI were admitted in 2015, 2016 and 2017, respectively. After the introduction of the STOP-IVH protocol, there was a decrease in the incidence of total IVH (from 24% to 12%); in particular, IVH grade IV decreased from 7.1% to 3.8%. Some aspects of the protocol have been adequately followed, while others need further implementation.

CONCLUSIONS

After our QI intervention, the incidence of total IVH and severe IV decreased by about half. Although this result may not only depend on the application of the protocol, our results are in line with other international centers that have adopted the same strategy. Nevertheless, many points of the protocol must continue to be implemented and monitored over time along with clinical outcomes.

LECT 16

MINDFULNESS IN HELP FOR THE OPERATORS IN NICU: AN EXPERIMENTAL TRAINING PATH AT THE S. ANNA TURIN HOSPITAL

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Psychological interventions based on Mindfulness have become increasingly popular throughout the Western world. These interventions are aimed at offering health professionals the tools to cultivate an attitude of non-judgmental awareness and acceptance of the present moment, and also to develop skills useful for modifying the attitude towards oneself and others, providing strategies to manage in more functional ways those situations with high emotional impact present in the daily work with families and small patients. In our experience there was a short training course of seven meetings, addressed to all health care workers of the neonatal intensive care of our S. Anna Hospital in Turin, with the main objective of bringing benefits not only to the staff but also to the patients. The course was intended as an opportunity for sharing among the operators aimed at improving and refining interpersonal skills and abilities through guided meditative practices. Mindfulness is a valuable resource to cope with the burnout of health operators of the NICU who are

engaged daily in handling highly complex events. Following this training, the operators, guided by keeping the practice alive in their daily work, were able to benefit from the use of more functional adaptive strategies in emotional terms. The course provided for the administration of a self-report test battery in a version adapted to the course recipients.

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LECT 17

KANGAROO MOTHER CARE: ITS BIRTH, WORLDWIDE DIFFUSION, SCIENTIFIC EVIDENCE

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Edgar Rey in 1978 in Bogotà (Columbia) initiated what later became known as kangaroo mother care (KMC), which is now recognized worldwide as a method for caring for preterm or low birth weight or sick newborns. Initially KMC was the response to lack of incubators in a technologically poor environment but since the 80's KMC has been associated with the promotion of protective factors for fragile infants' health and with the reduction in risk factors associated with preterm infants' survival, growth and development. Early and prolonged skin-to-skin contact is the basis of this method, which has become widespread at all levels of neonatal care, in both developed and low-income countries (LICs). In recent years, KMC has been provided in different modalities: intermittent KMC (some hours/day) is usually performed in the technological intensive care units whereas continuous KMC (almost 24/24 hours, at least 18 hours) is common in LICs where primary targets are the reduction of mortality and morbidity (by lowering infections and hypothermia, at first), the improvement of breastfeeding, the reduction of the time spent in the hospital, the empowerment of the mother's role. A "new role" of the mothers (together with a "new" involvement of the father and the finding of a "new" role for the family) in the care of fragile babies looks to become the primary target in modern intensive care units, in addition to the biological effects cited above, mainly the implementation of breast milk feeding. KMC reduces the mother-infant separation periods and consequently the negative effects of maternal deprivation for the infants and in the meantime reduces the stress factors due to over-stimulation by light, sound and repeated experiences of pain by the buffering role of the skin-to-skin contact. KMC has often been regarded as an "alternative medicine", not scientifically supported, but in the last few decades its biological and psycho-social effectiveness has been validated by thousands of studies. Its biomedical effectiveness and safety have been evaluated in observational studies and randomized clinical trials and now KMC is used worldwide by scientifically oriented professionals as a complement to standard care. In the last decade a large number of studies were conducted with the purpose of confirming the scientific evidence of the KMC method. In 2011, Conde-Agudelo and Díaz-Rossello [1] in 16 RCT meta-analyses on the prognostic value of KMC in 2,586 LBWIs demonstrated 40% less mortality and 58% fewer nosocomial infections as well as a shorter stay in the hospital in the KMC group. KMC was even found to increase the incidence of breastfeeding and to improve mother-child attachment. More recently (2015), by using a GRADE approach, KMC was identified by Lassi et al. [2] as one of six interventions clearly effective in reducing neonatal, infant or child mortality together with the antenatal use of corticosteroids to prevent respiratory distress and the early initiation of breastfeeding. In 2016, a large meta-analysis of Boundy et al. (124 studies, of which 63 were RCTs) demonstrated that KMC compared to conventional care was associated with 36% less mortality, 47% reduced risk of neonatal sepsis, 88% less hypoglycemia, 58% fewer readmissions, 50% more exclusive breastfeeding [3]. Finally, we see as of extreme importance the recent (2018) systematic review and meta-analysis of Akbari et al. [4] that was performed by screening of 3,177 studies to examine the relationship between KMC and infant/toddler bio-psychosocial outcomes: KMC administered to vulnerable neonates in a sensitive period of brain development was seen to be related to improved self-regulation, a very important feature for the long lasting social behavior of the infant. Even though the scientific bases of KMC are more and more evidenced, the worldwide diffusion of KMC is not uniform: poor knowledge of the role of early and prolonged skin-to-skin contact and its implication on biological and psychosocial development seems

one of the more relevant problems to solve. A scale-up process requires the alliance of the medical and nursing schools, health scientific societies, political authorities and international agencies (the latter two actors have particular importance in LICs). There is enough evidence to act to deliver a better start for the new generation of preterm and full-term infants [5].

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LECT 18

USE OF BUNDLES TO PREVENT CENTRAL LINE ASSOCIATED BLOODSTREAM INFECTION IN NEONATAL INTENSIVE CARE UNITS

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Central venous catheters (CVCs) are commonly used to provide long term venous access. They provide critical nutrition for growth as well as a portal for other vital intravenous fluids and medications [1]. The most frequent complication is central line–associated bloodstream infection (CLABSI). CLABSIs have come to be recognized as preventable adverse events that result from lapses in technique at multiple levels of care. This recognition is essential to instill the appropriate sense of personal accountability in individual healthcare workers necessary to trigger change. Strategies to reduce CLABSI described in the literature over the past decades. Successful changes have incorporated these strategies into bundles of practice that are more effective when introduced simultaneously. A bundle is defined as "a limited number of specific practices, each essential for effective and safe patient care and that, when implemented together, result in additional improvements in patient outcomes" [2]. The reduction of healthcare-associated infection is a nationally important issue, and a bundle of interventions has been shown to produce a significant positive impact within a single unit. Infections can be prevented during insertion of a vascular device or during maintenance of a central line [3]. Insertion bundles include a varied combination of: hand hygiene, maximal sterile barriers, choice of insertion sites, ultrasound guidance (always if possible), skin disinfection, transparent and semi-permeable polyurethane dressing, prompt removal of CVC. Maintenance bundles combine: aseptic techniques when accessing the line, disinfection of catheter hubs/ports, administration set and fluid change, use of needle-free connector, pulsatile flush with saline solution. Use of a chlorhexidine (CHG) solution is recommended in many situations. The residual effect of CHG-containing preparations gives them preference for prolonged anti-microbial action to inhibit extraluminal migration of organisms colonizing the skin surface once the catheter is placed. CHG-containing solutions have been shown to be superior to povidone-iodine in reducing the incidence of bloodstream infection. Concerns over sensitivity reactions with CHG have been raised, but these should be weighed against the relative benefits of this agent over those without residual effect. CHG 2% in isopropyl alcohol 70% is the recommended skin antisepsis agent in the Association of Women's Health, Obstetric and Neonatal Nurses/National Association of Neonatal Nurses skin guideline and is specified in Central Line Bundle. Local skin reactions can be mitigated by rinsing with sterile water after a 30-second application, as the residual effect will remain. Due to ongoing concerns over local reactions, many centers limit the use of CHG preparations in the most premature infants, at least in the immediate perinatal period, choosing povidone instead [4]. Many studies have demonstrated that staff compliance with the bundle has a direct effect

on catheter-related infection; greater compliance is associated with reduced infection [5]. Despite the promotion of bundles, questions still remain as to their adoption and effectiveness. Bundled policies do not guarantee reliable execution at the bedside; moreover, even though decreases in CLABSIs have been reported, these infections continue to be significant problems in many neonatal intensive care units. Quasi-experimental studies point to subsequent decreases in CLABSI rates following bundle implementation. In these publications, a key focus has been improving the culture of safety, and some have hypothesized that an overall heightened attention to one clinical issue leads to a positive "chain reaction" effect that prevents other complications. If this were the case, implementing one bundle would be expected to lead to a decrease in other non-targeted healthcare-associated infection rates in the same setting.

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LECT 19

NEONATE OF MOTHER WITH AUTOIMMUNE DISEASE

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Autoimmunity diseases have higher prevalence in women; up to 70% of patients with autoimmunity are women in fertile age. A characteristic of autoimmunity diseases during pregnancy is the transplacental transport of auto-antibodies that can affect the fetus and the newborn and probably may have effects later in childhood. Most of the scientific literature on the effect of autoimmunity in pregnancy on neonates concerns individual cases or small groups of patients. We will try to focus on the principal effects on neonates of maternal autoimmune thyroiditis and systemic lupus erythematosus. Autoimmune thyroiditis is relatively frequent in pregnancies; 1 out of 2,000 pregnancies are affected by this disease, the most frequent of which is Graves thyroiditis. It is characterized by autoantibodies stimulating TSH receptors that can cross the placenta. Fortunately, only 1% of neonates from mothers with Graves's thyroiditis may be symptomatic with neonatal thyrotoxicosis. Features of such neonates are to be SGA infants, excessive loss of weight, irritability, flushing, exophthalmos, goiter, tachycardia up to hyperkinetic heart failure. Maternal Hashimoto's thyroiditis can cause fetal and neonatal hypothyroidism for transplacental cross of autoantibodies blocking fetal thyroid function. Rovelli et al., showed that transient mild elevation of serum TSH above the normal reference value for age is frequently observed in the first month of life in neonates from mothers with autoimmune thyroiditis whilst persistent hyperthyrotropinemia requiring replacement therapy was observed in 2% of these neonates [1]. Therefore, follow-up is recommended in these newborns. Neonatal lupus syndrome is a rare condition affecting 1/20,000 newborn and less than 5% of babies born from mothers with systemic lupus erythematosus (SLE) with anti U1RNP, anti SSA/Ro and anti SSB/La autoantibodies. The cutaneous manifestation (macular rash, butterfly erythema and discoid skin lesions of face and scalp) are the most frequent neonatal lupus characteristics but complete heart block is the most serious feature of this syndrome. It affects less than 3% of neonates from mothers with SLE and is determined by the disarrangement of cardiac conduction tissue of the atrioventricular node caused by autoantibodies. Complete heart block (CHB) may be of first, second or third degree and can get worse after birth. Scarsi et al. showed in 42 children with CHB that all were previously identified with an ELISA screening for anti-Ro/SSA 60 kD Ab [2]. Moreover, Anti-p200 Ab were more frequently positive in such patients. Therefore, ELISA screening for anti-Ro/SSA 60 kD Ab in pregnant women may identify neonates at risk of this serious disease. Mortality rate of CHB is reported between 19-31% in the first months of life

whilst in those surviving, heart-pacing frequently needs to be implanted. Heart block may also cause cardiomyopathy in early childhood; therefore such neonates require regular cardiac follow up. Nalli et al., in 2017 published a long term follow up of 40 neonates born from mothers with SLE and/or antiphospholipid antibodies, median age 7 years, and demonstrated a normal neurological physical exam whilst a cognitive impairment or discrepant cognitive profile was found in 7% and 28% of children respectively [3]. In 2018, Hwang et al. published follow-up data on preterm and term neonates born from mothers with SLE [4]. They included 92 neonates and demonstrated that maternal flares during pregnancy were associated with lupus anticoagulant antibodies and with preterm birth. Moreover, in preterm neonates higher ANA positivity persists at 12 months of age. To date, the question remains as to whether children born from women with SLE and/or antiphospholipid antibodies may need long-term follow-up focusing on their neurodevelopment. To address the possibility of cognitive impairment in children of mothers with SLE and or antiphospholipid antibodies during pregnancy a large trial is needed also to overcome the confounding factor of prematurity that is more frequent in this maternal disease.

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LECT 20

RETINOPATHY OF PREMATURITY: DIAGNOSIS AND THERAPEUTIC APPROACHES BY THE OPHTHALMOLOGIST

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The clinical and instrumental follow-up of premature retinopathy begins in neonatal intensive care and continues throughout the life of the subject. In fact, the presence of risk factors for Retinopathy of Prematurity (ROP) requires starting the patient's control even before the possible clinical manifestation of the pathology; the newborn affected by ROP, even where totally regressed, still needs systematic lifetime checks. Remote outcomes of ROP, even of low stage, are described in adulthood. Indirect binocular ophthalmoscopy (clinical control benchmark), both retinography and angiography, OCT, ocular ultrasound, and electrophysiology are essential elements of the correct clinical framework of this complex pathology, with operational and medico-legal implications. Although ablation of the avascular retina with laser photocoagulation remains the current gold standard and well-established therapy for ROP, some new therapeutic options including angiostatic therapies are being explored based on our knowledge of the pathophysiology of the ROP and the complications and efficacy of laser treatment. However, prevention of the development of severe ROP and screening for ROP would seem to be the best strategy in avoiding the visual impairment caused by ROP in premature infants.

LECT 21

STRATEGIES FOR HUMAN MILK FORTIFICATION

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Provision of adequate qualitative and quantitative nutrition represents a priority in very preterm newborns (gestational age < 32 weeks) and very low birth weight infants (< 1,500 g). The best nutritional strategy has to sustain correct short-term linear growth and long-term neurological and cognitive performance, avoiding negative consequences for long-term metabolic and cardiovascular health [1]. During the early postnatal period, preterm infants are particularly exposed to an imbalance between intakes and needs. Human milk (HM) provides many and unique benefits to preterm infants (e.g. protection against infections, necrotizing enterocolitis,

retinopathy of prematurity, improvement of neurodevelopment outcomes) that are mediated by macro-components and trophic factors. Therefore, HM is strongly recommended and represents the first choice for preterm nutrition [2]. However, HM provides insufficient nutritional components (mainly proteins and minerals) to ensure adequate growth and mineralization of preterm infants when fed at the usual feeding volumes. Considering that nutritional profile of HM varies greatly throughout the course of lactation, adding a fixed amount of a multicomponent fortifier ("standard" fortification strategy) fails to meet recommended nutritional intake [3]. "Individualized" fortification strategy seems to be very promising. The targeted approach is based on milk analyses choosing a target protein intake. This fortification has a high cost and may not be adopted by each nursery. The "adjustable" fortification approach provides protein supplement for each infant in addition to standard multicomponent fortification and it is adjusted on the basis of the infant's periodic evaluation of blood urea nitrogen. This strategy overcomes the infant's protein requirements considering the metabolic response of each infant. Most commercially available multi-nutrient fortifiers are derived from bovine milk which has different protein content if compared to HM. Commercial fortifiers differ in casein to whey ratio and degree of protein hydrolysis. Many authors recently drew attention to a HM-based fortifier despite its being costly. Currently, there are limited efficacy data. A new Italian clinical trial is adopting a donkey milk-based fortifier [4] because of the observation of better biological effects and nutrient availability. These new products may give interesting possibilities in the field of infant nutrition [5].

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LECT 22

NEONATAL ACUTE KIDNEY INJURY: DIAGNOSIS AND TREATMENT CHALLENGE

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Neonatal definition of acute kidney injury (AKI) results as a challenging task due to the peculiar renal pathophysiology of newborn critically ill patients. The immature kidneys require careful management and neonatal AKI is frequently complicated by unfavorable outcomes. Glomerular filtration rate (GFR) in neonates increases steadily from a very low level to adult value in about 12 months. Hence, the neonatal high levels of creatinine, reflecting maternal concentrations, tend to decrease in a relatively slow manner, depending on GFR progressive increase. The urine flow is mainly regulated by tubular re-absorption that must couple a low GFR with high urine output. Such delicate equilibrium works perfectly well unless even small alterations in renal blood flow or nephrogenesis occur: in these cases, kidney dysfunction leads to imbalance in water regulation, patient swelling, electrolytes disorders and acid-base dis-equilibrium, typically metabolic acidosis. Careful clinical judgment, early recognition of kidney dysfunction and accurate fluid and electrolyte management are mandatory to avoid fluid overload and iatrogenic electrolyte disorders. Historically, broad definitions and varying diagnostic criteria complicate scientific reporting of AKI among the neonatal population. In the adult and pediatric populations, serum creatinine (SCr) levels in conjunction with GFR and urine output (UO) identify patients at risk for kidney dysfunction and potential failure. However, premature infants exhibit vast differences in these parameters. Currently, SCr levels of more than 1.5 mg/dL accompanied with UO of less than 0.5 to 1 mL/kg/h identify infants at risk for AKI; however, SCr and GFR can be difficult to interpret due to gestational age, postnatal age, maternal factors, and postnatal therapeutics. Cystatin C (Cys-C) was proposed as an alternative filtration marker for creatinine due to limitations of creatinine measurement. Cys-C is a low-molecular weight protein produced by all nucleated cells at a constant rate. It is freely filtered by the glomeruli and re-absorbed and catabolized by proximal renal tubular cells. Therefore, its serum value could be better and an early marker of neonatal kidney injury than serum

creatinine level. Urine biomarker measurement that indicates potential or actual renal injury may greatly enhance our ability to intervene sooner and reduce associated consequences. To date, only limited evaluations of biomarkers have been performed in neonates. Delayed recognition and management of AKI is likely, emphasizing the need for a standardized approach to AKI detection. In general, the most effective strategies in preventing AKI include ensuring adequate hydration, maintaining sufficient mean arterial pressure, and minimizing nephrotoxin exposure. After the diagnosis of AKI, it becomes important to prevent the development of sequelae. There are sparse data documenting interventions that can prevent AKI in at-risk patients or ameliorate AKI once it is established. The special conditions of the maturing kidney have to be appreciated in order to protect babies from undue renal injury. With the increasing knowledge of the mechanisms governing the development of ARF, progress has been made in the development of new treatment methods. In neonates with perinatal asphyxia, adenosine receptor antagonists (theophylline) may prevent AKI by inhibiting adenosine-induced vasoconstriction. Other drugs that have been studied to prevent the development of AKI and improve renal blood flow include dopaminergic agonists (dopamine and fenoldopam). Because of the lack of successful strategies to prevent or ameliorate AKI, in children the primary therapy for severe cases of AKI is renal replacement therapy. Indications for renal replacement therapy in neonates include refractory acidosis, uremia electrolyte abnormalities, inability to provide adequate nutrition, and fluid overload. Renal replacement therapy poses particular challenges in the neonate, as most equipment was designed for older children. Currently, peritoneal dialysis is the modality of choice in infants. The role that AKI plays in the development of chronic kidney disease (CKD) in the neonatal population is unknown. All patients who experience AKI should be evaluated after 3 months for new onset or worsening of CKD. They caution that even if CKD is not present at that time, those with AKI are considered to have increased risk for CKD long-term. Although these recommendations are likely pertinent to infants, currently there is not enough firm evidence to make formal follow-up recommendations after episodes of neonatal AKI.

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LECT 23

ROLE OF MILRINONE IN THE MANAGEMENT OF RIGHT VENTRICULAR DYSFUNCTION

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Milrinone is a derivative of amrinone belonging to the bipyridine compounds group of drugs, that selectively inhibits cyclic nucleotide phosphodiesterase 3 (PDE3) enzymes: it was used for the first time in 1995 in infants with low cardiac output syndrome (LCOS) following cardiac surgery. This multi-faced drug has several pharmacological effects: afterload reduction and improved diastolic function (lusitropy) with minimal increase in myocardial oxygen consumption. It is also named "inodilator 2" (inotropic with vasodilatory properties) because it improves left and right ventricular function [1]. It inhibits PDE3, which cleaves cyclic adenosine monophosphate (cAMP) of smooth muscle cells of arteries and myocardiocytes. In particular, milrinone increases the levels of cAMP, second messenger, which modulates intracellular calcium. The intracellular cAMP, causing an increase of calcium entry into cardiomyocytes, improves myocardial contractility through the activation of protein kinase A (PKA). PKA is an enzyme that phosphorylates many elements of the contractile machinery within the heart cell. In the short term this leads to an increased force of contraction. In a recent study [2] milrinone administration, used as a rescue therapy for term infants with pulmonary hypertension (PH), was followed by an increase in both right and left ventricular outputs. This was temporally associated with an improvement in the right ventricular strain and systolic strain rate, as well as left ventricular tissue Doppler and velocities in

addition to left ventricular myocardial performance index. This differential effect of milrinone on strain, systolic strain rate, and tissue Doppler parameters in the left and right ventricles is interesting and may reflect the physiological changes resulting from milrinone administration. All together these effects lead to an increased cardiac index and decrease in the mean arterial blood pressure (MAP) [2]. This PDE3 inhibitor produces dose-dependent increase in left and right cardiac output and decrease in left ventricular filling pressures as a result of the interaction of its positive inotropic, lusitropic, and peripheral vasodilator actions. Because of its vasodilating effects, milrinone is less likely than dobutamine to increase heart rate and myocardial oxygen consumption. Milrinone use is increasingly employed in the NICU, and it has been the focus of studies on the treatment of persistent pulmonary hypertension (PPHN), post patent ductus arteriosus (PDA) ligation syndrome, LCOS post corrective surgery for congenital heart defect [2]. Several studies [3, 4] show that it may be a promising therapeutic addition to PPHN of the preterm newborn and in a term neonate not responsive to inhaled nitric oxide (iNO).

Therefore, milrinone can play a role in pulmonary hypoplasia secondary to preterm premature rupture of membranes (pPROM) and twin-to-twin transfusion syndrome (TTTS) [3, 4]. Preterm infants with PPROM have a high perinatal mortality, presumably due to abnormalities of airway or vascular developments and associated PH. Early identification of PH and/or right ventricular (RV) dysfunction and initiation of treatment may enhance neonatal outcomes. TTTS complicates between 10 and 15% of monochorionic-diamniotic twins. The RV function in recipient fetuses is thought to be vulnerable to changes in loading conditions but data are limited. Inhaled nitric oxide (iNO) has been used in preterm infants with PH with little evidence of its efficacy [5]. A significant role is played by milrinone also in patients with left congenital diaphragmatic hernia (CDH). These patients may present hypoplasia and RV dysfunction. Patients with left sided CDH may have left ventricular hypoplasia and dysfunction. Such dysfunction may be associated with elevated left atrial pressure, pulmonary venous hypertension and poor LV output [1-5]. The systemic circulation may be dependent on right to left ductal flow due to elevated pulmonary vascular resistance (PVR). Pulmonary vasodilators such as inhaled NO may result in pulmonary arterial dilation and exacerbate pulmonary edema in the presence of pulmonary venous hypertension and decrease ductal-dependent systemic flow ("ductal steal"). IV PGE1 maintains ductal patency leading to reduced RV afterload and support systemic circulation. Milrinone, by improving left ventricular diastolic and systolic function reduces left atrial pressure and also dilates pulmonary vasculature resulting in improved oxygenation in CDH. The presence of hypoplastic lungs with remodeled pulmonary vasculature and volutrauma, barotrauma and oxygen toxicity contribute to poor response to pulmonary vasodilator therapy. In a recent randomized pilot trial [1] it was hypothesized that a combination of milrinone with "gentle" ventilation will improve oxygenation and response to pulmonary vasodilator therapy in CDH. Milrinone, in this context, can improve left and right ventricular diastolic function and reduce left atrial pressure [1-5]. These important properties of milrinone on myocardial performance and oxygenation are the basis of its use in critically ill preterm iNO non-responders in PH, in CDH and PPHN.

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LECT 24

MULTIDISCIPLINARY EXPERIENCE WITH A CASE OF OMPHALOPAGUS TWINS

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INTRODUCTION

Conjoined twins are one of the most challenging malformations in pediatric surgery. Depending on the anatomical structures involved, they can be separated, allowing each twin to lead a normal life. We emphasize the importance of meticulous planning with a multidisciplinary approach and its role in achieving the result of a good outcome.

CASE REPORT

A prenatal diagnosis of conjoint twinning was accomplished through an ultrasound performed prenatally at a gestational age of 12 weeks and confirmed as omphalopagus by a fetal MRI at 14 weeks of gestation. The twins, with a total birth weight of 4,700 g, were delivered at 34 weeks + 4 days of gestation by caesarean section. Throughout the duration of hospitalization, the identification of the twins was guaranteed by attribution of different colors (red and green). The fusion was extended from the epigastrium to the navel for 6 cm and with a thickness of 3 cm. In the umbilical region there was a small epithelial omphalocele and only one umbilical cord. After delivery, the twins underwent non-invasive ventilation (n-IPPV) for 4 days with regular cardiorespiratory adaptation and diuresis and meconium emission within 24 hours. Blood and hemoglobin tests were normal, as well as hepatic and renal function. A first evaluation of the pulmonary parenchyma was performed at birth with a plain x-ray. An abdominal ultrasound study was also performed after birth that confirmed the presence of a liver parenchymal bridge with two distinct hepatic hilum and two venous portal axes. The gallbladder of twin A was present, unlike that of twin B, which was not visible. No dilatation of the biliary tracts. One month after birth two gastrointestinal (GI) x-ray studies were performed, they did not show shared GI tracts among the twins. CT scan was acquired at the age of 4 months showing irregular lobules in the site of hepatic fusion, a porto-portal shunt and an arterio-arterial partially-extrahepatic shunt. Separate hepatic venous drainage into the inferior vena cava and right atrium was clearly demonstrated. The gallbladder was not clearly identified in twin B, therefore a TC-99 hepatobiliary scintigraphy (99mTc-Mebrofenin) was programmed demonstrating regular hepatobiliary function and the presence of two distinct gallbladders. After meticulous multidisciplinary preparation work, at 6 months of life with a total weight of 9.000 kg, the separation surgery was scheduled. Whole blood, fresh frozen plasma and platelet concentrate were available for each twin. The induction of anesthesia occurred separately for each twin followed by the placement of separate central venous and arterial lines. The surgical incision was made on the union bridge from the navel to the epigastrium through skin, muscles and cartilage ribs. A broad median fusion of the two livers was confirmed. Using intra-operative ultrasound, the presence of two vascular systems and the independence of the livers were confirmed. The median fusion point was identified and the separation was made. By keeping them on the same operating table, the wide wall defect in both twins was closed. The reconstruction was done by closing the anterior diaphragm and the abdominal wall with an acellular patch of porcine dermal collagen by direct suturing. After extensive mobilization and stretching of the subcutaneous plane the skin was closed directly with detached points. Vital parameters remained stable throughout the procedure. There were no complications during the postoperative period in the pediatric surgery intensive care unit. Extubation was performed on the third day for the red twin and on the fifth for the green. Re-feeding with breast milk in post-op started on day four. Both newborns had minor wound infection treated with silver-based dressings. Both newborns were in excellent health at a 6-month follow-up.

DISCUSSION

The estimated prevalence of conjoined twins in the literature varies from 1:50,000 to 1:200,000. It could be expected with about six or more operable cases per year throughout the world, that omphalopagus twins have the best chances of survival. Omphalopagus twins are joined ventrally in the umbilical region; the lower thorax may be included with the possibility of a shared pericardium; the heart is never involved. The stomachs and proximal small intestines are usually separate. Various imaging modalities have proved to be useful to evaluate the area of shared parenchyma, but CT has been recognized as the imaging modality of choice for an accurate description of vascular communications potentially present in omphalopagus twins [1-5]. Careful planning, a multidisciplinary approach and experience are important factors in dealing

with conjoined twins. The choice of the operative procedure depends on the complexity of the attachment and the degree and type of organs shared. A detailed anatomic study of the twins and careful surgical planning must precede separation. Pre-operative knowledge of shared anatomy is necessary for adequate preparation and planning. Despite meticulous pre-operative investigations, certain anatomical features can only be discovered at the time of surgery. A well-prepared pediatric surgery team and anesthesiologic team are necessary to surgically manage conjoined twins.

CONCLUSION

A complete imaging and physical examination should be performed in conjoined twins and the combination of these elements represents the union of medical, radiological and surgical skills aimed at guaranteeing the best chance of success in the twin separation procedure.

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LECT 25

NEONATAL CRANIAL ULTRASOUND: HOW TO OPTIMIZE ITS PERFORMANCE

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The cranial ultrasound is one of several techniques that capitalize on the bone-free anterior fontanelle to provide a window into the neonatal brain [1, 2]. Additionally, the use of the posterior fontanelle and of the mastoid fontanelle has markedly improved the value of ultrasonography in the evaluation of posterior fossa structures [1, 2]. Ultrasound is an irreplaceable, but not exclusive diagnostic tool; it is relatively simple to use in the majority of birth time points. The enormous value of the technique in the study of the neonatal brain has been documented in a vast number of original papers and reviews and in several books. The ultrasound method has a high diagnostic value in the evaluation of such diverse intracranial processes as the following: developmental aberrations; hypoxic-ischemic injury; subdural, germinal matrix-intraventricular, and posterior fossa hemorrhage; ventriculitis; tumors; cysts; and vascular anomalies [1-4]. Areas of increased echogenicity in the superficial cortex, in the region immediately below the brain surface, can be detected with ultrasound in some babies with hypoxic-ischemic encephalopathy. A 10-MHz transducer improves the accuracy of detection of cortical lesion [1, 4]. The ultrasound diagnosis of brain swelling requires more than a casual observation of "slit-like ventricles". Virtually all normal term babies have small lateral and third ventricular cavities, and a few hours spent imaging babies on postnatal wards will reveal the range of normal appearances at term. In congenital infections, ultrasound can easily identify some brain injuries, such as calcifications (**Fig. 1**), germinolytic cysts or ventriculomegaly. Cranial ultrasound imaging can be unaltered in patients with uncomplicated bacterial meningitis [5]. There is a wide spectrum of possible abnormalities, which can be categorized depending on the location: pathologic changes visible on the surface of the brain, in the ventricular system, in deep structures-brain tissue, and in the lumbosacral segment of the vertebral canal. Abnormal parenchymal echogenicity may be focal or diffuse and probably reflects cerebritis, brain edema, or infarction caused by vasculitis. Cerebral infarcts tend to be large and multiple. When the increased

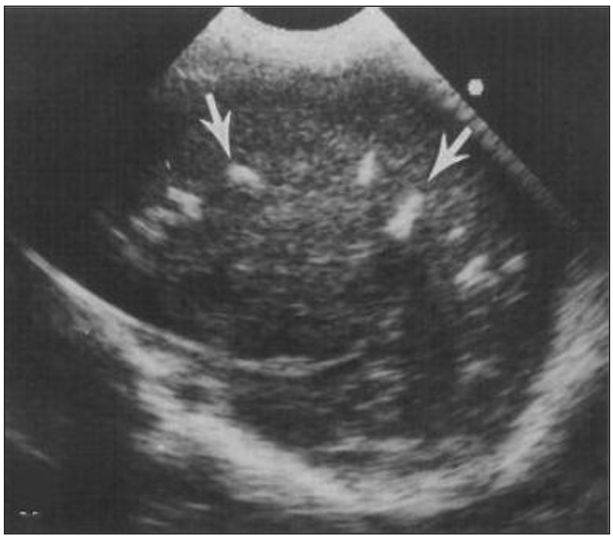

Figure 1 (LECT 25). Congenital toxoplasmosis: cranial ultrasound scan. This parasagittal scan shows parenchymal calcifications (arrows).

echogenicity is focal, particularly when limited to a gyral distribution, the likelihood of infarction increases [4, 5]. Approximately 30% of neonates with bacterial meningitis have cerebral infarcts related to associated vasculitis with venous thrombosis. Although technological advancements have permitted the production of economical ultrasound equipment with an acceptable level of quality, the gap in image quality and thus diagnostic power between top of the line and economical devices is generally abysmal. Currently, some ultrasound devices allow, under certain conditions, revelation of anatomical details that are almost invisible to the naked eye. A poor choice of depth setting results in a miniature image, which does not make the best use of the potential window for insonation. There is nothing that can be done about a very small fontanelle, but it is important to use a generous quantity of coupling gel in order to avoid loss of information at the extremes of the angle of insonation [1, 3].

Lack of coupling agent can also cause a series of "ripple"-like concentric rings to appear resulting from reverberation of ultrasound reflected between the transducer and the skin. Incorrect choice of setting on the TGC (time-gain compensation) control, or excessive "gain" (the amount of energy used to generate the ultrasound beam), can have a significant impact on the appearances of the image. It is essential to check the gain settings before making a diagnosis of "bright brain", which can be one feature of cerebral edema [1, 2]. An incorrect diagnosis of cerebral edema, based only on increased echo reflectivity in an image with excessive gain settings, is the commonest error we see in scans made by inexperienced operators [1-3]. However, the use of proper methodology is fundamental, which necessitates both accurate diagnostic and prognostic data, in order to avoid repetitive testing, and negative influences on future diagnostic – therapeutic decisions. It should be emphasized, however, that many ultrasound limitations are actually limitations associated with operator training and experience.

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LECT 26

A CLINICAL AND DIAGNOSTIC APPROACH TO A NEWBORN WITH MULTIPLE CONGENITAL MALFORMATIONS

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INTRODUCTION

A genetic syndrome is a clinical situation that combines major and minor malformations, anomalies of growth and of psychomotor development. Congenital malformations are prenatal structural abnormalities present at birth that occur in 2-3% live births. Malformations are divided into major and minor depending on their severity; a major malformation interferes considerably with the function of the child and has surgical, medical, or cosmetic importance; minor malformation does not. In 15-20% of the cases, two or more anomalies can be found in the same patient in different organs and systems, sometimes in the context of a specific syndrome. Distinguishing isolated malformations from genetic syndromes represents a special diagnostic and management challenge; a systematic approach is most useful. How to get to the right diagnosis?

HISTORY

The family history should include at least a three-generation pedigree, and contain information on spontaneous abortions, stillbirths, birth defects, geographical origin and consanguinity. This information can provide clues about inheritance pattern of a genetic condition. A history of recurrent pregnancy loss may detect a couple with an increased likelihood of fetal aneuploidy.

The clinical history includes important elements of the pregnancy history such as parental age, exposure to drugs, medications, alcohol, evidence of maternal infectious diseases or chronic illness, oligo- or polyhydramnios, ultrasound results and fetal movements. Other important information comes from the perinatal period: gestational age at delivery, mode of delivery, neonatal adaptation including evidence of asphyxia, neurological or biochemical abnormalities such as hypoglycemia or hypo-hypercalcemia. For example: when a "small for gestational age" newborn, with decreased cranial size and confirmed maternal alcohol exposure is observed, the diagnosis of fetal alcohol syndrome must be suspected; in case of a significant neonatal hypotonia with feeding difficulties the physician should evaluate the baby for suspected Prader-Willy syndrome.

