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Lectures

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LECT 1

COMPLEMENTARY FEEDING IN PRETERM INFANTS: MYTHS AND FACTS

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Optimal nutrition in the 1,000 days between a woman's pregnancy and her child's second birthday sets the foundations for health during both childhood and adult life. The relationship between nutrition in early life and long-term outcome is particularly relevant for preterm infants. Actually, preterm birth is inevitably linked to a certain degree of anatomical and functional immaturity: this situation, in conjunction with several comorbidities, makes nutritional management of these infants quite challenging. Over the years, literature has focused on numerous aspects of preterm infants' nutrition, including nutrition following hospital discharge: however, very little attention has been paid to complementary feeding, and no specific guidelines about the introduction of solid foods in preterm infants exist at present. Even the very recent ESPGHAN guidelines for complementary feeding, published in the *Journal of Paediatric Gastroenterology and Nutrition* at the beginning of this year, are aimed explicitly at "healthy term infants in Europe", and do not provide any specific recommendation for preterm ones [1]. As a consequence, clinicians' attitude towards complementary feeding in preterm infants is extremely variable both within and among countries. Italian guidelines for complementary feeding have been issued in 2015 but, similarly to the European ones, no specific recommendation for preterm infants has been made [2]. Most of the available literature about this topic has been produced in the UK. Some brief advice about preterm infants was first included in a Report about complementary feeding published in 1994 by the Committee on Medical Aspects of Food and Nutrition (COMA report) [3]: the authors of this report suggested that preterm infants should be weaned to solid foods once they had reached a minimum body weight of 5 kg, and that complementary feeding should be started once the infant had acquired some developmental milestones. The suggestions made in the COMA report have been later reviewed, mostly by dieticians' working groups and by professional associations in the UK, who have identified a temporal window between 5 and 8 months of uncorrected age, rather than a minimum body weight, when weaning should be started [4]. The choice of such a window takes into account two fundamental issues: the infant's oral motor development and the acquisition of taste with the readiness for new textures. Actually, between 5 and 8 months of age, virtually all preterm infants should have acquired the developmental skills which allow the consumption of foods other than milk, such as the progressive disappearance of the protrusion reflex of the tongue, the reduction of reflexive suck in favour of lateral tongue movements, and the gradual appearance of lip seal. In addition, this time window is the optimal one in term infants for introducing new flavours and textures: even if it is not known how this sensitive period is affected by preterm birth, it is highly likely that the later preterm infants are introduced to new flavours and textures, the less likely they are to accept a wide variety of foods. The proposed time window is based on chronological rather than corrected age: actually, correcting for prematurity and following the recommendations made for healthy term infants would result, for infants born at the lowest gestational ages, in a delay in the introduction of solid foods beyond 8-10 months uncorrected age, which could impair the entire process from both a nutritional and a developmental point of view. Despite the lack of specific guidelines, there is general consensus that the introduction of complementary feeding in preterm infants should be an individualized process whose timing has to be guided more by developmental acquisitions than by nutritional issues. Nevertheless, nutritional adequacy of weaning food should also be taken into account, and high-protein, energy- and nutrient-dense solid foods should be used for this purpose.

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LECT 2

NEONATAL HYDRONEPHROSIS

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Ultrasound carried out during pregnancy generally allows us to make a timely diagnosis of dilated fetal urinary tract, which represents the most frequent congenital anomaly detected *in utero*. The different managements of this pathology reflect how difficult it is to distinguish mere physiological differences of fetal and neonatal anatomy from cases related to the decline of kidney function; this lack of certainty can lead to an inappropriate use of tests, to expensive specialist examinations or exhausting follow-ups on healthy fetuses and newborns, causing unjustified and/or excessive anxiety and fears in parents [1]. A better understanding of the natural history of Congenital Anomalies of the Kidney and the Urinary Tract (CAKUT) [2] has contributed to shift the attention from hydraulic problems of urinary flow (and the related reparation techniques for obstruction and/or reflux) to genetic and biomolecular issues which seem to have a key role in the rising and the progression of renal parenchymal disease.

MANAGEMENT OF NEWBORNS WITH PRENATAL DIAGNOSIS OF HYDRONEPHROSIS

The primary objective of first ultrasound carried out in newborn is to discriminate between two separate populations [3]: 1) the population "at risk" of showing symptoms and/or function damage: in this case it can be advisable to start prophylaxis for infectious complications and schedule invasive methods of diagnosis or a careful follow-up; 2) the "benign" population: newborns with anomalies with no clinical significance, whose only risk is to undergo inappropriate tests. In the population "at risk" there are newborns with bilateral dilation, those with high-grade unilateral dilation (anteroposterior diameter of the renal pelvis: APD > 15 mm), those whose pelvis dilation is associated to signs of dysplasia, kidney malformations (in number, shape, position and volume) or ureter dilations. In the "benign population" there are newborns with mild or medium grade unilateral dilation, without anomalies in number, shape, volume or position of kidneys, or alterations visible with ultrasound.

NEWBORNS AT RISK: WHAT IF THEY HAVE VESICOURETERAL REFLUX?

Most of the times, after the first ultrasound, newborns considered "at risk" undergo antibiotic prophylaxis and invasive diagnostic tests which start with a micturating cystourethrography (MCU) in order to determine that 15-37% of cases which, according to literature, will show vesicoureteral reflux (VUR) [5]. VUR with hypodysplasia is still the main cause of chronic renal insufficiency (CRI) during pediatric age (25.8% of cases), but there are no significant differences in the progression of the disease between patients who have been diagnosed before or after the first six months of life. In newborns with high grade VUR and dysplasia (almost all are male) surgical procedures successfully repair the ureterovesical junction but they do not allow the recovery from the related parenchymal damage nor do they stop the evolution of the nephropathy. Also, the role of antibiotic prophylaxis is largely debated today: even though there is no evidence on its effectiveness to prevent UTI, antibiotic prophylaxis has been a common practice for years in the management of patients with VUR [6]. However, it is well documented in medium- and long-term follow-ups how cases of VUR with no congenital parenchymal damage have a good prospective of spontaneous recovery in the first years after birth, without consequences on renal function, if they are treated conservatively. The great amount of new and partly unexpected findings has produced a large body of work on this topic and several suggestions about the therapeutic and diagnostic management. Nevertheless, there is no certainty as is shown by an important *Cochrane* review, which concludes that it is not clear yet if the identification and the treatment of babies with VUR have a significant positive effect on the evolution of the pathology [7]. Postnatal management of congenital hydronephrosis has to take advantage from the ultimate new findings and diagnostic strategies have to minimize the number of unnecessary tests in order to reach the main goal, which is not the identification of VUR but the prevention of parenchymal damage.

NEWBORNS AT RISK: WHAT IF THERE IS AN OBSTRUCTION?

When newborns with hydronephrosis considered as "population at risk" do not have VUR or show a tendency to an increase of dilation in the first weeks after birth, this might be a case of obstruction [8]. Unlike VUR, in obstructive uropathies ultrasounds have a key role not only for the diagnosis and the follow-up but also for the grading of the anomaly, the formulation of the prognosis and the therapeutic approach. However, the only undisputable and unequivocal definition of obstruction is "an obstacle to the urinary flow which can cause a progressive decline of kidney function if it is not treated properly". As Gordon et al. explained, we can make this retrospective evaluation only after a periodic observation of the consequences of the obstructed urinary flow [9]. The less invasive and reasonably safe approach is at first conservative but it includes strict monitoring that considers the possibility of using surgery only in case of function reduction of the obstructed kidney, avoiding all those treatments that cannot prevent, restrict or compensate renal damage.

WHAT IF THERE IS NOTHING?

Most of dilations *in utero* are of mild or medium grade (2-5% of all pregnancies), they are unilateral, they do not show anomaly in form, position or structure revealed by ultrasound. Furthermore, they are not described in the works of medical pathology or pathological anatomy and they have drawn pediatricians' attention only after the spread of obstetric ultrasound, thus becoming one of the most debated topics of perinatal diagnostics. Newborns with these mild or medium grade dilations belong to that group we called "benign population": they are healthy babies but they still fill ultrasound and pediatric urology rooms because it is believed that in the future they might develop a pathology and in the meanwhile they are exposed to exhaustive instrumental and clinical monitoring, to diagnostic examinations and to their parents' anxiety about their future. This population of babies ("ultrasound victims") has proved to be above all our suspicions: they do not have renal function alterations, they do not show obstructive pathologies, they do not have an increased incidence of VUR or predisposition to UTI, but they are the ones who have paid the highest price for our lack of knowledge of the natural history of this condition in terms of pain (invasive examinations they underwent), in terms of side effects to drugs (very long periods of antibiotic prophylaxis), in terms of radiobiological damage (due to radiological tests used) and lastly in terms of parental anxiety.

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LECT 3

WHEN A NEWBORN DIES IN NICU

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INTRODUCTION

When a baby dies in NICU, parents are usually unprepared to face this event. Also the staff that took care of the baby feels pain together with the family and frustration, because all the medical efforts failed and the parents' hope was disappointed. To answer an increasing need of specific training on this subject we organized a course in order to train the healthcare professionals to support with empathy

families experiencing a perinatal death, of whatever culture or religion. The course involved various religious leaders (Catholic, Jewish, Orthodox, Muslim and Buddhist religion), to better understand the different cultures and beliefs.

OUR EXPERIENCE

After the course, we felt the need to work on institutional guidelines to help the NICU staff being able to support the families experiencing a perinatal loss, while having a particular attention to the requirements of different cultures and religion. The grief for the loss of a baby cannot and must not be avoided but, facilitating and supporting the mourning process, we can help the families involved and reduce the consequent traumatic effects and improve the care of the family. A multidisciplinary group composed by nurses, doctors and psychologists was created to elaborate an institutional procedure of mourning's management. We aimed to give suggestions on how to assist the families in a sensitive way, at the best of our possibilities, rather than a strict protocol of "what-to-do and what-to-say", as we know that "when facing a grief, there in no firm actions' sequence". The new of baby's death should be given, by the attending staff physician in a timely and unhurried manner, and in a private area, to let them recognizing the loss and to let them collect the less traumatic memories, images and emotions. It's important to create a private space, if possible an isolated room, and stay close to the parents. Don't minimize, don't try to comfort, don't distract the attention and don't leave the parents alone: these are the indispensable behaviours to have when supporting a family experiencing a perinatal loss. Also, it is necessary to answer all parents' questions, reassuring them that everything has been done to save their baby and to relieve his suffering. If required, the nurse can involve them in the care of the newborn, washing him, wrapping him in a blanket and putting him in their arms as long as they wish. If, at first, the parents refuse to do this, it is important to propose it again in the most appropriate moments because it was proved to be very useful during the mourning processing. Every parent can greet the baby respecting his cultural and religion tradition; also, there is the possibility to let the relatives come into the Neonatal Intensive Care Unit (NICU), subject to parent's approval. If a single parent shows up, it is good to suggest him to come in with a relative or a loved person, so he will not face alone the circumstance. We introduced the "Box of Memories", which has to be given to the parents, and contains everything of their baby: the identification bracelet, socks, hat, handprints and footprints, pictures and brother's drawings and votive images the parents placed close their baby. It has proved to be important, for the mourning processing, to have tangible signs of the baby's transition in this world. It's essential to facilitate the following passages and to give accurate information about the execution of autopsy and funeral arrangements. At the end of the path and after the death of babies we cared of for months, we organized staff debriefing meetings. Finally, the parents experiencing a perinatal loss can take part in follow-up meetings organized by the NICU's psychologists (*Auto-Mutuo Aiuto*).