CLINICAL EXAMINATION

The physical examination should be as accurate as possible, focused on detecting both major anomalies and minor dysmorphisms; it must document birth weight, length and head circumference and their relationship to gestational age. These biometric parameters should be compared to the reference charts for the specific ethnic group of the patient. Growth anomalies including overgrowth, asymmetric growth, significant growth retardation, and micro- or macrocephaly are other important considerations for genetic evaluation. For example: a disproportionately large head and asymmetry of the limbs may be some features of Silver Russell syndrome. Special attention should be given to minor anomalies that might provide clues to underlying diagnosis, despite being present in 4% of the normal population. Additionally, the presence of three or more minor anomalies may be associated with he presence of a major one in 20-90% of infants; so it has been recommended to search for major anomalies in newborn with multiple minor anomalies. It may be hard to distinguish these minor anomalies from normal variants. Each physical feature should be evaluated, normal and variant features should be accurately described using accepted standard terminology. Even if impressions are important, they are insufficient alone: every measurable parameter must be compared to standard references. For example, hypertelorism (widely spaced eyes) noted on casual observation may be an illusion caused by epicanthal folds; measuring interpupillary distance may reveal that eye spacing actually falls within the normal range. Greatest attention is given to the examination of the head and face, assessing symmetry, placement, and proportions both of overall appearance and of all paired structures (e.g., eyes and ears). The head shape, fontanelles, and suture width are examined, looking for the presence of a craniosynostosis. For example: large fontanelles and wide sutures are most notable for cleidocranial dysplasia. The forehead should be noted for contour and breadth; the placement, size, rotation and configuration of the ears should be evaluated, as also the presence of pre-auricular tags or pits. The eye distances should be measured; the nose should be evaluated for the configuration of the nasal bridge and tip. The configuration of the philtrum should be observed, along with the size of the mouth and features of the lips. Finally, the profile should be assessed for prominence or recession of the forehead, eyes, midface, and chin. For example: pre-auricular sinus and/or ear pits are common in the general population, but they may lead to the diagnosis of branchio-oto-renal syndrome when identified in a newborn with sensorineural hearing loss and renal anomalies. The chest, clavicles, ribcage, and spine should be examined for deformity or abnormalities of contour. The positioning and form of the nipples and sternum should be noted. Sacral spinal defects such as hair tufts or pits should be observed. Examination of the genitalia should include assessment of proper proportions and positioning of structures. Abnormalities of the skin, hair, and nails should be noted, and the joints examined carefully for any abnormalities, such as hyperlaxity or contractures. In noting any asymmetry or deformity of the extremities, it is important to look specifically for syndactyly or an abnormal number of digits. For example: the clinical examination of a neonate with ambiguous genitalia should include careful analysis of the toes, as cutaneous syndactyly (webbing) between the second and third toes. It could be Smith-Lemli-Opitz syndrome. Careful cardiac and neurologic examinations should be completed to look for evidence of congenital heart disease or central nervous system dysfunction, respectively. Any heart murmur, abdominal wall defect, or organomegaly should be noted.

ADDITIONAL EVALUATIONS

Imaging studies (fox example abdominal-renal ultrasound, echo-encephalography or echo-cardiography) are useful to search for malformations not evident at a first examination. Hearing and vision evaluations are as important

as some biochemical tests. A complete skeletal survey should be performed if skeletal dysplasia is suspected.

GENETIC TEST

Some genetic conditions are diagnosed on clinical grounds. Geneticists can assist in diagnosis, suggesting additional testing and referrals if warranted, helping with direct medical care, and providing counselling for affected patients and their families. There is a wide array of tests that may be used: molecular, chromosomal, and biochemical genetic testing. Other laboratory tests that measure the levels of certain substances in blood and urine can also help suggest a diagnosis. The choice of the test depends on the nature of the condition, the expense and availability of the test, and the specific clinical scenario. Certain resources (for example GeneTests Web, http://www.ncbi.nlm.nih.gov/sites/GeneTests) may be helpful in determining the type of genetic testing that is recommended or available, and in finding a laboratory that conducts testing for a certain genetic condition.

OTHER SUPPORTS AND CONCLUSION

The observation of the patient as a whole does not always permit immediate recognition of a specific and well known phenotype (e.g. Down syndrome). Sometimes a more analytic approach is necessary, based on the differential diagnosis, in which the recorded signs and anomalies, imaging, and blood tests are studied to fit a constellation of findings in a known syndrome. Several thousand syndromes have been delineated and many are described and catalogued in textbooks, such as Smith's Recognizable Patterns of malformations and Syndromes of the Head and Neck. With the wide availability of Internet access, databases have become an integral aspect of practice in clinical genetics and dysmorphology. Available resources to date include, among others, the OMIM (Online Mendelian Inheritance in Man) and Orpha.net. However, clinical genetists prefer specialized databases, such as the Winter-Baraitser Dysmorphology Database from the London Medical Databases and POSSUM (Pictures of Standard Syndromes and Undiagnosed Malformations), which are the most comprehensive resources for photos and information about syndromes, genes and clinical phenotypes. The prompt recognition of a genetic condition can improve the selection of appropriate and cost-effective diagnostic tests. Referral to a subspecialist and to well-informed genetic counselling must be immediate and related to issues such as prognosis and future family planning. Periodic evaluations are important when a diagnosis cannot be reached. During the follow-up the physical examination findings may have changed into a recognizable pattern consistent with a known diagnosis. Similarly, reviewing photographs of a child at various ages may detect phenotypic features classic for a particular condition that are no longer recognizable.

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LECT 27

BASIC ECHOCARDIOGRAPHY COURSE FOR THE NEONATOLOGIST

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In recent years, echocardiography has acquired an important role in the Italian Neonatal Intensive Care Unit and increasingly often it is performed by neonatologists. This role is acknowledged by the leading scientific societies in the field: the European Society for Neonatology (ESN) and the European Society for Paediatric Research (ESPR), that in recent recommendations refer to this practice as "Neonatologist-performed echocardiography" [1], and the American Society of Echocardiography (ASE) in collaboration with the European Association of Echocardiography (EAE) and the Association for European Pediatric Cardiologists (AEPC), that refer to this practice

as "Targeted Neonatal echocardiography" [2]. The Study Group of Neonatal Cardiology of the Italian Society of Neonatology is developing a structured training program and accreditation in neonatologist-performed echocardiography in Italy, in order to ensure standardization of training for neonatologists who perform echocardiography in day to day care. The main purpose of the neonatologist-performed echocardiography is to evaluate the hemodynamic status of the critical patient with an anatomically normal heart. This specific ultrasound examination, also named functional echocardiography, includes the evaluation of parameters such as cardiac output, systolic function, diastolic function and contractility. All these parameters differ from those measured in pediatric age or even more in adulthood, given the peculiar physiology of the neonatal age. Neonatologist-performed echocardiography findings are then compared with clinical examination, in order to obtain a comprehensive picture of the disease, to make targeted therapeutic choices and to monitor therapeutic effects. The routine use of functional echocardiography in neonatal intensive care units allows early identification of hemodynamic problems that might be missed using clinical examination alone. In order to perform an adequate functional evaluation, however, it is fundamental to establish the anatomical normality of the heart, which implies a good knowledge of basic echocardiographic techniques. Structural examination will be the starting point for functional evaluation. It is often the hardest part to learn and the one that most frightens those who approach this ultrasound technique. The aims of this course are to provide the basics of ultrasound technique applied to the study of the neonatal heart (2D, M-Mode, color Doppler, pulsed and continuous Doppler), to describe in detail the main standard views and the anatomical findings that can be evaluated in each of them and to describe the "sequential approach" to the anatomical study of the heart. Echocardiographic examination is based on the recent guidelines published by the European group of neonatal cardiology [1], that include the evaluation of: situs and position of the heart; systemic and pulmonary venous returns; shape and size of the four cardiac chambers; atrio-ventricular and ventricular-arterial concordance; integrity of interatrial and interventricular septa; morphology of atrioventricular, aortic and pulmonary valves; right and left ventricular outflow; aortic arch and coronary origin; main intra and extracardiac shunts (foramen ovale, arterial duct). Ultrasound scan views that will be examined in detail in this course will be the subcostal, the parasternal, the apical and the suprasternal ones. Each view will be discussed in a frontal teaching session. Subsequently, several normal and abnormal ultrasound scans will be reviewed, focusing on learning how to systematically approach the study of cardiac structures and to recognize normal cardiac anatomy. The diagnosis of structural congenital heart disease is beyond the scope of this course, as is functional echocardiography.

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LECT 28

MANAGEMENT OF SHORT BOWEL SYNDROME IN THE NEONATAL POPULATION

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Intestinal failure (IF) is defined by the reduction of the functional intestinal mass necessary to ensure adequate digestive and absorptive processes in order to meet nutrient, electrolyte and fluid requirements and to guarantee an appropriate growth. Congenital intestinal defects are the leading cause of IF in the neonatal population (up to 40%), followed by necrotizing enterocolitis (NEC) (30%), severe intestinal motility disorders (11.5%), intestinal obstruction and meconium peritonitis [1, 2]. The occurrence rate of intestinal failure is 0.1% among live-birth newborns and 0.5% among neonates at high risk, such as preterm infants [1]; due to their gut immaturity, this population is highly prone to

develop severe intestinal complications, such as NEC or spontaneous intestinal perforation, which often require surgical resection of the affected bowel. Short bowel syndrome (SBS) is defined as the need for parenteral nutrition (PN) for more than 6 weeks due to IF after bowel resection. SBS is more common among preterm compared to term infants, and its frequency is inversely related to birth weight [3]. The severity of SBS has been historically defined in terms of length of the residual bowel, measured from the ligament of Treitz; on this basis, a bowel length < 10 cm or < 10% of the expected length for age defines ultrashort bowel syndrome, which has long been associated with increased mortality, higher risk of gut transplant and poorer outcome [4]. Recent evidence, however, has shown that the likelihood of PN weaning and achievement of enteral autonomy in infants with SBS does not rely only on the length of the residual bowel, but the resection site, an intact ileocecal valve, the length of the remaining colon and the potential for intestinal continuity are also fundamental. Of interest, SBS secondary to NEC development has been associated with higher rates of enteral autonomy achievement [2]. The management of infants with SBS is a challenge for clinicians, as this population is at substantial risk for fluid and electrolyte losses, PN-associated complications (e.g., infections of central venous catheters, liver and metabolic disease etc.), and nutritional deficiencies, especially if PN is being tapered or discontinued. Hence, a stepwise and multidisciplinary approach, aimed at maintaining a good nutritional status, minimizing malabsorption and reducing the incidence of PN-associated complications, is required [5]. In the early phases of SBS, PN is fundamental to provide an adequate nutritional support and to maintain electrolyte balance. A close monitoring of stool output is also needed, with fluid replacement for losses > 20 ml/kg. Gut exposure to enteral feeds plays a major role on intestinal adaptation; hence, as soon as the patient stabilizes after intestinal surgery, enteral feeding should be promptly initiated. Small frequent feeds or continuous enteral feeding are initially preferred, along with the use of breast milk or amino acid-based formulas. The absorptive state and feeding tolerance of the infant need to be re-assessed frequently as adaptation progresses, and the composition and rate of enteral feeds should be adjusted accordingly, aiming to maximize the proportion of enteral nutrition, as tolerated. In this phase, particular attention should also be paid to minimize the risk of nutritional deficiencies. Due to the reduction of gut absorptive areas, the most common deficiencies occurring in SBS infants if PN is being tapered or discontinued are of fat soluble vitamins (A, D, E, and K), calcium, iron and vitamin B12; in order to avoid such deficiencies, during PN weaning it is common practice to initiate an enteral vitamin supplement using a water-miscible form of vitamins A, D, E, and K and to check regularly vitamin and mineral status by routine laboratory blood tests, in order to provide targeted supplementation as needed. Eventually, pharmacological strategies, such as acid suppression therapies and cholestyramine, may help in reducing gastric hypersecretion and bilious acid diarrhea, whereas antibiotic courses can be used to hinder bacterial overgrowth. In a proportion ranging from 3 to 13% from different cohorts of SBS infants [1, 2], however, enteral autonomy is not achieved despite maximal medical and nutritional therapies. In these cases, a surgical approach including intestinal tailoring or lengthening procedure may be of help, while gut transplantation represents the rescue approach for selected individuals with life-threatening SBS complications. Nevertheless, the progressive spread of a multidisciplinary approach to this delicate population of infants has allowed improved survival, higher rates of PN weaning, and reduced need for intestinal transplantation, and thus represents the pathway to follow in the challenging management of infants with SBS.

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LECT 29

STRATEGIES OF NUTRITION AND FORTIFICATION IN PRETERM SMALL-FOR-GESTATIONAL AGE OR GROWTH-RESTRICTED NEWBORNS

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In preterm small-for-gestational age (SGA) newborns there is large overlapping between the effects of prematurity and the consequences of impaired fetal growth, so the outcome of these infants will not only depend on the degree of pre-maturity, but also on the severity of fetal growth restriction (FGR). Recently, a consensus committee of international fetal medicine experts defined FGR by three solitary parameters, either estimated fetal weight (EFW) < 3rd centile, abdominal circumference (AC) < 3rd centile or absent umbilical artery end diastolic flow, and by four contributory parameters (AC or EFW < 10th centile combined with a PI > 95th centile in either umbilical or uterine artery) [1]. Nevertheless, currently no gold standard for the diagnosis of FGR is available. The acronyms FGR and SGA are often used interchangeably, but a distinction between the two terms should be made. SGA is usually defined as an infant with a birthweight < 10th centile of a given neonatal chart. By this definition, it is not possible to distinguish healthy fetuses with a small genetic growth potential (known as "constitutionally small") from those that are truly growth restricted because of abnormalities in the mother, the placenta, or the fetus itself. Although nutritional plans should be individualized, the main aim for the population of SGA/FGR newborns is to ensure a nutritional supply in order to achieve adequate growth in quantitative and qualitative terms, such that benefits (a better auxological and perhaps a better neurodevelopmental outcome) outweigh the short-term (NEC and feeding intolerance) and long-term risks (metabolic and cardiovascular disease in adulthood, associated to an early postnatal catch up growth). In term of enteral feeding, the main problem to be faced is the risk of NEC and feeding intolerance. The occurrence of NEC is becoming a rare event. Hence, the need is to identify premature and sensitive predictors of feeding intolerance. To date, a universal definition for this latter concept is lacking. This makes impossible a comparison among different studies and a unique approach in the clinical practice. Recently, different studies focused on feeding strategies and regimens. The ADEPT (Abnormal Doppler Enteral Prescription Trial) trial [2] included infants < 35 weeks, with birthweight < 10th centile, and abnormal antenatal umbilical artery Doppler. Subjects were randomly allocated to start enteral feeds "early" (day 2 after birth) or "late" (day 6). Authors concluded that preterm FGR infants with abnormal Doppler flow advanced more rapidly to full feeds if feeds were initiated early. Further analysis demonstrated that FGR infants born < 29 weeks' gestation with abnormal antenatal Doppler, compared to those born ≥ 29 weeks, failed to tolerate even the careful feeding regimen of ADEPT. Hence, the raising question is whether feeding tolerance is a function of maturity and GA rather than of the umbilical artery Doppler flow. From an etiologic point of view, feeding intolerance was thought to be due to the redirection of splanchnic circulation to the more vital organs like brain (known as "brain sparing" phenomenon). In 2016, Bozzetti et al. [3] showed that bolus feeding is more effective than continuous feeding in increasing splanchnic perfusion. Nevertheless, whether this effect leads to a clinical benefit for the patient is still not known. Recommended intakes are for guidance, as individual absorption and bioavailability may differ depending on the consumption of human milk (HM) or infant formula. Mother's own milk is the first choice for preterm infant, also with FGR, and strong efforts should be made to promote lactation. When mother's milk is not available, donor HM obtained from a well-established HM bank is the preferred choice. In a *Cochrane* review, preterm infants who were fed with donor milk were found to have improved feeding tolerance, reduced delay to enteral feeding, and a lower incidence of NEC, when compared to preterm infants who were fed with infant formula [4]. In preterm infants (with or without FGR), evidence suggests that HM alone may not be sufficient for growth: all preterm infants with a birthweight < 1,800 grams should be fed with fortified HM. HM should be fortified with protein, vitamins and minerals. The quantity of HM fortification should be sufficient to enable appropriate growth throughout the NICU stay. HM fortification should start with standard fortification: if infants do not grow appropriately, individualized fortification is advisable. There are two types of individualized fortification: "targeted" (based on milk analysis) and "adjustable" (based on blood

urea nitrogen-BUN measurements). Both are advisable depending on the NICU experience and facilities. Monitoring infant's daily caloric and protein intake, as well as daily growth velocities, is important. Calcium and phosphorous levels should be monitored to prevent hypercalcemia and osteopenia of prematurity, respectively.

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LECT 30

THE MUCOPOLYSACCHARIDOSES

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The mucopolysaccharidoses (MPSs) are a group of rare genetic metabolic disorders due to the deficiency of lysosomal enzymes required for glycosaminoglycans (GAGs) degradation. GAGs accumulate in the lysosomes, inducing cellular damage and multiple organ failure, with consequent reduction of life expectancy and neurocognitive impairment [1]. MPSs are classified into seven types based on the enzyme deficiency (**Tab. 1**). Because of the high variability in clinical symptoms, diagnosis is often delayed, particularly for patients without neurocognitive impairment, and many children and young adults suffer for years with an unrecognized MPS. Even those patients with severe neurocognitive and somatic disease may not be diagnosed until many months after the onset of symptoms, during which time permanent organ damage can occur. However, the symptoms of MPSs may already occur prenatally with fetal hydrops (FH) or congenital ascites. There are three MPSs (MPS-I Hurler syndrome; MPS-IV A; and MPS-VII) that can occur with FH and among these the MPS-VII is the one that presents with FH in about half of the cases [2]. The incidence of MPS could be underestimated because some cases with prenatal onset with FH could undergo intrauterine death and remain undiagnosed. The suspicion of MPS of the neonatologist must remain high in all cases of non-immune FH without a diagnosis that comes to his observation. The enzyme deficiencies are biochemically characterized by increased GAGs in urine, blood and cerebral spinal fluid. Measurement of urinary GAG levels serves as a screening test for the MPSs. A positive result is highly suggestive of an MPS, but false negative results are common and do not rule out an MPS. Enzyme activity assays based on cultured fibroblasts or leukocytes are the definitive method to diagnose a specific MPS [3]. Measurement of enzyme activity in cultured chorionic villi or amniocytes can be used for prenatal diagnosis. Gene sequencing can follow biochemical diagnosis to identify the genetic mutation. Given the clinical heterogeneity and rarity of MPSs, and the possibility to an enzyme replacement therapy (ERT) for most of them, newborn screening may be important for identifying affected patients before the onset of irreversible clinical disease. To date, the U.S. Food and Drug Administration has approved 4 recombinant human enzymes: laronidase for MPS-I, idursulfase for MPS-II, galsulfase for MPS-VI, and vestronidase alfa for MPS-VII [4, 5]. ERT is effective in controlling physical manifestations of MPSs, including organ enlargement, pulmonary insufficiency, and decreased joint mobility. However, bone and heart valves tend to be resistant to ERT. A major problem of ERT is its inability to cross the blood-brain barrier and to improve cognitive impairment.

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Table 1 (LECT 30). The mucopolysaccharidoses.

MPS-type	Deficient enzyme	Gene locus	GAG accumulated	Genetic inheritance	ERT	Clinical manifestations
MPS-I **Hurler syndrome** **Hurler-Scheie syndrome** **Scheie syndrome**	α-L-iduronidase	4p16.3	DS, HS	AR	laronidase	Coarse facies, short stature, dysostosis multiplex, joint stiffness, spinal cord compression, organomegaly, corneal clouding, hearing loss, cardiac and respiratory disease and mental retardation if severe
MPS-II **Hunter syndrome**	iduronate-2-sulfatase	Xq28	DS, HS	X-liked	idursulfase	Coarse facies, short stature, dysostosis multiplex, joint stiffness, spinal cord compression, organomegaly, diarrhea, retinal degeneration, cardiac and respiratory disease, pebbled skin and mental retardation if severe; no corneal clouding
MPS-III A-D **Sanfilippo syndrome**	A: heparan N-sulfatase B: N-Acetyl-α-glucosaminidase C: acetyl-CoA:α-glucosaminide N-acetyltransferase D: N-Acetylglucosamine 6-sulfatase	A: 17q25.3 B: 17q21 C: 8p11.1 D: 12q14	HS	AR		Severe mental impairment, aggressive behavior, sleep disturbances, dementia, and mild somatic symptoms
MPS-IV A, B **Morquio syndrome**	A: N-acetylgalactosamine-6-sulfate sulfatase B: β-galactosidase	A: 16q24.3 B: 3p21.33	A: KS, CS B: KS	AR		Short stature, ligamentous laxity, joint hypermobility, dysostosis multiplex, odontoid hypoplasia, pectus carinatum, kyphoscoliosis, genu valgum, corneal clouding, hearing loss, and cardiac disease; no mental impairment
MPS-VI **Maroteaux Lamy syndrome**	arylsulfatase B	5q11–q13	DS, HS	AR	galsulfase	Coarse facies, short stature, dysostosis multiplex, joint stiffness, odontoid hypoplasia, kyphoscoliosis, genu valgum, organomegaly and cardiac and respiratory disease; no mental impairment
MPS-VII **Sly syndrome**	β-glucuronidase	7q21.11	DS, HS, CS	AR	vestronidase alfa	Coarse facies, short stature, dysostosis multiplex, joint stiffness, spinal cord compression, odontoid hypoplasia, organomegaly, cardiac disease, corneal clouding and mild mental impairment. Fetal hydrops
MPS-IX	hyaluronidase	3p21.3–p21.2	Hyaluronan	AR		Short stature, polyarthropathy, periarticular soft tissue masses with painful swelling and acetabular erosion

MPS: mucopolysaccharidosis; GAG: glycosaminoglycan; ERT: enzyme replacement therapy; DS: dermatan sulfate; HS: heparan sulfate; KS: keratan sulfate; CS: chondroitin sulfate; AR: autosomal recessive.

LECT 31

FEEDING INTOLERANCE AND GASTRO-ESOPHAGEAL REFLUX

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The development of the gastrointestinal tract is continually evolving during fetal life and many of its functional characteristics (motility, enzymatic digestion, hormonal responses, bacterial colonization and local immunity) continue their maturation in the postnatal period, influenced by genetic and environmental factors (gestational and post-natal age, medications, diet, intestinal microflora). The development of the GI tract is a continuous process over gestation continuing in the post-natal life and involving both the anatomical and functional aspects. The developing of the absorbing area continues during the last trimester of gestation and beyond in the postnatal life until reaching, in the adulthood, an absorbing surface of approximately 200 m^2 [1]. Motility-related functions, such as sucking-swallow-respiration coordination, lower esophageal sphincter (LES) tone, gastric emptying and intestinal peristalsis may be profoundly immature in preterm infants. The esophagus of the premature infant shows slower peristaltic movements and prolonged esophageal clearance time than term infants; the low pressure and instability of the LES favors the development of gastroesophageal reflux disease (GER) due to transitory inappropriate LES relaxations. Gastric emptying is also slower in premature than in term infants. The small bowel motility patterns are poorly developed before 28 weeks of gestation, and the motilin receptor is not present until 32 weeks of gestation. Despite the immaturity of its gastrointestinal system, the preterm infant has important nutritional needs to maintain adequate growth standards. Parenteral nutrition undoubtedly allows us to offer adequate nutritional intake from the first days of life, thus promoting adequate growth. However, it exposes infants to infectious and metabolic risks and complications associated with the use of a central venous line. For these reasons, parenteral nutrition should be suspended as soon as possible in favor of the acquisition of complete enteral feeding. It is known that the time of achievement of full enteral feeding is related to better outcomes regarding development and reduction of hospitalization time in NICU. For these reasons, the rapid achievement of full enteral feeding and adequate growth must be one of the main aims of the neonatologist. Feeding intolerance (FI), defined as the inability to digest enteral feedings and expressed as increased gastric residuals, abdominal distension and/or emesis, is a frequent diagnosis in the very preterm infant. In most cases FI represents a benign condition related to the immaturity of the gastrointestinal function; however it may represent an initial step towards the necrotizing enterocolitis (NEC) [2]. Symptoms of FI induce clinicians to interrupt or reduce enteral feeding and consequently FI may lead to suboptimal nutrition, delayed achievement of full enteral feeding and prolonged intravenous nutrition supply. No standardized protocol guiding clinicians in managing the progression of enteral feeding on the basis of FI symptoms are currently available. However, it has been shown that the use of standardized feeding protocols that take into account the signs of feeding intolerance reduced the odds of NEC by 67% in VLBW infants [3]. Among symptoms of FI, regurgitation, vomiting and cardiorespiratory (CR) events (apnea, bradycardia, blood oxygen desaturation) are commonly associated with GER. GER is a physiological condition in infants, but the presence of symptoms of FI as increased gastric residual and abdominal distension, together with LES immaturity, can increase the frequency of GER and worsen GER characteristics. In preterm infants, GER can act as a trigger for CR events activating the chemoreceptors of the upper airways and the neuroreceptors sensitive to esophageal distension with vagal stimulation. Recent studies have demonstrated that in some patients with particular GER characteristics, there is a significant and causal association between these two events. However, the GER events involved in these associations are mainly weakly acidic suggesting that the empirical treatment with antacids in infants with CR and GER events is, in most cases, inappropriate [4]. The proper approach to the problem of GER in preterm infants should be aimed at improving feeding tolerance by adopting techniques and behaviors involving nutrition strategies (thickening, positioning, slow feeding) and able to reduce the frequency of refluxes.

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LECT 32

FAMILY-CENTERED CARE IN ITALIAN NEONATAL INTENSIVE CARE UNITS: PARENT EXPERIENCE AND SATISFACTION, A SYNTHESIS OF A MULTICENTER STUDY AND PRELIMINARY RESULTS

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INTRODUCTION

Family-Centered Care (FCC) is an approach to plan, deliver and evaluate health care grounded in a mutually beneficial partnership among patients, families, and health care practitioners [1]. Parent satisfaction is an indicator of the quality of FCC provided in the Neonatal Intensive care Unit (NICU). To evaluate parent experience and satisfaction with FCC in NICU, the Italian version of EMPATHIC-N was developed [2]. The original Dutch instrument is already shared at international level, and it offers the opportunity to explore parent satisfaction with the different domains of FCC [3, 4]. FCC is applied in Italian NICUs in variable ways and not always uniform with international standard. Moreover, it is important to investigate not only the daily activities of FCC that the health care providers (HCP) put in practice in NICU but also the activities they consider as necessary. Therefore, it could be important to identify the organizational or professional variables that are mostly associated with parent satisfaction in NICU. The study aimed to describe parent satisfaction with FCC in Italian NICUs with a validated instrument and explore organizational and professional variables associated with parent satisfaction.

METHODS

A cross-sectional multi-center study design was used. Study participants were parents of infants discharged from 31 Italian NICUs. The included infants had a duration of hospital staying longer than 48 hours. The Italian EMPATHIC-N was used to assess parent satisfaction. The instrument includes 57 items in five domains: Information, Care & Treatment, Parental Participation, Organization and Professional Attitude. The rating scale of the items is a 6-point scale; 1 "certainly no" to 6 "certainly yes". The instrument also measures the overall satisfaction through two questions. Moreover the questionnaire contains two questions to evaluate the physicians' and nurses' overall performances (10-point rating scale). The instrument has a demographic section and a free space to allow parents to write about their experiences. Moreover, the HCP of the same NICUs were involved in the study. The Italian version of Family-Centered Care Questionnaire-Revised (FCCQ-R) by Bruce (1997) [5] was used to explore HCP's perception of FCC principles applied in daily practice (current scale) or considered as necessary (necessary scale). The 45 items of the questionnaire describe several activities of FCC divided into nine subscales, using a Likert scale ranging from 1 "strongly disagree" to 5 "strongly agree". The instrument, in accordance with the author, was adapted for the use in neonatal setting. The study was approved by the Ethics Committee of Bambino Gesù Children's Hospital that coordinated the study. Participants were informed about the aim of the study and the data collection process. Moreover, they were informed

that their participation in the study was anonymous and voluntary.

RESULTS

Parents of 633 infants participated (90% of enrolled parents). They were mostly of Italian nationality (86.8%), and 36% of infants were very low birth weight. Mean value of the EMPATHIC-N domains ranged from 5.5 for "Professional attitude" to 5.7 for "Care & treatment". The level of parent satisfaction resulted in correlation with the general experience and the overall score that parents gave to the work of the physicians and nurses. FCCQ-R was completed by 1,061 HCPs. Mean value of the subscales ranged from 2.8 to 3.1 for the daily practice (current scale) and from 3.9 to 4.4 for the perception of necessity (necessary scale). The parent satisfaction was associated with the level of necessity of change in FCC issues, as perceived by HCPs (**Tab. 1**).

CONCLUSIONS

This is the first extensive national study about parent experience and satisfaction with FCC in NICU. It was proved that parents were satisfied with the received care in the participating NICUs. Moreover, the parent's satisfaction was associated with the need that HCPs feel to improve the daily practice of FCC in NICU. Finally, the results among the HCPs indicated the need for FCC education and training to improve the organization of NICUs.

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The members of Italian NICUs FCC Study Group are available at: https://it.surveymonkey.com/r/FCC_Italian_NICUs_study_group.

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Table 1 (LECT 32). Correlation between values of Family-Centered Care Questionnaire-Revised (FCCQ-R) and EMpowerment of PArents in THe Intensive Care-Neonatology (EMPATHIC-N) scales.

FCCQ-R subscales	EMPATHIC-n domains					
	Information	Care & treatment	Parental participation	Organization	Professional attitude	General experience
Family is the constant (CURRENT)	-.064	-.142	.274	.128	.180	-.264
Family is the constant (NECESSARY)	-.086	-.009	.388 [a]	.039	.353	-.104
Parent/professional collaboration (CURRENT)	.116	.038	.331	.135	.161	-.106
Parent/professional collaboration (NECESSARY)	-.303	-.074	.238	.099	.295	.080
Recognition family individuality (CURRENT)	-.040	-.089	.159	.190	.155	.000
Recognition family individuality (NECESSARY)	-.172	-.044	.298	.068	.369 [a]	-.112
Sharing information (CURRENT)	-.085	-.176	.169	.083	.127	-.127
Sharing information (NECESSARY)	-.306	-.181	.131	-.024	.244	-.074
Developmental needs (CURRENT)	-.177	-.294	.224	.027	.130	-.244
Developmental needs (NECESSARY)	-.173	-.014	.296	.036	.406 [a]	-.158
Parent to parent support (CURRENT)	.083	.068	.504 [b]	.347	.417 [a]	-.002
Parent to parent support (NECESSARY)	-.039	.109	.343	.135	.462 [b]	-.053
Emotional financial support (CURRENT)	.078	-.012	.369 [a]	.119	.276	-.009
Emotional financial support (NECESSARY)	-.077	.010	.273	.018	.431 [a]	.066
Design healthcare system (CURRENT)	.183	.189	.474 [b]	.219	.240	.092
Design healthcare system (NECESSARY)	-.034	.059	.328	-.008	.363 [a]	-.076
Emotional support for staff (CURRENT)	-.059	.062	.387 [a]	.187	.297	.086
Emotional support for staff (NECESSARY)	-.143	.017	.246	.008	.171	.036

FCCQ-R: Family-Centered Care Questionnaire-Revised; EMPATHIC-N: EMpowerment of PArents in THe Intensive Care-Neonatology.
[a] $p < .05$, [b] $p < .01$.

LECT 33

RESPIRATORY SUPPORT AND PHARMACOLOGICAL TREATMENT OF BRONCHOPULMONARY DYSPLASIA: TOWARDS INDIVIDUALIZED CARE

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Bronchopulmonary dysplasia (BPD) occurs in 20-60% of preterm neonates with an inverse relationship with gestational age [1]. Its pathogenesis includes several factors, such as volutrauma, hyperoxia and oxidative stress, inflammation, infection and undernutrition [2]. Cornerstones of BPD management are respiratory support, pharmacological treatment, and nutrition. However, BPD can present with a different stage of disease severity and different physiopathology characteristics that require an individualized approach. Currently, no studies are evaluating the effectiveness of different non-invasive respiratory support in infants with established BPD and, therefore, in the clinical practice the most commonly used support is nasal-continuous-airway pressure (NCPAP) [3] or high-flow-nasal-cannula (HFNC) [4]. To decide the optimal level of NCPAP (or flow) at bedsides, infants' clinical condition and chest X-rays are important: tachypnea and dyspnea, reflecting poor lung compliance, and atelectasis area suggest the need for a higher pressure level, while a cystic form of BPD with a possible tendency for gas trapping may suggest that high-pressure level cannot be tolerated [3]. On the other hand, nasal intermittent positive pressure ventilation (NIPPV) is superior to NCPAP in preventing extubation failure and may represent an effective non-invasive support in weaning infants with BPD from mechanical ventilation, particularly in the presence of hypercarbia [5]. High-frequency ventilation (HFV) is not usually used in infants with BPD, while patient triggered ventilation (PTV) may benefit these patients limiting agitation, fighting the ventilator, and need for sedation [3]. It is known that lung pathology in BPD may be heterogeneous, with alternating areas of atelectasis and over-expansion and most infants will have a compensated respiratory acidosis and some degree of persistent ventilation-perfusion mismatch. Thus, infants with BPD may require higher positive end-expiratory pressure (PEEP) with improvements in oxygenation without CO_2 retention [6]. As the time constant is often prolonged, high ventilatory rates are usually inappropriate and can favor the development of gas trapping. On the other hand, infants with BPD can present tracheomegaly, large floppy airways [7], and increased airways resistance. These conditions can benefit from an increase in tidal volume (TV), longer inspiratory and expiratory time (i.e.: low ventilator rate), and high PEEP [8]. Recently, it has been reported that there are three distinct phenotypes of severe BPD, namely the obstructive, restrictive, and mixed phenotypes [9]. These results should have relevant implications for the care of infants with severe BPD, demonstrating that there is a sub-group of patients who might benefit from bronchodilator therapy and quickly removed from mechanical ventilation [9] rather than treated with mechanical ventilation with large tidal volumes and a slow rate aimed at classic BPD with an obstructive component [10]. BPD can be complicated in 17-24% of patients with pulmonary hypertension (BPD-PH) with an associated mortality of 14-38% [11]. Therefore, all infants with BPD should be studied with serial echocardiography to point out the diagnosis of PH and plan the possible therapy. Nowadays, despite a lack of high-quality evidence and regulatory approval, sildenafil is the most used off-license drug for the treatment of BPD-PH [11, 12]. It has been demonstrated that infants with BPD have slower rates of postnatal growth compared with preterm infants without lung disease [13]. Their energy needs have been estimated to be 15-25% greater than infants without BPD in the range of 140-150 kcal/kg [14]. However, the recommended protein (3.5-4 g/kg/die) and lipid (3-4 g/kg/die) intake in infants with BPD are similar to those of infants without chronic lung disease [14]. In conclusion, infants with BPD need to be carefully evaluated to individuate their specific pathophysiological characteristics. This approach can allow optimizing the respiratory support, pharmacological treatment, and nutrition in these patients.

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LECT 34

DECREASING THE POLLUTION OF HUMAN MILK, WHILE DEFENDING THE GOOD REPUTATION OF BREASTFEEDING

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HUMAN MILK: A NATURAL LIQUID PRONE TO POLLUTION

Breastfeeding is an integral part of the reproductive cycle, and it is an unequalled way of providing food for infants. Despite the overwhelming benefits of breastfeeding, we should recognize that similarly to other human fluids (blood, saliva, seminal fluid, etc.) it might also transmit other possible dangerous substances to the baby [1]. Consequently, concerns have been raised on the transfer of different kinds of not nutritive substances (drugs, contrast media, pollutants) from the mother to the breastfed infant that might cause short-term adverse effects as well as long-term consequences. Public attention has been paid to environmental contaminants, particularly persistent organic pollutants (POPs), which, in a way that is different from other not nutritive substances, are assumed unintentionally and mostly inadvertently by the breastfeeding mother. This public health and nutritional paradox has been recognized in the literature and faced by International Health Agencies since the early '70s. POPs include a wide range of substances that consist of intentionally produced chemicals currently or once used in agriculture, disease control, manufacturing, or industrial processes (e.g., in electrical transformers, heat exchange fluids, additives to paints and lubricants). POPs persist for long periods of time in the environment, have halftime even longer than 10 years and pass almost unmetabolized from one species to the next through the food chain. Human milk is placed at the top of the food pyramid and consequently might carry a relevant burden of environmental pollutants. POPs are of concern for human health, most notably, because they might negatively interfere with the neurological development of the fetus and the nursing infant, might cause congenital malformation, particularly neural tube defects, and might produce endocrine disruption. To address the global concern of the environmental pollution due to POPs, the US, the EU, and many other countries agreed at the Stockholm Convention (May 2001), to reduce or eliminate the production, use, and/or release of 12 key POPs [2]. Since that time, other chemicals have been added to the Convention, which actually has played a prominent role in the control of harmful chemicals on both a national and global level.

FACTORS INFLUENCING CHEMICAL POLLUTION OF HUMAN MILK

The passage into human milk depends not only on the degree of environmental pollution and on the chemical characteristics of the individual pollutant (e.g., a higher passage for increased lipid solubility) but also on the personal history and the lifestyle of the mother. Many factors are recognized to increase the risk of exposure of the nursing infant to polluted human milk. These factors are presented below.

- High fat concentration. As pollutants are lipid soluble, the fat content of human milk represents a determinant of the burden of POPs vehiculated to the infant. The fat content of human milk varies between 1.5 and 12 g/dl, due to interpersonal differences and to the higher fat content of hindmilk compared to foremilk.
- Fat rich diet. Being highly lipophilic, POPs accumulate in fatty animal tissue. Milk produced by mammals (cattle, sheep, goats) [3], meat and seafood (e.g., tuna and salmon) represent major sources of contamination.
- High M/P ratio. The ratio between the milk and the plasma concentration of the individual pollutant indicates the degree it ultimately concentrates into breast milk.
- Polluted residential location. Proximity to pollution sites, such as hazardous waste incinerators, uncontrolled waste burning, and polluting factories, leads to higher POPs concentration in human milk.
- Parity. First born infants are prone to be fed with a mother's milk produced, while maternal fat depots are still intact, possibly containing a higher concentration of pollutants accumulated over time.
- Stage of lactation. The amount of pollutants in breast milk is lower as lactation proceeds [4]. Moreover, a reduced volume of milk is consumed by the infant during the weaning process, and consequently, the POPs exposure might be lower.

THE MILK DILEMMA

Avoiding breastfeeding has been suggested as an option to protect the breastfed infant from pollutants exposure through breast milk. Actually, this might represent a poor choice, as current scientific literature shows that children prenatally exposed to POPs showed better cognitive performance if breastfed. In other words, the cost/benefit ratio is still favoring breastfeeding [5]. In conclusion, breastfeeding is still the safest way to feed infants, independently of the concurrent antenatal and postnatal environmental contamination.

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LECT 35

CAN BLOOD GAS ANALYSIS BY UMBILICAL CORD ARTERY PREDICT CLINICAL OUTCOME IN NEWBORNS WITH APGAR SCORE ≥ 7 AT 5 MINUTES FROM BIRTH?

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BACKGROUND

Neonatal acidemia is correlated with an increased risk of admission in the neonatal intensive care unit (NICU) due to respiratory distress, hypoxic-ischemic encephalopathy, multi-organ dysfunction and neonatal exitus [1]. Umbilical cord blood gas analysis (BGA) is important to evaluate neonatal acidemia during delivery. Nowadays, there are not clear threshold value of pH, base deficit (BD) and lactate. Umbilical cord BGA is required only for Apgar score < 7 V and in newborns with a high risk of asphyxia. Is not clear if newborns with moderate acidemia and Apgar score ≥ 7 V must be monitored for development of adverse outcome. Literature shows that newborns with a good Apgar score have a residual risk of neonatal acidemia and adverse outcomes [1]. Furthermore, Hermansen at al. [2] describes the "acidosis paradox": newborns without acidemia at birth might still develop a hypoxic condition. Indeed, in newborns with a normal pH and catastrophic intrapartum events might occur adverse outcomes [2]. The main aim of a recent study was to understand the best marker of the BGA among pH, BE and lactate [3].

METHODS

A review of the literature was conducted on PubMed (up to June 2018) for original English articles that investigated the correlation among Apgar score, BGA and clinical exam in newborn. Researchers used the following key words: Acidemia, Apgar score, Adverse neonatal outcomes, Umbilical cord gas. The aim of this study is evaluating of BGA in newborns with Apgar score ≥ 7 V as a predictor of adverse neonatal outcomes.

RESULTS

During delivery, newborns with a pH < 7.0 and BE < -12 mmol/l or pH < 7.1 and BE < -10 mmol/l can suffer of meconium aspiration syndrome, respiratory distress syndrome, sepsis and NICU admission (0.7%, 1.1%, 0.2% and 4.4%, respectively; $p < 0.05$) [1]. Yeh et al. [4] proved that an umbilical cord arterial pH < 7.10 was associated with an increase of the adverse neurological outcomes (0.36%, RR = 2.22 [1.06-4.62], NNH = 509). Reference values for cord pH are 7.26-7.30, which are associated with the lowest risk for adverse neurological outcomes (0.16%, RR = 1) [4]. The main aim of the recent study was to understand the best marker of the BGA among pH, BE and lactate. The ROC curve analysis revealed that pH, BD and lactate had a similar predictive ability for neurological (AUC: 0.81; 0.78; 0.83, respectively) and systemic neonatal morbidity (AUC: 0.77; 0.82; 0.82, respectively) [3]. However, BD and lactate did not improve the predictive ability of pH alone for short-term neonatal outcomes.

CONCLUSION

Several studies evaluated the predictive ability of pH, base deficit and lactate for adverse outcome. It was not demonstrated an important difference between BD and lactate to predict an adverse outcome, and furthermore, pH alone had a strong predictive ability for the short-term outcomes. A retrospective study will be conducted to confirm these results.

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LECT 36

ULTRASOUND FINDINGS IN NEONATAL MENINGITIS

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INTRODUCTION

The central nervous system (CNS) and its covering membranes may become involved in a variety of infectious processes, with devastating effects on structure and function. Infections may occur during intrauterine development, in association with the birth process, or in the first postnatal days or weeks. The etiological agents include numerous bacteria, several viruses, but also a protozoan (*Toxoplasma gondii*) and a spirochete (*Treponema pallidum*). Cranial sonography (CS) plays an important role in the initial evaluation of neonates and young infants with suspected or proven meningitis or meningoencephalitis and in monitoring for complications of the disease. We will discuss below the main ultrasound aspects of neonatal bacterial and viral infections of the CNS.

BACTERIAL INFECTIONS OF THE CENTRAL NERVOUS SYSTEM

Neonatal bacterial meningitis is an uncommon but devastating infection. Although overall incidence and mortality declined over the last several decades, morbidity among survivors remains high and virtually unchanged. Meningitis is the acute inflammation of the meninges, subarachnoid space, and brain vasculature resulting from infection. Primary bloodstream infection with secondary hematogenous dissemination to the CNS is the most common mechanism in the development of neonatal meningitis. Bacteremia leads to CNS infection via seeding of choroid plexus, resulting in infection of CSF and subsequently ventriculitis. This is usually followed by infection of pia and arachnoid mater including the vessels traversing the subarachnoid space. The inflammatory response involves phagocytic cells and inflammatory cytokines, culminating in an increased membrane and vessel wall permeability, causing formation and accumulation of inflammatory exudates within the sulci. CS has high accuracy in evaluating initial signs as well as complications of bacterial meningitis. Ultrasound findings in neonatal bacterial meningitis include: echogenic sulci,

ventriculomegaly, ventriculitis, extra-axial fluid collection (EAFC), parenchymal changes. The echogenic sulcus is the earliest and most common finding, in neonatal meningitis, which is due to increased thickness as well as echogenicity of the sulci. Widening and increased echogenicity is due to accumulation of inflammatory exudate within the sulci, especially around the pia and arachnoid vessels. Ventriculomegaly is the enlargement of ventricles that occurs during acute phases of bacterial meningitis due to increased production as well as decreased CSF absorption, with resultant increased intraventricular pressure. Ventriculitis is identified as increased thickness, irregularity and increased echogenicity of the ependyma. EAFC displaces the brain away from the vault, so sonogram reveals detailed characterization of gyri, midline shift with falx deviation to the opposite side, and compression of ipsilateral ventricles and dilatation of contralateral lateral ventricle. Parenchymal changes are seen as areas of altered or increased echogenicity, which may be diffuse as in cerebritis or focal as in infarction, abscess formation, hemorrhage or focal cerebritis.

VIRAL INFECTIONS OF CNS

In the developed world herpes simplex virus (HSV) accounts for a large proportion of infectious encephalitis and is associated with significant morbidity and mortality. In the pre-treatment era the mortality was as high as 70%, but with the availability of the antiviral drugs acyclovir, it significantly declined to less than 10%. HSV infection of the neonate is uncommon with varying rates across the world due to differing birth rates and HSV seroprevalence. Both HSV-1 and HSV-2 have been recognized to cause neonatal herpes infection. Almost one-third of cases of neonatal herpes disease presents as encephalitis and is categorized as CNS disease, with or without skin involvement. Neonates usually present at 16-19 days of life, although it is possible to have disease manifestations start anytime within the first month of life. Infants present focal/generalized seizures, lethargy, irritability, poor feeding, temperature instability, and bulging fontanel. In all, 60-70% of these infants have skin lesions at some point during the course of the illness. Meningoencephalitis is characterized by: 1) inflammatory cells in the meninges, 2) perivascular infiltrates with inflammatory cells, 3) severe multifocal necrosis of all cellular elements of brain parenchyma, often with some degree of hemorrhage, 4) reactive microglial and astroglial proliferation and 5) occurrence of Cowdry type A intranuclear inclusions in neuronal and glial, especially oligodendroglial cells. These pathological findings are often accompanied by a considerable degree of brain swelling, and hemorrhage in the areas of necrosis may occur. The result of HSV infections of the perinatal brain most commonly is a devastating effect on neural structure and function. The subsequent failure of brain growth and microcephaly after the neonatal period are the rule. Multicystic encephalomalacia has repeatedly been documented. Cranial ultrasound and especially MRI can document these lesions readily. CS is also useful in the detection of parenchymal damage and evolution into multicystic encephalomalacia but is likely to miss cortical and brain stem injury.

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LECT 37

CONTAMINANTS IN INFANTS' FOODS

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Contaminants are substances not intentionally added to our food, which are found in aliments as a residue of production, preparation, packaging or following environmental contamination. They are distinguished in: chemical (e.g., substances used in agriculture as pesticides or nitrates), physical (e.g., foreign bodies) and microbiological (e.g., bacteria, mycotoxins). The pediatric age has a greater vulnerability to contaminants due to both organs' immaturity and infants behavior (e.g., to bring everything to the mouth); even more due to the consumption of specific foods, called "baby food". The high percentage of total body water, responsible

for a greater distribution of water-soluble molecules as many contaminants, makes children at higher risk of toxicity later in life than adults. For this reason, following food legislation, children's food must have an adequate composition and should not contain any harmful substance. Particular attention should be given to foods used in early childhood, such as formula milk and solid food used in the first months of life. Among the emerging contaminants, there are natural anthropic substances, called endocrine-disrupting chemicals (EDCs) that act on the endocrine system and may inhibit the release and action of several hormones related to body metabolism. In particular, the reproductive organs and the thyroid are the most susceptible organs in childhood. Examples are: persistent organic contaminants (POPs) such as polychlorinated biphenyls (PCBs); pesticides; industrial substances such as bisphenol A (BPA) which are used for food preservation in plastic; metals such as cadmium or mercury or arsenic and finally mycotoxins. Several scientific studies show pesticides neurotoxic effects (particularly, attention-deficit/hyperactivity disorder – ADHD), reproductive and immune-related effects on childhood. Nitrates, salts of nitric acid, transformed into nitrites in the gastrointestinal tract by bacterial flora or deriving from poor preservation of post-cooking vegetables, could cause methemoglobinemia in infants and accumulation of vitamin A in the liver. Furthermore, they can be transformed to carcinogenic nitrosamines, being toxic at high concentrations (by being converted back into nitric oxide via the entero-salivary recirculation, bacterial nitrate reductases, or acidic reduction of nitrite to nitric oxide). The EFSA (the European Food Safety Authority) affirms that infants and toddlers are highly vulnerable to heavy metal exposure (cadmium, lead, and mercury). For this reason, the recommendations are to eliminate fat from meat, choose small fish avoiding bottom fish (e.g., mollusks) and use a large variety of food to prevent accumulations of the same pollutant. Finally, mycotoxins are toxic chemicals metabolites produced by a variety of fungal genera. They are present on plant products (cereals), in milk or meat derived products from animals that ingested contaminated feeds. Mycotoxins can cause growth deficits and alterations of the immune system (in particular aflatoxins, deoxynivalenol, fumonisins). In conclusion, many substances have already been banned in children's products because of the greater vulnerability of the childhood. However, the real challenge for the future will be the use of biological products and above all, the constant check of food by the Authorities in order to decrease the presence of food contaminants, considering that their tolerated dose in the pediatric age is significantly lower than in adulthood.

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LECT 38

LEFT VENTRICULAR DYSFUNCTION: COULD BE FENOLDOPAM USEFUL?

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Fenoldopam mesylate, a selective dopamine-1 receptor agonist, has been approved since 1997, for the short-term management of severe hypertension in adults. It produces vasodilation of the renal, mesenteric and coronary arteries. The safety and efficacy of fenoldopam have not been established in pediatric patients, but the off-label or unlicensed use of medications commonly occurs in Neonatal Intensive Care Unit (NICU). Strauser et al., in 1999, reported the first pediatric use of fenoldopam for the management of hypertension [1]. Several reports suggest a potential benefit for fenoldopam to restore urine output in selected pediatric and neonatal patients. Therapeutic doses increase renal blood flow, creatinine clearance, urinary flow and sodium excretion. A randomized multicenter placebo-controlled study met FDA requirements for approval of the use of fenoldopam in children [2]. The study was designed to evaluate pharmacokinetics and pharmacodynamics as well as the side-effect profile of fenoldopam in pediatric patients. The results found that 0.2 mcg/kg/min was the lowest dosage at which a decrease in blood pressure was seen while 0.8 mcg/kg/min was the most effective dosage. The time of onset of effect was 4-5 minutes after initiation of IV infusion. The intravenous administration of fenoldopam in

pediatric patients was well tolerated. Higher doses could produce a reflex-mediated increase in heart rate and cardiac index. Fenoldopam is rapidly and extensively metabolized by conjugation in the liver. In contrast with dopamine, fenoldopam does not have dopamine 2 or beta-adrenergic receptor activity. A systematic review of randomized controlled trials (2015) of fenoldopam peri-operative administration concluded that it reduces the development of acute kidney injury (AKI) but did not significantly alter the requirement of renal replacement or hospital mortality. The analysis was limited by the inclusion of both surgical and non-surgical critically ill patients (i.e., sepsis). Subsequently, they performed another meta-analysis with a focus on studies in patients who underwent cardiovascular surgery. They concluded that fenoldopam significantly reduces the need for renal replacement and was associated with lower in-hospital mortality [3]. In a retrospective cohort study, Costello and coworkers (2006) evaluated neonates after cardiac surgery requiring cardiopulmonary bypass, and they found that fenoldopam improved urine output and promoted a negative fluid balance. For these reasons, it is used in peri-operative patients with or at risk for renal dysfunction [4]. In a recent article, fenoldopam reduces peak blood lactate level during cardiopulmonary bypass. This finding supports the hypothesis that fenoldopam exerts a protective action against vasoconstriction of the splanchnic area induced by endogenous and exogenous catecholamines. In case of hypotension requiring inotropic drugs (dopamine, dobutamine, epinephrine) administration, fenoldopam could be used after blood pressure normalization in order to promote peripheral vasodilatation. A recent article evaluates the effects of fenoldopam in patients with coronary artery disease and myocardial dysfunction [5]. The ultrasound derived strain rate represents a new Doppler myocardial imaging parameter, which can measure the local deformation independently of overall heart motion. In segments with pre-existing abnormal function fenoldopam significantly increased the peak systolic and diastolic strain rates in ischemic segments without effects on global ventricular function. This effect could be due to an increase in coronary blood flow. Other studies showed that fenoldopam, by lowering blood pressure, could ameliorate left ventricular function in patients with severe hypertension. Due to its vasodilating effect, fenoldopam has been used in congestive heart failure to reduce afterload.

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LECT 39

THE NEONATAL NETWORK OF THE ITALIAN SOCIETY OF NEONATOLOGY

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Premature birth (before 37 completed weeks of gestational age [GA] or 259 days of pregnancy) is the leading cause of neonatal death and second leading in children under five years old [1]. Globally, around 10-11% of all neonates are estimated to be born preterm. Preterm birth is also considered a major determinant of immediate as well as long-term morbidity and is associated with growth and developmental delay. To be able to determine the relative contribution of preterm birth to the burden of disease from National Health System both during the hospital stay and after discharge and to inform the planning of health care interventions to address this burden, a deep understanding of the main problems showed by babies born preterm is needed. To this effort, the Italian Society of Neonatology (SIN), which has the aim to promote any measure that can improve the well-being of newborn and neonatal care, in the past years developed and promoted the Neonatal Network of Italian Society of Neonatology (NNSIN). NNSIN is the first Italian network that offers the possibility to collect reliable information on a population of preterm (from 22^{+0} to 36^{+6} weeks

of GA) and to conduct descriptive and analytical analyses with the possibility of stratification for GA and weight classes. In the last three years, the number of participating centers has progressively increased. 68 neonatal care units were enrolled: 29% in the North of Italy, 41% in the Center and 29% in the South. We present some collected data to show the value of NNSIN. The average maternal age was 33 years with no differences for GA. Preterms from medically assisted reproduction were 14.3% (~18% between 28 and 33 weeks of GA). Higher rates of both spontaneous and indicated preterm birth in multiple gestations lead to a significant proportion of the moderate preterm and late preterm rates (40% in the 32-33 weeks of GA). Multiple gestations have an increased risk of pregnancy complications. Delay in childbearing and assisted reproductive techniques have remained common reasons for the increase in multiple gestations over the last few decades. Prenatal steroid administration was around 70% under 33 weeks of GA, in late preterm, the value drops to 35%. This data is in line with the recommendation to administer glucocorticoids at earlier GA to reduce the risk of respiratory morbidity. Preterm from cesarean section was 72%. Male sex was prevalent. Length of stay may be an index of care complexity and indirectly of the clinical conditions of the newborn. In preterm enrolled the median hospital stays were 18 days (lowest value of 6 days in 34-36 GA group, highest value of 70 days in 25-27 GA group). Our report confirms an increased risk of morbidity in preterm infants compared to babies born at term. Measures of morbidity included: need for hospitalization, need for transfer to neonatal intensive care units (NICUs), length of time in NICU, time spent in oxygen and time spent on a ventilator. Specific morbidities relating to preterm in NICUs are respiratory distress syndrome (RDS: 29%), apnea (11.3%), transient tachypnea (10.7%), bronchopulmonary dysplasia (BPD: 3.9%). 42% of preterm under 37 weeks of GA showed respiratory problems (RDS, apnea, transient tachypnea, pneumothorax). 35.2% of all preterm with any form of respiratory disease required oxygen therapy after the delivery room. The need for oxygen therapy is reduced with increasing GA. Respiratory support techniques and their frequency of use are shown in **Tab. 1**. Preterm < 32 weeks of GA showed the

Table 1 (LECT 39). Distribution of the main procedures and therapeutic supports in the different class of gestational age. The year 2017.

		22-24 (N = 63)	25-27 (N = 191)	28-31 (N = 703)	32-33 (N = 805)	34-36 (N = 3,474)	22-36 (N = 5,236)
Oxygen therapy after delivery room	**N**	58	177	576	410	622	1,843
	%	92.1	92.7	81.9	50.9	17.9	35.2
Conventional mechanical ventilation	**N**	50	146	280	99	108	683
	%	79.4	76.4	39.8	12.3	3.1	13.0
High-frequency ventilation	**N**	38	67	60	10	16	191
	%	60.3	35.1	8.5	1.2	0.5	3.6
High-flow nasal therapy	**N**	14	49	91	42	83	279
	%	22.2	25.7	12.9	5.2	2.4	5.3
Nasal-IPPV	**N**	16	61	161	65	70	373
	%	25.4	31.9	22.9	8.1	2.0	7.1
Nasal-CPAP	**N**	22	125	527	393	474	1,541
	%	34.9	65.4	75.0	48.8	13.6	29.4
Surfactant	**N**	56	143	368	126	120	813
	%	88.9	74.9	52.3	15.7	3.5	15.5
INSURE method	**N**	6	23	132	62	60	283
	%	9.5	12.0	18.8	7.7	1.7	5.4
Caffeine	**N**	43	157	544	269	118	1,131
	%	68.3	82.2	77.4	33.4	3.4	21.6
Nitric oxide	**N**	6	14	11	3	5	39
	%	9.5	7.3	1.6	0.4	0.1	0.7
Postnatal corticosteroids	**N**	20	49	59	4	14	146
	%	31.7	25.7	8.4	0.5	0.4	2.8

greatest need for respiratory support. Conventional mechanical ventilation prevailed under 27 weeks while high-frequency ventilation under 24 weeks of GA. Non-invasive ventilation showed a progressive reduction in frequency from 27 weeks onwards due to the decreasing risk of respiratory problems observed with increasing GA. Surfactant administration also involved mainly GA under 28 weeks. Newborn under 28 weeks of GA received post-natal corticosteroids for preventing and treatment BPD because this group has a higher risk of developing BPD. Other morbidities were patent ductus arteriosus (7.9%), late-onset sepsis (4.4%), periventricular leukomalacia (1.9%), early-onset sepsis (1.9%). Intraventricular hemorrhage, necrotizing enterocolitis, and retinopathy of prematurity showed instead lower rates. Mortality rate was 2.4% with highest values under 24 weeks (55.6%) and between 25 and 27 weeks (21.3%). NNSIN offered us all these data and showed to be a valid tool to perform effective and personalized data analysis in real time. This can represent a further help: to evaluate better the level of activities, outcomes and quality of care provided; to have reliable epidemiological data aimed at improving the quality and safety of neonatal care; to contribute to the better programming of perinatal care; to allow participation in coordinated research and training programs.

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LECT 40

VISUAL FUNCTION DEFICIT IN PRETERM NEWBORNS

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The visual function has a key role in children psychomotor development [1], being heavily influenced by the external environment and experience. The assessment of visual function in newborns could be useful to understand developmental processes and to detect ophthalmic and neurological deficits with predictive value. Premature infants show an increased risk of peripheral (retinopathy of prematurity refractive errors) and central visual system disorders (cerebral visual impairment, CVI) caused by early exposure of their immature visual system to light stimuli in NICU, nutritional deficiencies, systemic diseases and complications derived from preterm birth. CVI is a damage or malfunction of the retro-geniculate visual pathway (optic radiation, occipital cortex, and associative visual areas), without a major eye involvement. In subjects with CVI alterations of basic visual functions (fixing, tracking, saccadic movements), abnormal eye movements and strabismus are often detected. CVI is often related to hypoxic-ischemic injuries, typically found in preterms such as periventricular leukomalacia (PVL). Children with PVL show a high incidence of abnormalities in the different tests to assess visual function generally due to the involvement of optical radiation (via geniculo-calcarine) and associative areas. Frequent and early visual function evaluation might prove to be helpful in monitoring not only ophthalmological aspects but also central nervous system (CNS) maturation and potential cerebral readjustment after a brain lesion. The proposal of visual function evaluation tools specific for newborns is also crucial in order to implement habilitation strategies along the first months of life, a period in which the infant's brain shows the highest degree of plasticity. Different visual function evaluation tools have been developed for assessing in early age throughout the years, including behavioral and electrophysiological techniques. The primary aim of the study is to evaluate visual function in premature babies through a clinical instrument called NAVEG (Neonatal Assessment Visual European Grid) tailored to assess visual function in newborns, easy to administer, non-invasive. The secondary aim of the study is to correlate the visual profile with neurological assessment and neuroimaging in cases of CNS damage. We propose NAVEG as an instrument of visual function investigation, with both predictive and preventive aspects in subjects with high risk of visual and/or neurological impairment.

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LECT 41

CASE REPORT: SEVERE ACUTE BRONCHIOLITIS

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INTRODUCTION

Acute bronchiolitis is a viral infection of the lower respiratory tract characterized by acute inflammation, edema, necrosis of epithelial cells lining small airways and increased mucus production. Respiratory syncytial virus (RSV) is the most common viral pathogen in children under 2 years of age, with 30% of lower respiratory infection prevalence and almost 3% of hospitalized patients. Effective therapies remain elusive and clinical guidelines suggest for supportive measures while discouraging the use of pharmacotherapy and diagnostic testing. Between 3-10% of hospitalized patients require escalation of treatment with admission to the Pediatric or Neonatal Intensive Care Unit (PICU and NICU) and need of respiratory support (non-invasive or invasive). Bronchiolitis is associated with high mortality rates not only in developing but also in industrialized countries, especially for children with higher risk of developing severe forms of the disease (< 3 months of age or with pre-existing risk factors, such as prematurity, bronchopulmonary dysplasia, congenital heart diseases, and immunodeficiency) [1-4]. The clinical case we report aims at considering clinical guidelines in the management of acute bronchiolitis underlining the need to develop personalized therapeutic strategies in severe bronchiolitis.

CASE REPORT

We describe the case of a 27-day-old infant, born at 40 weeks of gestation, without risk factors for severe infection from respiratory viruses, who was admitted to the Pediatric Emergency Department due to respiratory difficulties, cough, episodes of vomiting and difficult breast suction; at home he had been treated for two days with salbutamol inhalations without showing improvement. In the emergency room, the patient showed symptoms of acute bronchiolitis with a persistent cough, fine crackles and wheezing in both lung fields auscultation, low O_2 saturation levels (90% in room air), high respiratory rate (70 breaths/minute), high heart rate (170 beats/minute), feeding difficulties, signs of respiratory distress were present (chest recession, nasal flaring) and the modified Wood's Clinical Asthma Score (m-WCAS) was 4. Given the concern for impending respiratory failure in an infant < 3 months of life with acute bronchiolitis, the patient was admitted to NICU. After admission in NICU, respiratory support began with high flow nasal cannula (HFNC) therapy at a flow of 2 L/kg/min, while FiO_2 had to be raised to 30% to achieve oxygen saturation > 92%. Because of oral feeding difficulties, also nasogastric nutrition was started. The etiological research of viral antigen on the nasopharyngeal swab, performed by rapid test, was positive for RSV, while serum C reactive protein was negative. Blood gas analysis was normal. Intravenous rehydration and nebulized hypertonic saline were started. After 24 hours of hospitalization there was a clinical worsening with increasing work of breathing and dyspnea (m-WCAS 6, Silverman score 4), tachycardia (180 beats/m), tachypnea (85 breaths/m) while capillary blood gas analysis showed moderate hypercapnia (pCO_2 62 mmHg, pH 7.25); respiratory support was changed to Heliox (8 L/min, FiO_2 0.4) for 6 hours with no amelioration and subsequently, for further clinical deterioration (m-WCAS 7), nasal continuous positive airway pressure (nCPAP) was started and oxygen supplementation was incremented to FiO_2 0.50. A clinical trial with nebulized adrenaline was done without no positive clinical effect while intravenous midazolam was started to facilitate nCPAP tolerance. 36 hours after admission, due to the onset of respiratory failure, clinical exhaustion and hypercapnia (capillary pCO_2 75 mmHg), increased FiO_2 (0.7), the infant was intubated and mechanical ventilation was started (synchronized intermittent positive pressure ventilation, volume-granted); meanwhile, a repeated etiological research through amplification and genomic isolation with a polymerase chain reaction (Multiplex®) on nasopharyngeal swab was positive for RSV, parainfluenzae virus 4 and *Haemophilus influenzae*. Additional laboratory studies revealed high positive serum C reactive protein. Intravenous antibiotic therapy was started. There was a temporary increase in oxygen requirements (FiO_2 max 0.8) associated with persistent hypercapnia (capillary pCO_2 70 mmHg). A clinical trial with nebulized adrenaline was done with positive clinical effect. Chest radiography showed atelectasis of the upper right lobe. After 3 days of mechanical ventilation, the first extubation failed due to abundant airway secretions and severe dyspnea; therefore he was intubated, and SIPPV was continued. After slow weaning from ventilation, it was possible to definitely extubate the patient on day 8 from admission; he continued respiratory support with nCPAP for 2 days and then with HFNC. After 14 days from admission, he was transferred from NICU to the pediatric ward. Clinical nutrition was maintained through a nasal

gastric tube, and respiratory support was continued with HFNC.

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LECT 42

ACUTE KIDNEY INJURY: DEFINITION AND CLASSIFICATION

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Acute kidney injury (AKI) is a serious disease (increases mortality and length of hospital stay, causes poor outcomes) and it is very common at all ages (with a peak in incidence among newborns in NICU). Its definition and classification have been made difficult by the variability of clinical manifestations (ranging from asymptomatic forms to severe symptoms secondary to alterations of hydroelectrolytic homeostasis and acid-base balance) and by the heterogeneous etiology (intrinsic or consequent to different and complex extrarenal diseases). In the recent past, we had dealt with AKI only when it manifested itself with clinical symptoms and/or the values of serum creatinine (SCr) indicated a severe decrease in renal function. To define this pathology, we used the term "acute renal failure" (literally "deterioration or decay"). Due to the lack of a universally recognized definition and a shared classification, epidemiological data referred to limited, non-comparable clinical records and the results were not statistically significant. To solve this problem, nephrologists and emergency doctors gathered in 2004 in a joint working group, to propose a simple but inclusive classification of all forms of renal damage, to be called RIFLE, an acronym of the 5 degrees in which renal damage was stratified (Risk, Injury, Failure, Loss, End-stage kidney disease). This classification was subsequently amended to adapt it to pediatric (pRIFLE) and neonatal use (nRIFLE), but in a short time it was replaced, first by Acute Kidney Injury Network (AKIN) and currently by Kidney Diseases: Improving Global Outcomes (KDIGO), which is the result of a synthesis between RIFLE, AKIN, and pRIFLE. The numerous and often unsuccessful attempts to systematize this topic had at least the merit of supplanting the old definition of "failure" and replacing it with "injury". The term "failure" remains reserved for the late stages of this pathology when renal function is lost or severely impaired, and it is necessary to resort to renal replacement therapies (peritoneal dialysis or hemodialysis). This variation of the terminology is not a lexical finesse, but the evolution necessary to spread and stress the concept that the injury, unlike the failure, includes pathological situations of varying severity; moreover, it is necessary to recognize it in the early stages, when the renal function is "at risk" or, at least, when the function, still sufficient, is guaranteed by compensation mechanisms, but the damage has already been established. Recently, Jetton and Askenazi proposed an adaptation of the KDIGO classification for use in neonatal age (< 120 days) which, in 2013, was evaluated by the National Institute of Diabetes and Digestive and Kidney (NIDDK) workshop. The conclusion was that "at this time, this definition offers a reasonable starting point and would allow for consistency throughout studies". The neonatal KDIGO (nKDIGO, **Tab. 1**) establishes the criteria for the diagnosis of AKI and distinguishes it in three stages based on two simple parameters: rise in SCr and decrease in urine output (UO). SCr rise > 0.3 mg/dL within 48 h or SCr rise > 1.5-1.9 are considered pathological compared to the reference SCr (defined as the lowest previous SCr value); the UO is considered pathological if < 0.5 mL/kg /h for more than 6 h. Unfortunately, both these parameters are very popular, but far from "ideal", representing the late outcome of renal failure and not markers of the injury itself. The SCr has many limitations: in the first 48/72 h of life it reflects the renal function of the mother and not of the newborn, varies according to muscle mass, hydration status, age, and sex,

Table 1 (LECT 42). Neonatal AKI KDIGO classification.

Neonatal AKI KDIGO classification		
Stage	**SCr**	**UO**
0	No change in SCr or rise < 0.3 mg/dL	≥ 0.5 mL/kg/h
1	SCr rise ≥ 0.3 mg/dL within 48 h or SCr rise ≥ 1.5-1.9 x reference SCr within 7 d	< 0.5 mL/kg/h for 6 to 12 h
2	SCr rise ≥ 2.0-2.9 x reference SCr	< 0.5 mL/kg/h for ≥ 12 h
3	SCr rise ≥ 3 x reference SCr or SCr rise ≥ 2.5 or receipt of dialysis	< 0.3 mL/kg/h for ≥ 24 h or anuria for ≥ 12 h

AKI: acute kidney injury; KDIGO: Kidney Diseases: Improving Global Outcomes; SCr: serum creatinine; UO: urine output.

changes only when the loss of function is = or > 25-50%. Moreover, due to tubular secretion, when glomerular filtration is reduced, SCr overestimates renal function. Lastly, the different dosing methods (Jaffe vs. enzymatic reaction) produce different values, and some drugs or hyperbilirubinemia can alter its value. SCr's luck as a biomarker is due to the lack of valid alternatives, for this reason there are numerous studies researching more precocious, non-invasive biomarkers of kidney injury such as serum Cystatin C, serum and urinary neutrophil gelatinase-associated lipocalin (NGAL), urinary interleukin-18 (IL-18), kidney injury molecule-1 (KIM-1), while interesting results are also reported with the use of metabolomics. Oliguria is also a not very sensitive marker of AKI, considering that over 1/3 of neonatal AKI cases and 60% of AKI in asphyxiated infants are not associated with a reduction of UO. Despite these limitations the nKDIGO classification has had the merit of unifying the terminology and standardizing the grading of the AKI, allowing the realization of the first large multicentric, multinational cohort study, carried out in 24 NICU of four countries (Australia, Canada, India, United States) and recently published in the Lancet by Jetton and collaborators. This work has estimated the incidence of AKI in intensive care neonates at around 30%, and has shown that it is more frequent in the lower gestational ages (< 29 weeks), minimum between 29 and 36 weeks and returns to increase > 36 weeks, describing a U-shaped curve. The conclusion is that newborns with AKI have four times higher odds of death and longer independent hospital length of stay.

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LECT 43

HEALTH-RELATED QUALITY OF LIFE OF FORMERLY PRETERM INFANTS FROM CHILDHOOD TO ADULTHOOD

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INTRODUCTION

In recent decades, research on preterm infants has had increased interest on the assessment of short and long-term outcomes, not only in the motor, cognitive, language, and behavioral areas but also in the field of Health-Related Quality of Life (HRQoL) [1, 2]. HRQoL has become an even more crucial outcome to consider adding to traditional information about mortality and morbidity. However, it is well known that HRQoL widely changes according to the age of assessment and the assessment approaches. We aim to review the main recent articles that evaluated HRQoL in formerly preterm infants from childhood to adulthood and to analyze the trajectories through ages and the differences between parental and self-report measurements.

RESULTS

In the analysis of research about HRQoL in formerly preterm infants, three different periods should be considered: childhood (0-12 years), adolescence (12-18 years) and adulthood (> 18 years). Preterm children generally display a lower HRQoL than their full-term peers. However, these results could have been influenced by the parent-report measures of HRQoL, as below 12 years of age there are very few tools to evaluate self-reported HRQoL. The differences remained even after adjusting for gender and socioeconomic status [1, 2]. The role of gestational age is still debated and requires further investigations. Adolescent preterm-born individuals reported a satisfactory HRQoL, with a similar level to healthy term-adolescents, except for subjects with moderate and severe disabilities [1]. The overall agreement between parents and adolescents on the description of HRQoL was good, even if adolescents reported more problems in cognitive and emotional aspects. These differences could be related to the particular developmental age [1]. During adulthood, despite there being more chronic diseases and psychological disorders, self-reported HRQoL shows positive results when compared to full-term individuals. Formerly preterm subjects seem to transition well into adulthood [1]. Recent reports also focus on the trajectory of HRQoL of formerly preterm subjects through time in the same cohort of infants followed in longitudinal studies. A wide heterogeneity in the results is reported, varying from a clear worsening of reported HRQoL in preterm individuals through time, in Saigal et al. [3], to stable values in German and Dutch populations [4, 5]. Probably the most important issue is to identify, through longitudinal studies, the specific trajectory of the infants we care for, to tailor our follow-up approach. This is done in order to analyze and possibly modify the different factors that influence self-perceived HRQoL.

CONCLUSION

The impact of preterm birth on HRQoL is greater during childhood, but the influence also remains into adolescence and adulthood, mainly in subjects with any sensorineural disabilities. Different results on HRQoL in former preterm individuals have been reported according to self or parental reports; parents' assessment is not only worse but also focused on physical health, whereas preterm individuals referred worse HRQoL in mental and emotional domains. Despite debate on the real trajectories of HRQoL through life in formerly preterm infants and the different role of parents or self-reported results, it is mandatory to consider HRQoL as an important outcome in matters of public health and epidemiology.