CONCLUSIONS

After the adoption of a common procedure to assist families experiencing a perinatal loss, the parents gave us a positive feedback of the support they received in the units when their baby died. Some of them came back later in the NICU, to thank the staff for the support they received. All the staff found positive having a common procedure to support families facing a perinatal loss. We noticed that, after the adoption of this procedure, when supporting families when a baby dies, we are more coordinated and helpful. While at the beginning the staff encountered difficulties in moving closer to the parents because of a sense of awkwardness, now all occurs with more composure and most of the times we find ourselves in a group to support the parents during the hard circumstance of their baby's death.

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LECT 4

RED REFLEX TESTING IMPLEMENTATION IN THE NURSERY: COMPARING EXPERIENCES

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INTRODUCTION

A screening eye examination is an essential part of the newborn assessment. Red Reflex testing allows detecting eye diseases such as coloboma, cataracts, glaucoma, retinoblastoma, retinal and vitreous abnormalities, systemic diseases with ocular manifestation and serious refractive disorders. The test is performed using an ophthalmoscope with a non-invasive technique, of simple and rapid execution and well tolerated by the newborn. The American Academy of Pediatrics recommends 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. Diseases identifiable with this method can lead to serious and irreversible effects on visual function and overall health of the child, 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.

MATERIALS AND METHODS

In the last months of the year 2014, under the stimulus of a non-profit organization (NPO) focused on prevention and treatment of visual disorders, a Project of care improvement was established. It aimed at the implementation of Red Reflex testing, in collaboration with the Unit of Neonatology and Neonatal Intensive Care and Ophthalmology of the Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milan, Italy. During October and November 2014, the neonatologists were instructed by ophthalmologists to Red Reflex testing through a short theoretical and practical course in various lessons addressed to all medical personnel of Neonatology and Neonatal Intensive Care Unit. At the same time, 5 ophthalmoscopes were purchased. On 12 January 2015, screening of congenital cataracts and other congenital eye abnormalities through the Red Reflex testing started. Neonatologists examined the Red Reflex in all infants before discharge from the Unit of Neonatology and Neonatal Intensive Care. In the event of a missed test screening before discharge and in doubtful cases, patients were sent to an outpatient consultation room dedicated to detecting the Red Reflex by ophthalmologists. In these cases a date was already set and indicated on the letter of discharge from the Neonatal Unit, within the first month of life. This outpatient consultation room for the Red Reflex testing was sponsored by the NPO regarding the ophthalmologists who took part.

RESULTS

In the interim from 12 January 2015 to 11 January 2016, the number of newborns discharged from the Neonatology and Neonatal Intensive Care Unit was 6,447. Of them, 5,508 were tested successfully presenting a normal Red Reflex; 337 infants showed a doubtful Red Reflex testing and therefore were sent to the outpatient consultation room dedicated to Red Reflex control; in 233 babies, Red Reflex testing was not run before discharge due to difficulties linked to the eyelid edema typical of the early days of life: these neonates were sent to the outpatient consultation room dedicated to Red Reflex control; 309 infants underwent comprehensive ophthalmologic visit during hospitalization for clinical indications and/or medical history. 60 babies were not tested by Red Reflex screening (0.9% of all newborns discharged): 16 died during hospitalization; 17 were transferred to pursue admission to another Hospital; 3 were directed to the primary care pediatrician; 24 (0.37% of the initial population) definitely were not subjected to Red Reflex screening. Five cases of lens opacities were detected: 3 cases of opacity restricted in one eye, with clear crystalline lens in the remaining scope, so not worthy of surgical indication. They are followed up in the Pediatric Ophthalmology consultation room. Two infants, instead, showed a dense cortical opacity causing amblyopia in one eye and were referred to surgery.

CONCLUSIONS

After the Red Reflex Project, which lasted a year and implemented this screening testing at the Neonatology and Neonatal Intensive Care Unit of the Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milan, Italy, although the outpatient consultation room dedicated to Red Reflex control by ophthalmologists does not exist anymore, neonatologists continue to run the test before discharge from the nursery and during subsequent clinical controls, sending in the Pediatric Ophthalmology consultation room the doubtful cases. This has enabled to identify new cases of congenital cataract deserving of prompt treatment.

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LECT 5

PAIN MANAGEMENT IN PREMATURE INFANTS. PAIN SEMIOLOGY AND ASSESSMENT. ANALGESIA FOR SKIN BREAKING PROCEDURES

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Neonatal Intensive Care Unit (NICU) professionals face the challenge of implementing developmental, supportive interventions that reduce stress and provide pain treatment, support parental presence and involvement in the care, improve brain development [1] and positively impact infants physiological and neurodevelopmental outcomes [2]. Pain management is of great importance for the infants admitted to NICUs because they require many painful procedures, which are associated with both negative short- and long-term outcomes. This is because the pain experienced occurs during a critical time of neurological maturation. The first step in controlling pain in NICU is to minimize the total number of painful iatrogenic procedures, where possible. Routine pain assessment and implementation of guidelines for pain control are basic components of developmental supportive care [3]. The Pain Study Group of the Italian Society of Neonatology (PSG from here onwards) has highlighted the importance of these aspects for a long time and developed guidelines based on evidence and clinical practice for preventing and controlling neonatal procedural pain. Also, the PSG offers training courses to Health Care Professionals throughout Italy, just like the one that is going to be provided during the XXIII National Conference of the Italian Society of Neonatology. I've been a Board member of the PSG since November 2015, when two NICU nurses were officially recognized as part of the Board. So I'll be a trainer of the above-mentioned course and I'm going to explain the part of the course that I manage. How can the premature infant express its pain if it can't verbalize it? It can communicate in other ways: it can respond with behavioral, physiological and hormonal changes (catecholamines and cortisol) to painful stimuli. Behavioural indicators of pain are posture/tone, sleep patterns, facial expressions, skin colour and crying. Physiological indicators of pain are respiration, heart rate, saturations and blood pressure. Assessing pain in infants relies mostly on observing behaviour. Regular assessment and documentation of pain with an established pain tool is a specific intervention to pain management. Several validated scoring systems exist to assess pain in neonates, even though there is no standardized or universal approach for pain management. The PSG suggests using routinely validated, reliable pain scales as PIPP (Premature Infant Pain Profile) [4], DAN (*Douleur Aiguë du Nouveau-né*) [5], EDIN (*Échelle Douleur Inconfort Nouveau-né*) [6] and NIPS (Neonatal Infant Pain Scale) [7], illustrates and offers a space where participants can practice the proposed scales. Each infant should be assessed for pain and/or stress at least every 4 hours or during each infant interaction. Each infant should be assessed for pain and/or stress during all procedures and caregiving activities. Non-pharmacologic and/or pharmacologic measures should be utilized prior to all stressful and/or painful procedures and the infant's response to pain and/or stress relieving interventions should be documented. During the course I will address effective non-pharmacological interventions in the management of pain and stress during painful procedures. They are presented below.

- Environmental changes: protecting infants from high levels of light and sound and educating staff and parents about the effects of light and noise.
- Timing: always considering medical needs, NICU professionals should choose the best time for the infant, to try to fit in with the infant's sleep pattern.
- Facilitative support:
  - swaddling and positioning: infants should be supported in comfortable positions which help to protect their behavioural organization and stability and facilitate self calming behaviors like hands to face and mouth, grasping and bracing feet;
  - skin-to-skin holding, breast milk and breastfeeding: parents should be involved in the plan for managing their infant's pain during procedures. NICU staff should support parents as soon as possible to observe their infant's behavior, to read their

baby's cues and responses and help them with supportive holding, grasping fingers, gently talking to the infant, whenever possible;

- when completing a pain assessment, healthcare professionals can gain information from the parents about any behavioural cues that their baby may be displaying. Healthcare professionals can give explanations to parents regarding the rationale for pain observations and interventions. This can be done by teaching them about cues of distress in their baby, and how they can provide developmental care. This will improve their confidence as parents and enable them to be more involved in the care and comfort of their baby;
- administration of oral sucrose is a recommended intervention to relieve procedural pain in newborns. The use of sucrose is most effective when used in combination with other non-pharmacologic therapies like non-nutritive sucking and sensorial saturation (another method of pain reduction that involves multisensorial stimulation, including tactile, gustatory, auditory and visual stimulation);
- non nutritive sucking.

These interventions should be provided on an individual basis, separately or in combination prior to, throughout, and following all caregiving interventions, so that the baby is calm and comfortable during and after the interaction [10-15]. Nursery staff should receive continuous training and guidance for the awareness of painful procedures and for pain and stress management of infants. All pain management should be individualized, monitored and reliably reassessed and adapted in order to achieve the best outcome [16].

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LECT 6

VISUAL EVOKED POTENTIALS: WHY AND WHEN PERFORM THEM

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Current recommendations of the AAP advise for an early assessment of the red reflex in neonates and during subsequent visits [1]. An abnormal red reflex is an easy and fast way to detect ocular abnormalities that span from anterior segment alterations, such as

congenital cataract, glaucoma, corneal opacities, to posterior segment disease, such as retinoblastoma and vitreoretinal abnormalities. It is important to perform the red reflection test at birth and repeat it to the third month of life; if the test is altered, the child must be examined by the paediatric ophthalmologist. Following up on an abnormal red reflex test, the paediatric ophthalmologist has the possibility to better examine the child with a slit lamp examination, indirect ophthalmoscopy, RetCam and hand-held OCT imaging. Ocular electrophysiology still plays an important role in the diagnosis of complex infantile cases. Visual evoked potentials record the electrical responses generated by the occipital cortex after visual stimulation of the visual pathways. The flash stimulus input to the retina is transmitted to the optic nerve, optic chiasm, optic tract, lateral geniculate body, optic radiation (geniculocalcarine tract), and visual cortical area, and the Visual evoked potentials waveform is recorded from the occipital region [2]. Particularly, they are used to target and quantify paediatric conditions linked to a suspicious reduction in the visual function, or in cases where anterior opacities or posterior pole abnormalities prevent the correct visualization of ocular structures, in the preoperative evaluation of surgical cases [3]. For instance, Visual evoked potentials are performed in the routine evaluation of children with congenital cataract or in cases where there are associated diseases of the vitreous, retina or optic nerve, which may affect the quality of postoperative vision. Infants with retinal disorders, including retinal detachment, are better evaluated with flash Visual evoked potentials, especially to identify eyes with a good postoperative visual prognosis. In congenital retinal dystrophies with nystagmus and poor visual function, like Leber's congenital amaurosis, flash Visual evoked potentials are fundamental in the detection of electrical activity in the visual cortex when flash ERG is not recordable [4]. Even if the Visual evoked potentials are usually performed in the office, several times general anesthesia is required. In the case of reduced Visual evoked potentials, the examination shall be repeated within 6 months. Do not forget that Visual evoked potentials are used in children affected by amblyopia to detect the real amplitude of residual visual function. In fact, several studies demonstrated that Visual evoked potentials gave better results compared to standard methods of visual acuity measurement (Teller Acuity Cards). By the way, amblyopia is due to a multitude of ocular and brain diseases, thus abating a clear relationship between the two, but making Visual evoked potentials a precious instrument to monitor the visual development of these children [5].