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LECT 44

COMPUTERIZED MANAGEMENT OF THE EMERGENCY: FROM THE REQUEST TO THE APPROPRIATE HOSPITALIZATION

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BACKGROUND

The study aims to evaluate the performance of the Coordinating Center of the Neonatal Emergency Transport Service (NETS) of the Lazio region through the computerized management of the emergency to improve effectiveness and efficiency and reduce the risk of deterioration of clinical conditions related to the transfer [1]. To activate the transfer, the Coordinating Center acquires the anamnestic, clinical and instrumental information of the pathological newborns. It formulates a diagnostic evaluation, verifies cot availability on-line in hub centers or those of high specialization (congenital heart disease, neurosurgical or malformations pathologies, etc.). Mortality Index for Neonatal Transportation score (MINT) [2] is

used for determining intervention priorities in case of simultaneous transfer requested or forwarded *in itinere*.

METHODS

16,649 primary transports (average/year: 1,189) were evaluated from January 2004 to December 2017. 764 electives transport for diagnostic investigations and 325 back-transport were excluded from the analysis. The NETS of the General Hospital Umberto I in Rome uses the information system OPTIN (Occupation of cot in Neonatal Intensive Care) for the on-line connection with the centers of NICU and Neonatal Surgery and the collection of data on transfers in real time. OPTIN is available on the reserved website of the Programming Area of the Hospital Network and Risk Management of the Lazio region (www.regione.lazio.it/asponline/servizi/tin/tin_login.php).

RESULTS

In our region in 2017, there is a neonatal transfer index (NTI) of 2.3 per 100 live births higher than in other European countries. The analysis of the transport indicators showed the following results: an activation time with a median of 25 minutes and an interquartile range (IR) of 15-45 minutes from call for transport and departure for referring hospital after the availability of cot; a time of assistance and stabilization with a median of 25 minutes (IR 15-35) and a total transfer time, from departure to new availability of the team for another transport, with a median of 130 minutes (IR 85-190). The search time for cot availability is different for transport for surgical pathologies (median 0 minutes, IR 0-10) compared to medical conditions (median 10 minutes, IR 0-20) [3, 4]. The rationale is due to the prenatal diagnosis of major surgical pathologies and to the rational planning of birth. Qualitative assessment is determined by the type of patients transported stratified by gestational age and by pathology classes. The medical conditions of the respiratory system or originated in the prenatal period (especially the preterm birth) concern 42.3% of the transfers, the infectious diseases 17.3%, the metabolic ones 9.9% and the neurological the 6.8%. In 2017, 303 newborns were transferred to surgery centers. The diagnosis at the referring hospital was: congenital diaphragmatic hernia, esophageal atresia, omphalocele, gastroschisis, bladder exstrophy in 53.8% of cases, congenital heart disease in 38.9% of cases, neurosurgical diseases in 7.3% of cases. In 2016, 45% of newborns were transferred in the first day of life (51.7% in the first 4 hours of life and 75% within the first 8 hours) to reach 68.6% in the first week of life. 3.3% of transports involves newborns with EG ≤ 27 weeks (1.8% with EG ≤ 25), 6.2% with GA between 28 and 31 weeks, 21.1% between 32 and 36 weeks and 69.3% with GA ≥ to 37 weeks. There is a gradual increase in age in days for transport (10%) of infants up to two months of correct postnatal life (ex-preterm, small infants with cardiological, surgical or malformative diseases) coming from the emergency room of regional hospitals or airborne transport from other regions. As an indicator of efficacy and outcome the MINT score presents a homogeneous distribution in infants transferred with GA < 28 weeks while the Transport Risk Index of Physiological Stability Score (TRIPS) [5] shows two distinct clusters with a reduction of the score to the increase of the GA up to the 36th week and another with directly proportional increase for GA between 37 and 41 weeks. In transfers of newborns with medical conditions the improvement of the TRIPS score, from referring unit to admission at receiving hospital, varies from 8.9% (class 0-1) to 34.9% (class ≥ 21). The "pre" and "post" TRIPS score classes are stable in 93.1% of transfers for medical conditions and show an improvement in 4.9% of cases. In transfers of newborns with surgical diseases, the TRIPS score classes in 95.7% remain unchanged, and an improvement of 3.2% is observed.

CONCLUSION

The OPTIN system managed by the NETS Coordinating Center has allowed a significant improvement in the management of the alarm phase and extra-hospital research of the cot with optimization of the hospitalization suitable for centers of reference or highly specialized.

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LECT 45

SEX-RELATED DIFFERENCES IN THE OUTCOME OF PRETERM INFANTS: A REVIEW

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Gender medicine investigates the differences between man and woman in physiology, pathophysiology, and diseases. In recent years the awareness of sex differences even during intrauterine life and neonatal period has increased, though being presently mechanisms responsible for these differences not completely understood. Sexual dimorphism between male and female has been reported in term of mortality, birth defects, preterm birth, and short and long-term outcome. In 1971 Naeye speculated on "the male disadvantage hypothesis" on the basis of the higher mortality and morbidity in the male during childhood and later life. This hypothesis has been related to Barker's hypothesis (The Developmental Origins of Health and Disease – DOHaD) that postulated that many of the adulthood diseases origin during intrauterine life and the first few years of life. Male disadvantages may be secondary to a minor adaption to the environment of males compared to females. Many data confirm those two hypotheses. For example, a minor adaptation might be the cause of the different incidence of preterm birth in the two sexes. A 2016 review on 574,358 pregnancies confirmed a higher incidence of preterm delivery (RR 1.26) and pregnancy-induced hypertension (RR 1.07) in the presence of a male fetus. Sexual dimorphism of placental function has been advocated to explain this different incidence: pregnancies with a male fetus show a lesser activity of the decidual renin-angiotensin system and a lesser β-HCG production. Moreover males "invest" lesser in the placenta so that a lower placenta weight to birth weight ratio is present in male infants. Placenta represents a defense for the fetus to the external environment; therefore the higher occurrence of preterm birth in male infants in case of unexpected stressing conditions might be due to a less efficient system in males. This may also explain the higher incidence of death in male fetuses at the end of the second trimester and during the third trimester: a big review on more than 30 million of pregnancies confirmed a higher incidence of male death after 24 weeks of gestation. The higher risk of preterm birth in males could be even partly due to the higher incidence of birth defects in male infants that may lead to preterm delivery. A study on about 850,000 neonates considered 779 different birth defects: the overall prevalence of major defects at birth was 3.9% among males and 2.8% among females. Differences of the two sexes also regard the type of defects: males presented a higher incidence of congenital heart diseases, urinary tract defects, and gastrointestinal tract defects, while the endocrine system and central nervous system defects are more prevalent among females. After birth, male infants still present disadvantages in term of short- and long-term complications compared to females. Respiratory complications have a higher incidence in male preterm infants: both for extremely preterm and late preterm neonates. A review on 500,000 preterm newborns showed both a higher incidence of respiratory distress syndrome (RR: 1.56-1.84) and chronic lung disease (RR: 1.22-1.38) in males; this vulnerability persists in the first few years of life, with a higher risk of bronchiolitis in boys. Other studies regarding respiratory markers highlighted male disadvantages: need for oxygen (RR: 1.14-1.54), respiratory support (RR: 1.0-1.50), surfactant administration (RR: 1.10-1.60) and pneumothorax (RR: 1.09-1.62). A recent investigation on mixed-gender twins confirmed, even in the presence of identical intrauterine conditions, a higher need for mechanical ventilation (RR 1.31) and a higher incidence of respiratory distress (RR 1.45) in male compared to his female twin. Even in terms of neurological outcome male preterm infants have the worst outcome. Two recent studies report a higher risk of intraventricular hemorrhage and periventricular leukomalacia in extremely preterm male neonates. The "male disadvantage" has been confirmed even at 2-3 years of age with a higher prevalence of moderate to severe functional disability in males (RR 1.87). A 2014 study compared extremely preterm infants at 30 months of life: boys had lower mean cognitive composite scores and lower mean language composite scores compared with girls. MRI analysis confirmed dimorphism between male and female: delayed myelination was found more frequently in boys, whereas cerebellar abnormalities were more common in girls. Nevertheless, data are still uncertain: a recent study on more than 42,000 preterm infants (up to 32 weeks of gestation) did not show a difference in term of neurological outcome between male and female neonates. This review underlines some of the differences that may regard

male and female preterm infants. Understanding all mechanisms behind the "developmental origins of health and disease" and reaching a better knowledge of sexual dimorphism may lead in future to more personalized care and more specific prevention strategies.

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LECT 46

GROWTH ASSESSMENT AND NUTRITION

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The increased survival of preterm infants has arisen concerns regarding their long-term health. Adequate nutrition in early life contributes to the limitation of postnatal growth failure and associated nutritional deficits, prevents the development of morbidities and plays a critical role in the optimization of neurofunctional development. Thus, in the light of long-term health programming, postnatal growth monitoring during the early postnatal period is of major importance. Within this context, the opportunity of promoting accelerated growth has been questioned, as it may be associated with increased adiposity and adverse metabolic outcomes. Moreover, there is no consensus on the optimal postnatal growth pattern that preterm infants should follow. The current availability of preterm postnatal growth standards, the Intergrowth-21st growth charts, represents an important, useful tool in monitoring preterm infants' postnatal growth up to the 64th week of corrected age time when the Intergrowth-21st growth charts are complemented by those of the World Health Organization for infants born at term. These charts have been specifically constructed including preterm infants born from low-risk pregnancies, with no evidence of intrauterine growth restriction and fed according to feeding protocols based on the promotion of exclusive breastfeeding up to 6 months. Hence, the implementation of these charts could allow for a more comprehensive assessment of preterm infants' growth, taking into account the peculiar characteristics of this population that significantly differs from infants born at term. Emerging evidence indicates that not only weight, length, and head circumference growth patterns but also fat mass and fat-free mass gains play an important role in the developmental programming of health outcomes. Preterm infants have been reported to accrue a fat-free mass deficit during hospital discharge that tends to persist beyond the first years of age. On the other hand, rapid fat mass accretion appears to take place mainly in the early postnatal period leading to a fat mass content similar to that of term infants within the first months of life. Remarkably, in a cohort study including 20 preterm infants, higher percent fat mass gains form term to 4-month corrected age were associated with lower working memory performance at 4 years whereas higher 4-month corrected age to 4-year fat-free mass gains were associated with better cognitive outcome and speed of processing performance. These data indicate a relationship between the alterations in body composition development that take place early in life and later neurocognitive outcomes. Concerning metabolic outcomes, no clear evidence has been reported linking an increased fat mass accretion during early life with an augmented risk for developing the metabolic syndrome. However, a tendency towards central fat mass deposition, a well-known risk factor for the adverse metabolic outcome has been reported in infants born preterm. By the available data, body composition assessment has been thus recommended to be included in preterm infants' postnatal growth assessment. In this scenario, the importance of promoting and supporting breastfeeding must be adequately taken into consideration. In healthy and stable infants born preterm and assessed between discharge and term corrected, human milk feeding has been shown to promote an adequate growth with a higher nitrogen balance in comparison to formula feeding. Moreover, human milk feeding has been independently associated with fat-free mass deposition. Specifically, infants fed human milk

between discharge and term corrected age show a gain in fat-free mass of 124 g. Accordingly, a meta-analysis including 642 preterm infants demonstrated that fat mass content at term corrected age was lower in infants fed human milk in comparison to formula-fed infants (mean difference 0.24; 95% CI 0.17, 0.31 kg). Thus, by the available data, it can be hypothesized a potential role of human milk feeding in promoting the recovery of a fat-free mass deficit in preterm infants. There is still no agreement on the usefulness of human milk fortification after discharge since conclusive evidence on its positive effect on outcomes such as growth rates is lacking whereas its implementation may potentially interfere with feeding directly at the breast. When human milk is not available, no clear evidence indicates a beneficial effect of being fed a nutrient-enriched formula after discharge even though it has been suggested an improvement in growth parameters, including fat-free mass accretion, with no effect on neurodevelopmental outcomes. Taking into consideration the critical role of nutrition in long-term health programming, health care professionals should exert efforts in implementing regular follow-up and growth monitoring, both in terms of quantity and quality, in this vulnerable population.

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LECT 47

BREASTFEEDING GUIDED BY NEWBORN

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Breast milk is the most complete nutriment for babies in the first six months of life since its rich and balanced composition contains all the essential nutrients for a proper physiological growth. Breastfeeding patterns can change significantly. Two different approaches are often used to determine when and how long the baby is breastfeeding. The first one is led by the baby and is known as baby-led or breastfeeding on demand. The other one is led by the clock and is known as scheduled, timed or restricted breastfeeding. From the 20th century, women in healthcare centers or hospitals were advised to breastfeed according to the timing and restricting both the frequency and length of breastfeeds. This practice varied when baby-led or demand breastfeeding was supported. With baby-led breastfeeding, the amount of milk produced is determined by the baby's request. In this way the baby can control the supply of milk, ensuring that enough milk is produced to meet his needs. With this approach, close contact between the mother and her baby is encouraged with no time restrictions. However, the mother may not always be in a position to breastfeed her baby on demand due to, for example, being separated from her baby for any reason, and there can be uncertainty for the mother if and when her baby does not demand a breastfeed. Every newborn, when placed on her mother's abdomen, soon after birth, has the ability to find her mother's breast and to decide when to take the first breastfeed. This is called the "breast crawl". This is the most studied input and is believed to be the most important. Babies prefer their mother's unwashed breast to her washed breast, soon after birth. The mother is the source of an array of olfactory, visual, auditory and tactile stimulation that the infant may perceive and respond to when placed on her bare chest [1]. The mother's voice is reported to be the most intense acoustic signal measured in the amniotic environment. A preterm fetus also is capable of responding to speech stimuli. Also, the typology of birth influences breast crawl and breastfeeding. It was found that emergency cesarean delivery negatively affects mother bonding and opening emotions and originates in mother feelings like sadness and disappointment for the unplanned delivery evolution [2]. After birth, the healthy newborn often undergoes a quiet alert phase, which has been referred to as the first phase of reactivity.

When placed skin to skin on the mother's chest shortly after birth, the infant often becomes quiet and starts exploring its environment [3]. Infants separated from their mothers cry excessively. Smell, vision and taste, touch and motor outputs help the newborn to detect and find the breast. Auditory inputs and touch help to create a suitable environment. A mother's feeling of love for the baby may not necessarily begin with birth or instantaneously with the first contact. During the breast crawl, while staying skin to skin and looking fixedly eye-to-eye, they begin to learn about each other. For the mother, the first few minutes and hours after birth are a time when she is uniquely open to begin the new relationship with her baby. Suckling enhances the closeness and new bond between mother and baby. Mother and baby appear to be carefully adapted for these first moments together [4]. Many studies have confirmed that breast crawl helps mother-baby bonding, and gets better the breastfeeding. We can consider that "bonding" is a dialogue, a physical, emotional, hormonal and relational experience between mother, child, and father, an articulated and complex path that begins in the prenatal period, is consolidated at birth and continues during the first year of life. The mother (and the relationship with her) provides the child with a "secure base" from which he can move away to explore the world, entertaining forms of relationships with family members. The development of personality is affected by the possibility of having experienced a solid "secure base", as well as the individual ability to recognize if a trusted person can or wants to offer a secure base [5]. Current scientific guidelines encourage breast crawl, bonding, breastfeeding and baby-led breastfeeding as the fundamental point of future baby health and his proper physiological growth. It is important to review the evidence systematically, to inform women's decisions on the relative effectiveness of each method.

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LECT 48

TEAMWORK AND ON THE JOB TRAINING IN NEONATAL INTENSIVE CARE UNIT

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Training plays a strategic role in promoting organizational and structural changes; it is an ongoing effort to improve through development and enhancement of healthcare employees' professional skills and to promote the workers' personal and professional growth and self-fulfillment. Training increases each person's ability to work, improving the quality and safety of the healthcare provided. The training need can be defined as the difference between the skills and the knowledge possessed by a healthcare professional and those that he/she should have to reach the standard needed to provide optimal performance. The most accepted way to analyze the training needs is to start from the professionals' selection of the topics to be improved. The on the job learning is defined as an activity in which the setting and the skills of the operators are actively involved in welfare activities for learning and improving purposes. This training method, which includes participation in research activities, committee, and improvement groups, offers the maximum chance of being involved into the specific needs and topics of the work environment resulting in the real possibility to practice what learned directly on the job. The assumptions that support the need to enhance training are presented below: adults are motivated to learn if the training activity is perceived as relevant; on the job training is built on previous experiences; it directly involves the learners and promote their active participation; it's based on practical and specific problems to be solved; everyone becomes responsible for his/her learning; it is possible to practice what has been learned right into the work context; it provides a series of actions and reflections; it is supported by the organizational context when training and professional development are promoted. The workplace becomes the privileged setting for: using experience as a source of learning; sharing training processes and their operational outcomes with colleagues, leaders and other professionals; stimulating professionals to question themselves about problems that are yet unsolved by researching

and interpreting new knowledge to be later applied to their professional practice; providing the opportunity to ponder mistakes and critical issues of their daily practice through a structured audit process; making continuing education "truly continuous" and not a sporadic activity. The followings can be focused: individualized training; groups of improvement; research activity; clinical and/or assistance audit. With this presentation we would like to focus on the groups of improvement that can be designed within a unit: research teams; drafting/review teams of procedures/protocols; teams to improve the quality of care. In our Neonatal Intensive Care Unit, the first step in assessing the "training needs" has been their precise identification. A first meeting was held, a kind of brainstorming aimed to identify and analyze the problems. Through this method, it was possible to identify the following study groups: neonatal care team; breastfeeding team; peripherally inserted central catheter (PICC) team; infections team; skin injuries team; parenteral nutrition team; lullabies team; drug management team; nursing diagnosis team; ventilation devices team. According to their specific needs, the teams were formed by a minimum of six to a maximum of ten voluntary professionals, some multidisciplinary; all participants were assigned medium-long term goals to achieve yearly. Through scheduled meetings, the head nurse supervised the progress of the works motivating the staff and managing conflicts. When the goals are achieved, further editions of internal courses are organized, accredited by the ECM (Educazione Continua in Medicina) system, founded to promote the knowledge updating of all health professionals. This method of organizing and managing internal training has various advantages; it increases group cohesion and teamwork, improving, subsequently, the quality of the healthcare delivered and the satisfaction of both the professionals and the patients.

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LECT 49

THE ROLE OF THE NURSE IN THE PROMOTION OF THE KANGAROO MOTHER CARE IN THE NEONATAL INTENSIVE CARE UNIT

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The kangaroo mother care (KMC) was developed in 1978 by Rey and Martinez in Bogotà (Columbia), as an alternative to the conventional care of low birth weight infants. In the 2003 World Health Organization (WHO) published the *Kangaroo Mother Care Guide*: a powerful, easy-to-use method to promote the health and well-being of infants born preterm and full-term. The recommended minimum period is 2 hours. In the last 20 years, a high number of studies demonstrated the benefits of the KMC practice. Skin-to-skin contact (SSC) is associated with a reduced risk of hypothermia, apnoeas, and periodic breathing, nosocomial infection, desaturation events and it facilitates parent-infant bonding and empowers mothers in the breastfeeding process. The KMC does not require high-tech and expensive equipment, and it can be implemented everywhere. Despite its well-documented benefits, in some neonatal intensive care units (NICU) the KMC is not considered as a necessary care practice in the daily routine. The KMC should be started as soon as possible in the NICU. The nurses play a key role in the promotion of the KMC because he/she is the caregiver who spends most of the time with the infants and their parents. The nurse welcomes the parents and invites them to do the SSC with their infant as soon as possible; he/she helps the mum or the dad to lie the baby on the chest; he/she helps the mum to dress her baby for the KMC and to wrap him close to her chest to maintain temperature, comfort, contact, and stability. The nurse also invites the mum/dad to kangaroo his/her baby every day and after discharge as well.

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LECT 50

BREASTFEEDING PROMOTION IN NEONATAL INTENSIVE CARE UNIT

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The scientific evidence on the benefits of breast milk has supported the spread of breastfeeding practice worldwide. In a unique contest as a Neonatal Intensive Care Unit (NICU), the use of human milk, mother's own milk or donor milk has to be considered as a medication. Indeed, it improves the neurological outcome, is associated with a reduction in the risk of developing sepsis and necrotizing enterocolitis and improves feeding tolerance, reducing parenteral nutrition and length of hospital stay. Breastfeeding may not be an option for several weeks or months in sick or premature infants. Thus, it is essential to implement strategies aimed at the collection of human milk. The aim should be the promotion of mother-infant bonding to encourage the maintenance of milk production and to assure the psychological well-being of the mother and her baby, identifying and breaking down barriers resulting from hospitalization. To achieve this aim, the World Health Organization (WHO) and the United Nations Children's Fund (UNICEF) launched the Baby-Friendly Hospital Initiative (BFHI). The initiative is a global effort to implement practices that protect, promote, and support breastfeeding. The document describes the 10 basic steps, and some authors adapted them to the context of the NICU, to the different situations faced by premature and sick infants and their mothers. This requires a breastfeeding-oriented policy and healthcare professionals with specific knowledge and skills able to transfer information and techniques to the feeding mothers. NICUs should implement procedures aimed at supporting mothers of infants admitted into the NICU that cannot stay with their babies in the first hours after birth involving and making them conscious of their role: they should begin the early stimulation of the breast as soon as possible and be informed on how to maintain milk production and manage its collection and storage. The same attention should also be given to mothers of the outborn infants. Written information, shared between hub center and spokes centers, should be delivered to mothers at the time of the transfer of the baby, so the infant will dispose of the milk of his mother in NICU, as soon as he or she can start enteral nutrition. The beginning and continuation of breastfeeding should be guided only by the competence and stability of the infant, using a semi-demand feeding regimen during the transition to exclusive breastfeeding. Pacifiers should be offered to infants only to relieve pain or calm them down when necessary. The discharge program should include adequate parental training, information for breastfeeding support facilities and a post-discharge follow-up plan. There is a wide gap between breastfeeding rates and a shorter duration of breastfeeding in preterm infants at discharge from hospital compared to healthy children, especially in very low birth weight infant. In 2016 in Italy, the Ministry of Health issued a recommendation to promote the use of breast milk and the access of parents in the Neonatal Care Units, as part of the breastfeeding support policy. As a consequence, in the last years, the number of NICUs open 24 hours a day to the parents has been progressively increased, to promote the well-being of hospitalized infants and that of their families. It is desirable that the

number of NICUs open 24 hours will increase over the whole country in the near future.

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LECT 51

PERINATAL PALLIATIVE CARE IN 2018: A NATIONAL SURVEY

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BACKGROUND

In Italy, neonatal mortality accounts for 70% of pediatric mortality as well and is mainly due to perinatal or congenital disorders. Recently, improvement of perinatal care allows for the survival of newborns with chronic diseases, which are sometimes incurable, and require dedicated clinical care pathways. Thus, facilitating perinatal palliative care (PnPC) protocol must be mandated. PnPC and its focus on the fetus and newborn are not intended only as care for terminal conditions, but as the framework of interventions for "incurability". PnPC starts from the moment of diagnosis and lasts throughout the neonate's life; it does not preclude concomitant curative therapy, having a quality of life (QoL) as its primary goal for the newborn and family by identifying and treating distressing symptoms of life-threatening or complicated conditions. PnPC requires multidisciplinary interventions, which demand the expertise of several practitioners (i.e., obstetricians, neonatologists, pediatric palliativists, counselors, nurses, psychologists, neuropsychiatrists, spiritual assistants, and geneticists), who collaborate closely in their overall care to meet the multiple needs of the situation. We identified three categories of patients in which PnPC is necessary: newborn viability at its limits, pre- or post-natal diagnosis of a life-limiting condition (e.g., trisomy, anencephaly, skeletal dysplasia, and Potter's disease) and those who develop a severe clinical condition during hospitalization; this can lead to a poor long-term outcome (e.g., severe respiratory insufficiency, massive cerebral hemorrhage, and ventricular leukomalacia). Little is known in Italy about the growth of the PnPC infrastructure: the purpose of this survey is to explore the emergence, diffusion, and application of PnPC in Italian NICUs.

MATERIALS AND METHODS

A 16-item online questionnaire concerning the presence of a PnPC pathway, along with other aspects of its attainment, was sent to referring neonatologists of 91 Italian NICUs; these were registered with the Vermont Oxford Network (VON) in December 2017. A second reminder was sent in February 2018.

RESULTS

Seventy-six NICUs of 91 (83.5%) answered, while 71% of them were non-teaching hospitals and 29% of them were university NICUs. The median number of NICU beds was 8 (range 4-24). The median number of yearly admissions was 400 (range 110-3,000), with 6 median deaths per year (range 0-31) and 2 median deaths for newborns per year (< 24 weeks' gestational age [GA]). Only 23 NICUs (30%) presented a structured PnPC, while 34% had an expert consultant for problems related to end-of-life and palliative care issues. A pediatric palliative care team is present in 23.7% of the NICUs. Regarding the management of patients with an incurable disease in 32 NICUs (42.2%), there was a delineated healthcare plan, which provided the possibility of early discharge (for in-house management to assist with end-of-life conditions). In 65 NICUs (85.5%), there was a health care provider who could assist staff and parents before and after the birth of those with life-limiting conditions. Seventy-eight percent of practitioners were psychologists, 18.4% were coroners, 17% were pediatric palliativists, and 10% were bioethicists. The palliativists for adult, counselors, obstetricians, and geneticist were rarely involved though. The decision to use a PnPC approach was cooperatively handled in most cases (88%) by the team of neonatologists. Sixty-two percent of

those interviewed answered that they documented PnPC decisions for the medical record. Reasons for underreporting included limited knowledge of the subject (62%), fear of legal consequences (21%), or both (17%). Almost all NICUs (90%) disclosed that they performed regular prenatal counseling for high-risk pregnancies, with the help of an obstetrician, neonatologist, and pediatric surgeon (75%), as required. Sixty-eight percent of Italian NICUs set the limit of viability at the 23rd week of GA. Only 4% of neonatologists would resuscitate all vital fetuses. Seventy percent of NICUs had a local ethics committee for end-of-life decisions, but only 17% used it. Less than one-third of the NICUs (28%) organized ad hoc PnPC structured training over the last 3 years.

CONCLUSION

One-third of Italian NICUs use a structured PnPC program, although in most cases there are dedicated practitioners, with compassion and proficiency in end-of-life decisions, as well as palliative care, adequate perinatal counseling activity, and an early discharge program. Our results confirm extreme variability in the application of PnPC in Italian NICUs. Therefore, it is important to promote training for healthcare providers to help remove these barriers, which could ostensibly prevent the implementation of PnPC.

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LECT 52

METABOLIC ACIDOSIS IN CONGENITAL HEART DISEASES

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Metabolic acidosis in newborns is a common life-threatening event that, for its management, has been widely debated in the literature. In infants with congenital heart disease (CHD), metabolic acidosis secondary to hypoxia is the most common cause of death, far surpassing heart failure and cyanosis, *per se* [1]. The discrepancies between the supply of oxygen and its metabolic requirements underlie the entire problem and form the bases for treatment. In daily practice, clinical indicators reflecting tissue perfusion and systemic oxygen delivery are needed to discriminate between infants at high and low risk of a poor outcome both before and after surgery for CHD. Since the most frequent reason of metabolic acidosis with high anion gap is lactacidemia secondary to tissue hypoxia, the rate of increase in serum lactate was identified as an early marker of increasing tissue oxygen debt, predictive of poor outcome; moreover, lactate level can be followed serially for the treatment response [2]. In critically ill neonates, sodium bicarbonate therapy is thus not recommended to treat metabolic acidosis secondary to hypoxia and ischemia, not only for lack of benefit but also evidence of harm. Since the effect of catecholamines on the myocardium is blunted in the presence of acidosis, the direct adverse inotropic action of sodium bicarbonate has been demonstrated. About that, experimental models established that administration of sodium bicarbonate might, under certain circumstances, result in a "paradoxical" decrease in the intracellular pH [3]. A consequence is worsening myocardial contractility as pH ions compete with Ca^{2+} ions for binding to troponin. In addition, extracellular alkalosis shifts the oxygen-hemoglobin saturation curve to the left, which impedes oxygen release to the tissues, exacerbating the situation.

On the other hand, intrauterine cerebral blood flow varies with each particular cardiac lesion and post-natal hypoxemia, hypotension, and elevated oxygen demand exacerbate pre-existing injuries. Administration of sodium bicarbonate is associated with dose-dependent fluctuations in cerebral blood flow and consequent high risk of intraventricular hemorrhage [4]. In treating metabolic acidosis, neonatologists should avoid administering bicarbonate, instead concentrating their efforts on understanding and treating the underlying cause of the acidosis. In the case of CHD, correction of the underlying defect is considered to be the most important therapeutic measure in the management of metabolic acidosis. Considering, furthermore, the severity of metabolic acidosis reflects the gravity of

the underlying cardiac defect, mortality occurs mainly in patients with severe forms of CHD requiring immediate surgical intervention in the first month of life. Secondary to the improvement of surgical techniques over the last decades, mortality has already decreased dramatically. Achieving a further decrease in mortality and morbidity predominantly require improved preoperative stabilization of the patient. About that, prenatal diagnosis of CHD enables multidisciplinary therapeutic intervention immediately after birth, including planned delivery at a cardiac center and immediate postnatal stabilization, which may include the initiation of prostaglandin therapy and intubation and ventilation if required [5]. These measures prevent neonatal hypoxemia, hypoperfusion, and acidosis and optimize the preoperative condition of the patient to the advantage of an improved long-term outcome.

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LECT 53

RECENT ADVANCES IN BREASTFEEDING

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Mothers' milk is essential for the survival of all mammals and marsupial newborns, including humans. Only in recent times, technological advances have allowed the development of formula milk as a valid nutritional alternative to breast milk when the latter is not available. Human milk has been the subject of deep investigation since ancient times. The presence of lactose was described in 1633, the concentrations of macronutrients in 1884, and the presence of non-lactose carbohydrates in 1929 [1]. Together with the discovery of *Lactobacilli* and *Bifidobacteria* and their importance for health and disease, researchers discovered differences in the microbial composition of stool samples from breastfed and bottle-fed infants. Breast milk is composed of fat, proteins, and sugar, in a 1-to-3-to-7 ratio. Until recently, breast milk has been considered as a simple food for the rapidly growing newborn, with strictly nutritive functions [2]. However, breast milk has also been shown to contain factors – bioactive components with some functions – that promote the gut development, enhance the immune system and help the gastrointestinal microbial flora to form the intestinal microbiome (the ensemble of bacteria that naturally reside in the human bowel) [3, 4]. The composition of breast milk varies according to the infant's postnatal age. The changes in the composition from colostrum to transitional milk and then to mature milk consist of a progressive increase in lactose, lipids and caloric content. Conversely, the total protein concentration progressively decreases, depending on both a decrease in the so-called "true proteins" (responsible for the infant's growth) and a decrease in the "bioactive proteins" [4]. The colostrum contains components of the innate immune system, such as lactoferrin, lysozymes, lactoperoxidase, complement, cytokines and components of the adaptive immune system, including lymphocytes and antibodies like immunoglobulin A (IgA), IgG, and IgM. sIgA concentration in colostrum is 2.0 g/L and decreases to approximately 0.5 g/L in mature milk. As the first line of defense, sIgA are active throughout the newborn's gastrointestinal tract. sIgA block the adhesion of toxins to the intestinal epithelium and modulate the inflammatory reactions upon binding of commensal or pathogenic microorganisms. Lactoferrin concentration is approximately 7 g/L in colostrum and 1 g/L in mature milk. It has bacteriostatic functions in the newborn's intestinal mucosa, a direct cytotoxic effect against bacteria, viruses, and fungi, and immunomodulatory functions [4]. Kuhn and György were awarded the Nobel Prize for medicine and physiology for the discovery, about fifty years ago, that the human milk is enriched in active molecules called "human milk oligosaccharides" (HMOs). Nowadays, a link between breast milk HMOs and the neonatal microbiome has become

the focus of intense research [2]. Each HMO is an oligosaccharide containing lactose at the reducing end. Most HMOs have a polylactosamine backbone and contain terminal fucose, sialic acid, or both. The HMO content has been reported in the range of 1-10 g/L in mature milk and up to 15-23 g/L in colostrum. In term breast milk, HMOs can be fucosylated (35-50%), sialylated (12-14%), or neutral (nonfucosylated, 42-55%). HMO composition is influenced by maternal genetics, including secretor and Lewis Blood Group status [1, 3]. Lebrilla et al. identified nearly 200 unique HMOs that selectively promote bifidobacterial growth in the infant's gut, particularly *Bifidobacterium longum biovar infantis* [2]. Further considerations on breast milk's protective functions for the newborn concern the potential role as a probiotic food. Sources of bacteria for milk include the mammary gland itself, and two likely sources: external, via the mammary ducts, and internal, via an entero-mammary pathway (GI tract to mammary tissue) [5]. Finally, the human milk contains a wide variety of proteases along with their relevant inhibitors and activators; thus i) allowing a tightly regulated level of digestion within the mammary gland and in the infant's gastrointestinal tract, ii) maintaining some proteins intact for bioactive functions, and iii) promoting the development of the infant's protease system [2, 4]. Overall, the gain in knowledge on the composition and function of each breast milk component has implications both for the full-term newborn's and the preterm infant's health. Human milk is not just a perfect nutritional supply but has complex biological, protective functions deserving the focus, for its promotion, of regulatory agencies and healthcare systems.

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LECT 54

CONJOINED TWINS: NEONATAL MANAGEMENT

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Conjoined twins (CT) are a rare embryologic developmental accident of uncertain etiology. Since antiquity, CT captured the attention of people around the world. Interest has ranged from fear of their birth, being a sign of impending disaster, through exhibitionism and curiosity to intense media attention. The most celebrated case of CT was Chang and Eng Bunker of Siam, by which the term "Siamese twins" was coined. Born in 1829, these omphalopagus twins were joined together at the chest with a narrow band that could stretch enough for them to stand side by side [1]. The incidence of CT, although variable, has been estimated to be 1 in 50,000-100,000 pregnancies but, since about 60% of the cases are stillborn or die shortly after birth, the actual incidence seems to be approximately 1 in 200,000. Females predominate in the ratio of 3:1 [2]. It is generally understood that CT is a rare and abnormal form of monozygotic twinning, but the process by which monozygotic twins do not entirely separate and form CT is not well understood. Two opposing theories have been suggested to explain the sequence of events of CT. According to the fission theory, there is incomplete splitting or cleavage of the embryo at the primitive streak stage, leading to a junction. In contrast, the fusion theory, supported primarily by Spencer, suggests that the embryo is re-joined after complete initial separation at vulnerable sites where the ectoderm is compromised during normal development [3]. In any case, reaching a definite answer to the question of how CT is formed is hindered by our inability to carry out conclusive experiments, as well as by the relative rarity of the event. There is no record in the literature of familial aggregation of this phenomenon, nor for preferential association with maternal exposure to chemical agents or radiation. Recently it has been reported that chronic low dose radiation exposure could favor the occurrence of twinning and the prevalence of CT, but numbers were too small to reach significant conclusions. Equally, no preferential combination with anomalies unrelated to the site of the union has been reported. Although some malformations occurred more frequently with certain CT types, numbers are still too small to suggest specific associations. CT

can be classified according to the most prominent site of union with the suffix "pagus", the Greek term for fixed. The main types are omphalopagus (abdomen), thoracopagus (thorax), cephalopagus (ventrally head to umbilicus), ischiopagus (pelvis), parapagus (laterally body side), craniopagus (head), pygopagus (sacrum), and rachipagus (vertebral column). Each class has its unique embryological basis of origin, giving rise to their complicated anatomies [1]. Survival of CT is precarious and mainly depends on the type, the shearing of organs and timely and appropriate surgical or no surgical treatment. Developments in imaging modalities and radiology have enabled physicians to diagnose and assess the extent of fusion at an early developmental stage in most cases of CT. Prenatal assessment, made primarily through the use of ultrasound, with the addition of fetal MRI, currently allows defining the anomalies and the anatomical details of two fetuses so that it is now possible for physicians to predict the outcome more precisely and, if necessary, to obtain a manikin for high fidelity simulation. The latter is important to define the resuscitation team and to develop strategies for assessing vital signs, establishing an artificial airway, planning invasive procedures and administering medications [4]. Options for therapy include emergency or planned separation. CT is not usually separated immediately after birth unless the life of any one or both of the twins is threatened. A delay in separation provides the twins with sufficient time to grow, past the critical post-birth period, increase the likelihood that they will be able to withstand rigorous treatment procedures as well as to obtain an accurate clinical assessment and preparatory imaging. Detailed investigations, including chest and abdominal computed tomography, MRI, with particular attention to the anatomy of heart, liver and genitourinary system, are essential in the separation planning. Once the parents and physicians agree to perform a separation procedure, physicians are required to assemble a multidisciplinary team for proper preoperative, intraoperative, and postoperative management including laboratory staff and psychologists. Following separation, management in the intensive care unit is essential for close monitoring of fluid requirements, ventilatory support, pain relief, attention to the closure of wounds, to infections and adequate nutrition. Fortunately, the success rates of separation procedures and prognosis of post-separation survival have significantly improved thanks to modern techniques and to the dedicated team working together with the purpose of achieving the best outcome for the twins [5].

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LECT 55

INTRACAVITARY ECG FOR CENTRAL CATHETER'S TIP LOCATION IN INFANTS

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Central vascular access is frequently required in critically ill newborns; it is an everyday procedure in neonatal intensive care units. The main problem faced by inserting a central venous line is to determine its tip position. According to current literature, the tip of any central line should lie in the lower third of the superior vena cava at the junction with right atrium or in the upper part of the right atrium [1]. Malposition is associated with a high risk of complications: a central venous catheter that is positioned too high ("short" catheter) in the superior vena cava or subclavian veins can

lead to an increased risk of venous thrombosis, intimal damage, erosion to the wall of the vein and formation of fibrin sleeve with frequent catheter malfunction. Catheters that are positioned too low ("long" catheter) into the right atrium can cause arrhythmias, atrial thrombosis, and cardiac tamponade. In neonates, it is more difficult to place the tip in a correct location. In infant patients, the surface landmark for estimating the length of the catheter from puncture site to the cavo-atrial junction is less reliable than in adults; the interpretation of radiological images is more difficult, as there are no clear-cut criteria for defining where the cavo-atrial junction is located. The radiological assessment of the tip position is post-procedural, so it is frequent that after radiological evaluation, the catheter has to be repositioned. Catheter tip repositioning requires a new procedure, a second radiological assessment, significant discomfort for the patient and for the physician, a significant time delay, repeated x-ray exposure and increased costs [2]. Intra-procedural methods for verifying the location of the tip are to be preferred since they avoid the risks, delays, and costs of repositioning the tip. Among the intra-procedural methods, the electrocardiography method has many advantages. IC-ECG has many advantages: it is effective, inexpensive, safe, easy to perform, easy to teach and easy to learn. Many studies in adult and pediatric populations have proven the higher success rate and a decreased incidence of complications of malfunction, using intracavitary-ECG. These studies have demonstrated a high overall success rate and that the technique has no complications. The basic principle of the intracavitary-ECG method is that the position of the tip inside the venous system can be detected by regarding the catheter itself as an intracavitary electrode when it is filled with saline solution. Three electrodes are used, yellow on the left shoulder, red on the right shoulder, green on the left flank. The intracavitary-ECG focuses on lead II (red to green), which is ideal for the visualization of the P wave. Whenever the P wave is evident on surface ECG on lead II, the IC-ECG is applicable. The catheter is threaded further on into the venous system. When it approaches the target area, the red electrode is detached from the shoulder and connected with a special transducer device. The surface ECG is switched to the intracavitary ECG so the reading of lead II will show a P wave whose shape and height will be a reflection of the closeness of the intracavitary electrode (the tip) to the seno-atrial node. As the catheter proceeds into the superior vena cava, the P wave gets higher and reach its peak at the cavo-atrial junction; proceeding further, a progressive reduction of the P wave amplitude and/or the appearance of an initial negative component in the P wave occurs; deeper on, the P wave becomes diphasic [3]. There are very few studies demonstrating the effectiveness of the IC-ECG on neonates. We verified the feasibility of intracavitary electrocardiography method for tip location of a central venous access device in infants and evaluated the accuracy of the method in comparison with post-procedural radiographic and echocardiographic verification of the tip position. We used IC-ECG method to verify the tip position of 74 central venous catheters, 42 central venous catheters periferically inserted (epicutaneous cava catheters) and 32 central venous catheters centrally inserted (CICC). We concluded that the intracavitary electrocardiography method is safe and accurate in neonates [4, 5].

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LECT 56

RESPIRATORY VIRUS INFECTIONS IN CHILDREN: PREVENTION AND TREATMENT

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The disease burden from respiratory tract infection (RTI) is higher than that of any other cause of disease. RTIs account for increased mortality and

morbidity in children under 5 years. RTI occur with increased frequency in early life compared to adulthood, with approximately 5-6 infections per year. Several viruses are responsible for RTI: rhinovirus (HRV), respiratory syncytial virus (RSV), influenza virus, parainfluenza virus, coronavirus, adenovirus, metapneumovirus, enterovirus, bocavirus. Most respiratory virus infections in early childhood are confined to the upper respiratory tract, leading to relatively mild symptoms, presenting as a common cold. However, some children have a more severe course of a disease and develop lower respiratory tract symptoms, such as pneumonia and bronchiolitis. The leading cause of severe viral RTI in young children is RSV, but influenza virus, HRV, parainfluenza virus, adenovirus, and metapneumovirus can also cause severe respiratory disease. The severity of infection is complex and is determined by both environmental and genetic risk factors. The disease can be either immune or virally mediated and most probably is a combination of both. Early life affects both virus- and immune-mediated damage. The infant immune system is skewed to a hyporesponsive phenotype, with a reduced type I interferon response leading to a higher viral load. The adaptive immune response is also skewed and limited in its effect.

ANTIVIRAL DRUGS AND VACCINES CURRENTLY IN USE

Tab. 1 summarizes the current treatment and prevention strategies for the 3 most common respiratory viruses occurring in infants. The anti-RSV palivizumab reduces the number of RSV cases requiring hospitalization for at-risk infants if given prophylactically. High-risk groups for whom prophylaxis is recommended include premature infants, children under 2 years of age with chronic lung disease or with congenital heart disease [1]. Importantly, palivizumab does not have beneficial effects on established RSV bronchiolitis in immunocompetent infants. A new anti-RSV antibody derived from palivizumab with enhanced anti-RSV neutralizing activity *in vitro*, motavizumab, did not receive the license from FDA primarily due to concerns over a lack of greater efficacy and increased hypersensitivity reactions relative to palivizumab. Ribavirin is an antiviral drug that is very effective against RSV *in vitro*. However, regarding clinical use, ribavirin has generally been thought to be disappointing and to provide little or no benefit. For influenza viruses, the neuraminidase inhibitors oseltamivir and zanamivir are licensed as antiviral drugs but only for patients aged 1 and 5 years, respectively, and not for infants. These drugs can be used for post-exposure prophylaxis and the treatment of influenza virus if they can be given within 48 h after exposure or 36 h after first symptoms. Neuraminidase inhibitors are recommended only for children with chronic morbidity at increased risk of severe influenza-induced disease. Treatment shortens symptoms by about 1 day and may reduce disease severity. There are no approved antiviral agents for the prevention or treatment of HRV infection. Several drug candidates have been progressed into clinical trials, including a viral protease inhibitor, and different compounds that prevent virus attachment and entry into cells. However, none of these candidates were commercialized.

RESVERATROL

Resveratrol is a polyphenol produced by several plants in response to stress or injury induced by microorganisms and protects fruits and vegetables against infections. Resveratrol displays a wide range of biological and pharmacological activities including anti-inflammatory, antioxidative, anti-

Table 1 (LECT 56). Treatment and prevention of the 3 most common respiratory viruses occurring in infants.

	RSV		Influenza virus	HRV
Drug	Palivizumab (Monoclonal antibody)	Ribavirin	Oseltamivir Zanamivir	None
Viral target	Envelope F glycoprotein	Guanosine analogue	Envelope neuraminidase	-
Mechanism of action	Inhibit virus entry into the cell	Binding to the RNA polymerase leading to a reduction in viral replication or to the production of defective virions	Inhibit virus release from infected cell	-
Vaccine	None		Subunit. Trivalent or quadrivalent	None. More than 100 serotypes

RSV: respiratory syncytial virus; HRV: rhinovirus.

bacterial and antiviral effects [2]. Several studies have demonstrated that resveratrol exerts antiviral effect against different DNA and RNA respiratory viruses, including adenovirus, influenza A virus, RSV, and HRV [3-5]. The benefits of resveratrol may be associated with its general activity as a modulator of the transcription factor NF-kB, of the cell cycle, apoptosis, and possibly as an activator of SIRT1 [2]. Of note, NF-kB transcription mediates the production of cytokines and chemokines in response to Toll-like receptor recognition of viral infections. HRV, the most prevalent respiratory viruses, are responsible for at least 50% of the common colds and are also associated with severe infections and asthma. HRV infection of airway epithelial cells induces the production of cytokines and chemokines and has pro-inflammatory effects that correlate with the severity of cold symptoms. It has been recently demonstrated that Resveratrol exerted exerts a high, dose-dependent, antiviral activity against HRV replication in nasal epithelia and reduced reduces virus-induced secretion of IL-6, IL-8, and RANTES to levels similar to that of uninfected nasal epithelia [5]. Basal levels of IL-6 and RANTES were also significantly reduced in uninfected epithelia confirming an anti-inflammatory effect of the compound. HRV-induced expression of ICAM-1 was also reversed by resveratrol. A central role of resveratrol anti-HRV activity is played by the modulation of transcription factor NF-kB, known to be involved in rhinovirus infection and cytokines production. Resveratrol may be useful for a therapeutic approach to reduce HRV replication and virus-induced cytokine/chemokine production.

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LECT 57

COMMUNICATION, MEDIA, AND MASS-MEDIA: HOW CAN WE GET READY TO DEAL WITH ALL OF THIS?

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Since the 1950s the relationship between men and machines in the field of communication has always been involving those scientists who have focused their attention on communication to meditate on how systems are ruled, how they learn and change. In our daily experience, media represents a significant "meeting point" of every aspect of our life: in our way of looking at the world, behaving, communicating, creating relationships and making sense and significance of ourselves and of what surrounds us. As professionals, we must be aware that, with the new technologies, the message cannot overlook the medium. Paraphrasing an axiom of communication, the medium categorizes the content: the medium that we choose is not neutral but determines certain behaviors and ways of thinking. Each medium has some specific qualities, promoting some experiences and inhibiting others. The digital and network revolutions bring about innovative and improving aspects but also other elements that, if not controlled, could generate critical situations. Let's try to analyze how the digital and media context takes part in the doctor-patient/family communication and in the whole care relationship. 1) The computer, from being a facilitating tool to be a communicative barrier: the enhancement of its storage and connection/interconnection potentialities has increased the bureaucratic duties and the administrative load of every single visit. 2) The possibility of remote communication and the consequent misunderstandings: sending emails or using chats are important tools and continuous information exchange can happen with little effort, but they can be dangerous as they represent an actual sanitary link with all its implications and responsibilities, concealed by the virtual appearance. 3) The doctor's new competitors and the patient's new enemies are information without

intermediation, fake news, the information overload and the confirmation bias. On one side we now have "doctor Google", who is apparently more available and faster; on the other, the patients and their family, who believe to be competent and well-informed. Anything can be found online: it is enough to type whatever keyword on a browser to have a series of information immediately. Speed and abundance become the main characteristics. If we write "preterm", we get 11,300,000 results! This abundance of information, known as "information overload", and the consequent "information bias", are not helpful for the patient to properly use notions, data, indications, nor to clarify their first questions and requests. The "information bias" is the patient's inability of deciding because of the amount of information to be analyzed. In the majority of the cases the information represents a "noise", a "bother" rather than gaining of awareness. The obtained result is not useful but can cause as much confusion and concern. Even when people acquire later evidence that denies the starting idea, they keep holding to that first idea created by preliminary information. This phenomenon is attributed to the high amount of information to be managed without any mediation, to the lack of time and the resulting stress. Another element is the heuristic of the availability, that is the fact that a person tends to choose by the last available information, last not like the most recent but the last in the emotive sphere. Then, professionals are facing two obstacles: the need to correct the information and to look after the emotive impact that the incorrect information has. The caring relationship, if it is constructed on trust and reciprocal emotion, can become a place of listening rather than the chaos of the background noise. If that is generated, the doctors can and must take on a new role of "filter" of data, guides, facilitators in the use of the applications for self-management and the use of devices for long-distance health-checks. The digital can meet the new requirements of professionals and patients, only if it is carried by high-quality communicative ways, reflection and reinforcement moments that can contribute to increasing the maturity of the patient-family request. Doctors and specialty schools have become sensitive to communication themes that allow improving the transversal expertise that can make the doctor not only a professional who nurses, but who takes care of someone. Counseling and the ability to communicate become precious expertise that can be developed but also taught and learned. To let the words become therapy, "training" is necessary. New technologies can be useful for educating purposes: simulation, video-recording with reflection on communicative and relational modes adopted, software that allow the analysis and monitoring of conversations. Technology can improve the communications and decrease the misunderstanding, the discomfort, the risks, and can help doctors to strengthen a new identity that joins digital and human nature.

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LECT 58

GENETIC ASSOCIATION WITH CONGENITAL HEART DISEASE

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Prevalence of congenital heart disease (CHD) is 5-10/1,000 newborns per year, and at least one-third of patients have got extracardiac manifestations, including genetic associated complex syndrome. The primary cause of CHD remains not understood, but genetics is a major contributor to CHD. In this paper, I will make a short review of some of the most popular genetic causes of CHD and try to give a general guideline to practitioners for genetic tests.

CONGENITAL HEART DISEASE IN ABNORMAL CHROMOSOMAL NUMBER

Thirty percent of children with an abnormal chromosomal number will have CHD. A simple karyotype can be used to detect chromosomal abnormalities from 10 Mb. Fifty percent of children with trisomy 21, the most common aneuploidy, can have CHD, varying from atrial septal defects, ventricular septal defect, and tetralogy of Fallot. Left-sided obstructive lesions (aortic coarctation, subaortic stenosis) are very rare in this population. Surprising, surgical outcome from atrioventricular canal defect in children with Down syndrome is better than in patients without the syndrome. All patients with trisomy 18 will have some degree of CHD, usually septal defects. One-third of patients with Turner syndrome will have CHD, usually left-sided abnormalities including bicuspid aortic valve, aortic stenosis, coarctation of the aorta.

CONGENITAL HEART DISEASE IN CHROMOSOMAL MICRODELETIONS

Chromosomal microdeletions up to 10 Mb can be detected in twenty percent of patients with CHD. Fluorescence *in situ* hybridization (FISH) can be used in babies with suspected Williams syndrome and 22q11.2 syndrome. Williams syndrome is due to microdeletion of chromosome 7p11.23 that can cause the typical elfin face, neonatal hypercalcemia, renal abnormalities, developmental delay, and CHD. CHD in Williams syndrome are due to haploinsufficiency of elastin and most commonly are supra valvular aortic and pulmonary stenosis. 22q11.2 deletion causes abnormal pharyngeal arch development that leads to different types of cardiac malformation in association with thymic and parathyroid hypoplasia. CHDs are present in 75-80% of patients with 22q11.2 deletion, most commonly conotruncal defects (tetralogy of Fallot, pulmonary atresia, truncus arteriosus, ventricular septal defect) and aortic arch anomalies. FISH cannot detect the most distal lesions, so in patients with few clinical features can be useful to use genome-wide microarrays. Comparative genomic hybridization (CGH) array can be used to detect submicroscopic deletions and duplications that can cause changes in gene dosage. CGH array can be used in children with CHD with associated other abnormalities that cannot directly refer to a specific syndrome. Del8p23 includes the cardiac transcription factor GATA4 and can be associated with various cardiac abnormalities, developmental delay, and congenital diaphragmatic hernia. More recently, whole exome sequencing (WES) and whole genome sequencing (WGS) can provide more information about this small structural abnormalities.

CONGENITAL HEART DISEASE IN SYNDROMES WITH SINGLE GENE MUTATIONS

Analysis of single genes can be useful in children with a specific phenotype. Fibrillin 1 (FBN1) mutation can cause Marfan syndrome, a genetic disorder characterized by abnormalities in connective tissue, which usually causes flexible joints, scoliosis, cardiac problems like progressive aortic root dilatation and increased risk of aortic dissection. RAS-mitogen-activated protein kinase (RAS-MAPK) pathway can be mutated by different genes abnormalities, and different syndromes exhibit dysregulated signaling through RAS-MAPK cascade. This disorders, so-called RASopathies, includes Noonan syndrome, Costello syndrome, LEOPARD syndrome, cardiofaciocutaneous syndrome and neurofibromatosis type 1. Type of CHD in RASopathies depends on the gene involved: pulmonary vein stenosis is frequently associated with PTPN11 mutations, hypertrophic cardiomyopathy is associated with RAF1 mutations.

WHAT TO DO IN CASE OF SUSPECT GENETIC ASSOCIATED CONGENITAL HEART DISEASE

1) Pregnancy and neonatal history; 2) family history; 3) clinical observation of the patient: phenotype, associated symptoms and signs; 4) genetic tests: karyotype (in case of suspected aneuploidy), FISH (Williams, DiGeorge), CGH Array (congenital heart disease plus other important extracardiac manifestations: brain malformations, gut malformations etc.), specific phenotype (analyzing specific genes), WES (in case of negative tests with high suspect of genetic associated CHD).

CONCLUSIONS

Just 50% of CHD have a known causative event, and 30% of CHD are associated with a complex genetic-based syndrome. CHD can be the first manifestation of a precise genetic syndrome, and early genetic diagnosis is essential in order to organize a correct follow up for the patients.

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LECT 59

EARLY STRESS AND EPIGENETIC EFFECTS IN PRETERM INFANTS

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Behavioral epigenetics is revealing biochemical mechanisms linking individual developmental phenotype and early adversity exposures to later-in-life detrimental outcomes. Preterm birth represents a major adverse condition in human development, including both the immature neurobehavioral profile at birth and the hospitalization in the

Neonatal Intensive Care Unit (NICU). During NICU stay, preterm infants are exposed to life-saving yet pain-inducing and invasive procedures (e.g., skin-breaking procedures and mechanical ventilation) and protective care interventions (e.g., developmental care strategies including skin-to-skin contact and breastfeeding support). DNA methylation and telomeres length regulation are two promising epigenetic markers of early stress exposure. DNA methylation consists in alteration of the gene expression related to environmental factors. Telomeres length is genetically determinate, but cumulative exposure to adversity experiences produces DNA damage and can increase telomere shortening. The application of behavioral epigenetics to the field of preterm studies (i.e., Preterm Behavioral Epigenetics, PBE) is rapidly growing and holds promises to provide valid insights for research and clinical activity. We will provide evidence from our longitudinal research program on PBE including: 1) the effects of NICU-related stress exposure on DNA methylation and telomere length regulation from birth to NICU discharge; 2) the association between altered epigenetic markers and phenotypic outcomes at 3 months and 4 years of age in preterm infants compared to control full-term counterparts; 3) the study of the neurological and brain-imaging correlates of altered epigenetic signatures in preterm infants at 12 months of age; 4) the investigation of the potential buffering role played by maternal behavior and sensitivity during the post-natal period on the association between pain exposure, increased DNA methylation and behavioral stress regulation in preterm infants. This pool of findings suggests that post-natal adverse exposures (e.g., NICU-related pain-related stress) affect the developmental trajectories of preterm infants and children via epigenetic alterations and usually occurring variation in post-natal maternal caregiving can only partially mediate this effect. As the potential epigenetic vestiges of early care and protective interventions in NICU have not been investigated yet, the field of PBE research presents open questions and future directions for clinically relevant epigenetic-applied research will be discussed.

LECT 60

FOLLOWING UP THE RESPIRATORY CONSEQUENCES OF PRETERM BIRTH

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Whether it is associated with bronchopulmonary dysplasia (BPD) or not, preterm birth has been correlated with adverse pulmonary outcomes in infancy, childhood, and adolescence. Although several consequences of prematurity – especially in lung function – have emerged from longitudinal follow-up studies, there are still nor consensus nor recommendations on how monitoring pulmonary outcomes in these children. Functional and imaging studies may both have a role for clinicians. Follow-up studies on survivors of preterm delivery, with or without BPD, demonstrated an increase in the incidence of respiratory symptoms in the early years of life, with an up to 5-fold higher risk of wheezing disorders than in term-born infants, especially if there are other risk factors involved, such as RSV-related infections, exposure to smoke, and atopy. Asthma and the use of asthma medication also tend to be more common in the first decade of life in children born extremely preterm, and significantly so for exercise-induced respiratory symptoms. Wheezing in children born very premature seems to be independent of a neonatal diagnosis of BPD, which on the opposite may be a predictor of the use of asthma medication [1]. However, the pathophysiology of BPD differs from that of asthma, as demonstrated by the low exhaled nitric oxide values seen in these subjects. In the first 2 years of life, lung function and volumes can be assessed using rapid thoracoabdominal compression techniques, gas dilution or washout, and whole-body plethysmography (which can provide a measure of hyperinflation and gas trapping), but these techniques are not without their disadvantages [2]. Studies exploring the respiratory function of preterm-born infants in the neonatal and early post-natal period have found a reduced compliance of the respiratory system (Crs) and an increased resistance (Rrs) in the first weeks of life, as well as a lower functional residual capacity (FRC). These findings seem to be more evident in infants with BPD than in those who do not develop this condition [2, 3], but the Crs tends to normalize by 2 years of age [3, 4]. While compliance and lung volumes seem to improve with time, the same cannot be said of the airflow limitation, which appears to be a persistent problem. From their first months of life, preterm infants have reduced expiratory flows judging from their maximal forced expiratory flow at functional residual capacity ($Vmax_{FRC}$), with no

changes up to 24 months of age [4]. Spirometry, to assess pulmonary function during childhood and adolescence, confirms a persistently limited airway flow in individuals born prematurely. From school age onwards, longitudinal studies have documented a persistent reduction in expiratory flow parameters (FEV_1, FEV_1/FVC, FEF_{25-75}) until early adulthood, with an estimated mean 16.2% and 7.2% reduction in %FEV_1 for preterm-born individuals with and without BPD, respectively, compared with term-born controls [5]. Those born late preterm, at 33-34 gestational weeks (GW) have a reduced airway function at 8-9 years of age too, to much the same degree as in children born extremely preterm (25-32 GW), although there is some improvement by 14-17 years of age. There is evidence of tracking in lung performance in preterm-born individuals with or without BPD. In fact, the longest follow-up study performed in a cohort of BPD survivors born in Padua demonstrated a persistent airway obstruction from infancy into adulthood, with a positive correlation between $Vmax_{FRC}$ at 2 years and FEV_1 at 24 years of age, and no significant changes in mean z-scores for expiratory flow measures (FEV_1, FEV_1/FVC, FEF_{25-75}) [4]. This airway obstruction pattern seems to affect both the "old" and the "new" form of BPD, and the use of noninvasive ventilation techniques at birth does not appear to have improved lung function outcomes [6]. Physiologically, lung function tends to increase gradually throughout childhood and adolescence, reaching a plateau at around 23-25 years of age. It is now clear that people entering adulthood with a lower than normal lung function is at higher risk of developing chronic obstructive pulmonary disease (COPD) in later life. BPD and prematurity are clear examples of how an insult occurring in the perinatal period can be associated with a lung function impairment that persists into adulthood. Future studies should address both pharmacological interventions to reduce the development of BPD and the benefits of long-term respiratory function monitoring in individuals with BPD.

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LECT 61

NEONATAL BLEEDING DISORDERS AND PLASMA TRANSFUSION

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Neonatal bleeding is often a severe problem and a life-threatening event because of cardiovascular effects associated with a loss of blood and the damaging effects of bleeding on neonatal tissues, especially the brain. The diagnostic approach needs to consider the theory of "developmental hemostasis" for interpretation of tests. The most common abnormality is thrombocytopenia, but clotting derangements can also occur and co-exist. Acquired coagulation defects are often present in sick neonates, while inherited coagulation defects can present in otherwise healthy neonates. We review bleeding in the neonate with attention paid to inherited and acquired coagulation disorders, interpretation of laboratory test as well as treatment with Fresh Frozen Plasma (FFP).

CLINICAL ASSESSMENT

The clinical setting of the neonate presenting with bleeding often indicates the likely cause. A sick premature infant is much more likely to have an acquired coagulopathy, such as a disseminated intravascular coagulation (DIC) or a liver failure. Bleeding in the well newborn suggests an inherited coagulation disorder such as hemophilia or other congenital clotting factors deficiencies, vitamin K deficiency or immune-mediated thrombocytopenia. Family history of bleeding disorder, maternal risk factors for sepsis that may affect the fetus and maternal thrombocytopenia need to be identified. Maternal medication history is also important, particularly of drugs, such as anticonvulsants,

rifampin, and isoniazid that may be associated with severe vitamin K deficiency.

LABORATORY ASSESSMENT

Blood should be withdrawn from a venous site, as capillary samples are more prone to errors due to clot formation. First line investigations should include full blood count and standard coagulation tests: prothrombin time (PT), activated partial thromboplastin time (APTT) and fibrinogen. The results of these tests can lead to a specific diagnosis of coagulopathy that needs to be confirmed by testing the single coagulation factors. According to the "developmental hemostasis", the hemostatic system is not entirely developed at birth. APTT and PT can be prolonged, the first due to physiologically low concentrations of the contact factors and the second due to decreased concentrations of many vitamin K-dependent coagulation factors, respectively. For this reason, age-specific reference ranges are needed to adequately understand clotting results in term and preterm neonates (**Tab. 1**).

FRESH FROZEN PLASMA ADMINISTRATION IN CONGENITAL COAGULATION DISORDERS

Due to the availability of recombinant, highly purified, viral-inactivated, plasma-derived concentrates of factor VIII, factor IX, von Willebrand factor and antithrombin, the use of FFP and cryoprecipitate is no longer considered the first choice treatment for these congenital clotting factor deficiencies. However, FFP may be given if treatment is urgently required before the diagnosis of inherited clotting factor deficiency has been confirmed. Furthermore, FFP use is recommended for the treatment of single inherited clotting factor deficiency without safer replacement product available. Currently, this applies only to factor V.

FRESH FROZEN PLASMA ADMINISTRATION IN ACQUIRED COAGULATION DISORDERS

DIC is a common problem in sick neonates and is usually associated to birth asphyxia, systemic hypothermia, acidosis, respiratory distress syndrome, sepsis, necrotizing enterocolitis. Treatment of the underlying condition, with attention paid to oxygenation and circulation, needs to be prompt, effective and combined with the restoration of the hemostasis by platelet, FFP and cryoprecipitate transfusions in the presence of bleeding. Indeed, the use of FFP, at a dose of 10-20 mL/kg, is indicated in cases of active bleeding associated with coagulopathy, defined by age-specific reference values (see **Tab. 1**). In case of bleeding due to vitamin K deficiency, FFP transfusion, at a dose of 10-15 ml/kg, should be combined with intravenous infusion of vitamin K. In the absence of bleeding, prophylactic administration of FFP is indicated only for invasive surgical procedures in the presence of coagulopathy (see **Tab. 1**). In a recent Italian study, involving 17 NICUs, it was found that FFP administration was a quite frequent intervention, with 8% of admitted neonates receiving one or more FFP transfusions. This study reported a high proportion of FFP transfusions non-compliant with current guidelines, and FFP was administered prophylactically to 63% of transfused neonates, without any evidence of bleeding. Current evidence does not support FFP administration in the absence of bleeding for preventing intracranial hemorrhage in preterm babies, for treating hypovolemic hypotension, for

Table 1 (LECT 61). Defining coagulopathy in the premature and term neonate, at birth (**A**) and during the first 3 months of life (**B**), according to prothrombin time (PT), activated partial thromboplastin time (APTT) and fibrinogen values.

A.

Gestational age at birth (wk)	PT, upper limit [a] (sec)	APTT, upper limit [a] (sec)	Fibrinogen, lower limit [a] (mg/dL)
< 28	> 21	> 64	< 71
28-34	> 21	> 57	< 87
30-36	> 16	> 79	< 150
≥ 37	> 16	> 55	< 167

B.

Gestational age at birth (wk)		PT, upper limit [a] (sec)	APTT, upper limit [a] (sec)	Fibrinogen, lower limit [a] (mg/dL)
30-36	and postnatal age of 5 days	> 15	> 74	< 160
	and postnatal age of 30 days	> 14	> 62	< 150
	and postnatal age of 90 days	> 15	> 51	< 150
≥ 37	and postnatal age of 5 days	> 15	> 60	< 162
	and postnatal age of 30 days	> 14	> 55	< 162
	and postnatal age of 90 days	> 14	> 50	< 150

[a] The upper limit of PT and APTT, and the lower limit of fibrinogen are defined for values outside the 95% confidence limits of the age-related reference ranges.
PT: prothrombin time; APTT: activated partial thromboplastin time; wk: week; sec: second.

improving the immune function during sepsis, or for preventing hemorrhagic/thrombotic complications in neonates with hypoxic-ischemic syndrome in treatment with systemic hypothermia.

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LECT 62

ASSESSMENT OF NURSING SKILLS: THE EXPERIENCE OF A NEONATAL INTENSIVE CARE UNIT

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OBJECTIVE

The primary objective is to describe the process of assessment of nursing skills in a neonatal intensive care unit (NICU), with the identification of specific profiles of membership. The instrument adopted to pursue this objective is, in addition to the analysis of the job description, the proposal for a new nursing skills assessment form.

METHODS

The nursing skills assessment sheet is inspired by the Italian version of Meretoja's "Nurse Competence Scale". The context analysis performed has removed or modified a substantial number of items from the original evaluation. Each item has been broken down into four levels of development: junior, senior, professional and specialist. A legend has been constructed to evaluate each item according to the definition of the level of development, which follows the common logic of: the nurse knows, the nurse knows and apply, the nurse knows and applies and transmits and collaborates in updating knowledge, the nurse knows and applies and teaches and actively participates in research. The evaluation of each item gives the professional a score of 1-4. The weighted sum of the scores places the professional in one of the four profiles of membership. The nursing assessment by the nursing coordinator is preceded by a self-assessment. The compilation of the evaluation form and the relative processing of the data took place through the implementation of software.

RESULTS

The application of the scale of evaluation allowed mapping the competencies of all the nurses of the area, in order to promote a balance of work groups. The knowledge of nursing skills allows the possibility of providing a specific training, in order to fill in the gap of knowledge and to promote the strengths of the single nurse.

CONCLUSIONS

The mapping of skills allows the nurse coordinators to identify the strengths and weaknesses of their organizational structure and to promote the development of the skills of their employees. On the other hand, the verification of professional development allows professionals to get an answer to the need for recognition and self-fulfillment, highlighting their professional development.

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LECT 63

EMERGING BIOMARKERS AND METABOLOMICS FOR MANAGING NEONATAL SEPSIS

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Over the last decade, sepsis is dramatically increased, potentially leading to approximately 6 million deaths per year worldwide [1]. Based on data reported in a recent meta-analysis, approximately 2,202 babies every 100,000 live births develop neonatal sepsis with a mortality rate ranging 11-19%; this corresponds to 3.0 million cases of neonatal sepsis

annually [2]. Unfortunately, the meta-analysis did not include any data from low-income countries, and thus the true global burden of sepsis is likely to be higher and is far to be accurately quantified. In May 2017, the United World Health Assembly and the World Health Organization (WHO) adopted a resolution to improve, prevent, diagnose, and manage sepsis [3]. Sepsis was recognized a global health priority, marking a quantum leap in the global fight against this disease; the 194 United Nation member States were pushed to implement appropriate measures to reduce the human and health economic burden of sepsis, including innovative diagnostic approaches. The resolution also acknowledged that sepsis is a major factor in childhood morbidity and mortality. The presence of life-threatening organ dysfunction discriminates sepsis from uncomplicated systemic infections, being the former the result of a dysregulated host response to infection [4]. Sepsis and septic shock are two different entities; actually, the latter is a subset of sepsis marked by deep circulatory, cellular, and metabolic abnormalities and associated with a greater risk of mortality than with sepsis alone [4]. In its early stages, sepsis is often confused with other conditions, especially in critically ill newborns; this leads to a delayed recognition of signs and symptoms that in turn causes an abrupt multi-system organ failure and ultimately death. As a result, the early and accurate diagnosis of the disease is a key issue in reducing neonatal morbidity and mortality. Although blood culture remains the gold standard for diagnosis, some critical perinatal factors (e.g., maternal intrapartum antimicrobial exposure, low or intermittent bacteremia) together with several analytical pitfalls (e.g., small blood volume obtained from newborns, high turnaround time for culture results) make inaccurate and insensitive the microbiological approach. In addition, the absence of a timely microbiological response on blood culture leads to empiric antimicrobial therapy; frequently this strategy is excessive, unnecessary and promotes antimicrobial resistance, an additional harmful effect on newborns' outcome [5]. A huge number of biomarkers for sepsis and septic shock have been tested in hundreds of clinical studies; curiously, there is an inverse correlation between the plethora of biomarkers proposed for diagnosing and managing sepsis and the number of reliable biomarkers currently used in clinical practice. C-reactive protein (CRP) and procalcitonin (PCT) are the most extensively investigated acute-phase reactants. These two proteins significantly differ each other in their clinical and biological features: serum levels increase within 6-10 hours for CRP and within 2-4 hours for PCT, reaching the serum peak level after 2-3 days and after 18-24 hours, respectively [6]. As a consequence, they are not interchangeable with each other: CRP accurately depicts the monitoring of the disease, especially the response to the treatment. PCT is highly sensitive, allowing an early diagnosis at the onset of the disease. Serum levels of both proteins are influenced by gestational age and post-natal age, requiring "dynamic" decision levels [7]. Among the plethora of potentially emerging biomarkers, such as serum amyloid A protein (SAA); lipopolysaccharide binding protein (LBP); neutrophil CD64; various cytokines (e.g. IL-2, IL-6, IL-8, TNF); soluble form of urokinase-type plasminogen activator receptor (suPAR); soluble triggering receptor expressed on myeloid cells-1 (sTREM-1); liver-type fatty acid-binding protein (L-FABP); intercellular and vascular adhesion molecule-1 (ICAM-1 and VCAM-1, respectively); and mannose binding lectin (MBL), the soluble CD14 subtype (sCD14-ST), also called presepsin, seems to fulfill most of the characteristics of an ideal biomarker for managing neonatal sepsis [8]. In a recent meta-analysis, both pooled sensitivity and specificity of sCD14-ST were 91.0%, and the diagnostic odds ratio was 170.28 [9]. Receiver operating characteristic (ROC) analysis showed an area under the curve (AUC) of 0.975, significantly higher than those of CRP and PCT (0.858 and 0.783, respectively). Several studies investigated the role of metabolomics in patients with sepsis and septic shock [10]. Most of the published studies found that metabolomics clearly distinguishes the metabolic profile of septic patient from that of non-septic patients; in neonatology, the metabolic profile of the early-onset neonatal sepsis (EOS) is significantly different from that of late-onset neonatal sepsis (LOS) [11]. The urinary metabolic profile of septic newborns assessed by proton nuclear magnetic resonance spectroscopy (^{1}H-NMR) is marked by the increase in acetate, glycine, glucose, acetone, lactate, and lysine and by the decrease of citric acid and creatine [12]. In conclusion, the holistic vision of biological systems as a whole provided by metabolomics seems to be more than a promising tool for improving the early diagnosis and monitoring of neonatal sepsis.