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LECT 7

NURSING NEONATES SUPPORTED ON ECMO: ORGANIZATIONAL FEATURES AND CARING ASPECTS

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Neonatal Extra Corporeal Membrane Oxygenation (ECMO) procedure is a challenge for nursing staff: special skills and training are necessary as to offer an appropriate quality of care. Launching a new ECMO program requires the ECMO team to receive a structured, specific training on extracorporeal techniques in order to master the procedure. Combining theoretical training and practical simulations provides a complete preparation for caregivers, as it permits to both apply extracorporeal concepts and coordinate a multidisciplinary team. The ECMO group should be continuously active and updated in order to improve the ECMO program and ensure the best assistance for the neonate supported by ECMO procedure. In September 2015, the Neonatal Intensive Care Unit in Milan launched the Neonatal Respiratory ECMO Centre, performing a training program based on these concepts.

ORGANIZATIONAL FEATURES

Performing a new ECMO program includes specialist skills and resources, ongoing training,

setting organization, protocols drafting and review. In our Neonatal Intensive Care Unit, ECMO nurses' training is based on frontal theoretical lessons and practice exercises with medical staff. The purpose is to reach the same skills for each team component. The training program is characterized by continuous training (once a month) and by practical simulations; both apply skills achieved by theoretical lessons and coordinate ECMO members in the best way possible. Setting organization has a central role: taking the best option for every team member – including nurses, neonatologists, surgeons, perfusionists – is a gut issue in order to permit optimal environmental conditions for a good staff coordination. Setting organization comprehends choice of adequate caring devices, selecting equipment disposal and, last but not least, evaluating these decisions through planned simulations. Evidence-based guidelines are indispensable for the quality of care. It is mandatory to periodically review international literature as to apply the best practice. Drawing up specific protocols and checklists leads ECMO team in both routine care and emergency procedures in order to permit the safest caring possible. Applying protocols permits their constant updating: as a matter of fact, some inadequate aspects commonly emerge when put into practice. Our nurse staff draws up an ECMO protocol based on these features, constantly reviewed as to guarantee the best quality of nursing care.

NURSING ASPECTS

Role of the NICU nurse begins before the "start-ECMO" procedure and includes setting organization and devices checking. Preparing neonate to cannulation comprehends: positioning the baby supine with head turned to the left and a roll under the shoulders, monitoring patient's vital signs, positioning central and peripheral venous and arterial lines, maintaining patent airways and pointing out any impairment as to take action quickly. Preparing medications needed for anesthesia and resuscitation, providing neonate's station with devices to start any emergency procedure is indispensable because of the critical patient's conditions and the procedure invasiveness. Special attention is needed to anticoagulant therapy management: anticoagulation is required for proceeding to cannulation and is established assessing ACT (Activated Clotting Time) value. After cannulation is performed, the neonate is connected to the circuit and supported on ECMO. Nursing care is characterised by preventing and solving complications due to the procedure, based on constant extracorporeal circuit monitoring and managing and continuous intensive care of the neonate, exposed to both disease and procedure risks. Alongside the typical nursing care of a neonate in NICU, ECMO procedure requires specific monitoring and interventions. As the first complication for patients supported by ECMO is bleeding – due to anticoagulant therapy – it is necessary a regular monitoring of every possible bleeding, such as invasive devices insertion site or surgical wound. As to prevent bleeding, it is forbidden to remove any visible cloth. Blood secretions may be observed during airways suctioning, as well as blood gastric retention, hematuria or melena. Physicians must be informed of these conditions as to take action promptly if necessary. Anticoagulation is monitored through regular blood exams (PT, PTT, D-dimer, factor X-a, ACT, platelets). It could be necessary to change heparin dosage or administer platelets, plasma, antithrombin III or other specific therapies. Cannulas insertion point dressing may be performed if there are no bleeding signs with a transparent material, which should not adhere to cannulas. Water balance is another important aspect of ECMO procedure as to minimize risks associated with fluid impairment. The neonate should have a urinary catheter as to perform water balance hourly. Passive movement of the neonate should be performed at least every two hours as to prevent skin ulcers, paying attention to any ECMO parameters change. Neonate posturing is constantly related to these parameters, because it may modify cannulas position. Managing emergency events correlated to ECMO procedure must be one of the first skill of the ECMO nurse, who should take action promptly with other ECMO members or alone, if necessary. Parents care during this difficult and critical moment is important as to maintain parents-child bond so that, when possible, it is ethically significant to involve them during their childcare.

CONCLUSION

In conclusion, neonatal ECMO is a complex procedure that requires both organizational and caring skills. Constant training and update are necessary as to perform the best assistance for the neonate.

LECT 8

NEONATAL HYPO- AND HYPERGLYCEMIA: WHAT TO KNOW, WHAT TO DO

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HYPOGLYCEMIA

There are several methods (epidemiologic, clinical, neurophysiologic and endocrine) that have been used to define hypoglycemia [1]. Therefore, we have no consensus for a specific level that defines hypoglycemia or when and how much treatment should be provided. During the first 48 hours of life, neonates' plasma glucose (PG) concentrations are lower than later in life because of hypoketotic hyperinsulinism. After the first 48 hours of life, PG does not differ to any great extent with age (> 70 mg/dL) [2]. Currently there are two main guidelines for the evaluation and management of hypoglycemia: the guidelines of the Pediatric Endocrine Society (PES) and the ones of the American Academy of Pediatrics (AAP). Both underline the importance of identifying newborns at high risk for severe hypoglycemia during the first 48 hours. For at-risk neonates without a suspected persistent hypoglycemia disorder, a "safety" fast of 6-8 hours should be considered before discharge [3-4]. After 48 hours, in patients with persistent hypoglycemia a "critical sample" should be obtained to identify the etiology of hypoglycemia. In our clinical practice, the PG cut-off value to treat asymptomatic hypoglycemia used by APP, lower than the one used by PES, with subsequent vigilance to identify persistent hypoglycemia syndromes after 48 h, might be the best compromise to prevent overscreening and overtreatment.

CONGENITAL HYPERINSULINISM

Congenital hyperinsulinism (CH) is defined by an unsuppressed detectable plasma insulin level at the time of spontaneous hypoglycemia or fasting test. Other signs of inappropriate insulin excess are: NEFA < 1.7 mM, ketonemia < 1.8 mM, hyperglycemic response to glucagon administration and high glucose demand (> 10 mg/kg/min) [5]. Currently, mutations in 11 genes that control insulin secretion have been associated with CH. Two different histological aspects of the endocrine pancreas have been identified: a diffuse form and a focal form. Patients should undergo a NGS screening for known genes causing CH. When genetic analysis is consistent with the suspicion of focal CH, patients should undergo 18 FDOPA PET/CT to look for a focal form, which is an elective indication for partial pancreatectomy [6]. Near-total pancreatectomy should be considered only in the case of unresponsive diffuse CH because this procedure is often associated with later appearance of diabetes, exocrine pancreatic failure, and does not guarantee the remission of hypoglycemia [7]. Diazoxide is considered the mainstay long-term therapy. In diazoxide-unresponsive patients, who still need i.v. glucose infusion after 5 days at a maximal dose, the second line drug is octreotide [8]. Despite diagnostic and therapeutic advances, CH remains an important cause of morbidity in children, still accounting for 26-44% of permanent intellectual disabilities and for 18-25% of epilepsy [9].

HYPERGLYCEMIA

Neonatal hyperglycemia is a frequent complication in VLBW infants during the first week of life. The most common causes include high glucose intake and stress situations. The appropriate definition is unclear. Hyperglycemia could be defined according to two different approaches: statistical (PG value of 125-150 mg/dL) and clinical (glycosuria). The incidence of hyperglycemia varies between 20% and 80% due to lack of consensus related to its definition. Current knowledge does not support the treatment of hyperglycemia when it does not lead to glycosuria. Target is maintaining blood glucose levels between 150 and 200 mg/dL [10-13]. Interventions that might be used to treat hyperglycemia in the parenterally fed VLBW/ELBW neonate include:

- reducing the rate of parenteral glucose infusion with or without early introduction of parenteral lipid;
- slow rate of advancement of parenteral nutrition;
- treating with insulin, primarily by intravenous infusion.

NEONATAL DIABETES

Neonatal/infancy onset diabetes mellitus (NDM) is a monogenic form of diabetes with onset within 6 months from birth and does not show the typical laboratory features of type 1 diabetes (negativity of antibodies and HLA associated with type 1 diabetes). Two distinct types of NDM have been recognized: transient (TNDM), with remission within 3-6 months, and permanent (PNDM) [14].

Efforts should be made to establish a molecular genetic diagnosis as early as possible. This is particularly important, since patients with *Kir6.2* and *SUR1* defects can now be effectively treated with oral sulfonylureas [15]. Continuous subcutaneous insulin infusion (CSII) is used most frequently for insulin treatment in this age group. Continuous glucose monitoring will give additional online information [16]. There are diabetes that arise after 6 months with identified mutations typical of neonatal diabetes, so the definition should perhaps focused more on genetics than on the age of onset.

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LECT 9

THE ESSENTIAL CARE LEVELS: INDICATIONS FOR THE NEWBORN

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In Italy the National Health System is universal guaranteeing free access to appropriate health services all over the country, respect of free choice and a pluralistic offer based on public or private accredited structures. All these characteristics make this system directed to all the population, with no gender, citizenship, age, income, and job discrimination. At the same time these characteristics promote the equity of the system that means not to give all to all the people but to ensure that everyone's needs are satisfied going beyond social and local differences. Current health systems show yet the differences in our society due to different social and economic conditions; for this reason it is very important to promote the goal of equity and balance of health resources in relation to health needs of different social contest. In this perspective the new Essential Care Levels (DPCM January 12th, 2017, published in the G.U. n. 65 of March 18th, 2017) represent a gold standard for all the Regions to ensure a common and better level of assistance to guarantee overall health protection. With a focus on the newborn, the health and wellbeing of children and adolescents are a priority for national and international health policies, as stated in the Minsk Declaration of October 2015, and the Italian Ministry of Health devotes a lot of attention, not only to the period of birth, but also to the actions in the first 1,000 days of life: from the conception to two years of age. In fact, believing that timely preventive interventions made in this period lead

to positive short-, medium- and long-term health outcomes, in the new Essential Care Levels we find many articles related to this period:

- Art. 24 – Social and health assistance for minors, women, couples, families which provides, among other things:
  - education and counseling for maternity and parenthood;
  - means necessary for responsible procreation;
  - preconception counseling;
  - assistance to pregnant women and protection of the newborn's health also through the prevention of the related psychological discomfort;
  - birth preparation courses in collaboration with hospital;
  - assistance and support in the infant's care;
- Art. 59 – Outpatient specialist care for pregnant women and maternity care which updated the previous decree about preconception of September 10th, 1998 on "Protocols for access to laboratory examinations and instrumental diagnostics for pregnant women and maternity protection";
- Art. 38 on early diagnosis of congenital illness, hereditary metabolic diseases, deafness and hypo-vision,
- Art. 4 – Basic health care which provides the activation of child-friendly care pathways, including taking care of the first month of life, controlling the physical, psychological and sensory development of the child and research of risk factors, with particular regard to the early detection of suspected neuro-sensory and psychological handicaps and the early detection of health-related issues; in the article mandatory vaccinations and vaccinations recommended to the at-risk population are also included;
- Art. 14 – Delivery of dietary products, the National Health System also guarantees delivery of breast milk substitutes for newborns born to HIV-infected mothers up to the sixth month of age.