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LECT 64

ENTERAL FEEDING IN PRETERM INFANTS: NOT AS TRIVIAL AS IT IS SUPPOSED TO BE

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The beginning and progression of enteral nutrition (EN) is a critical moment in the nutritional management of the premature infant. More and more data from the literature confirm that an individualized nutritional approach represents the most appropriate modality to promote growth and therefore the discharge of these little patients. However, many obstacles may interfere with this critical process: fetal growth restriction, immaturity of the gastrointestinal system, compulsory and prolonged passive feeding, high caloric needs and all possible complications arising during the hospitalization (such as necrotizing enterocolitis, retinopathy of prematurity and bronchopulmonary dysplasia). All these factors should not be taken lightly. The scientific evidences on the benefits of the use of breast milk have supported the spread of breastfeeding practice worldwide. In a special context such as the neonatal intensive care unit (NICU), the use of human milk (HM), mother's own milk or donor milk, has to be considered as a medication. Human milk enhances immune function, promotes gastrointestinal maturation, improves neurological outcome and decreases the risk for comorbidities of prematurity. It also improves food tolerance while reducing the need for parenteral nutrition and length of hospital stay. For all these reasons NICUs should implement procedures aimed at supporting mothers separated from their babies in the first hours after birth: they should be involved and made conscious of their role, should begin early stimulation of the breast and be informed on how both to maintain milk production and to manage its collection and storage. Despite all these advantages, several barriers remain that could interfere with and often overshadow the opportunities to promote and provide human breastfeeding. Although HM is the most desirable feeding for VLBW infants, evidences suggest that it does not provide adequate amounts of calories and protein to meet the increased demands of the growing preterm infant, so that fortification of HM with protein, vitamins, and minerals is necessary. Competent feeding is a multifactorial skill and several mechanical functions, such as suck-swallow-respiration coordination, gastroesophageal sphincter tone, gastric emptying and intestinal motility, may be profoundly immature in the very preterm infant. This means that preterm infants born at less than 32 weeks of gestation are not usually able to feed

effectively from the breast or a bottle and therefore need gavage feeding. Sucking on a pacifier during gavage feeding may encourage the development of sucking behavior and improve digestive functions. The quality of a feeding relies on the assessments, decisions, and actions of a caregiver who is knowledgeable about feeding the infant at hand, sensitive to the infant's behavioral and physiologic communications, and who has competent feeding skills. In addition, babies born before 34 weeks of gestation often present with gastroesophageal reflux (GER), gastric residuals, delayed meconium passage and bowel distension. Feeding intolerance (FI), defined as the inability to digest enteral feedings associated to increased gastric residuals, abdominal distension and/or emesis, is frequently encountered in the very preterm infant and often leads to a disruption of the feeding plan. In most cases FI represents a benign condition related to the immaturity of gastrointestinal function; however its presentation may largely overlap with that of an impending NE. Symptoms of FI induce clinicians to interrupt or reduce enteral feeding leading to suboptimal nutrition, delayed reaching of full enteral feeding and prolonged intravenous nutrition supply. Furthermore, many symptoms of FI such as regurgitation, vomiting and cardiorespiratory events can mimic GER. The presence of increased gastric residual and abdominal distension, together with the instability of LES secondary to immaturity, promote GER. Another critical period is the intestinal rehabilitation after a surgical event. Enteral nutrition must be started as soon as intestinal recanalization has been reached firstly combined with parenteral nutrition, according to intestinal tolerance.

CONCLUSIONS

Successful nipple feeding by breast and/or bottle without major cardiorespiratory compromise maintaining optimal growth standards is one NICU discharge criterion. This objective must be achieved by giving a correct interpretation of the symptoms of FI, providing adequate nutritional inputs and promoting the maturation of gastrointestinal functions and suction and swallowing suction mechanisms, taking into account the particular characteristics of each newborn. The use and implementation of breast milk, the personalized nutritional strategies to promote feeding tolerance and to achieve full oral feeding are the key points on which the neonatologist must act, especially in complicate neonates like severe preterm infants with intrauterine growth restriction and newborns with surgical problems.

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LECT 65

KANGAROO MOTHER CARE AND PROMOTION OF BREASTFEEDING: THE BREASTFEEDING WHEEL

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Breast milk is the ideal food for preterm. Despite its known benefits for newborn babies and mothers, the percentage of breast-fed preterm infants discharged from the Italian neonatal intensive care units is still unsatisfactory. It is therefore mandatory to understand that a generic attitude of favor towards breastfeeding has proved to be ineffective, and that specific programs are needed to support breastfeeding in the preterm infant. The early involvement of parents in caring for their baby in neonatal intensive care, starting from the early and continuous implementation of skin-to-skin is one of the fundamental steps to implement this process. It is, therefore, necessary to support skin-to-skin overcoming fears and false contraindications and to allow parents to be an indispensable part in the care of their preterm infants. During skin-to-skin, the little newborn will be able to try out his first tactile, olfactory and gustatory experiences, recalling those smells and flavors familiar to him since they have been memorized from the intrauterine life. During skin-to-skin the mother can make him taste small quantities of colostrum and then milk through the manual squeezing of the breast, and as time goes by, one step after the other, just like in a wheel that progresses slowly, she can arrive to attack the baby, always followed and supported by a sensitive, welcoming and competent multidisciplinary

team. In this way the "breastfeeding wheel" will become a simple and objective method with which both parents and operators can follow and check the progress made by the newborn, guiding and accompanying step by step the mother-child dyad towards new goals, supporting and enhancing day by day the skills of the newborn and his mother.

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LECT 66

NEUROLOGICAL COMPLICATIONS DURING RESPIRATORY SYNCYTIAL VIRUS INFECTION

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Respiratory syncytial virus (RSV) is the most common cause of severe infections of the lower respiratory tract of the child and the primary cause of hospitalization of the child < 5 years of age. The literature reports an incidence of neurological problems caused by RSV of 1.2-1.8% (overall 1,500-2,250 cases/year) [1], but until to 40% in some articles, an incidence that is probably underestimated. In particular, the incidence of RSV-related encephalopathy is reported as 0.08% of RSV-positive patients but rises to 10.7% in patients undergoing brain MRI for neurological symptoms. In Japan, RSV is the fourth most common causative agent of acute encephalopathy (after influenza virus, herpes virus, and rotavirus). The RSV-related neurological problems are: central apnea, various types of convulsions (febrile convulsions, non-febrile or sine cause, febrile epileptic status, convulsions secondary to hyponatremia with the syndrome of inappropriate secretion of ADH, SIADH) and the real encephalopathy. Apnea, the most frequent complication, is common in the infant under two months of age, is the most common cause of intubation and has central pathogenesis. Febrile seizures and febrile epileptic status are more common in the young child and may also occur in the absence of bronchiolitis symptoms and is associated with a high risk of neurological deficits. The hyponatremia is frequent in small child during RSV infection; in 4% of cases it is associated with convulsions when sodium values ≤ 123 mEq/L; they are due to excessive secretion of the antidiuretic hormone (ADH) produced during RSV pulmonary infection and related to the degree of air-trapping, often aggravated by an incorrect rehydration with hypotonic solutions. The encephalopathy is shown up with convulsive crises and alterations of state of consciousness, but also hypotonia, reduced responsiveness, exotropia. The pathogenesis has not been clarified: it could be linked to a direct action of the virus or to a secondary action caused by the increased production of cytokines that were found in the CSF in the acute phase of encephalopathy. The acute RSV encephalopathy shows like as a "toxic excitement", characterized by the production of large amounts of inflammatory cytokines in the circulation and the liquor, which induce endothelial damage, cerebrovascular dysfunction and cerebral edema, but also glial damage and ultimately neuronal death by apoptosis, with an immune-mediated mechanism. Clinically it manifests itself mostly with generalized tonic-clonic seizures. In a large retrospective study on children hospitalized for bronchiolitis, brain MRI showed abnormalities in 10.7% of those undergoing brain MRI for neurological symptoms, with encephalitis, ADEM-like encephalitis and limbic encephalitis [2]. Often the involvement is temporal-parietal, in particular of the hippocampus. The electroencephalogram is often positive in this type of injury. The liquor is almost always within the limits of the norm. A decisive role in the pathogenesis of RSV-encephalopathy is due to IL-6, IL-8 and TNFα cytokines. Produced by the epithelium of the infected airways, these cytokines may lead to increased blood-brain barrier permeability, vascular permeability causing cerebral edema, but also direct damage to neuronal cells.

Other cytokines, such as brain-derived neurotrophic factor (BDNF) and NOx (nitrogen oxide), may represent markers of neurological prognosis having been found to increase their correlation to a worse neurological prognosis [3]. Studies on mice infected with RSV have shown that RSV is a neurotropic virus, capable of spreading from the olfactory bulb in the cerebral cortex and the choroidal plexuses of the cerebral ventricles. It is able to alter the functions of the hippocampus (learning and memory) [4]. As there is no etiologic therapy for the RSV encephalopathy, the forms characterized by important cerebral involvement and with the demonstrated hyperproduction of inflammatory cytokines could benefit from modulating therapy with high doses of steroids, i.v. immunoglobulin, and plasma exchange.

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LECT 67

SEDATION FOR NEUROIMAGING IN INFANTS

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Computerized Tomography (CT) and Magnetic Resonance (MR) allow acquiring increasingly important images regarding the care of newborn infants and the study of the brain development. The execution of the CT scan is speedy while the MR has proven to be harmless and can be performed even on preterm infants, but can be annoying especially for the noise and the forced position. The immobility of the subject throughout the examination is essential to obtain good quality images and avoid diagnostic errors. It can, therefore, benefit positively from sedation or anesthesia but these can carry some risks.

The AAP published guidelines on the management of pediatric patients in sedation for diagnostic investigations, claiming that in the newborn and former preterm infants "it would seem prudent to avoid unnecessary exposure to sedation if the procedure is unlikely to change medical management". A systematic review indicated practical advice on how to perform in safety MR in premature infants [1]. Pharmacological sedation is feasible but not essential in the neonate. In recent years only 60-70% of neonatal intensive care units (NICUs) interviewed used sedation for brain MR.

Available literature allows us to say that MR can be performed simply with behavioral measures up to 6 months of age. Feed with milk the baby about 30' before the examination, actuate good acoustic isolation, wrap the infant by a specific device and administer sweet solutions, allow getting good images even in 95% of cases [2]. *Quality of evidence: moderate.* A further aid can be offered, especially in the premature, by the use of incubators that are compatible with the MR or by MR devices located within the NICUs.

If pharmacological sedation is needed, it is important to consider that only some molecules can be used in the neonates and outside the intensive care units and that the premature infants are at greater risk of respiratory adverse events.

Chloral hydrate was banned in Italy by AIFA for carcinogenic and genotoxic risk in animals. Midazolam is a good anxiolytic and sedative with amnesic effect, has an antagonist (flumazenil) but is a bitter taste. It causes irritation of the mucous membranes and burning sensation, also if nebulized with a special device (MAD); aerosolization on the oral mucosa produces the same sedation, causes less discomfort but requests more time than nasal aerosolization; one author added lidocaine spray to nasal administration in a pediatric population [3]. *Quality of evidence: low.*

Table 1 (LECT 67). Quality of evidence and grade of recommendation for neuroimaging in infants.

	Quality of evidence	Grade of recommendation
Eventually reliable examination		
milk meal administration 20-30' before the examination + ear occlusion + wrapping (better by immobilization device) +/- sweet solution (20-33%, 0.5-3 ml)	moderate	strong
Urgent or not reliable, venous access absent		
ear occlusion + wrapping (better by immobilization device) +/- sweet solution (20-33%, 0.5-3 ml)	moderate	weak
+/- midazolam: aerosolized nasal 0.3-0.5 mg/kg or aerosolized buccal 0.3-0.5 mg/kg or oral 0.5 mg/kg	low	weak
dexmedetomidine nasal 2-3 gamma/kg, 30' before the examination	very low	weak
Urgent or not reliable, venous access present		
+ ear occlusion + wrapping (better by immobilization device) +/- sweet solution (20-33%, 0.5-3 ml)	moderate	weak
midazolam ev 0.1 mg/kg +/- 0.05 mg/kg	low	weak

Dexmedetomidine is an agonist of the central and peripheral alpha2 receptors. It acts as hypnotic and anxiolytic, but it also binds to the peripheral receptors of the sympathetic system determining a reduction of heart rate, changes in blood pressure and reduction of cardiac index. It has less impact than other sedatives on respiratory activity and airway patency and tone. It can be administered intravenously, intramuscularly or intranasal with good efficacy; the oral route is less effective. The drug is tasteless and odorless and the nasal administration, unlike the midazolam, is not painful. Nasal administration leads to sedation after about 30-40', and a wake-up time of up to two hours, more time than with midazolam. Its intravenous use as a single sedative in the execution of the high number of sedations in pediatric age has shown proper sedation but significant side effects [4]. The nasal administration of dexmedetomidine has been used in the pediatric population to perform various diagnostic investigations obtaining proper sedation and no adverse event while its nasal use in the newborn is only mentioned [5]. *Quality of evidence: very low.*

Propofol is an intravenous hypnotic drug. It is an excellent sedative agent for non-painful procedures but can cause loss of protective reflexes of the airways and, sometimes, respiratory depression. It, therefore, requires the presence of expert personnel. **Tab. 1** summarizes the quality of evidence and the recommendations. The GRADE method was used for the analysis of the literature and the attribution of the quality of evidence and grades of recommendation.

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LECT 68

PERINATAL STROKE: CLINICAL CLUES AND DIAGNOSIS

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Perinatal stroke is an acute neurological syndrome, often associated with chronic sequelae, due to a cerebral injury of vascular origin occurring between 20 weeks of gestation and 28 days of postnatal life. Considering the time of detection more than that of occurrence, clinical features, and cerebral imaging, three categories can be identified;

1. Fetal, diagnosed before birth by fetal echography or Magnetic Resonance (MR) or in stillbirths on the basis of a neuropathological examination or in case of cerebral lesions detected within the first week after birth, with clear signs of tissue loss. Affected newborns show a chronic and static neurological impairment without acute perinatal sentinel events and/or neonatal resuscitation.
2. Neonatal, occurring from birth to 28 days of postnatal life, characterized in most of the cases by an acute neurologic dysfunction and concomitant specific radiologic and EEG features.
3. Presumed perinatal stroke, related to events whose exact time of onset, based upon clinical and imaging findings, are presumed, but not sure, to be perinatal (20 weeks of gestation – 28 days of life). The classical clinical presentation is that of a chronic, static neurologic deficit emerging during the first year of life in the absence of acute neonatal encephalopathy. Cerebral imaging identifies a periventricular venous infarction or an arterial territory infarction as a primary lesion [1-3].

Perinatal stroke syndrome includes four major clinical-anatomic subtypes:

1. Arterial ischemic stroke (AIS) is related to vascular occlusion in an arterial territory. The middle cerebral artery (MCA) as the main branch (with a worse prognosis), the distal cortical branch and lenticulostriate branches are most frequently involved in comparison to anterior cerebral and posterior cerebral arteries. Lesions are unilateral in nearly 75% of cases, and in about 80% involve the distribution of the left MCA. AIS can occur from: emboli of cardiac, transcardiac, or aortic arch origin; thrombosis due to disturbed hemostasis; disorders of the cerebral arteries. Fetal AIS (FAIS) can be related to monochorionic twinning with twin-twin transfusion syndrome or death of a co-twin, maternal illicit drug use as cocaine or amphetamines responsible for vasoconstriction or spasm, fetal-maternal hemorrhage, infectious arteritis related to TORCH fetopathy. Neonatal AIS (NAIS) birth prevalence is 6 to 17 per 100,000. Four main risk factors are identified: first pregnancy, male sex, intrapartum hypoxia, and fetal/neonatal infection. Other conditions associated are: injury from traumatic stretching at birth or arterial occlusion with cerebral edema, paradoxical thromboembolism associated with cyanotic congenital heart disease, portal vein thrombosis, iatrogenic vascular catheter-related thrombosis and ECMO. Main clinical signs are seizures with onset rarely beyond day three, lethargy, hypotonia, feeding difficulties, or apnea. EEG shows asymmetry of background activity, presence of focal spikes and focal seizures. Ultrasound has low sensitivity for early detection, being useful to exclude other pathologies, while diffusion-weighted imaging (DWI-MRI), showing a decrease ADC, can detect ischemic injury within 24 h of its onset, and the extent of the ischemic lesion between day 2 and day 4 after injury. Seven, ten days after the injury, established changes should be evident on conventional T1- and T2-weighted MRI.
2. Cerebral sinovenous thrombosis (CSVT) is secondary to a complete or partial occlusion from a thrombus in a cerebral venous sinus, a large deep cerebral or a smaller cortical vein. Incidence is 0.6-12/100,000 live births. Superior sagittal sinus is involved in 65% of cases. Parenchymal lesion in the area draining into the involved vein frequently from an ischemic venous infarction converts to hemorrhagic. Superior sagittal sinus occlusion is associated with parasagittal subcortical hemorrhage and internal cerebral vein occlusion with thalamic-ventricular hemorrhage. Pathogenesis is related to multiple factors; preeclampsia, maternal diabetes, neonatal maladaptation, dehydration, polycythemia, congenital cardiac disease, ECMO, sepsis or thrombophilia. Seizures and lethargy in the first 48 hours are frequent. Ultrasound and Doppler investigations can detect thrombosis, but MRI with the addition of MR venography is the best choice to identify the venous

occlusion and define secondary consequences such as infarction or hemorrhage.
3. Hemorrhagic stroke (HS) including intraventricular, lobar cerebral, cerebellar, subarachnoid, epidural and subdural hemorrhage should arise suspicion of a coagulation disorder or vascular malformation. Apnea and acute encephalopathy, in some affected newborns, could constitute life-threatening conditions.
4. Periventricular venous infarction (PVI) is a focal acute or chronic infarction in the periventricular white matter, not conforming to an arterial territory, often associated with evidence of germinal matrix hemorrhage in preterms [4, 5].

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LECT 69

ULTRASOUND GUIDED CENTRAL VENOUS ACCESS IN CRITICALLY ILL NEONATES AND INFANT BABIES

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The insertion of a centrally-inserted central catheter (CICC) has many advantages in the Neonatal Intensive Care Unit (NICU) setting because the use of these devices allows obtaining a stable and central venous access for the fluid resuscitation and infusion of vesicant solutions and drugs and the hemodynamic monitoring of patients. The procedure to insert a central line is complex and at high risk of complications, and its success significantly depends on the operator's skills. In the last years, the use of ultrasound guidance has been increasingly utilized for vessel visualization and puncture, thus decreasing complications and increasing success rates (level of evidence: A; degree of consensus: very good; strength of recommendation: strong) [1]. For this reason, ultrasound guidance is routinely used for short- and long-term central venous access in children and neonates as recommended by various international scientific societies and institutional guidelines [2]. However, ultrasound-guided venous cannulation in critically ill neonate and infant babies is more complicated and requires more training and a longer learning curve than in adults [3]. In order to achieve competence in ultrasound-guided central vein cannulation and to help neonatologists to fill these specific cognitive and procedural gaps, we organized a brief and specific training course with both theoretical and hands-on sessions in collaboration with two scientific societies called AMIETIP (Accademia Medica e Infermieristica di Emergenza e Terapia Intensiva Pediatrica) and GAVeCeLT (gli Accessi Venosi Centrali a Lungo Termine), accordingly to the recommendations for minimal education and training for central venous device insertion and management of the WoCoVA (World Conference on Vascular Access) 2017 (**Fig. 1**). As there is no ideal place for cannulation in children, ultrasound vessel screening should be routinely used before central vein puncture to select the ideal vein to cannulate for that specific patient according to the RaCeVA (Rapid Central Vein Assessment) protocol as described by Pittiruti and colleagues, which is a rational choice of the most appropriate vein to cannulate [4]. The frequencies of ultrasound transducers for vascular access range from 5 to 15 MHz. The higher frequencies (10-14 mHz) are preferred for the smaller babies to best visualize the most superficial veins. All the

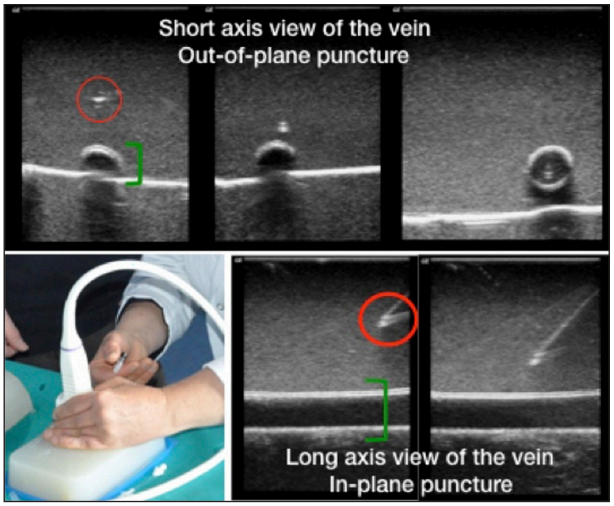

Figure 1 (LECT 69). Simulation-based training of an ultrasound-guided central venous catheterization.
The figure illustrates the ultrasound-guided vessel puncture technique by using phantoms. The trainee visualizes the simulated vessel in transverse scans (short axis) and longitudinal scans (long axis) and advances the needle tip (red circle) towards the vessel (green square bracket) during the procedure.

techniques must be accurately sterile. Ultrasound vessel imaging in transverse view is associated with an out-of-plan puncture of the vein and may be preferable in the setting of small target vessels. In contrast, the in-plane puncture technique (longitudinal view) is particularly relevant when we need not penetrate the posterior wall of the vein, but more training is required to direct the needle exactly within the plane of the probe. The utilization of the in-plane technique leads to higher precision and fewer complications and should be used when possible (**Tab. 1**). The measurement of the anteroposterior wall of the vein is important for the choice of the proper size of the catheter that should not exceed 1/3 of the internal diameter of the vein in order to avoid the risk of venous thrombosis. The tip of the catheter should be located in the proximity of the junction between the superior vena cava and the right atrium. Confirmation of tip location by post-procedure chest radiograph remains an acceptable practice currently even if the intra-procedural "intracavitary ECG" method is considered more rapid and accurate. The use of echocardiography for tip location is more beneficial in the neonate and infant babies and in emergency settings instead of chest radiograph [5]. After central venous catheter placement, the ultrasound equipment should remain easily accessible at the patient's bedside to detect early life-threatening catheter-related complications such as pneumothorax, cardiac tamponade, and hemothorax. Many aspects of ultrasound-guided central venous access are unknown to neonatologists who classically deal with umbilical and epicutaneous-caval catheters. So they need specific training before dealing with critically ill neonate and infant babies requiring a CICC.

Table 1 (LECT 69). Ultrasound-guided punctures of different central veins performed in "out of plane" or "in plane".

At neck	Internal jugular vein (out of plane)
In the supraclavicular area	Internal and external jugular, subclavian, brachial-cephalic vein (in plane)
In the infraclavicular area	Axillary, cephalic vein (out of plane/in plane)
At the groin	Femoral, saphenous vein (out of plane)

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LECT 70

NATIONAL NETWORK OF THE ITALIAN SOCIETY OF NEONATOLOGY: DATA SOURCE FOR SCIENTIFIC PAPERS

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INTRODUCTION

The National Network of the Italian Society of Neonatology (NNSIN) collects data on neonates with GA < 37 weeks which represents about 10% of all newborn and which constitutes more than 50% of the neonatal mortality in Italy. We aimed to evaluate the use of the NNSIN data for retrospective area-based studies on the example of the Lazio Regional Network UTIN online (NICU online), whose data have been analyzed to obtain a ten years mortality trend from 2007 to 2016 among neonates of 23-28 weeks of GA.

METHODS

We conducted a retrospective analysis on 2,181 neonates born at 23 to 28 weeks of gestational age in Lazio Region between 2007 and 2016, recorded on the UTIN online Network. Statistical Analysis was performed: maternal and neonatal characteristics have been analyzed over time windows of four years. The chi-square test has been used for statistical significance. Multiple logistic regression models were conducted to compare mortality and maternal and neonatal risk factors.

RESULTS

The study shows an increase in neonates with less than 25 weeks of GA and a significant reduction in transferred patients. An increase in maternal age and the number of women from developing countries have also been observed, as a significant reduction in intubation at birth. The overall mortality rate was 33.3% with a reduction in mortality rate in the birth weight group of 750-1,000 g and the GA group of 25-26 weeks. The logistic regression models show the highest mortality at lowest GA and in the group of neonates who did not receive antenatal steroids.

CONCLUSION

There has been a significant increase in assisted neonates with less than 25 weeks of GA. Maternal age, gender, maternal country of origin and twin pregnancies were not found to be mortality risk factors, while lower gestational age and the lack of antenatal steroids still represent mortality risk factor.

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LECT 71

ANTIBIOTIC PROPHYLAXIS IN THE NEONATE?

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Infections are still a major cause of morbidity and mortality in the neonatal period worldwide, especially in preterm infants. Although antimicrobial prophylaxis plays an important role in reducing infection, it exposes neonates to the risk of adverse effects related to antibiotic use, besides altering the gut microbiota development. Therefore, the use of prophylactic antibiotics should be carefully evaluated. In daily clinical practice, clinicians are likely to start antibiotic prophylaxis in the presence of risk factors for early-onset sepsis (EOS), in neonates with a central catheter in place, and in case of surgery. The main risk factors for EOS are well known, including maternal group B streptococcal (GBS) colonization, chorioamnionitis, maternal urinary tract infection, and prolonged rupture of the membranes. However, the lack of agreement among current guidelines does not help physicians, and identifying healthy-appearing neonates with a high likelihood of EOS who require antimicrobial agents soon after birth is still a challenge for the neonatologist. In 2010, revised guidelines from the Centers for Disease Control and Prevention (CDC) recommended that well-appearing neonates of any gestational age whose mother received adequate and inadequate intrapartum GBS prophylaxis should not receive antibiotics, while well-appearing neonates born to mothers with clinical signs of chorioamnionitis should undergo diagnostic evaluation and receive antibiotics pending culture results. However, in the last few years, some doubts have raised about the appropriateness of antibiotic prophylaxis in asymptomatic late-preterm and term neonates born to mothers with chorioamnionitis, because of the extremely low risk of EOS in this group of infants. Polin et al., in a commentary published in 2015, emphasized that it is time to abandon the policy of treating well appearing late-preterm and

term neonates because of chorioamnionitis alone. Certainly, there is a need for strong and unique recommendations for management of neonates at risk for EOS, in order to avoid unnecessary antibiotic therapies and standardize behaviors among physicians. Anyhow, it is crucial that antibiotic prophylaxis, when started, is discontinued after 48, maximum 72 hours when the neonate is well appearing and blood culture negative. As for the use of antibiotic prophylaxis in neonates with a central catheter in place, most of the authors agree that this practice should be avoided because insufficient evidence from randomized controlled trials exists to date to support or refuse the use of prophylactic antibiotics when a central catheter is inserted in a neonate. Finally, antimicrobial prophylaxis plays an essential role in case of surgery to prevent surgical site infection (SSI) and/or a bloodstream infection after surgery. Very few studies of surgical antibiotic prophylaxis have been conducted in the neonatal population, and specific guidelines about perioperative prophylaxis in the neonate are not available. Neonates are at high risk for SSI due to various factors: immunodeficiency, co-morbidities, prematurity, prolonged hospitalization in the Neonatal Intensive Care Unit (NICU) before surgery, colonization by multidrug-resistant organisms. Therefore, in the absence of specific guidelines, we believe that antimicrobial choice should take into account the above and may undergo changes based on the type of surgery, type of neonate, and pathogens circulating in the NICU. The optimal time for administration of preoperative doses is within 60 min before surgical incision. Additional intraoperative doses are needed to ensure adequate serum and tissue concentrations of the antimicrobial if the duration of the procedure exceeds two half-lives of the drug, or there is excessive blood loss during the procedure. New recommendations for a shortened postoperative course of antimicrobials involving a single dose or continuation for less than 24 hours are provided. Recent studies have demonstrated that non adherence to CDC "12 Step Campaign to Prevent Antimicrobial Resistance" in NICU was mainly due to prolonged (> 48 hours) postsurgical antibiotics. This attitude demonstrates that physicians are more concerned about the risk of SSIs than the risks related to an excessive or inappropriate antibiotic use. Further studies are needed to draw up appropriate recommendations for neonatal surgery.

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LECT 72

ETHICAL ISSUES AND NEONATAL RESUSCITATION

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The neonatal intervention in the delivery room is needed to verify the normal adaptation of the newborn infants to extrauterine life. In a small number of cases, neonatologist is essential to ensure survival as in the case of infants with a very low gestational age, with severe neonatal asphyxia or with severe congenital anomalies. In these cases, neonatologists are often faced with the ethical issues of deciding who is to be resuscitated and who is not. Severe prematurity affects less than 2% of all births. In the case of infants with severe prematurity, the current practice tends to refer to the detailed national or international recommendations or, less likely, to individual institutions guidelines. It is now clear that infants with gestational age < 22 weeks are not resuscitated in the absence of a spontaneous heartbeat due to the absence of adequate respiratory structures. For these newborns, a palliative intervention is recommended to relieve the pain of the newborn and to give psychological support to the family. Major problems are posed by the birth of newborns with gestational age of 23 weeks for which resuscitation is mandatory in the presence of vital signs (heart rate, breathing, and spontaneous movements), verifying its effectiveness already in the delivery room or in the neonatal intensive care unit to decide the continuation or withdrawal of intensive care. No doubt about the need to resuscitate prematures with gestational age > 24 weeks [1, 2]. Full-term newborns with severe asphyxia must be resuscitated in any case; the recent postnatal intensive care techniques (hypothermia)

can guarantee a favorable outcome even in case of severe prolonged asphyxia. The resuscitation of full-term neonates that have an Apgar score of 0 at 10 minutes since the beginning of resuscitation is more problematic. Many guidelines define within 10 minutes the time needed to cease resuscitation in the absence of vital signs (heart rate) despite maximal cardio-respiratory and pharmacological interventions. Indeed, recent data suggest that a good percentage of these newborns can survive without major disabilities or minor handicaps, especially after intensive resuscitation and postnatal treatment (hypothermia). In particular, it is reported that the percentage of disability of infants in which intensive care was continued over 10 minutes is similar to that accepted for severely preterm infants. Hence the question is: why not continues resuscitation if you can get results that are defined as acceptable for other categories of babies? I think it could be argued that preterm birth is itself at high risk of long-term disability and that it is less easy to accept that a full-term newborn, free from severe congenital abnormalities, may have long-term disabilities. In any case, even the most conservative recommendations suggest continuing resuscitation until it does not appear beneficial for the neonate (which is mostly impossible in the delivery room) [3, 4]. The decision to resuscitate newborn infants with severe congenital anomalies is still problematic. For these newborns, in fact, there is the need to define in the best way the possibility of life or the possibility of autonomous life. For malformations incompatible with life, often with prenatal diagnosis, the neonatologist, after extensive discussion before birth with the family, must only implement palliative care for newborns in respect of the human and religious beliefs of the family. In case of anomalies not easy to identify or not certain, the neonatologist has the duty to resuscitate the newborn infant. Any decision must be postponed when the diagnosis was made. The new diagnostic technologies (Rapid Whole Genome Sequencing and Precision Neonatology) will certainly help the neonatologist in the intensive care unit and, in the future, also in the delivery room [5]. Who has lived and lives with the complex problems of resuscitation in the delivery room knows that the neonatologist is often only with himself, his professionalism and his ethical and religious belief. It is fine to remember F. Barrington's words about newborns preterm: "decisions regarding appropriate resuscitation and treatment of the ELBW infant should neither be the triumph of hope over reason nor the victory of ego over uncertainty".

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LECT 73

NUTRITIONAL PROBLEMS IN SURGICAL INFANTS: WHICH IS THE GOAL?

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The most common diagnoses requiring intra-abdominal surgery during the neonatal period are esophageal atresia (EA), diaphragmatic hernia (CDH), volvulus with malrotation, intestinal atresia, megacolon and anorectal malformations. Both preterm and at term infants can be affected, and usually, the surgical intervention takes place in the first days of life. In the whole of these cases, the parenteral nutrition (PN) can offer the right liquids and nutrients intake in order to sustain the critical period of growth and aide the surgical wound repair. Postoperative infants had PN initiated immediately. As soon as possible, when the intestinal canalization is reached, the enteral nutrition (EN) can be started, firstly combined with PN, through bolus or continuous administration regarding the intestinal tolerance. Once EN is tolerated, the overall caloric intake from EN is calculated, and the difference between total caloric needs and those provided with EN is supplemented with PN. The aim of re-feeding is not also nutritional, but trophic for the bowel mucosa in order to avoid the leak of nutrients and bacterial translocation. The first choice for re-feeding is the fresh mother's milk. Secondly, the Donate Human Milk or hydrolyzed milk can be utilized. The hydrolyzed formula can

be implemented mainly in case of re-feeding of necrotizing enterocolitis (NEC) operated preterm newborns or in case of alimentation through a jejune-duodenal stoma. The raise of daily intake of milk has to be modulated depending on the intestinal tolerance. Usually, the right option for preterms is 10-20 ml/kg/d, and also the fortification of milk can take place in these situations when the total intakes reach the 80 ml/kg/d. Finally, it has to be start and promote breastfeeding as soon as possible, which is the most important objective to gain. During the re-feeding the appropriate weight gain is accounted for 15-20 g/kg/die for infants 24-36 weeks and for infants 36-40 weeks is 8-10 g/kg/die. Looking for more details, any disease has specific nutritional barriers. In the case of surgical intervention for NEC, the enteral feeding is started after 14 days. However, the advancement strategy allows for individualization as needed based on defined patient intolerance parameters. In the case of a diaphragmatic hernia, milk is delayed until recanalization is reached, that takes time because of typical cardio-respiratory difficulties, which affects these newborns. The major nutritional problems are related to newborns affected by gastroschisis. Enteral feeding practices for infants with gastroschisis are highly variable, and there are few published guidelines. In the case of "surgical" NEC or intestinal atresia or malrotation or megacolon or anorectal malformations, an entero or colon stoma is created. When the stoma is "functional", the newborns can be re-fed. Mucous fistula re-feeding is commenced if no stricture is identified. An Fr8 infant feeding tube is inserted into the mucous fistula and secured to the skin using adhesive tape. Proximal enterostomy effluent is collected every 4 h and subsequently infused continuously into the mucous fistula using a syringe pump. The infusion rate is gradually stepped up until it matched the total proximal stoma output. When patients reach reasonable body size with good bowel opening per rectum, closure of enterostomy is arranged. The mucous fistula re-feeding is safe and can decrease the risk of anastomotic complication and parenteral nutrition-related cholestasis. The position of the stoma and subsequently the residual length of bowel influence the absorption capacity and then the weaning of PN. To evaluate the continuation of PN, it is important to take into account the weight gain and the number of intake losses (tolerated until 1/3 of enteral intake). The re-feeding is a good option to accelerate the weaning of PN and to reduce the consequences linked with this, such as PN-associated liver dysfunction (PNALD) or central line-associated bloodstream infections (CLABSIs). In case of extended intestinal resection or short bowel syndrome (SBS) (extended NEC or necrotic bowel followed volvulus), EN is integrated to PN for a long period. The prognosis after intestinal resection depends upon the extent of resection, the function of the residual intestinal mucosa and the intestinal motility. The intestinal insufficiency linked to SBS is characterized by malabsorption of all nutrients, gastric hypersecretion, pancreatic insufficiency, leak of water and electrolytes, hyperoxaluria, biliary lithiasis, hepatopathy, and osteopathy. In these cases, it appears essential the use of human milk which has trophic factors such as epidermal growth factor, or hydrolyzed formula in order to help the intestinal adaptation and the restore of intestinal function and precocious weaning of PN with a low risk of PNALD.

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LECT 74

SYSTEMIC THROMBOEMBOLISM AND CEREBRAL SINOVENOUS THROMBOSIS IN NEONATAL AGE

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Thromboembolism is increasingly considered and diagnosed in hospitalized newborns and children [1]; neonates are at highest risk of thromboembolic events (TEs), especially those with critically ill conditions [2, 3]. Data from neonatal TEs are needed in order for clinicians to develop appropriate management guidelines as well as prevention strategies; indeed, despite a significant advancement in diagnosis and treatment of neonatal TEs, randomized-controlled trials are not available, and most current recommendations are still extrapolated by adult studies or are based on case series and data from registries [4]. The Italian Registry of Pediatric Thrombosis (Registro Italiano Trombosi Infantili [RITI]), a national prospective registry, was established by a multidisciplinary network of Italian investigators in 2008 through a secure web database (http://www.trombosinfantili.it), with the aims of improving knowledge about neonatal and pediatric TEs in Italy and providing preliminary sources of data for the development of specific clinical trials and diagnostic-therapeutic protocols. Following a pilot enrolment performed only by members of the founding team, the Registry was then launched in March 2010. In 2017, a new web platform (REDCAP) with a new database was created in order to improve the quality of recordable data; therefore, the phase of reintegration of old patients in the new registry and at the same time the insertion of new enrolled cases has begun on September 2017. The number of total TEs in the Registry is over 900. We present preliminary data analysis on neonatal systemic venous and arterial TEs (75 cases), and cerebral sinovenous thrombosis (CSVT) (78 cases) enrolled in neonatal sections of RITI from neonatology centers between January 2007-July 2013.