In the new Essential Care Levels, a special attention is given also to people with autistic spectrum disorders and the list of rare diseases and that of disabling chronic diseases have been updated. Last but not least, Art. 62 ensures the equity of care for foreign children present on national territory, too. Special attention has been dedicated to the policies regarding healthcare for mother and child through the December 2010 Agreement between the Central Government and Regional Governments (titled "Guidelines for the promotion and improvement of the quality, safety and appropriateness of care interventions during the birth pathway and for the reduction of caesarean sections"). The agreement established an organizational model of assistance, which accompanies women or couples and their newborn before, during and after the birth under the continued monitoring of the Ministry of Health by the National Birth Pathway Committee. Another agreement titled "Guidelines for the promotion and improvement of the quality, safety and appropriateness of care interventions in paediatric and adolescent field" is ongoing. In addition to promoting programs and actions, the Ministry of Health monitors their implementation with annual reports (birth pathway monitoring, essential levels of care monitoring) and their efficacy through specific surveillance systems on maternal mortality, perinatal mortality, "first years" – surveillance for children aged 0-2 years, "Okkio" for children school aged and "HBSC" for adolescents. The primary goal of the Ministry of Health is to promote a National Health System always in line with the technological and scientific innovation, and with citizens' needs, so also the Essential Care Levels are always being updated. For this reason, DPCM June 16th, 2016, established the National Commission for the Essential Care Levels update that has the task of continually monitoring their contents, by omitting outdated services and activities, and by evaluating to add innovative and effective therapies for patients' health.

LECT 10

VITAMIN D: OLD AND NEW

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Vitamin D, old vitamin and newly a hormone, is primarily made in the skin after exposure to ultraviolet radiation, and only a small amount derives from dietary sources [1]. When vitamin D enters the circulation, it is associated with vitamin D binding protein, which transports it primarily to liver. Here, it is metabolized to 25-hydroxyvitamin D (25OHD), which is used to determine patient's vitamin D status; subsequently 25OHD is metabolized in kidneys to its active form, 1,25-dihydroxyvitamin D (1,25OH2D) [2, 3]. Vitamin D also is circulated to all tissues in

the body, many of which are now known to contain the activating hydroxylase (e.g. placenta): therefore, those tissues achieve autocrine production of 25OHD. Furthermore, the vitamin D receptor is present in most tissues of the body, including osteoblasts, bowel, activated T and B lymphocytes, beta-islet cells, brain, skin, and mononuclear cells; thus, a vitamin D deficiency (as defined by 25OHD levels < 20 ng/ml) may affect not only the skeletal system. Probably, maternal and infant vitamin D status influence many tissue functions. In fact, it is involved in multiple developmental processes, including intrauterine programming: an adequate vitamin D status is important for neonatal and adult health and it is determined by adequate maternal nutritional and mineral homeostasis and adequate fetal hormonal stocks [4]. During pregnancy 25OHD readily crosses the placenta. The fetus at birth (cord blood) has 50-60% of maternal circulating concentration of 25OHD and this relation appears to be linear even after supplementation [5]: the newborn is dependent on maternal store to ensure an adequate vitamin D status at birth. High rates of vitamin D deficiency have been reported in pregnant women, especially in winter months and at higher latitudes: low levels during pregnancy have been associated with intrauterine growth retardation and hypertension, all of which increase the risk of low birth weight [6, 7]. A number of observational studies indicated a linear association between maternal vitamin D deficiency and adverse maternal and neonatal outcomes. Preeclampsia certainly is linked with vitamin D deficiency [8]: one of the leading theories is that 1,25OH2D is an important immune modulator involved in maternal tolerance to the foreign fetus whose DNA is only half that of the mother's. Experimental animal models have also strongly suggested vitamin D deficiency as a potential mechanism of placental dysfunction [9]. A recent meta-analysis of observational studies supports the premise that maternal vitamin D deficiency increases the risk of preterm birth [10]. Animal studies demonstrate an important biologic role in lung development and maturation, including differentiation of type II pneumocytes, surfactant phospholipid synthesis and secretion, as well as an immunomodulatory role in epithelial cells, neutrophils and macrophages [11]. In preterm infants, vitamin D has a weighty role in early lung development and innate immunity [12, 13]. Many observational studies indicated that maternal vitamin D deficiency is a significant risk factor for adverse neonatal outcomes including asthma [14], multiple sclerosis [15, 16] and other neurological disorders [17]. While there have been numerous observational studies that suggest vitamin D role in maintaining maternal and fetal health, there have been few randomized clinical trials with vitamin D supplementation. The Vitamin D Antenatal Asthma Reduction Trial, a randomized, double-blind clinical trial, has shown that pregnancy supplementation with 4,000 vs 400 IU/day during 2nd and 3rd trimesters of pregnancy was safe, led to an increase in mean maternal circulating 25OHD levels into the sufficiency range (as defined by 25OHD levels > 30 ng/mL), determined a significant increase in newborn weight and height, resulted in an enhanced broad-spectrum proinflammatory cytokine response of cord blood mononuclear cells to innate and mitogenic stimuli, which can contribute to protection from asthma-related, including infectious, outcomes in early life [18]. A recent prospective study was performed prescribing vitamin D during pregnancy to mothers of children with autism at a dose of 5,000 IU/day. The newborn siblings were at high risk for the recurrence of autism. The newborn infants were also prescribed vitamin D, 1,000 IU/day to their third birthday. The newborn siblings were followed for three years and were assessed for autism at 18 months and 36 months of age. The final outcome was 1 out of 19 (5%) developed autism in contrast to the recurrence rate of approximately 20% in the literature [17]. In conclusion, it is essential that pregnant mothers and newborns be adequately supplemented from the early days of life. Decreased vitamin D levels in the mother result in decreased transplacental transfer and reduced stores at birth. 25OHD has a short half-life (2-3 weeks): newborn vitamin D concentrations decrease rapidly during the neonatal period unless an exogenous source is provided.

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LECT 11

NURSING-SENSITIVE OUTCOMES IN NEONATOLOGY

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Nursing is a science that attempts to answer or alleviate human needs for care. It is both a science and an art, technical and ethical, cultivated to better understand and satisfy patients' needs in a fashion that is measurable, effective and efficient [1]. Establishing a set of internationally accepted outcomes expressed in consistent and measurable language is a priority for international nursing. The difficulty in measuring the efficacy of nursing care and its impact on individual patients' final outcomes represent a significant lacuna in the care process. What is meant by Nursing-Sensitive Outcomes (NSO) in today's context? According to Dorian [2], they represent the consequences or effects nurses obtain, manifesting as changes in health status, behaviour or perception, and/or the resolution of the problem the nursing care was intended to address. Griffiths holds that NSO are aspects of a patient's experience, behaviour and health status, wholly or partially resulting from the nursing care received, with variations based on the quality and quantity of said care. Although no universal definition exists, it can essentially be described as a measurable condition or perception on the part of the patient or his family that is influenced or "sensitive to" nursing care [3]. This concept encompasses a broader vision of care, one that goes beyond the outcome of nursing care on the patient to include every facet of nurses' professional conduct. This description has given rise to the idea of categorizing and subsequently defining the issues neonatal nurses face every day in their field, concretizing the often intangible aspects of their work. NSO is a complex topic, given that neonatology is a young science; it has now begun to examine its own efficacy and the correlations that exist between it and its outcomes. The research was conducted using biomedical databases such as CINAHL, JBI, and PubMed with the parameters "newborn 0-1" and "paediatric care". Database queries performed in February 2017 returned 21 pertinent articles. The studies evaluated were performed on either complex patients or ones requiring highly specialized care. Most outcomes are the result not only of the care the nurse provides to the patients, but also of nurse/patient relationships, the department's degree of complexity, each individual's skills, and knowledge. The outcomes list has been derived from the collection of data from specific patient outcomes or interviews with care providers. Our review process revealed that the concept of NSO was initially introduced in adult medicine. Only in the last 10 years has it entered the paediatric field, and the neonatal field even more recently. Some authors we reviewed referred specifically to

a categorization of NSO, but we found that most of them were negative in derivation. This is probably because nursing care, if not provided in a linear fashion, can result in negative patient outcomes, but perhaps it is also because such data is more easily collected when conducting a study. A linear model, including structure, process and outcome of a given healthcare service, would provide a clear guide into which to insert quality indicators for every phase and improve overall results. If we accept these statements as a point of reference, then we must quantify what we do, whether our actions lead to outcomes that are negative (safety-related), positive (effectiveness) or expressions of risk that a given event might happen which is conducive to another (compassionate care). In the complex field of neonatal intensive care, newborn infants are particularly vulnerable, due the undeveloped nature of their physiology, functions and immune systems. Given their inability to express themselves with language, the behaviour of caregivers and the care they provide in the NICU can significantly influence the newborn's outcome as well as its growth and development. Assessment of the quality of care and the choice of nursing-sensitive indicators that encourage specific outcomes are critical and lie at the core of nursing management. Objective, scientific, nursing-sensitive indicators can not only effectively measure the quality of care, but can also help to guide clinical care and monitor ongoing quality improvement. The development of nursing-sensitive quality indicators could contribute to harmonizing treatments, improving the quality of clinical care at every level and increasing patient safety. This task must serve as the starting point for further studies and for the categorization of neonatal outcomes, providing nurses not only with greater awareness regarding their work, but also a clear and objective vision of care as influenced by the environment and by workplace dynamics, in relation to the direct outcome on the patient and his family, while accepting that these dynamics may have less than positive real-world impacts.

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LECT 12

REQUIREMENTS OF MACRONUTRIENTS AND MINERALS IN PARENTERAL NUTRITION OF PRETERM INFANTS

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Survival of preterm infants (< 37 weeks gestation) has increased dramatically in the last few years. Along with this improved survival, clinicians must now face the challenge of providing nutritional support to infants born as early as 23 weeks gestation weighing just 500 grams or less. Nutritional support of the very low birth weight (VLBW) infants represents a daily challenge in every neonatal intensive care unit (NICU). The nutritional goal for premature infants is the achievement of intrauterine growth rates, while maintaining adequate body composition and avoiding metabolic impairment; this goal may be impossible due to limitations in preparation of parenteral nutrition (PN) bags, the increased metabolic demands of critically ill infants and the necessity of fluid restriction. PN is necessary when an infant is not able to tolerate an adequate amount of enteral nutrition within 3-5 days. Enteral nutrition should be initiated as soon as possible when the infant's medical condition allows, while simultaneously weaning total PN, at the same time ensuring provision of adequate nutrients for the best growth possible [1]. Nitrogen requirements are supplied using a solution of crystalline L-amino acids. The VLBW preterm infant needs approximately 3.5-4 g • kg^{-1} • day^{-1} of amino acids to produce nitrogen retention similar to that found *in utero*. In term infants 2.5 g • kg^{-1} • day^{-1} amino acids (equivalent to 300-360 mg of nitrogen • kg^{-1} • day^{-1}) is adequate for growth. Comparative studies do not show a difference in the occurrence of metabolic acidosis (as pH or base deficit) between groups administered different amino acid doses (initial amino acid dose ranged from 0 to 3 g/kg/day with a target range of 2.4-4 g/kg/day) [2, 3]. Current recommendations suggest 2-3.5 g/kg/day of amino acids on the first day of life, increasing to 3.5-4 g/kg/day in the first week of life [2-4]. In Italy the current amino acidic formulations available are Primene® 20% and TPH® 6%. Glucose is the carbohydrate of choice for PN, is metabolized by all cells, and it is an essential nutrient for central nervous tissues,

erythrocytes and renal cortex. High infusion rates may lead to hyperglycemia, glycosuria and osmotic diuresis thus impairing the metabolic state of the infants. The optimal intake remains uncertain. In preterm infants, it has been suggested to start with a carbohydrate intake of 6-8 g/kg/day (equivalent to approximately 4-6 mg/kg/minute) increasing over the next 2-3 days to around 12-14 g/kg/day, although higher intakes may also be tolerated. Preterm infants have small volumes of insulin-sensitive tissues (fat and muscle) and limited insulin secretory capacity. For these reasons, preterm infants are prone to develop hyperglycemia, with incidence as high as 80% in very preterm infants [5, 6]. Routine basal use of insulin in preterm infants (in order to promote lean mass accretion) showed no benefit, and was associated with a higher incidence of hypoglycemia [7]. The initiation of lipids within the first 2 days of life in very preterm infants appears to be safe and well tolerated but few data support the early initiation of parenteral administration of lipids to improve growth or decrease long-term morbidity. Delayed administration of lipid can also lead to essential fatty acid deficiency. Increased cumulative intake of lipids during the first 2 weeks after birth has been associated with improved neurodevelopment at 1 year corrected age. Starting with lipids intake at 2 g/kg/day is safe; it is recommended an increase to 3 g/kg/day over the next 1-2 days as continuous infusions (i.e. not cycling). Intakes over 4 g/kg/day are generally not recommended, and lower intakes are almost certainly sufficient in term infants. There are no proven advantages to using anything other than 20% lipids emulsion [8, 9]. Metabolic bone disease is very common in the preterm infant and is mainly due to insufficient mineral intake and excess losses (due to steroids, diuretics, malabsorption etc.), although the *ex-utero* environment (decreased movements due to the effects of gravity and lack of uterine wall to stretch against), lack of breast milk growth factors and sub-optimal vitamin D intakes also contribute. Parenteral administration of 50-75 mg of calcium/kg/day can prevent early neonatal hypocalcaemia in preterm infants. Through the parenteral administration of calcium and phosphorus (40-70 mg/kg/day and of 25-45 mg/kg/day respectively) it is possible to achieve 60-70% of intrauterine mineralization [10, 11]. Plasma phosphate should generally be kept above 1.8 mmol/L in the very low birth weight infant. Low concentrations impair muscle function and may therefore worsen respiratory difficulties, and may prevent optimal lean mass accretion, since phosphate is an essential component of lean tissue. Phosphate is a vital component of cellular membranes and enzyme systems and plays an important role in energy conversion to adenosine triphosphate (ATP) [12]. Growth outcomes of preterm infants remain suboptimal, because they do not receive enough amount of nutrients, including total protein, essential amino acids, total energy, and essential fatty acids. Growth failure among preterm infants includes brain growth failure and consequent neurodevelopmental deficits. Much research is still needed to determine optimum nutrition for extremely preterm and VLBW infants and those who experience significant postnatal growth restriction, especially to enhance growth and development of the brain [13, 14].

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LECT 13

KANGAROO MOTHER CARE (KMC) AND NEUROPROTECTION

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Kangaroo Mother Care (KMC) is an approach to the care of preterm infants which engages and empowers mothers and families as the main providers of the biological (warmth and food, at first) and emotional (contact, bonding, wellness) development of their newborns. The cornerstone of the KMC is the kangaroo position whereby the infant is placed and held in direct skin-to-skin contact on the mother's chest in an up-right position under her clothes. Since KMC was developed in Colombia in the '70 two trends in clinical application emerged, with substantial differences between low-income countries (LICs) and high-tech environments. In the low-income settings KMC consists of continuous and prolonged mother or parents skin-to-skin contact (24 h/day, 7 days/week): thermal regulation, promotion of exclusively breastfeeding and improvement of mother-child bonding are the main targets. Several studies [1, 2] show that KMC reduces the neonatal mortality in the LICs together with the reduction in infections, the improvement of weight gain, length and head circumference, the reduction of risk of hypothermia, a better long-term child development [2, 3]. In the last years KMC has been endorsed by the WHO [4], because of the additional evidence [2] that KMC reduces neonatal mortality among LBWIs < 2,000 g, the leading cause of under five mortality in LICs. In the well-developed countries and high-tech settings intermittent KMC sessions of one or few hours for limited periods is common. As a result of the increasing evidence [5] of the benefits of KMC for both infants and families KMC is now at the center of various conferences and workshops [6] where several dates about rates of breastfeeding, physiological regulation, maternal bonding, emotional issues, long-term quality of life are presented and discussed. The multisensory experiences in the NICUs and the mother-child separation are considered the main risk factors for the development of preterm infants, besides the biological factors (e.g.: lungs immaturity). In the traditional NICUs the preterm infants receive stressful stimuli – for which their immature brain is not ready – as various medical interventions, excessive ambient noise and light, painful procedures, negative touch experiences, sleep disruptions; moreover, in the incubators preterm and small infants are deprived of positive sensorial stimuli as skin-to-skin contact, mother smell, containment, gentle touch, mother's vocalization. This multisensory conflagration is quite different from the positive sensory experiences that a fetus lives through at the same gestational age in the mother's womb [7]. The mother-child separation worsens the sensorial stress experience that often assumes the feature of "toxic stress" [8, 9] that is characterized by a prolonged activation of the body's stress management system in the absence of the buffering relationship of mother support with consequences on neuroendocrine patterns. A growing body of evidence in both humans and animals suggests that brain development may be influenced by the quality of care given, including physical and emotional closeness and parent empowerment [10]. The knowledge that neonatal emotional experience and associated learning processes are critical in the maturation of prefrontal-limbic circuits emphasizes the importance of neonatal care. KMC may be a very important tool to reduce toxic stress and negative sensory experiences that influence the brain maturation and to promote a better quality of development. KMC may influence positively the limbic system that includes subcortical regions (hypothalamus, amygdala, nucleus accumbens among others) and cortical cortex (hippocampal formations and regions of neocortex including the insula, the orbitofrontal cortex, the cingulate and parahippocampal gyrus) with consequences on emotional pattern, memory and cognitive potential of the infant [11]. KMC is related to a better organization of sleep-awake rhythm of preterm infants, less sleep disruptions

and prolonged periods of sleep [11]. The positive effect on development is related to a better cerebral plasticity – sleep dependent – that is the brain capacity to adapt his function to environmental stimuli with improvement of self-regulatory system. Infants may experience numerous painful procedures during their course of stay in the NICU. The short-term and long-term effects of untreated pain include physiologic instability, poor self-regulation, altered CNS development and behavioral anomalies. KMC is effective in reducing pain with PIPP scores significantly less in KMC group compared to control group [12]. Moreover KMC infants have less level of cortisol, expression of less activation of HPA axis, and an increase in oxytocin levels and brain growth-promoting factor IGF-1, potentially having positive effects on the brain functioning and development [10]. The mothers of premature infants are at risk of psychological stress because of the separation from their infants. KMC is one of the methods influencing the maternal mental health in the neonatal period by ameliorating negative maternal mood [13] and promoting more positive interactions between pre-term infants and their parents with positive effect on breastfeeding (incidence and length) and on the attachment process and emotional development [14]. KMC is protective against a wide variety of adverse neonatal outcomes. This safe, low-cost intervention has the potential to prevent many complications associated with preterm birth and NICU environment. The consistency of these findings provides support for widespread implementation of KMC as standard of care for newborns [15, 16]. In spite of that, well-defined guidelines (ideal duration, adequate setting, start time) about how to implement this method of care are lacking [17]. As a consequence too many restrictions are applied in many NICUs. The main point is to remember that KMC is not an isolated action but is an integral part of individualized family centered strategies where free access of the parents to the NICU is a cornerstone together with pain control policies, physical environment adaptation to sensory needs of infants, individualized assistance organization. Successful strategies for KMC implementation in various contexts should be disseminated.