NEONATAL SYSTEMIC THROMBOEMBOLIC EVENTS

Results on clinical data have been previously reported [5]. Among 75 systemic events: 55% were venous (VT), 29% arterial (AT) and 16% intracardiac thrombosis (ICT); males represented 65% and 71% were preterm. In 25% TEs was clinically diagnosed on the first day of life and 10/19 "early onset" TEs were clinically diagnosed at the time of delivery. In this "early onset" group, prenatal-associated RFs (maternal/placental diseases) were reported in 70% and inherited thrombophilia in 33%. Post-natal RFs were present in 73%: infections and central vascular catheters in 56% and 54% VT, respectively, and in 67% ICT vs 27% AT ($p \leq 0.05$). Treatment and outcome. Supportive therapy alone was given in 16%; in the remaining 59 cases, anticoagulant (mostly LMWH, UFH in 13%) or thrombolytic treatment (in 15 cases: 75% urokinase, 26% rt-PA) was performed. No surgical treatment was reported. Complete clot resolution was reported in 78%. Therapy-related adverse events were reported in 10%: major/relevant bleedings in 5 and heparin-induced thrombocytopenia in 1 case; all were preterm. Overall mortality rate was 15%: in 4% directly related to TE, including one rt-PA related intracranial hemorrhage. Among 52 of 64 discharged infants, outcome assessment at 12-24 months confirmed sequelae affecting the quality of life in 5 children; neither clinically significant post-thrombotic syndrome nor TE recurrence was reported at 5-10 years.

NEONATAL CEREBRAL SINOVENOUS THROMBOSIS

Among 78 neonatal CSVT male predominance was observed (64%) and most neonates were full term (73%). Multiple risk factors were present in 63%. Inherited thrombophilia was reported in 27% of tested patients (14/51). A total of 42 neonates presented early symptoms within 48 h after birth. Associated clinical conditions were: congenital heart defect (24%), maternal preeclampsia/HELLP syndrome (15%), intubation/mechanical ventilation at birth (23%), iatrogenic factors (19%), infections (18%) and resuscitation at birth (15%). RFs significantly associated with early presentation were intubation/mechanical ventilation at birth ($p = 0.03$) and infections ($p = 0.01$). Presenting symptoms consisted mainly of seizures (70%), and 41 cases needed antiepileptic therapy. Sinuses most commonly involved were the transverse and the sagittal ones; venous infarct was present in 51% and correlated with deep system involvement ($p < .001$). The diagnosis was confirmed in 90% by combined magnetic resonance imaging/venography. Treatment and outcome: anticoagulant therapy (mainly with LMWH) was performed in 41%, including 27% of those presenting intracranial hemorrhage at diagnosis. Nor hemorrhagic complications were reported neither thrombus recurrence. At discharge, neurological sequelae were present in 30% and at 6 months' follow-up in 29%. No one died due to CSVT. Predictors of poor outcome were the presence of one or more neonatal RFs and the presence of one or more generalized or focal neurological signs/symptoms at onset. Neonatal systemic and

cerebral thromboses are multifactorial diseases with a significant risk of serious adverse sequelae; randomized clinical trials are still critically needed in order to help neonatologists to manage newborns with TE efficaciously but safely.

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LECT 75

USE OF SUCROSE IN MINOR INVASIVE PROCEDURE: WHAT'S NEW?

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Infants hospitalized in the neonatal intensive care unit (NICU) are still exposed to frequent painful tissue-breaking procedures, but treatment for prevention or relief of procedural pain varies widely in practice and is generally insufficient. Untreated pain in neonates, particularly in preterm infants, during a critical time in brain development, may result in significant immediate and long-term consequences that include: changes in somatosensory processing and altered sensitivity to future painful stimuli; impaired neuro-anatomical development; and behavioral, emotional and learning disabilities. Administration of oral sucrose with or without non-nutritive sucking or other sweet solutions (e.g., glucose) before and during painful procedures are the most frequently studied interventions for relieving procedural pain in neonates. Analgesic effects persist up to one year of age, although the strength of the effect may decline in older infants. Analgesic, calming and stress-reducing effects of sucrose were firstly reported in infant rats. These effects occurred rapidly, persisted for several minutes and were blocked by systemic opioid receptor antagonists. In human infants it is hypothesized that the sweet taste of sucrose promotes the activation of endogenous opioids that attenuate nociception or processing of noxious information at the level of the dorsal horn, demonstrating strong support for the beta-endorphin release. NIRS and EEG evoked potentials, recorded after oral sucrose administration, showed that sensory cortex activation persisted after a painful stimulation, despite the use of sucrose, in small trials. However, administering sucrose before heel lancing reduced the clinical expression of pain in newborn infants (as by observational pain score) and this is the so-called "analgesic effect". A recent 2016 *Cochrane* review on "sucrose for analgesia in newborn infants undergoing painful procedures" included seventy-four studies enrolling 7,049 infants, including updates completed in 2001, 2004, 2010 and 2013 which is a substantive update of the original 1998 *Cochrane* review (Stevens 1998). The Authors conclude that sucrose is effective for reducing procedural pain from single events such as heel lance, venipuncture and intramuscular injection in both preterm and term infants (high-quality evidence). However, sucrose does not provide effective pain relief during circumcision. There is conflicting evidence for whether sucrose reduces pain for other minor painful procedures. Twenty-nine studies reported on adverse events and found that the number of minor adverse events (e.g., choking or gagging) was very low and was similar in the different groups (so not attributable to the sucrose treatment). No major adverse events were reported. Therefore oral sucrose (24%) is recommended in both term and preterm infants in almost all national and international guidelines. The optimal dose of oral sucrose has yet to be established, but a dose in the range 0.2-0.5 ml (4-10 drops) in preterm and 1-2 ml (20-40 drops) in term neonates is suggested, placed on the tongue with a syringe two minutes before the procedure. Recent studies suggest that this interval is not needed, and the interval between sucrose administration and pain relieving effect might be shorter, but these data need to be confirmed in RTCs. Other more recent (unpublished) studies focus on the effectiveness of multiple sucrose doses before and during the skin breaking procedure. Preliminary results showed the

same effectiveness of one versus two doses of sucrose during the procedure; meanwhile, previous studies demonstrated the greater effectiveness of multiple doses. Recommendations for practice include: using small volumes for painful procedure only, avoiding use for calming irritable infants, giving solutions in aliquots over the duration of the procedure for prolonged procedure, avoiding use of greater than 10 doses in 24 hours, especially during the first week of life, using other effective strategies during pain procedures and bearing in mind that the first step in preventing pain is to avoid any painful procedures that are not strictly necessary, and preferably reporting the amount of sucrose administered in g/kg body weight. Nowadays it is still not identified an optimal dose due to inconsistency in effective sucrose dosage among studies.

Further investigation of the repeated administration of sucrose in neonates is needed. There is some moderate-quality evidence that sucrose in combination with other non-pharmacological interventions such as non-nutritive sucking is more effective than sucrose alone. Further research of sucrose in combination with pharmacological interventions and of sucrose use in extremely preterm, unstable, ventilated neonates and to determine the minimally effective dose of sucrose during a single painful procedure and the effect of repeated sucrose administration on immediate (pain intensity) and long-term (neurodevelopmental) outcomes are in future needed.

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LECT 76

CARDIOVASCULAR ABNORMALITIES IN BRONCHOPULMONARY DYSPLASIA (BPD). BPD IS NOT A MATTER OF PULMONARY HYPERTENSION ONLY

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Bronchopulmonary dysplasia (BPD) is one of the most common and significant complications associated with preterm birth. Pulmonary circulation is primarily involved, and it is characterized by abnormal growth, including decreased angiogenesis, altered pattern of vascular distribution within the lung interstitium and increased vascular tone and vasoreactivity. These anomalies account for pulmonary vascular disease (PVD) in BPD. Pulmonary hypertension (PH) is a severe form of PVD. Other than PH, further cardiovascular abnormalities are found to be associated with bronchopulmonary dysplasia and to be critical for course and prognosis. Impaired left ventricle hemodynamics is a complication that is retrieved in late BPD and can have a significant impact on BPD prognosis. Both diastolic and systolic function can be compromised. Left ventricular diastolic dysfunction (LVDD) has been firstly described in severe BPD [1]. It augments ventricular filling pressure, reducing stroke volume on one side, causing pulmonary venous congestion and edema on the other. Persistent late pulmonary edema due to LVDD often requires aggressive diuretic treatment, with an inadequate response; alternatively pulmonary edema worsens in response to pulmonary hypertension treatment with vasodilators. Post-capillary pulmonary hypertension develops eventually. High level of suspicion is required from the clinician to avoid missing it since the clinical picture is overlapping with underlying lung disease and often referred to it. LVDD diagnosis can be difficult by echocardiography, evaluation of the left ventricular diastolic function is complex and echocardiographic findings might be subtle. A combination of different echocardiographic markers may be used. In selected cases, cardiac catheterization is required. It is a potentially treatable complication, that benefits from afterload reduction therapy, such as milrinone and captopril that may improve prognosis. Veno-occlusive disease in subjects with a normal pulmonary venous connection has a strong association with preterm birth, up to 61% according to Drossner [2], having

BPD as a significant associated medical condition. Moreover, the incidence of pulmonary venous stenosis (PVS) in BPD patients with PH is high, up to one-third according to recent studies [3], mainly involving left pulmonary veins. Pathogenesis of PVS in preterm infants with BPD is not clear; however, published data would support the notion that it is an acquired condition. As with LVDD, it causes pulmonary venous congestion and edema in patients with three or more affected veins, resulting in PH; otherwise, it can cause the overflow to unaffected lobes with no contribution to PH. PVS is often a progressive disease and outcome appears to be quite poor, despite surgical or transcatheter techniques. Cardiac shunts are significantly associated with BPD, mainly atrial septal defect, patent ductus arteriosus and systemic to pulmonary collateral vessels; with PVS they account for up to 65% of BPD patients with PH [3]. Large left to right shunts aggravate pulmonary edema; however even small shunts can affect pulmonary hemodynamics. Pulmonary vascular bed in BPD patients is reduced; therefore small or moderate shunts can correspond to relatively high shunts and have a more significant impact than expected by shunt entity. Shunt lesions should be evaluated for closure in BPD patients, especially in severely ill infants where contribution to pulmonary edema and decreased compliance might be significant. Intrapulmonary shunts have also been described. Galambos et al. provided histological evidence of intrapulmonary arteriovenous anastomotic vessels (IAAV) in the lungs of infants with severe BPD, that bridges pulmonary arteries and veins, similarly to those found in late gestation fetus [4]. They hypothesized persistence or expansion of these vessels after premature birth providing the anatomic basis for intrapulmonary shunt and hypoxemia in neonates with severe bronchopulmonary dysplasia. Diagnosis remains histological and clinical contribution can only be presumed. Other cardiovascular abnormalities associated with BPD include left ventricle hypertrophy and systemic hypertension. Pathophysiology is poorly understood. Some advocate a possible association with high catecholamine levels or significant renal vascular or urinary tract disease. According to consensus recommendations for the care of children with BPD-PH as developed by the Pediatric Pulmonary Hypertension Network, complete echocardiograms should be routinely performed in preterm infants meeting clinical criteria for BPD at 36 weeks' PMA and with a continued need for significant respiratory support at any age [5]. Outpatient echocardiographic follow-up should follow, in order to possibly establish a prompt diagnosis and treatment.

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LECT 77

NEUROPROTECTION IN ADDITION TO HYPOTHERMIA

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Hypoxic ischemic encephalopathy (HIE) is a severe disease involving grey and white substance of the brain. It is generally caused by perinatal hypoxic ischemia and has an incidence of 2-3/1,000 live births. It is estimated that 700,000 affected children and more than 1,000,000 every year, respectively die or develop neonatal encephalopathy after perinatal ischemia. Despite the improvement in obstetric practice, the incidence of HIE has not changed in recent years, and HIE is still the second cause of neurodisability worldwide with enormous social and economic repercussions. The term neonatal encephalopathy refers to an impairment of neurological functions of the newborn that manifests itself with several symptoms including difficulty in starting or maintaining respiration, depression of tone and reflexes, alteration of the state of consciousness, poor feeding and seizures. Hypothermia, currently, is the only approved therapy to reduce mortality and improve survival without disability in cases of moderate or severe

HIE. However, only 1 in 6 newborns benefits from therapeutic hypothermia. For this reason, it is essential to find new therapeutic strategies to be used in combination with hypothermia. For this purpose, we must consider the complexity of the pathophysiology of the HIE that offers many chances for therapeutic interventions. The pathophysiology of the HIE includes several phases. The first one is that of the hypoxic-ischemic insult with the primary death of some neuronal cells depending on the severity of the insult and the energy failure with the decrease of ATP. The loss of cell homeostasis causes excessive calcium entry that activates the excitatory neurotransmitters and triggers a neurotoxic cascade with increased nitric oxide production and drastic reduction of endogenous antioxidants. After this acute phase, there is the latest one, which begins about half an hour after the acute ischemic insult and lasts up to 6-24 hours. It is commonly believed that the therapeutic window is only during this period. In the secondary phase, we observe energy failure again. This secondary phase starts between 6 and 24 hours and lasts for days and is characterized by cytotoxic edema, because of the release of cytotoxic neurotransmitters and free radicals with the depletion of ATP reserves. The third phase is characterized by inflammation and epigenetic changes that lead to an impairment of the proliferation, migration, and differentiation of neuronal cells and interfere with synaptogenesis. Based on these different phases of neuronal damage (acute, subacute and repair), there are many studies in progress about the efficacy of different neuroprotection strategies to be combined to therapeutic hypothermia in HIE patients. For this purpose, magnetic resonance spectroscopy was often used to evaluate the effects of some neuroprotective drugs. Melatonin, a neuroendocrine molecule produced for the regulation of the sleep-wake cycle, has essential anti-oxidant, anti-apoptotic, anti-inflammatory actions and promotes the development of neuronal and glial cells. Melatonin acts in the acute phase of encephalopathy. Some studies showed that, in combination with therapeutic hypothermia, melatonin improves survival and 6-month neurobehavioral outcome. Magnesium sulfate binds to the magnesium site of the glutamate channel; therefore, different trials are ongoing to demonstrate the efficacy of magnesium sulfate in reducing mortality and improving damage-free survival when administered in the acute phase. Recent studies are evaluating whether topiramate administered with hypothermia improves the outcome of newborns with HIE compared to those receiving only hypothermia. The neuroprotective effect of topiramate occurs in the subacute phase and more specifically in the secondary phase. Clinical trials are ongoing to prove the efficacy of erythropoietin (Epo) in association with hypothermia in improving outcome. Epo has an anti-oxidative, anti-apoptotic and anti-inflammatory effect; however, the leading role is in the repair phase, participating in the proliferation and differentiation of neuronal, glial and endothelial cells. Stem cells would act in the same repair phase (tertiary phase). Currently, the pathophysiology and timing of some endogenous neuroprotection and neuroregeneration mechanisms are not fully understood. Increasing these endogenous responses has shown a neuroprotective effect in preclinical studies. In the future, infants with HIE may be treated with a combination of tailored therapies with appropriate doses and timing.

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LECT 78

STRATEGIES FOR STIMULATION OF ORAL FEEDING CAPACITY IN PRETERM

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BACKGROUND

World Health Organization defines preterm or premature infants born before the 37th weeks of gestational age. ELBW (extremely low birth weight) babies belong to a category of premature whose birth weight is below 1,000 grams. The infant's feeding capacity is directly proportional and closely linked to the ability to coordinate sucking, swallowing and breathing. Premature dysphagia is defined as the set of problems related to the development of suction/

swallowing coordination and its maturation, related to the maintenance of the stability of respiratory and cardiac function. The highly specialized nursing care, in the neonatal intensive care unit, can favor, through the positive sensory experiences, the achievement of complete autonomy in oral feeding. Aim: to identify and analyze through a literature review, the best strategies for achieving autonomy in oral feeding, in order to reduce hospitalization length.

MATERIALS AND METHODS

Research of scientific articles in the main databases, such as Pubmed, Cinahl and Cochrane Library. Through the use of some search strings, whose main keywords were "preterm infants", "dysphagia" and "non-nutritive suction" and setting the presence of full text and the date of publication not prior to five years, about 40 articles were found; after abstract reading, the actual number of articles examined was reduced to 20.

RESULTS

Correct and early stimulation of the newborn, can favor complete autonomy in oral feeding. In the literature, the strategies identified and analyzed were the following: non-nutritive suction, usable immediately, even in the lowest gestational age, promotes the coordination of sucking and swallowing; sensory stimulation, which involves tasting the milk, massaging the cheeks and proposing familiar perfumes to the newborn; motor rehabilitation of the muscles of the face and of the oral cavity, (which, after the negative stimuli received during the hospitalization due to endotracheal tube, nasogastric tube, aspirations, patches applied and removed, need relaxation to overcome more easily the problems that prevent the babies to achieve the exclusive oral feeding); early attachment of the newborn to the breast, which favors the reflection of rooting and the protrusion of the tongue to lick the nipple. The analyzed studies report suggestive data also on the reduction of length of stay which, on average, seems to decrease by 4 days and about the exclusive oral feeding that is achieved with an average time of 15 days lower than in the newborns in the control groups on which the strategies mentioned above have not been performed.

CONCLUSIONS

It is clear that the nurse, through high-quality care levels, can put in place these positive strategies towards the newborn, to ensure a better evolutionary development and a more rapid transition from SOG feeding to the exclusive oral diet. The benefits of these practices also affect the time of hospitalization, which is reduced because the skills acquired with greater speed by the newborn, allow a more rapid discharge.

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LECT 79

EARLY, PROTECTED AND ASSISTED NEONATAL HOSPITAL DISCHARGE

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The length of hospital stay of the mother and her newborn after delivery has been discussed for a long time in the last few years. The average length of hospital stay of the mother-infant dyad after delivery declined from '70s until '90s. The early newborn discharge was implemented in the '90s. Early discharge is still a controversial topic, especially for the possible newborn readmission, due to the appearance of other possible diseases that cannot be assessed during hospitalization and that might influence the newborn's state. According to the literature, early discharge occurs when the length of hospital stay is lower than that defined for the diagnosis-related group (DRG). The major risk is new readmission. Currently, in Italy, many neonatal centers discharge healthy newborns between 48 and 72 hours after birth. This kind of discharge must be "appropriate" regarding mother and newborn health status; the presence of social and relational risk factors and their management; care opportunities on the territorial services. It also must be "agreed" with the parents. Early discharge (< 48 hours) should be limited to selected situations. For newborns discharged before 48 hours after birth,

an appointment should be made for the infants, to be examined within 48 hours of discharge, to assess infant general health, weight, hydration, degree of jaundice, review feeding patterns and technique, encourage and support breastfeeding, perform metabolic screenings, according to state regulations. Protected hospital discharge is a process that accompanies the patient and the family from the hospital to home. It should be a personalized process, planned together by the hospital and territorial professionals, which includes social and health assistance, aimed at satisfying further health and autonomy needs of the patient and family. In Italy, the problem was managed at the regional level, with differences in timing and organization. Some regions defined the protected discharge as the continuation of the hospital-residential path, through the planning of interventions and the predisposition of medical-assistance supports. Protected discharge is the activity performed in the ambulatories of the hospital. It is aimed at ensuring continuity of care for people discharged from the ward, who no longer require hospitalization but who require care and controls, to complete the diagnostic-therapeutic procedures. The protected discharge of the mother and her newborn should provide home care support in the puerperium and preferential access to the hospital services for the family and the pediatrician if new diagnostic tests are necessary. As indicated by the AAP, the hospital stay of the mother and her healthy term newborn should be extended enough to allow the identification of neonatal diseases, often related to the transition from intra to extrauterine environment (e.g., cardiopulmonary problems, jaundice, congenital heart disease, etc.) and significant maternal complications; to ensure that the mother is sufficiently recovered and prepared to care for herself and her newborn. The length of hospital stay should be based on maternal health, health and stability of the newborn, ability and confidence of the mother to care for the newborn, adequacy of support systems at home and access to appropriate follow-up care in a medical home. The newborn and the mother should be simultaneous discharged, after considering the input from the obstetrical care provider, nursing staff and social services. The specific criteria that should be met to ensure discharge and appropriate follow-up of a healthy term newborn are indicated in **Tab. 1**. The final document delivered to the newborn's discharge represents an essential source of continuing health care and it should contain all the information relating to pregnancy, childbirth (screening, instrumental and laboratory tests carried out), as well as any pharmacological indications, useful to the family pediatrician and other territorial services, of which should be provided their telephone numbers. The family pediatrician is the leading healthcare provider after discharge. The pediatrician's assignment should take place before the baby is discharged, so that the infant's first visit can be scheduled, with him, within 4-5 days of discharge. If this is not possible, the infant's first visit should take place in the hospital outpatient setting or a territorial service. If family, environmental and social risk factors are present (maternal or parental use of illicit substances, child abuse, mental illnesses, homelessness, history of domestic violence, adolescent mother, barriers to adequate follow-up care, lack of social support, etc.) discharge should be delayed until they are resolved, or a plan to safeguard the newborn is

Table 1 (LECT 79). Criteria to meet before discharge of a term newborn.

Physiologic stability of the newborn: • normal physical examination and clinical course; • infant's vital signs within normal range and stable for the 12 hours before discharge, such as: axillary temperature, respiratory rate, heart rate, pulse oximetry screening for congenital heart defects; • the infant has urinated regularly and passed at least 1 stool spontaneously; • the infant has completed at least two successful feedings and is able to coordinate sucking, swallowing and breathing while feeding; • clinical significance of jaundice, if present before discharge and appropriate management and/or follow-up plans; • adequate evaluation of infection diseases of mother and newborn; • review of mother and newborn laboratory tests for blood type and direct Coombs test; • administration of the first dose of Hepatitis B vaccine, if necessary; • newborn metabolic, hearing and eye screening tests and possible repetition during the follow-up visit.
Parents adequate training and information about the skills to provide newborn care at home, especially regarding: • importance and benefits of breastfeeding; • appropriate urination and stooling frequency for the newborn; • umbilical cord, skin and newborn genital care; • recognition of clinical signs of illness, particularly jaundice; • infant safety, such as use of an appropriate car seat, correct position for sleeping, safe home environment.
Availability of social support and access to health system and resources.

in place (adequate family care support can be guaranteed, involving the social services).

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LECT 80

NEONATAL PAROXYSMAL MOTOR PHENOMENA: FROM SEMIOLOGY TO CLINICAL DIAGNOSIS

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INTRODUCTION

Paroxysmal motor phenomena occurring in the neonate may represent a wide range of medical diagnoses ranging from benign transient events to severe genetic or metabolic neurological disorders. Clinical clues to early diagnosis are important to address efficiently and timely further diagnostic workup. The first diagnostic step is to observe and characterize spontaneous and paroxysmal motor activity. A further step is to search for triggers of paroxysmal events as well as for inhibitory factors. It is also essential to evaluate the relationship between neonatal behavioral states.

NEONATAL PAROXYSMAL MOTOR PHENOMENA: THE DIFFERENTIAL DIAGNOSIS

The differential diagnosis includes four main diagnostic groups. First, paroxysmal events may represent abnormal control of spontaneous motor activity as in pathological general movements or brainstem release phenomena. Ferrari, Cioni, and Prechtl [1] categorized spontaneous motor activity based on observation of the so-called General Movements. They defined their quality as normal when variable in intensity, speed, and strength; motor activity is normal when organized in complex sequences lasting seconds to minutes involving all parts of the body, with gradual onset and end. By contrast, abnormal spontaneous motor activity has a poor repertoire, may be chaotic with sudden onset of big movements in a chaotic sequence or cramped synchronized. Thus, abnormal general movements can mimic epileptic phenomena. Second, epileptic seizures occurring in the neonatal period often do not have typical clinical manifestations, due to immature brain circuits. Thus, the differential diagnosis with other paroxysmal motor events may be challenging and often require video-EEG polygraphic recordings [2]. This technique is not necessary for all the paroxysmal motor events of the neonate but is mandatory to diagnose epileptic seizures and to monitor the efficacy of treatment. Third, paroxysmal motor phenomena may be part of genetic neurological syndromes with onset in the neonatal period as a movement disorder with or without associated epileptic seizures or epileptic encephalopathy. It is important for example to distinguish benign infantile kinesigenic dystonia that is a paraphysiological phenomenon from dystonia as the prevalent phenotype of a neurological syndrome. Finally, in the neonatal period, the central nervous system immaturity may allow to paroxysmal, benign and self-limited motor phenomena, which can occur in neurologically normal infants as well as in those with perinatal brain damage, these are the focus of the following paragraphs.

FOCUS ON PAROXYSMAL BENIGN NON-EPILEPTIC MOTOR PHENOMENA

The most frequent neonatal paroxysmal non-epileptic motor phenomena are the neonatal benign myoclonus, tremors, tonic reflex episodes and benign paroxysmal dystonia; the Sandifer syndrome is a subtype of tonic reflex episodes. Tremor is defined as an involuntary rhythmic movement of equal amplitude and frequency on a fixed axis. It can be localized to hand or feet or be more diffuse. Restraint can interrupt tremor. The onset is in the first hours of life and spontaneously disappears within the first months. Tremor can occur in healthy neonates or in mild hypoxic-ischemic encephalopathy, in preterm babies or in electrolyte imbalance. It is a feature also of abstinence syndrome. Benign neonatal myoclonus typically occurs in normal neonates often with the family history of the same disorder. Repetitive myoclonus occurs during quiet sleep, disappearing at awakening characterize the episodes. Benzodiazepines exacerbate tremor because they favor quiet sleep. The onset is usually

around the end of the first week of life and disappears before six months, the development is normal, and the EEG is normal, even if it is not necessary to perform the EEG in the typical cases. Tonic reflex episodes consist of diffuse tonic contraction with the extension of the four arms. The episode can cause apnea and cyanosis. It is the equivalent of an extreme Moro reflex with sudden onset and 3 to 10 seconds duration. Episodes occur only in a vertical position in the awake state and are favored by shaking; the EEG is normal and helps to differentiate these episodes from tonic seizures. The Sandifer syndrome is a subtype of tonic episodes characterized by paroxysmal lateral deviation of the head and trunk associated with gastroesophageal reflux. It can occur in healthy infants or in cerebral palsy. An important differential diagnosis is hyperekplexia, characterized by a sustained startle response with generalized hypertonia involving respiratory muscles. Episodes occur only in the awake state and are elicited by tactile stimulation typically of the face, without habituation. The flexion of the legs on the trunk can stop the episode and save from this life-threatening condition. Hyperekplexia was in the past classified as a neonatal paroxysmal non-epileptic motor phenomenon. However, it is now recognized that is a genetic disorder of inhibitory glycine-mediated circuits (GLRA1 gene Cr 5q33.1 SCL6A5 Cr 11p15.2) and is more appropriately classified in the metabolic movement disorders.

CONCLUSIONS

Paroxysmal benign non-epileptic motor phenomena frequently occur in the neonatal period. They can be distinguished from other less benign disorders by the identification of specific triggers and the possibility of inhibition by specific maneuvers. They generally occur only in a specific behavioral state, depending on the subtype. It is important to ask parents specifically for triggers or inhibition since they will not often report on them; during the neurological examination, it is also possible to verify triggers. The electroencephalogram is normal by definition and is an important diagnostic tool when the differential diagnosis is unclear on clinical grounds. Surface polymyographic recordings help the characterization of the movement. It is essential to recognize timely these disorders for reassuring and counseling families as well as to avoid unnecessary diagnostic load.

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LECT 81

REIKI AND HEALTH: THE MEETING BETWEEN AN ANCIENT ORIENTAL DISCIPLINE AND SCIENCE

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INTRODUCTION

Reiki is a natural healing method that consists of transmitting energy to the person through contact or proximity of the hands of a Reiki operator. Reiki is not yet scientifically demonstrable, but has brought and brings many benefits and, above all, has no side effects or toxicity. Intelligent energy can be transmitted to anyone by anyone who is a Reiki operator. The aim is to illustrate Reiki, focusing attention on how it can be used within healthcare facilities, exploiting its multiple benefits both on the patients and on the operators.

METHODS

I have therefore analyzed the applications of Reiki in the health sector, comparing different realities and examining the benefits and the actual applicability of this technique in the health field, mainly in the hospital.

RESULTS

Reiki can be used practically in the treatment of all known diseases and disorders, bringing benefits ranging from the simple relaxation of the recipient to the reduction of edema and swelling to the normalization of arterial blood pressure. Generalizing, Reiki brings well-being and balance to everything that is channeled, accelerating all the psychic, spiritual, emotional and material evolutionary processes. Reiki is indicated for adults, the elderly, but also for newborns and children. The primary applications are seen in oncology, algology, but also in surgery and neonatology. In Italy, projects have been carried out on the use of Reiki in the hospitals of Turin (Oncology, Neonatology), Milan (for the treatment of migraine), Asti (Oncology), Vicenza (treatment of drug addiction), Naples (Oncology), Cefalù (Oncology, Obstetrics and Gynecology), Lido di Camaiore (Oncology), Florence (treatment of HPV infection). Moreover,

the use of Reiki is very interesting in the treatment of the burnout syndrome of the professional.

CONCLUSIONS

Reiki has a high potential in the health field because it is practicable by lay personnel; it is applicable in all areas, on newborns, children, adults and the elderly; the technique is standardized; no specialized equipment is required. Reiki is easy to learn and is within everyone's reach; there are no side effects; it can be applied on itself and can be taught to the patients to continue the treatments independently at home.

LECT 82

PREDICTIVE ROLE OF URINARY METABOLIC PROFILE FOR ABNORMAL MAGNETIC RESONANCE IMAGING SCORE IN PRETERM NEONATES

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BACKGROUND

The metabolomics technique provides the quantitative analysis of an impressive amount of low molecular weight metabolites that are intermediates or final products of all the metabolic pathways in living organisms. Metabolomics can be applied to all biological fluids and the obtained profiles are the result of the interaction between gene expression and the environment. This technique can be used to identify human diseases based on the variations in the metabolic profile [1]. Metabolomics analytical techniques are the nuclear magnetic resonance (NMR) spectroscopy or the mass spectrometry (MS). Both allow the analysis of biological fluids or tissues and the extraction of latent metabolic information such as metabolic spectra, to enable the identification of biomarkers of human diseases [1, 2]. Applications of metabolomics in the field of neonatology are very promising. Studies on intra-uterine growth retardation, prematurity, bronchiolitis, cytomegalovirus infection, diabetes, sepsis and inborn errors of metabolism showed important results and pave the way for future research [3-5]. Although all biological fluids can be used for metabolomics analysis, urine is particularly suited in the neonatal population due to its non-invasive method of collection and large availability. In the present study we aimed to evaluate the urinary metabolic profile at 2 and 10 days after birth in preterm neonates with and without severe magnetic resonance imaging (MRI) abnormalities at term equivalent age.

MATERIALS AND METHODS

Thirty preterm infants with a GA < 28 weeks were consecutively enrolled, and urine samples were collected at 2 and 10 days after birth and analyzed using proton magnetic resonance spectroscopy (^{1}H-NMR). A 3T MRI was performed at TEA and images were scored for white matter (WM), cortical grey matter (cGM), deep GM (dGM) and cerebellar abnormalities, using the Kidokoro MRI score. Infants were divided into two groups: one with normal MRI or mild abnormalities and one with moderately to severely abnormal MRI score. Receiver-operating characteristic (ROC) curves analyses were performed to distinguish infants with moderately/severely abnormal MRI score.

RESULTS

The principal component analysis (PCA) did not show significant clustering between normal/mild abnormal MRI score and moderate/severe MRI abnormalities for all regions (cGM, WM, dGM, and cerebellum) at both time points, 2 days and at 10 days after birth. The ROC curves distinguished neonates at both 2 and 10 days after birth who later developed a markedly less mature cGM score from the others (2 d: AUC 0.72, specificity [SP] 65%, sensitivity [SE] 75% and 10 d: AUC 0.80, SP 78%, SE 80%) and moderately to severely abnormal WM score (2 d: AUC 0.71, SP 80%, SE 72% and 10 d: AUC 0.69, SP 64%, SE 89%).

CONCLUSIONS

^{1}H-NMR urinary spectra of extremely preterm infants at 2 and 10 d were able to discriminate between different metabolic profiles in patients with moderately to severely abnormal cGM score and WM scores at TEA. Further research on urine spectra as promising for the early identification of neonates at high risk of brain damage will probably allow understanding the multifactorial pathogenesis of altered neonatal brain development better.

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LECT 83

PARENTERAL NUTRITION IN PRETERM NEONATE

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In the last decades, there has been a significant increase in the survival rate of preterm infants, especially very low birth-weight (VLBW, < 1,500 g) neonates. The nutritional problems of preterm babies have become particularly relevant, as numerous studies underlined the importance of early feeding on short- and long-term development. Many pieces of evidence suggested that nutrition in early life may influence long-term growth and neurodevelopment. The vast majority of infants born at a gestational age lower than 29 weeks do not achieve the median birth weight of the reference fetus at theoretical term or 40 weeks postmenstrual age (PMA). At discharge the estimates of growth failure range from 30 to 67%. Prevention of extra uterine growth restriction (EUGR) by optimizing early nutrition of neonates is still a challenge for neonatologists. During the early adaptive period of life (from birth to approximately day 7), hemodynamic instability associated with immaturity of the gastrointestinal tract limit the use of enteral nutrition [1, 2]. Parenteral nutrition represents the primary route of administration of nutrients in this period. Recent guidelines for parenteral nutrition recommend an increased caloric and protein intake for preterm neonates, similar to that received by the fetus during intrauterine life in order to improve growth and avoid EUGR [3]. According with current recommendations premature infant should receive up to 90-120 Kcal/kg/die with about 3 g/kg/die of amino acids, 12-14 g/kg/die of carbohydrates, 3-4 g/kg/die of lipids and adequate amounts of electrolytes, minerals, trace elements and vitamins, since the first hours of life (**Tab. 1**) [3]. The implementation of current parenteral nutrition (PN) recommendations is still scarce. Some recent surveys observed high variability in PN composition, supply, and administration, in the healthcare organization and the quality assurance. A "good standard of care" was only observed in 24% of cases with frequent delay in recognizing the need for PN (28%), delay in the administration of PN (17%), inadequate intakes for needs (37%), inadequate monitoring (19%), and few multi-disciplinary nutritional team. This aspect could be due to a non-optimal evidence quality that supported many aspects of nutritional recommendations. Available evidence suggests a positive effect of the implementation of nutritional guidelines on early postnatal growth, but not on long-term growth and neurodevelopment. However, many aspects remain to be clarified, including possible immediate side effects and long-term adverse effects on neurodevelopment. Further, well designed, studies are advocated to evaluate and possibly improve effects of implementation of recent nutritional guidelines in the current clinical practice. Possible area of future research in preterm nutrition may be summarized in four issues: 1) the evaluation of

Table 1 (LECT 83). Nutritional intakes for a very low birth weight neonate.

	Starting dose	Target dose
Amino acids, g/kg/day	2	3
Glucose, g/kg/day	6	12-14
Lipids, g/kg/day	1	3-4
Energy, kcal/kg/day	40-60	90-120
Water, mL/kg/day	80-100	110-170
Sodium, mmol/kg/day	0-1	3-5
Potassium, mmol/kg/day	0-1	2-3
Chloride, mmol/kg/day	0-1	3-5
Calcium, mmol/kg/day	0.6-1	1.6-2.5
Phosphorus, mmol/kg/day	0.6-1	1.6-2.5
Magnesium, mmol/kg/day	0.1-0.2	0.3-0.4

the metabolic complications associated with high protein and energy intakes; 2) the study of long-term neurologic effects of early high intakes; 3) the study of the relation between macronutrients intake and micronutrients metabolism [4, 5]; 4) the study of the efficacy and safety of individualized compared with standardized parenteral nutrition solution.