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LECT 14

HEMODYNAMIC PRINCIPLES AND MANAGEMENT OF EXTRACORPOREAL MEMBRANE OXYGENATION SUPPORT

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The management of the critical patient in Extracorporeal Membrane Oxygenation (ECMO) requires the knowledge of the physical laws of fluid dynamics and the extracorporeal circulation dedicated equipment by all members of the ECMO team. The law of Poiseuille states that flow is inversely proportional to the viscosity of the fluid and the length of the conduit and directly proportional to the pressure difference at the extremities of the conduit as well as to the fourth radius power ($Q = \frac{\Delta P\, r^4 \pi}{8\, L\, \eta}$). Therefore, choice of the gauge of the ECMO circuit and its length is crucial in determining variations in flow velocity. In fact, stasis, due to the passage from a smaller to larger radius and the loss of a laminar flow to a turbulent, are responsible for increased blood clotting activation and increased risk of thrombus formation during ECMO. ECMO assistance drains deoxygenated blood and reinfuses oxygenated and decarboxylated blood in the circulatory stream through mono or dual lumen cannula. The correct choice of type and cannula gauge ensures optimal flow for the level of support desired. The incorrect selection of these two variables reduces the success of the extracorporeal procedure. Venous blood is drained to a pump that generates the flow to be delivered to the patient (liters per minute) by generating a certain number of revolutions per minute, which is displayed on the console. Pumps are classified into two groups: occlusal pumps (roller pumps) and centrifugal pumps. In occlusal pumps rollers propel the blood, which is drained by gravity, mechanically crushing the raceway without the possibility of back flow. The second, using the centrifugal force generated by the axial rotation of the pump itself, produces a negative pre-pump pressure able to drain the blood actively and at the same time a post-pump propulsion force that can push the blood through the artificial lung and to the patient. In the last, back-flow is a risk, although preventable and pre- and afterload influence the flow generated. The membrane lung is the component in which heat and gas exchange occurs through the passage of blood between the fibers that make it up. Similarly to what happens in the lung, gas exchanges occur by diffusion: venous blood releases CO_2, acquiring oxygen from a mixture of air and oxygen delivered by a gas blender to the membrane; CO_2 removal increases as the airflow increases, while oxygen concentration is increased by increasing the "inspired" oxygen fraction administered. Heat exchange is regulated by a heat exchanger connected to the oxygenator. Fluid overload in neonates on ECMO is very common as a consequence of systemic inflammatory response due to the exposition to the circuit. Moreover, the volume required to administer drugs is high relative to a newborns blood volume resulting in a delicate handling of fluid balance and significant risk of fluid overload. The hemofilter is one of the systems that, through a convective method, allow the elimination of excess fluid. Since ECMO is a highly invasive procedure, it is advisable to monitor pressure blood at three points of the circuit: pre-pump (where excessive negative drainage pressure is associated with hemolysis), pre- and post-oxygenator, because the pressure difference between these two values reflects the resistance of the membrane, the increase of which may be a sign of progressive or sudden thrombosis of artificial lung. Furthermore, post-oxygenator pressure can be used to evaluate post-loading and reinfusion pressure in the cardiovascular system (**Fig. 1**). Monitoring of blood gas values is essential to modulate the assistance to perfusion and to assess the need for any metabolic and ionic corrections. A venous sample, generally pre-oxygenator, and a post-membrane sample must be collected to assess efficiency. An arterial sample from the patient will allow verifying the correct mixing between the native and the ECMO blood flow. Blood gas parameters allow deriving those, which are considered to be good "perfusion indices", among the most important: oxygen delivery (DO_2), oxygen consumption and CO_2 production. DO_2 is mainly influenced by flow, hemoglobin and oxygen saturation. During ECMO, to improve perfusion, it is necessary to act on the pump flow rather than on hemoglobin saturation and concentration. The use of continuous blood gas monitoring systems enhances the management of care by recording real-time values that provide good perfusion derived indices. ECMO assistance involves blood interaction with the non-autologous material, so it is necessary to keep the circuit clot free, without hemorrhage in the

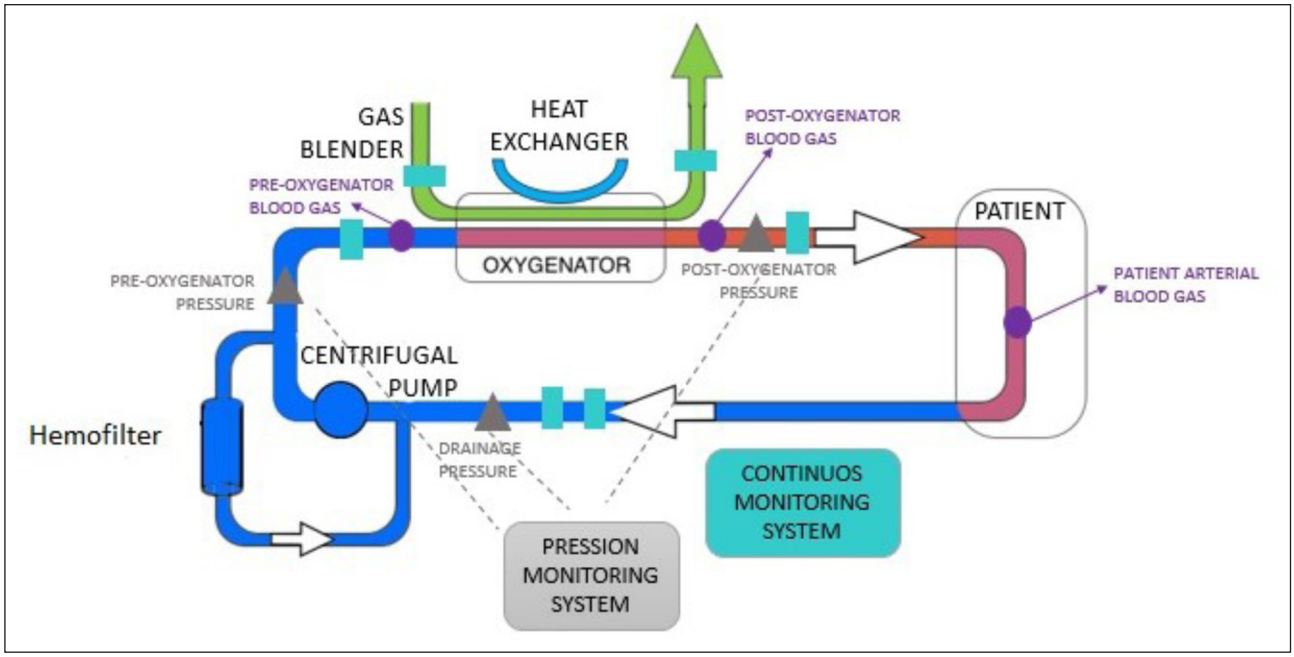

Figure 1 (LECT 14). ECMO circuit.

patient, ensuring a balance between prothrombotic and prohemorrhagic factors. Consequently, it is useful to perform standard coagulation tests and thromboelastography at regular intervals. One of the most common mechanical complications is the formation of thrombi in the ECMO system; according to the Extracorporeal Life Support Organisation Registry, clot formation occurs in 16.7% in the oxygenator, 8.5% in the circuit and 3.1% in the hemofilter. High percentages are due to cannula problems (11.5%) and oxygenator failure (5.6%), while the incidence of complications such as air-to-circuit, cracks in connectors, pump malfunction, heat exchanger failure reported is less than 5%. The resolution of these mechanical complications must be immediate and in most cases requires interruption of the assistance. In conclusion, the management of the patient in ECMO is highly complex and requires the collaboration of a multidisciplinary team that involves nurses, perfusionists, neonatologists, anesthetists, and surgeons who need to know the system and physical laws of extracorporeal circulation.

LECT 15

THE STABILIZATION OF THE NEWBORN BEFORE THE TRANSPORT

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Irrespectively of care levels, all hospitals worldwide that provide obstetric services must be prepared for birth, resuscitation, stabilization and treatment of premature or sick infants. Initial management is outlined in the Neonatal Resuscitation Program (NRP). The NRP textbook establishes that approximately 90% of infants pass to extrauterine life without difficulty and just about 1% needs a resuscitative approach [1]. The neonatal resuscitation program is effective if neonatologists are able to identify at-risk or sick babies and provide effective stabilization. There are two babies populations: those who require post resuscitation care, and those who are well at birth but may become sick. Among the babies who seem recovered after resuscitation within five minutes from birth, the 62% have short-term complications that require a new evaluation and treatment [2]. Even babies, who need a mild resuscitation at birth, can be often assessed and treated. A prolonged clinical observation is necessary for all resuscitated infants, especially if they need an ongoing support and for all infants at risk of infections or maternal drugs side effects. Observation may simply consist in clinical inspection with assessment of heart rate, respiratory rate, glucose test, temperature and arterial saturation monitoring. The observation period depends on the clinical conditions of babies and can range from several minutes to a few hours. It is very important for each perinatal center to have guidelines on the maximum observational time in order to decide if a baby's transfer should be made. What should

clinicians do to optimize the care of sick newborns while waiting for the NICU transport team? It is important to early identify all newborns who are unstable after the transitional period to increase the application of timely protocols, evidence-based, and to improve the neonatal care in the first hour of life. During the first hour called Golden Hour, the team's haste and the sequence of interventions have an impact on mortality and short- and long-term outcomes [3].

IDENTIFICATION OF BABIES WHO ARE SICK OR AT RISK FOR BECOMING IT

Looking for the causes of neonatal death worldwide, many of them may be recognized before birth or soon afterward. Premature births, intrapartum complications such as abruption placentae and antepartum bleeding, neonatal sepsis, pneumonia and meningitis always show abnormal clinical signs. The first step to improve neonatal care after birth is to train the team for the risk factors of instability. Knowing all risk factors (short gestation, maternal fever) guarantees an earlier intervention during labour and delivery and the transfer to NICU with more adequate resources. The clinical signs of stability should reflect the normal function of vital organs in extrauterine life and should be validated by clinical trials to confirm their validity as signs of normality and predictors of normal outcomes. The Risk Index of Physiologic Stability (TRIPS) and Clinical Risk Index for Babies (CRIB) have used such indicators of stability and would be a good starting point for establishing the vital sign of stabilization [4, 5].

EDUCATION PROGRAMS FOR SICK BABIES

Most of the programs of stabilization recognize that a stable respiratory activity must be considered a priority after resuscitation. There are many education programs that train the team for the neonatal stabilization. These differ slightly in their approaches and targets but generally follow the same principles: to identify the sick baby, to list which organs are unstable and to resolve systematically the instability [6-8]. Following this programs the neonatologists can quickly assess the vital organ function and provide the care identifying infant's needs. The S.T.A.B.L.E. neonatal stabilization program, founded in 1990 by Kris Karlsen, is the only neonatal continuing education program that focuses exclusively on the post-resuscitation/pre-transport stabilization care of sick neonates. This program is considered by experts to be the complementary follow-up to the American Academy of Pediatrics' NRP [9]. The goals of the S.T.A.B.L.E. program are two: the first one is to educate healthcare providers in stabilization of preterm and ill neonates after delivery and before the transport to III level neonatal center. A mnemonic algorithm helps them to remember the 6 key areas of care for the management and stabilization of high-risk neonates before being transported (**Tab. 1**). The second one is to provide patient safety. So, in the mnemonic algorithm the "S" is not only referred to blood sugar stabilization but also to patient's safety. Early transitional care improves the health of high-risk infants, thus reducing infant morbility and mortality. In VLBW infants a protocol of stabilization that improves the quality of care must be used in the golden hour (GHP) to avoid the detrimental short-term outcomes including hypothermia, hypoglycemia, respiratory compromise, late-onset sepsis and for intraventricular hemorrhage risk factors [10].

Table 1 (LECT 15). Mnemonic algorithm for the S.T.A.B.L.E. program.

S = **S**ugar and **S**afe care
T = **T**emperature
A = **A**irway
B = **B**lood pressure
L = **L**ab work
E = **E**motional support

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LECT 16

NEONATAL EXTRACORPOREAL MEMBRANE OXYGENATION: THE BASICS

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Despite advances in neonatal intensive care, each year hundreds of neonates worldwide still need extracorporeal membrane oxygenation support (ECMO). According to the Extracorporeal Life Support Organization (ELSO), last year 571 neonates required ECMO for acute respiratory failure, while 327 of them received it for cardiac impairment and 130 were implanted on cardiac arrest (extracorporeal cardiopulmonary resuscitation – ECPR). Over the years this procedure has remarkably progressed, and nowadays it represents an invaluable tool for acute, severe, reversible cardio-respiratory failure, unresponsive to conventional treatment. ECMO is not a disease-modifying therapy but rather a supportive treatment; it always should be referred to the right patient, in the right way (configuration), at the right time (not too early nor too late), in the right place (experienced ECMO center). Here we discuss basic principles, modality, indications, monitoring, outcomes, and complications.

BASICS

ECMO is a form of cardiopulmonary support, in which blood is drained from the venous district (right atrium or vena cava) through a venous (drainage) cannula, circulated extracorporeally by a mechanical pump, oxygenated and decarboxylated through a membrane oxygenator, warmed and reinfused to the vascular system through an arterial (reinfusion) cannula. The arterial cannula may be placed either in the venous (dual-lumen cannula in the right jugular vein in veno-venous ECMO [VV-ECMO]) or arterial side (right carotid artery in veno-arterial ECMO [VA-ECMO]). Oxygenation is mainly determined by blood flow, while CO_2 removal is modulated by adjusting the gas flow through the membrane. The amount of oxygen provided is directly related to blood flow, which generally ranges from 100 to 160 ml/kg/min, with variations according to patient's conditions. Duration of support varies widely; the mean duration reported is 6 days for VA-ECMO and 8 days for VV-ECMO, ranging from 3 days up to two months.

MODALITY

VV-ECMO guarantees adequate gas exchange in hemodynamically stable patients, being the circuit in series to the native heart and lung. Conversely, VA-ECMO bypasses both the heart and the lungs, also providing hemodynamic support. In neonates, VA configuration is the most frequently used modality. Cannulation may be peripheral (more common in respiratory patients) or central (especially in postcardiotomy ECMO). Choice of the cannula size is critical to guarantee adequate support.

INDICATIONS

ECMO can be instituted for medically refractory respiratory and/or cardiac failures and one of the crucial issues is patient selection. In the majority of cases (77%) neonates require ECMO for respiratory support in meconium aspiration syndrome, congenital diaphragmatic hernia, persistent pulmonary hypertension, sepsis, pneumonia, respiratory distress syndrome and air leak. The main cardiac indications to ECMO are largely represented by congenital cardiac defects, followed by cardiomyopathies, cardiogenic shock, and myocarditis.

MONITORING

The daily clinical evaluation of a neonate on ECMO should be integrated by a close multisystemic monitoring: hemodynamics (continuous invasive blood pressures, echocardiography, hourly urinary output, fluid balance), pulmonology (daily X-ray, lung ultrasound, bedside lung function measurements), neurology (continuous cerebral near-infrared spectroscopy, daily head scans), infections and hemostasis. Routine hematological, biochemical and microbiological parameters should be complemented by hemolysis indices (LDH, direct bilirubin, free hemoglobin). A close coagulation monitoring is imperative, as hemostatic imbalances may occur secondarily to the exposure to extracorporeal surfaces, systemic anticoagulation, dysfunctional platelets and clotting factor hemodilution. Along with conventional coagulation tests (PT, aPTT, fibrinogen), antithrombin and anti-factor Xa assay are useful tests to monitor heparin activity and guide antithrombin supplementation, whenever indicated. Some centers use bedside global tests such as activated clotting time

Table 1 (LECT 16). Main clinical complications during respiratory/cardiac extracorporeal membrane oxygenation support (ECMO) and related survival rates (derived from Extracorporeal Life Support Organization [ELSO] registry – January 2017).

Complications	Respiratory ECMO				Cardiac ECMO			
	N reported	% reported	N survived	% survived	N reported	% reported	N survived	% survived
Cannula site bleeding	2,374	7.9%	1,505	63%	769	10.7%	242	31%
Surgical site bleeding	1,871	6.2%	791	42%	2,084	29.1%	644	31%
CNS hemorrhage	2,285	7.6%	979	43%	824	11.5%	202	25%
CNS infarction	2,033	6.8%	1,075	53%	241	3.4%	64	27%
Creatinine 1.5-3	1,927	6.4%	964	50%	737	10.3%	175	24%
Creatinine > 3	378	1.3%	139	37%	130	1.8%	39	30%
Dialysis required	935	3.1%	364	39%	534	7.4%	103	19%
Hemofiltration required	4,794	16%	2,566	54%	1,863	26%	537	29%
CAVHD required	658	2.2%	279	42%	481	6.7%	85	18%
Inotropes on ECLS	6,887	23%	4,180	61%	4,014	56%	1,416	35%
Hypertension requiring vasodilators	3,559	11.9%	2,507	70%	687	9.6%	283	41%
Hyperbilirubinemia (> 2 direct; > 15 total)	2,174	7.3%	1,326	61%	356	5%	116	33%

(ACT), thromboelastography (TEG) or rotational thromboelastometry (ROTEM), which allow a more comprehensive view of the hemostatic process.

OUTCOME AND COMPLICATIONS

Since 1989 around 29,942 newborns have been supported for respiratory indication, 7,169 for cardiac problems, 1,532 for ECPR with a survival rate of the procedure of 84%, 64%, and 67%, respectively. Of note, newborns with congenital diaphragmatic hernia have a survival rate on ECMO of 50%. During an ECMO run, technical and clinical complications may arise, with a potential impact on patient outcome regarding morbidity and mortality (**Tab. 1**). Generally, VV-ECMO course is more favorable than VA-ECMO, across all age groups. The most frequent complications reported from the ELSO registry are hemostatic disorders with a potential neurological involvement. Hemodynamic and fluid imbalances may lead to acute kidney injury, requiring some kind of replacement therapy. Some patients may experience infectious and metabolic derangements. It is important to consider that all these aspects may be related to the underlining conditions, which required ECMO and shouldn't be seen purely as a direct consequence of the circuit itself. As one may expect, duration of support impacts negatively on rate and entity of events. Therefore it is crucial, as a team work strategy, to look for early and safe weaning from ECMO, whenever the patients are "ready" for decannulation.

LECT 17

MONITORING THE PRETERM INFANT'S TRANSITION AT BIRTH

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The preterm infants' hemodynamic and respiratory stabilization in the Delivery Room (DR) is the main challenge for the neonatologist. Preterm babies, in fact, need an adequate support to achieve an effective lung aeration and subsequent raise of pulmonary blood flow, with the onset of a physiologic blood oxygenation [1]. To avoid hypoxia and its consequences, such as neurological impairments, NRP guidelines have established well-defined steps and timing for resuscitation. However, the neonatologist must be particularly careful during resuscitation, since pitfalls during the first minutes of life can lead to potential severe injuries (i.e. ventilatory-induced lung injuries [VILI], prolonged hypoxia). All these initial injuries have long-term effects on the lung parenchyma and can determine adverse outcomes such as bronchopulmonary dysplasia (BPD) [2], or neurodevelopmental complications [3] such as intraventricular haemorrhage (HIE) or periventricular leukomalacia (PVL). In the DR, maintenance of an adequate body temperature (target range of 36°C to 38°C) [1] is one of the most important supportive therapies

during fetal-neonatal transition for preterm infants. For this reason, early control of the body temperature in the DR is a duty as it is widely stated that hypothermia is associated with higher mortality rates in preterm infants [4]. Then, an immediate monitoring of the vital parameters is mandatory to optimize resuscitation. The heart rate (HR) reading should be obtained as soon as possible after birth and it is essential to guide the different steps of the resuscitation [5]. Moreover, targeting oxygen saturation on SpO_2 percentiles in the first minutes of life is crucial to avoid hypoxia but also hyperoxia peaks, which can induce early oxidative stress and tissue damages [6]. Delivering controlled pressure to preterm infants during early respiratory stabilization with continuous positive airway pressure (CPAP) or during positive pressure ventilation (PPV) via face mask is now widely but still not universally spread in the DR management. The use of a T-piece resuscitator connected to a face mask or to an endotracheal tube (ETT) can provide controlled CPAP, positive end expiratory pressures (PEEP) and peak inspiratory pressures (PIP) during neonatal respiratory support, which cannot be assessed with a flow-inflating bag or a self-inflating bag [7]. To date, another device is available to add further information on the respiratory support provided in DR. The respiratory function monitor (RFM), in fact, can integrate and show the resuscitating team real time information about pulse-oximetry and the main respiratory data, reflecting the efficacy of the resuscitation manoeuvres. In particular, a pneumotachometer connected between the resuscitator device and the patient interface provides data of delivered pressures and flows [8, 9]. Integration of the flow signal provides data on inspiratory and expiratory tidal volumes (Vti and Vte), allowing the neonatologist to perform changes in the PIP level to achieve adequate ventilation (**Fig. 1**). Moreover, real time observation of the flow signal can provide information regarding face mask leaks or obstructions, which remain relevant factors influencing a successful mask ventilation. In addition, the flow signal can help in determining the efficacy of endotracheal intubation. Upon informed parental consent, RFM can also video-record the DR stabilization process and be used in debriefing sessions of the resuscitation team or for educational purposes with students. These records are extremely useful to improve the neonatologist skills and to identify and correct mistakes. Even if it is a new technique which must be further investigated to be standardized as a routine practice in the DR, end-tidal CO_2 ($ETCO_2$) monitoring has been recently shown to be a promising measurement to evaluate the degree of lung aeration and the onset of

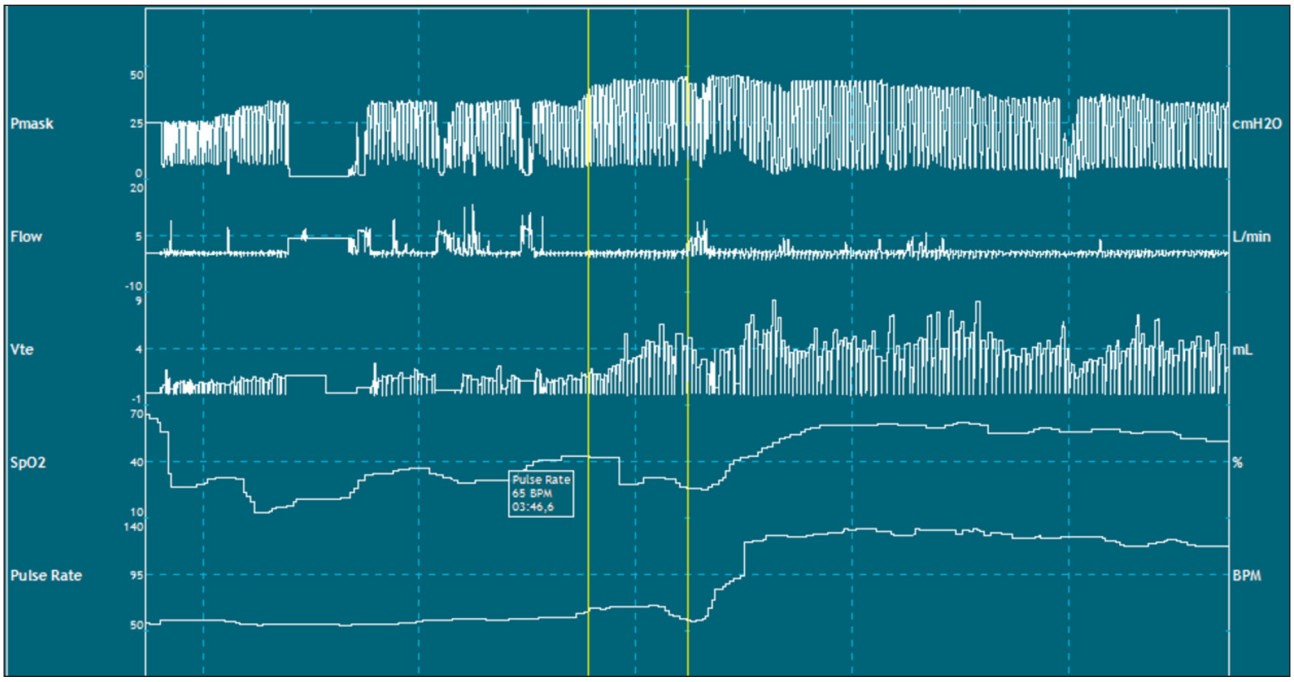

Figure 1 (LECT 17). The picture shows signals recorded by a respiratory function monitor (RFM) during a Delivery Room (DR) stabilization of a preterm infant: Pmask is the signal of pressures delivered during mask positive pressure ventilation (PPV). Flow signal, expired tidal volume (Vte) calculation, oxygen saturation (SpO_2) and pulse rate are simultaneously recorded. Pulse rate and SpO_2 raise in this example is clearly correlated with raise in peak pressures during mask PPV with subsequent increase in Vte.

pulmonary gas exchange [10]. Recent studies have also shown its feasibility to monitor the efficacy of PPV during neonatal resuscitation [11] and the presence of spontaneous breathing efforts [12].