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LECT 84

CARE IN LOW-INCOME COUNTRIES

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The term "care" refers to all kind of cares that address the premature babies. Their goal is to minimize the stress to which they are subjected, acting at different levels: improving the environment (reducing visual and auditory stimulation), reducing painful stimulation, favoring periods of sleep, reducing periods of destabilization and ensuring early contact with the mother in order to ensure adequate neuro-behavioral development. It is therefore clear that in high-resource countries, care is a technique applied in the neonatal intensive care unit especially for premature infants. Neonatal mortality accounts for the 46% of the under-five year's mortality and the low-resource countries are those most affected by the problem, in which the care of the newborn child after birth is still scarcely widespread. The primary causes of neonatal mortality are prematurity, asphyxia at birth and infections. The attention to the newborn and the application of the principles of perinatal/essential newborn care (safe delivery, delayed umbilical cord clamping, skin to skin, thermoregulation, early nutrition, infection prevention, kangaroo, data collection, etc.) and comprehensive newborn care are the WHO' strategies for the reduction of neonatal mortality in the world; however, they are still poorly known and developed in many contexts. The care is sometimes the only tool that allows a quality treatment to the small premature and the mother in low-income countries lacking scarce human and technological resources and infrastructures (roads, water, electricity, transports). In contexts where oxygen and electricity are non-existent, it is impossible to use modern technologies while we know that the care leads to a lower need for oxygen, less duration of mechanical ventilation, less number of apnea crises, periods shorter parenteral nutrition, better behavioral organization, shorter duration of hospitalization, faster acquisition of neuro-evolving stages, better maternal relationship and competence, contributing to higher survival of premature and premature mild neonates. Kangaroo is a low-cost, high-impact method in many low-resource countries. Therefore, the care in low-income countries could be identified as a method to: take on all healthy and pathological infants as individuals at any gestational age and weight, to reduce neonatal mortality and to provide individualized care that follows evolutionary stages of the newborn according to the developmental care approach in every context. Our evidence is based on practical experiences such as International Cooperation Projects between the Tuscany Region and three Hospitals in Uganda and Kenya since 2005 in collaboration with Ngo Doctors with Africa Cuamm.

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LECT 85

MIGRANTS AND EMERGING INFECTIOUS DISEASES

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In the last year, more than a million refugees and migrants cross European borders [1]. In Italy, the number of foreign citizens residing has doubled in the last ten years representing 8.3% of the resident population [2]. As a result of these movements, there has been increasing attention to the potential health impact of migration across Europe. Despite the common perception of an association between migration and the importation of infectious diseases, there is no systematic association [3]. Migrants often come from countries affected by war or economic crisis where public health systems are weak or disrupted and undertake long journeys that increase their risks for diseases that include communicable diseases. Communicable diseases such as tuberculosis (TB), measles, rubella or vector-borne diseases like malaria have been for a long time very common in Europe, but their burden has been significantly reduced because of better hygienic conditions, valid health systems and vaccines and antibiotics availability. TB and other communicable diseases have not, however, been eliminated and still exist in Europe, regardless of migration. Moreover, there is little evidence that newly imported and rare pathogens are spreading. Late last year, the European Center for Disease Prevention and Control (ECDC) estimates that the risk of outbreaks of emerging pathogens due to migration is "extremely low" [1]. TB is still the single leading cause of death from infectious disease worldwide, with more than 10.4 million incident cases and 1.3 million deaths in 2016 alone. Between 2015 and 2016, there was a 4.6% decline in TB incidence in Europe, one of the faster trends in reduction among all WHO regions. The incidence in the migrant population is variable, but it appears to be, in all European countries, up to 20 times higher than in the native population. Migrants' risk of being infected or developing TB depends on the TB incidence in their country of origin and on factors related to socio-economic conditions in the host country [4]. As for Italy, 4,032 TB cases were notified in 2016, with an estimated rate of 6.6 per 100,000 inhabitants, in reduction compared to the last ten years. Italian Ministry of Health also indicates that the percentage of new TB cases referring to foreign citizens has exceeded that of natives, going from 47% in 2006 to 56% in 2016. When these cases are put in relation to the increase of the foreign population in Italy – which has more than doubled in the last ten years – a decrease in the occurrence of TB (with frequencies more than halved: from 84.1 cases for 100,000 foreign residents in 2006 to 44.5 per 100,000 in 2016) is noted. This data confirms that the risk of illness is also falling in this population group, but it is also true that the difference in terms of relative risk between foreigners and Italians continues to be high (RR = 6.7) [2]. TB is not easily transmissible, and active disease occurs in only a proportion of those infected (from 10% lifetime risk to 10% per year in HIV-positive people) and is not often transmitted from migrants to the resident population because of limited contact [1]. In recent years there has also been a slow but progressive increase in resistance to antituberculosis drugs. The recent epidemiological picture of TB in Europe and Italy shows an increase in the number of multidrug-resistant (MDR)-TB cases, in particular among people from Eastern Europe. In Italy, according to the data reported in the ECDC report, in 2015 the percentage of MDR-TB cases was 2.7% [5]. Today malaria is endemic in large areas of Asia, Africa, Latin and Central America, the Caribbean islands, and Oceania, with about 500 million sufferers every year. In addition to being endemic in many areas of the planet, malaria is increasingly imported even in areas where it has been eradicated [6]. The European Region was the first in the world to achieve interruption of indigenous malaria transmission, but imported malaria remains a public health concern. Travelers, foreign workers, and migrants represent the main sources of imported malaria, as seen by the recent resurgence of malaria in Greece that was directly linked to an influx of migrants from Pakistan. Pregnant women are particularly at risk. Non-immune pregnant women risk acute and severe clinical diseases, with consequences of up to 60% of fetal losses and over 10% of maternal deaths. Semi-immune pregnant women risk severe anemia

and compromised fetal growth, even if they do not show symptoms of severe illness. About 10,000 of these women and 200,000 of their newborns die each year following malaria infection during pregnancy [6]. The transmission of infectious diseases is influenced by the socioeconomic conditions of a population as well as by the state of public health of a nation. Maintaining efficient infection prevention and control facilities is an essential element to prevent the emergence or re-emergence of infectious diseases.

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LECT 86

EVALUATION OF EFFICACY OF GLUCOSE GEL VS. GLUCOSE SOLUTION USED FOR PAIN RELIEF IN NEWBORN BABIES. A RANDOMIZED BLIND CLINICAL TRIAL

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INTRODUCTION

In neonatal wards, newborn babies undergo diagnostic procedures that may cause pain in the infants. As a result of systematic research of the literature, we found references regarding the administration of glucose solution analgesia but not the use of glucose gel analgesia. In our research, we tested a glucose gel 10% compared to a glucose solution 10%.

MATERIALS AND METHODS

A randomized blind clinical trial of glucose gel (test case) vs. glucose solution (control) was conducted in a neonatal ward using the following steps: 1) selection of newborn babies according to criteria of inclusion/exclusion; 2) parent informed consensus; 3) preparation of glucose gel; 4) administration of the gel during the painful procedure; 5) disclosure of the data using the NIPS scale; 6) comparison between the two groups (solution vs. gel).

RESULTS

Sample size

- 20 vs. 20 newborn babies;
- number of procedures 63 vs. 63.

Descriptive analysis

- *Gel*: age (average/trend/median/SD: 39.15; 39; 39; 1.38).
- *Solution*: (average/trend/median/SD: 39.5; 39; 39; 1.23).

Research results

T Test: age T test (α 0.01) t critical a t 2 code 2.9 P (T<=t) two (presence/absence codes 0.50 comparable 99% CI) (comparable groups).

Risk measurement: procedural pain:

- experimental group (gel) (presence/absence): Yes: 10, No: 8;
- control group (solution): Yes: 55, No: 8;

RR 0.18 (95% CI: 0.10-0.32); Chi square 99%.

Equal evaluation with other studies: NIPS < 3 vs. ≥ 3:

- (gel): with pain ≥ 3: 0; with pain < 3: 63;
- (solution): pain ≥ 3: 15; with pain < 3: 48;

RR 0.000 95% CI; RRR -1.000 (95% CI: 0-0).

LECT 87

PERSISTENT PULMONARY HYPERTENSION OF THE NEWBORN NOT RESPONSIVE TO NITRIC OXIDE THERAPY; TWO CASES REPORT AND REVIEW OF LITERATURE

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INTRODUCTION

Persistent pulmonary hypertension (PPHN) is characterized by sustained elevation of pulmonary vascular resistance (PVR) and often related to low systemic vascular resistance (SVR). PPHN is estimated to occur in 2/1,000 of the live-born term, while in preterm babies with precocious distress syndrome it may also reach 2/100. PPHN may be idiopathic, due to intrauterine pulmonary vascular remodeling, or secondary to delayed or impaired relaxation of the pulmonary vasculature, associated with many neonatal pathologies. The diagnosis of PPHN is based on clinical evidence of labile hypoxemia and confirmed by echocardiography showing indirect signs of high pulmonary pressure and often right ventricular dysfunction.

CASE REPORTS

E.O. was born after a pregnancy complicated by cervical cerclage, pPROM and 1 course of betamethasone. Born at 29.1 weeks of gestational age from spontaneous labor, birth weight (BW) 1,360 g after a vigorous crying soon developed cardiopulmonary depression. Ventilated with a positive pressure, led to neonatal intensive care unit (NICU) and initiated with high-frequency oscillatory ventilation (HFOV). For the worsening of the respiratory pattern, surfactant was administered, and ventilation parameters were increased. She developed hypotension, hypoalbuminemia, and coagulopathy, so inotropic therapy was started, and albumin and fresh frozen plasma were infused. At 10 hours after the diagnosis of atrioventricular canal defect and pulmonary hypertension, nitric oxide (iNO) was started at 20 ppm, increased to 40 ppm, with a partial response. At 48 hours persistence of pulmonary hypertension and worsening of oxygenation index (OI) so milrinone associated to noradrenaline was introduced. Early improvement of saturation allowed a gradual iNO reduction. Milrinone was discontinued after 96 hours and mechanical ventilation after further 48 hours. Non-invasive ventilation was maintained for 4 weeks, chronic lung disease (CLD) was treated with spironolactone-hydrochlorothiazide. She was discharged at 37 weeks with a weight of 2,290 g.

H.F. was born at 27.6 weeks of gestational age from urgent cesarean section for reversal umbilical arterial end diastolic flow and IUGR in an ICSI pregnancy. A complete cycle of betamethasone was performed. BW was 572 g. At birth, he was ventilated and transferred into the NICU in nasal CPAP. He soon presented increasing respiratory distress that needed surfactant administration and HFOV support, after lungs recruitment. Dobutamine was started for hypotension. At 18 hours a diagnosis of PPHN was performed, ventilation parameters were increased, and iNO was started from 5 ppm to 20 ppm with inotropic drugs for hypotension. After an initial response, due to a new worsening of the OI milrinone was added to therapy, with a fast response and gradual iNO suspension. Extubation after dexamethasone course was reached in 23 days. Non-invasive ventilation was continued until 38 weeks, CLD was treated with furosemide plus aldactazide and a second cycle of dexamethasone. As a consequence of persistent elevated pulmonary pressure associated with right superior pulmonary vein stenosis, sildenafil therapy was attempted, with a poor response. Thus, at 5 months of age, a transcatheter dilation was performed.

CONCLUSIONS

General management principles for the newborn with PPHN include maintenance of normal temperature, electrolytes, glucose, and intravascular volume, improvement of systemic hemodynamics and cardiotonic therapy, in order to enhance cardiac output and systemic O_2 transport. Gentle ventilation strategies with an optimal PEEP, relatively low peak inflation pressure or tidal volume, and a degree of permissive hypercapnia are recommended as the first action, but then HFOV is frequently necessary to optimize lung inflation and minimize lung injury. HFOV with early surfactant administration and optimal oxygenation improves iNO therapy. Hypotension treatment with inotropic agents is set to improve heart function. If the response to iNO is not satisfactory, milrinone may be associated: it inhibits phosphodiesterase 3 (PDE3), increases cAMP levels in arterial smooth muscle cells and cardiac myocytes and relaxes pulmonary arteries, improving oxygenation and heart dysfunction. Sildenafil inhibits PDE5 and increases cGMP levels in pulmonary arterial smooth muscle cells, inducing pulmonary vasodilation too. Both are generally well tolerated, but they can induce hypotension. Prostaglandin E1 (epoprostenol) and non-specific endothelin-1 receptor blocker (bosentan) act on pulmonary endothelium, but they are less used in preterm babies for a higher risk of a ventilation-perfusion mismatch, of pain and variable gut absorption. ECMO is an option when these measures fail. Despite the treatment modality, PPHN is a disease with significant long-term morbidity, with neurodevelopmental impairment in 14-30% of the cases at 18-24 months and with the frequent need of post-discharge therapies, home oxygen, and enteral nutrition support, worsening the quality of life and long-term outcome of these preterm babies furthermore.

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LECT 88

RESPIRATORY PHENOTYPES IN NEONATAL CHRONIC LUNG DISEASE: WHAT IS BEHIND THE OXYGEN REQUIREMENT?

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The bronchopulmonary dysplasia (BPD) is the most frequent lung morbidity diagnosed among survivors of preterm infants. BPD is a multifactorial disease, which takes its origin from an impaired alveolar-capillary maturation both during the fetal and neonatal life. One of the main problems in BPD is the inadequacy of the current definitions, for their inability of capturing the severity and the different clinical phenotypes of the disease itself. Actual definitions take into account the patient oxygen requirements and the respiratory support at specific time points only, that is BPD is a disease which is defined oddly by its treatment rather than its pathophysiology. The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) held a workshop on BPD in October 2016. The expert panel underlined the need for better phenotypic characterization of infants with BPD [1]. Recognizing the spectrum of respiratory phenotypes associated with individuals born preterm can, first of all, provide comprehensive and personalized care to these individuals before the BPD itself has been established. Second, it can help to modulate adverse respiratory outcomes in later life. Determining the potential phenotypes in patients with BPD will pave the way for better therapeutic strategies, modify disease progression, and/or improve the hospital course. Some respiratory phenotypes are often described in the literature. The alveolar disease component of BPD may clinically manifest as gas exchange abnormalities, including hypoxemia and hypercarbia. The airway component of BPD (obstructive lung disease), which clinically can manifest similar to asthma, is a common presentation among infants and children with a history of prematurity [2]. Lung function abnormalities as assessed by pulmonary function testing are not part of the current criteria to diagnose BPD, likely reflecting pulmonary function testing is not routinely available in all neonatal intensive care units. The American Thoracic Society critically reviewed the available techniques for ventilated and spontaneously breathing infants and children in the ICU [3]. The possibility to use functional tests to characterize the determinants of BPD would allow better insight into the pathophysiology of the disease. In 2015 Greenough and Pahuja published an update on functional characterization of BPD [4]. In this work, they reported the results of several studies, concerning the mechanical properties of the respiratory system, with the aim of predicting BPD development. They conclude that, up to that date, it was not possible to conclude whether assessment of lung mechanics is helpful in predicting BPD development. The discrepancy in the results likely reflects that different techniques were used in different populations. Almost all the studies in the literature focus on the possibility to predict BPD development and on the long-term respiratory outcome after BDP is well established. Few studies are focused on the initial phase of the disease with the specific aim of driving the therapeutic choice in term of ventilator strategy or pharmacological therapies. Shepherd et al. [5] used infant pulmonary function testing to reveal distinct phenotypes in patients with established severe BPD during the initial NICU stay. They demonstrated that there are 3 distinct phenotypes in patients who are diagnosed with severe BPD: obstructive, restrictive, and mixed. This fascinating work once again was conducted at the median postmenstrual age of 52 weeks, once the disease was well established. The authors underline that different phenotypes may require different therapeutic approaches, highlighting the necessity of characterizing this population in the early phase of the disease. To overcome these limitations, we have tried to define a diagnostic algorithm to encompass the entire scope of clinical signs and symptoms, to evaluate response to treatment and personalize patient therapy. We have used the forced oscillation technique, that has been recently integrated into a mechanical ventilator available at the bedside, for the study of mechanically ventilated patients and patients receiving non-invasive ventilation. Very preliminary results have shown the possibility to define respiratory phenotypes during the acute phase of the disease, well before the chronic lung disease has been established. The possibility to derive information about the mechanical properties of the respiratory system and its compartments

(airways, lungs, chest wall) from the relationship between the driving pressure and the resulting flow (the forced oscillation technique) could allow to better objectivize the respiratory impairment, to follow its evolution over time and to monitor the efficacy of the different therapeutic strategies. At last, remembering the impaired alveolar-capillary maturation origin of BPD, we cannot neglect the vascular component that is becoming an increasingly recognized disease phenotype among preterm infants.

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LECT 89

THE PARENTAL OPEN VISITATION POLICY IN NEONATAL INTENSIVE CARE UNIT AS HUMANIZATION OF CARE MODEL

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From the very beginning, in Italy, the neonatal intensive care unit (NICU) has been an isolated ward for the safety of the newborns' health, characterized by insufficient access to the parental visits. Assuring proper isolation was not only part of the measures of surveillance made to avoid the infectious diseases spreading within the NICU, but it was also aimed to avoid any parental discussions and/or interference with the diagnostic and therapeutic decisions taken by the caregivers, to avoid the raising of parental anxiety and, last, to respect the right of privacy. In the twentieth century, in Italy, the mother-baby separation soon after birth has become a regular hospital rule. However, this practice appears to be in contrast to what the human history teaches regarding the chance of survival that, for newborns, depends on the close and continuous mother-baby contact. From a scientific point of view, the reasons for limiting NICU parental visitation are not evidence-based. The family-centered care is a recently introduced practice aimed to favor parental, namely mother and father, presence and participation in care at NICU that has now been proven to offer multiple advantages for both baby and parents. In the past few years, also in Italy, we are assisting to a change because of the increasing number of NICU starting the practice of open visitation for parents, even if with still a significant difference compared to the level already reached in other countries. As a matter of fact, this is a practice not yet completely extended to our national territory, as parental visitation policy varies between neonatal units, and the mother-baby close contact is still too often limited to a few hours per day, mostly in occasion of the lactation schedule program. Several sources in literature have reported that family-centered care in NICU is associated with decreased parent anxiety and stress as it improves parental knowledge in their baby care. Becoming themselves active partners in collaborating with their baby caregivers, parents learn to trust more the NICU staff.

Moreover, it favors the kangaroo mother care or skin-to-skin technique used especially in the care of the preterm baby for the many positive effects on the body temperature and metabolism, the cardio-respiratory stability and the neurologic development. A fundamental aspect of the open visitation policy is that it favors the breastfeeding on-demand, which allows optimal milk production from the mammary glands, so important for both beginning and maintaining lactation. Failures in the breastfeeding of preterm and ill infants are often due to the too long time of maternal separation. Parental open visitation policy in NICU is in agreement with 1) the Convention of the Rights of the Child proclaimed by the United Nations in 1991, which states: "the family should be afforded the necessary protection and assistance, so that it can fully assume its responsibilities"; 2) the *European Charter of Children's Rights in the Hospital* that affirms:

"Children in the hospital shall have the right to have their parents or parent substitute with them at all times"; 3) the Italian *Carta dei Diritti del Bambino nato prematuro* that at the Art. 4 states: "the preterm has the rights of immediate and continuous contact with the family… as for that the preterm infant should always be supported by the active presence of the parent"; 4) the Italian Ministry of Health that has a document on "*Promoting breastfeeding and parental open visitation policy in the NICU*" where it recommends the NICU directors to allow open parental visitation for 24 hours/day, in order to reduce anxiety and to favor breastfeeding.

CONCLUSIONS

The transition of NICU from "close" to "open" parental visitation policy is both scientifically and rights evidence-based. Considering the multiple positive outcomes, both in short and long terms, NICUs should always be open at best benefit for babies and their families. This transition also implies that our NICU will move from being an "intensive critical care units" to rather a place for the "intensive care of critically ill newborns" where besides professional skills also exist great supportive relationships for humanization of the care.

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LECT 90

PHARMACOKINETICS IN THE NEONATAL PERIOD

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A reasonable goal of pediatric dosing is to ensure levels of drug exposure comparable to those achievable in adults and which approximate those for which the efficacy of the drug has been established. Therefore it will be of clinical relevance to ascertain the dosages that produce an equivalent amount of drug exposure compared to that observed in adults. Drug therapy, prescription, and dosing studies should consider the differences between neonates, infants, and young children, children, and adolescents regarding drug disposition. Changes associated with age in many physiological functions have often been implicated in altered drug absorption, metabolism, distribution and excretion, and hence in drug response, and safety in neonates compared to adults. The kinetic parameters change with development; therefore the pharmacokinetics must be studied to optimize drug therapy. The covariate analysis is an important tool for translating information from the newborn population into the single newborn, who needs individualized drug therapy. The covariates are specific characteristics that partly explain the inter-individual and intra-individual PK/PD variability. The variability related to maturation is further exacerbated by the characteristics of the interfering disease or by the treatment modalities. In critically ill neonatal patients, multiple drug therapies for acute and chronic conditions are often administered simultaneously, thus promoting the risk of adverse drug reactions or drug-drug interactions. Further pharmacokinetic studies are needed to ensure that the recommended dose for pharmacological treatment in the neonate is based on evidence. Innovative analytical techniques such as the use of dried blood spots, population pharmacokinetic analyses, and sparse sampling can help maximize efficacy and safety.

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LECT 91

ORAL FEEDING: A TEAMWORK FOR THE PRETERM

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INTRODUCTION

Successful nipple feeding by breast and/or bottle without major cardiorespiratory compromise maintaining optimal growth standards should be one of the NICU goals for discharge. However, that is not so easy to improve. Low birth weight infants are often at high risk for developing feeding disorders. The ability of infants to breast- or bottle-feed safely and competently is not routinely a concern for the majority of mothers. Unfortunately, 25-45% of normally developing infants/children and up to 80% of developmentally delayed infants/children, e.g., those born prematurely, do experience oral feeding difficulties. Being born preterm presents numerous challenges for the baby including neurodevelopmental immaturity, physiologic instability, and behavioral state disorganization. Oral feeding readiness can be defined both in terms of readiness to initiate oral feedings and readiness for any particular oral feeding event. The development of oral feeding skills is a complex process and requires an efficient interaction of well-coordinated sucking, swallowing and breathing patterns. Only preterm infants > 32 weeks of GA are neurologically capable of producing a rhythmic suck-swallow-breathe pattern and physiologically ready to increase their oral feeding skills.

STRATEGIES TO IMPROVE ORAL FEEDING IN PRETERM INFANTS

Achieving full oral feeding early in preterm infants can shorten hospitalization time, reduce hospital costs, and enable more significant interaction between the mother and child. Strategies such as non-nutritive sucking using a pacifier, sensorimotor stimulation, and actively pacing suck-feed, have been used to facilitate suck-swallow function and have been reported to be effective in reducing the time to reach full oral feeding in preterm infants. Sucking on a pacifier (non-nutritive sucking) during gavage feeding may encourage the development of sucking behavior and improve digestive functions on of the feeding. Tight integration of the behavioral state with sucking, swallowing and respiration is considered one of the most organized behaviors of the preterm neonate. Tube dependency is a potential, unintended side-effect of enteral nutrition support and can appear as early as one week after starting enteral nutrition support. It is characterized by an active disinterest in oral feeding skills or natural eating habits. It may occur in combination with frequent vomiting, hypersensitivity to oral stimuli, and/or other behavioral issues. So it is necessary that the oral stimulation is not standardized but is carefully evaluated. However, feeding is not only necessary for the preterm to growth and go home, but is one of the earliest, recurrent opportunities for development of the mother-infant relationship. So the mother contribute is critical to achieving a successful feeding. Correlated strategies for preterm infants during feeding include initiation of feeding based on the infant readiness, regulation of milk flow to support the infant's sucking and breathing rhythms, and minimization of infant stimulation during feeding. Infant feeding, by its nature, is an interactive, developmental task. Current research in preterm infant feeding shows that the infant's ability to feed well is closely related to the caregiver's ability to understand and sensitively respond to his physiology and behavioral communications. While breastfeeding is by far the superior means of feeding, the vast majority of infants in American newborn intensive care units are fed by bottle. Human milk is the optimal nutrition for both term and preterm infants, but only a few preterm infants are discharged by breastfeeding. Initiation of lactation is impaired, and the duration is shortened in mothers of preterm infants compared to those of term infants. Mothers of hospitalized infants reported that the maintenance of lactation was especially difficult. Mothers may need "more guidance or support" to assure sufficient human milk from the beginning until discharge. Maintaining breastfeeding during the hospitalization is important to promote the bonding between mother and preterm infants, especially when the preterm baby is able to suck without problems. The kangaroo mother care represents a very important moment to promote the passage to the nipple in a safe way.

CONCLUSION

The delay in acquiring feeding skills is the most frequent cause of prolonged hospitalization in the neonatal intensive care unit. Early feeding difficulties with the transition from tube feeding to oral feeding are prominent and often persist beyond discharge to home. Oral stimulation improves feeding performance, weight gain rate and reduces hospital stay in preterm infants. So it is very important to recognized and support the preterm infants during this critical phases. We must not forget the importance of breastfeeding that has been sustained day by day during the hospitalization. In the meantime, it is important to allow the preterm baby to get close to the mother's breast as soon as possible.

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LECT 92

RESVERATROL PLUS CARBOXYMETHYL-β-GLUCAN IN INFANTS WITH COMMON COLD: A RANDOMIZED DOUBLE-BLIND TRIAL

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BACKGROUND

The common cold is an acute viral disease affecting the upper airway. Human Rhinovirus (HRV) is the most common cause of common cold. The symptomatology is characterized by rhinorrhea, nasal congestion, sneezing, cough and other general symptoms [1]. Symptomatology may be more severe in infants, and this may be complicated by otitis media, bronchiolitis and pneumonia with a negative impact on the quality of life of both patients and parents [2]. No specific treatments are available for the common cold, and symptomatic treatments are not indicated for infants. Previous studies have shown that a resveratrol/carboxymethyl-β-glucan (CM-glucan) combination inhibits rhinovirus replication and expression of inflammatory mediators in nasal epithelia [3]. No studies on a population of infants were conducted.

OBJECTIVE

This study aimed to demonstrate the efficacy of common cold symptoms of the resveratrol/carboxymethyl-β-glucan solution compared with saline solution treatment in an infant population.

METHODS

Consecutive outpatient infants (0-6 months) with common cold symptoms were enrolled and randomly divided into two groups: resveratrol plus carboxymethyl-β-glucan solution or saline isotonic solution randomized treatment (3 drops in each nasal fossa, 4 times daily for 7 days). Each patient underwent clinical evaluation at enrollment, after 48 hours and after 7 and 30 days. Common cold symptoms were specifically evaluated. Nasal swabs for HRV research were also performed at the same times.

RESULTS

89 infants finished the 30 days-period study (CM-glucan: n = 43 vs placebo: n = 46). The resveratrol/carboxymethyl-β-glucan combination significantly reduces episodes of sneezing ($t = 2.47$; $p = 0.016$) and cough ($F = 2.88$; $p = 0.006$) after 7 days of treatment. 30-day relapses decreased mainly in the actively treated group without significant differences between the two groups ($X^2 = 2.508$; $p = 0.15$) probably due to the reduced sample. The nasal swab was positive at HRV in 41% of all infants at enrolment. After 7 days the originally positive nasal swabs were reduced by 65% in the actively treated group and by 50% in the control group without significant differences between the two groups ($p = 0.364$).

CONCLUSIONS

This preliminary study suggests that the solution containing resveratrol plus carboxymethyl-β-glucan might be an interesting option in the treatment of infant common cold symptoms and relapses with a positive impact on both clinical and socio-economic aspects.

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LECT 93

PROPHYLAXIS AND TREATMENT OF ACUTE BRONCHIOLITIS: STATE OF THE ART

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INTRODUCTION

Acute viral bronchiolitis is one of the leading causes of hospitalization in young infants. Usually, epidemics of this disease occur every year, mostly in the winter season. Several viruses may be implicated, including Rhinovirus, Adenovirus, Parainfluenza viruses, Metapneumovirus and others, but the most common cause remains the respiratory syncytial virus (RSV). In about 15-25% of cases mixed viral infections may be present. Although bronchiolitis is a self-limited disease, clinical manifestations may quite vary, ranging from mild respiratory symptoms to severe forms requiring intensive care treatment, including invasive mechanical ventilation. Given the heavy burden of the disease, researchers are struggling to reduce the incidence of bronchiolitis, as well as to optimize its clinical management in the hospital setting. Evidence-based guidelines for the treatment of bronchiolitis have been recently released by several international bodies [1, 2]. However, very few interventions have been discriminated as effective and safe, and much controversy and variability remain about the best management for these infants [3]. Our purpose was to summarize key information related to contemporary strategies for the prophylaxis and treatment of acute viral bronchiolitis.

THERAPEUTIC OPTIONS

Depending on the severity of the illness, an array of therapies have been attempted, e.g., bronchodilators, inhaled and systemic steroids, epinephrine, hypertonic saline, montelukast, antiviral agents (e.g., ribavirin) heliox and exogenous surfactant. However, most guidelines indicate the use of hydration and supplemental oxygen as the only beneficial treatments, as convincing data do not support other drugs. Nonetheless, respiratory support may be needed in the most severe forms, either using non-invasive or invasive ventilatory modes, including high-flow nasal cannula (HFNC), continuous positive airway pressure (CPAP), non-invasive and invasive mechanical ventilation. Interestingly, a major change in the management of bronchiolitis has been observed in the last decade, showing a marked shift from invasive to non-invasive support and a higher threshold to the admittance of bronchiolitis patients to the PICU. In a large multicenter RCT, 1,472 infants who had bronchiolitis and a need for supplemental oxygen were randomized to receive either high-flow oxygen or standard oxygen therapy. Patients treated with high-flow oxygen therapy had significantly lower rates of escalation of care than those receiving standard oxygen therapy [4]. The effect of HFNC in bronchiolitis has been tested in several other studies, suggesting HFNC may be an effective treatment for these patients, being even more comfortable than nasal CPAP. However, in a randomized study performed in 142 young infants with acute bronchiolitis, the effectiveness of HFNC was inferior to that of CPAP as the initial respiratory support, with a majority of the failures with HFNC occurring within 6 h after initiation [5]. Of note, about two-thirds of patients failing with HFNC did successfully respond to CPAP. Thus, further research is still needed to clarify the role of HFNC for successfully treating bronchiolitis and avoiding an escalation of care with more aggressive therapeutic options.

PROPHYLAXIS OF VIRAL BRONCHIOLITIS

Given the limited effectiveness of therapy, once viral bronchiolitis is established, as well as the huge costs related to its management, much research has been focusing on preventive strategies for decades. General hygienic measures, including careful hand washing and other behaviors to limit the viral infection within the hospital setting, are commonly recommended. In addition, many efforts to identify safe and effective immunoprophylactic agents have been carried out. Though, only passive immunoprophylaxis against RSV (Palivizumab) is currently available for certain high-risk patients, including infants with severe prematurity, chronic lung disease or hemodynamically significant congenital heart disease. Future options will have to provide new agents, ideally with a more extended half-life and a more favorable cost-effective profile.

CONCLUSIONS

Acute viral bronchiolitis is a common respiratory tract infection in infancy. Supportive care, including hydration and supplemental oxygen, remains the mainstay of treatment in the milder forms of this disease. Other adjuvant agents, including bronchodilators, steroids, and many others, still lack convincing evidence of effectiveness. Respiratory support and even mechanical ventilation, preferably by non-invasive modes, may be required in most severe cases. Although several international guidelines are available, a large variability of treatment practice persists among different centers. Further research is still needed to clearly define the best therapeutic practice to adopt in these patients, as well to optimize preventive measures, e.g., using active or passive immunoprophylactic strategies.

DECLARATION OF INTEREST

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NEONATES OF DIABETIC MOTHER: METABOLOMICS

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Gestational Diabetes Mellitus (GDM), as defined by the World Health Organization, is a carbohydrate intolerance resulting in hyperglycemia of variable severity with onset or first recognition during pregnancy [1]. This metabolic alteration have consequences for both mother and fetus, and the results showed by *Hyperglycemia and Adverse Pregnancy Outcomes* study of 2008, underlined the importance of findings diagnostic criteria which can recognize in time and prevent GDM, that is strongly related to increased birth weight, cord-blood serum C-peptide levels, and to several and severe health consequences [2]. Untreated women with GDM are more exposed to preeclampsia, cesarean section, early rupture of membranes (PROM) and stillbirth. Consequences of GDM for the fetus can be short-term as macrosomia or large for gestational age (LGA), neonatal hypoglycemia, respiratory distress syndrome, and long-term as Type 2 Diabetes Mellitus, childhood obesity and metabolic syndrome in adults [3]. A neonate with a birth weight above the 90th centile for gestational age is defined as LGA. The others major risk factors for LGA than GDM are maternal pre-pregnancy overweight and obesity. If the metabolic change in women with onset of GDM became early recognized, also with non-invasive technique, became preventable and it will be possible to avoid the risk due to hyperglycemia in the organism of both mothers and their child. In the seek of metabolite markers of prediagnostic gestational diabetes and other pathology which can occur during pregnancies, Graça and his research group apply metabolomics to study the metabolites compositions of amniotic fluid (AF) of a woman at second trimester of pregnancies. With the use of ^{1}H-NMR spectroscopy, the AF specimen of the 27 subjects with prediagnostic GDM showed a small increase in glucose and decreased levels of others compound, especially amino acids as glutamate, glycine, proline, serine and taurine [4]. Afterward, this study was enlarged, including a total of 198 pregnant women and this time object of the ^{1}H-NMR analysis were metabolites in plasma and urine samples. The urine of prediagnostic GDM group revealed higher levels of 3-hydroxyisovalerate and 2-hydroxyisobutyrate, associated with other metabolic changes which suggesting alterations in the metabolism of choline and nucleotide. The plasma showed a decreasing in trimethylamine oxide and betaine. Other authors instead, using ^{1}H-NMR spectroscopy and urine sample taken by pregnant women at three different time visits, had investigated only GDM with the purpose of discovering a way to early make diagnosis of GDM. What data showed in this study is the significant changes in lactose, alanine, and glycine among the visits. Another method for studying metabolites in urine of women affected by GDM was elaborated by Lorenzo et al. [5], and consisting in the optimization of a chiral GC-MS to determinate free d-amino acids ratio in human urine. For testing and validate this method were collected and analyzed urine from 20 women with GDM and 20 pregnant women as a control. Among all the amino acids found in urine a statistically significant increased level were observed only for d-Phenylalanine, found in the GDM group. The authors suggest that d-Phenylalanine could be involved in the compensation during the onset of insulin resistance, but this is just a hypothesis which needs further confirmation. Confirm are also needed

in a promising metabolomic study, which tried to predict the risk of macrosomia by the evaluation of serum profile of women in the first semester of gestational age. The study aims to found early biomarkers of fetal development, and enrolled 770 healthy and pregnant women between the 12th and 14th gestational week. The results showed that lower serum levels of phospholipids characterize macrosomia, while bilirubin increased. How the fetal metabolism change in infants born by mothers with GDM, was the topic of urinary metabolomic research. The authors supposed that infants delivered from diabetic mothers (IDM) have a different metabolism if related to metabolism of infants born to healthy mothers. The samples analyzed were urine, and the method applied ^{1}H-NMR spectroscopy. IDM had an alteration in metabolites that are involved in the biochemical pathway of the tricarboxylic acid cycle: glucose, formate, fumarate, citrate, and succinate. Using serum and not urine, but still looking for the determination of newborns metabolome of infants delivered from mothers with GDM, Dani et al. evaluated metabolic differences in the serum of 30 term IDM and 40 controls infants. IDM, in this case, showed a lower level of glucose and a higher level of pyruvate, histidine, alanine, and valine [6]. Although metabolic alterations such as hyperinsulinemia and hypoglycemia had been observed, metabolic pictures that can be considered "specific" of this pathology had never been described in neonates of diabetic mothers, and in this field, metabolomics seems to be a promising method.

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