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LECT 18

CEREBRAL PRENATAL DAMAGE: WHICH IS THE BURDEN OF INFECTIONS?

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In the past two decades the link between maternal infection, abnormal brain development and later onset of neuropsychiatric disorders has increasingly emerged [1]. Epidemiological studies suggest that exposure to prenatal infection such as influenza, rubella, measles, herpes simplex virus, and bacterial infections may increase the risk for the offspring to develop cerebral palsy, sensory deficit, bipolar disorder [2], schizophrenia [3], or autism [4-6]. This may be a starting point for neonatologists to review the relevant aspects of early diagnosis of maternal-fetal infection through clinical setting, laboratory biomarkers and imaging. The complex interaction between genetic and environmental factors in guiding and shaping brain development has been stressed by current research [7]. Cerebral development is a highly elaborate process that occurs predominately during the prenatal period, starting with the proliferation and migration of neurons to their final position in the brain, followed by the establishment of synapses and neuronal circuits. Considering the highly sophisticated processes of neural development, inflammation in the mother during pregnancy can compromise several vulnerable steps of fetal brain development [8]. These perturbations in the normal trajectory of brain formation and maturation during prenatal period may contribute to a causal chain of events that can become progressively magnified over time. This can lead to a wide spectrum of long-term changes in cerebral architecture and cognitive, behavioural functions that may persist into adulthood [9]. Microglia constitute the primary immune mediators of neural functions, directing and maintaining neuronal differentiation and maturation while playing a pivotal part in synaptic pruning, neural circuit formation and homeostasis. Inflammation-induced microglial priming refers to an exaggerated response to an inflammatory stimulus that is much stronger than that observed in stimulus-naive microglia [8]. Moreover, microglial activation component may persist for a period of time resulting in ongoing neuroinflammation as seen in patients with autism-spectrum diseases and periventricular leukomalacia (PVL) [10]. One hypothesis explaining the pathophysiology of the infective damage is that altered expression levels of inflammatory molecules in the fetal compartment in response to immune activation may disrupt brain development and neural connectivity, which may, in turn, have long-term effects on the individual's mental functions later in life [6]. As demonstrated by Nelson et al. [11], elevated inflammatory cytokines TNF-α, IL-1, IL-6, IL-8, along with interferon-γ (IFN-γ), vasoactive intestinal peptide, substance P, and calcitonin gene-related peptides in the neonatal

blood correlate with PVL, ventriculomegaly, and severe germinal matrix hemorrhage assessed by ultrasonography. On the contrary, cytokine elevation did not reflect the development of cerebral palsy in the population studied, leading the authors not to suggest cytokine measurement during the first days of life. In a second study [12], plasma levels of IL-6, IL-8, IL-10, TNF-α, and IFN-γ were not associated with cerebrospinal fluid concentrations of these cytokines nor did they reflect brain injury as assessed by MRI [13]. The lack of a decisive interpretation of the role of cytokines and their uncertain correlation with the long-term neurological outcome led to the emergence of the imaging techniques to assess brain injury. The use of imaging may provide a more accurate approach to assess inflammatory injuries, specifically to the brain. The clinical use of transfontanellar cranial ultrasound in detecting brain inflammation is the most prevalent technique used due to its relative safety, convenience of bedside scans, and cost-effectiveness that allows serial scanning of preterm infants at high risks and repeatable cot-side monitoring. It is able to detect ventriculomegaly, peri/intraventricular hemorrhage, cystic PVL and cerebellar hemorrhages. However, MRI and electroencephalography may be more sensitive at detecting mild white matter injury, such as diffuse PVL. Identifying ongoing brain injury in the setting of infection/inflammation will aid in recognizing newborns needing neuroprotection [13]: the earlier the suspicion of infection and treatment initiation, the better the outcome. Some clinical cases have highlighted the pivotal role of early detection of signs in other body districts such as skin, lung and gut, considering that these are the first ports of entry for fetal invasion as illustrated by Kim et al. [14]. The invasion then proceeds to bone marrow, thymus and immune system. The brain is one of the last target of fetal infection thanks to its protection by blood brain barrier. This sequence of organ involvement should always be taken into consideration in clinical practice. Moreover, Stolp et al. described the crucial function of blood brain barrier in the interaction with the immune system. Any structural deficits within the barrier junctions resulting from any type of injury in early life may increase the risk of early onset of neurodegenerative conditions [15]. Given the relationship between inflammation and brain injury, it is crucial to prevent prenatal infection, to early diagnose chorioamnionitis [16] and to screen probably infected neonates soon after birth with the aid of neuroimaging and clinical, biological surveillance.

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LECT 19

NEONATAL INFECTIONS: RECENT ADVANCES

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Neonatal bacterial, viral or fungal infections are the most important consequences of problems of the immune system adaptation from intra- to extra-uterine life. At birth immune system is immature, and antigenic experience is largely missing, as the fetus lives in a germ-free environment. Indeed, both the innate and the adaptive immune systems are incompletely developed, and the inflammatory response dysregulated, the more preterm the neonate, the more severe and prolonged the immunodeficiency [1]. The combined neonatal deficiency of lymphocytes, natural killer, immunoglobulin, complement and neutrophil activity results in increased susceptibility to systemic infections from encapsulated pathogens, such as *Group B Streptococcus*, *Staphylococci spp.*, and *Klebsiella spp.*, that require opsonization for efficient phagocytosis and killing, while the immaturity of pattern recognition receptors (PRR) response to pathogen-associated molecular patterns (PAMPs), and the impaired TLR4 (Toll like receptor) signaling, may contribute to the vulnerability to Gram-negative bacteria. It should be noted, however, that B cell development starts early in the fetus, advancing from 12 to 26 weeks, and neonatal T cells at birth are capable to raise type 1 and 2 immune responses upon appropriate stimulus [2]. Neonatal immunization does not generally lead to rapid antibody synthesis, however, it may result in efficient immunologic priming, which can act as a basis for future responses. It is therefore possible to induce early protection by immunization at birth [3]. The possible negative consequences of neonatal immunodeficiency are mitigated by some natural compensatory mechanisms. The transfer of high-avidity IgG antibodies through the placenta from the mother to the fetus during the second half of the pregnancy provides the newborn with the immunoglobulin protection, while after birth the maternal-neonatal immune link is maintained through the immunomodulatory and anti-infective properties of breast milk [4]. Recently, however, it has been hypothesized that, in selected rare circumstances, anti-cytokine neutralizing maternal antibodies may induce increased susceptibility to infection by specific pathogens such as *Group B Streptococcus* [5]. Both pre- and post-natal protection by specific maternal antibodies may be significantly improved by active vaccination (particularly against influenza or pertussis) during pregnancy [6]. The efficacy of neonatal infections treatment is closely related to a timely intervention. It is therefore necessary to have quick and accurate diagnostic tools. Indices with high (as close as possible to 100%) sensitivity and negative predictive value are preferred for the diagnosis of neonatal infection. If the infection is present, the result should always be positive, while when the outcome is negative, the infection should always be absent. However, specificity and positive predictive value are also important to avoid the side effects related to excessive treatment due to false positivity. The main tools used for the diagnosis of neonatal systemic infections are microbiological investigations for the isolation of the pathogen from biological samples, and the evaluation of sepsis biomarkers (either hematological, or inflammatory markers as acute phase proteins and procalcitonin, or cytokines and receptors assay). More recently, molecular diagnosis (as polymerase chain reaction [PCR], real-time PCR, NASBA, FISH, NAAT) has allowed obtaining the diagnosis during antibiotic treatment, while "-omics" technologies have shown particularly interesting. Screening panels, which contemplate the simultaneous evaluation of different indexes of infection, are commonly used in the clinical setting [7]. The complexity of infection manifestations requires an integrated therapeutic approach, which includes specific antibiotic therapy, in combination with general supportive therapy, and the enhancement of natural defense mechanisms, depressed in the neonatal age. The treatment outcome may be significantly influenced by the peculiar characteristics of the newborn, as adaptation problems, birth weight, gestational age, intrauterine growth restriction, postnatal age, and the immaturity of renal and hepatic function. The use of antibiotic therapy in the neonatal age, in particular the route of administration, the dosage and the interval of administration, should therefore take into account the differences in absorption, distribution, biotransformation, metabolism and excretion of the drug in the infant, In order to obtain the best efficacy and to limit adverse effects. The appropriate use of antibiotics is extremely important, particularly through the adoption of a "stewardship" program, which includes, among others, the use of restricted spectrum antibiotics for empirical therapy, and the timely stop of treatment as soon as the clinical picture and biochemical and cultural investigations exclude the presence of an infection [8-12].

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LECT 20

THE ENGINEER AND THE SINGLE FAMILY ROOM (SFR): THE ALLIANCE WITH THE CLINICIAN

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Health professionals and technicians do not always communicate effectively. Sometimes doctors think about technical professionals as if they were simple performers of maintenance tasks, not fully understanding the complexities associated with the systems they manage. On the other hand, technicians often ignore the impact of processed data on clinical workflows. In the design and construction of the new Single Family Room (SFR) NICU in Monza, one of the main strengths during the design and implementation phase was the creation of a multidisciplinary group of doctors, nurses and technicians. The value of this group was that all members have been able to work proactively with each other. The point of view of each different professional figure has been evaluated and taken into account in order to produce a series of functional requirements. As for the "engineer", it was crucial to participate in the NICU life in order to know and understand in detail, not only at the organizational level but also at the operational level, the needs, expectations and wishes of the staff. In the same way, it was important to attend meetings on the design and layout of each of the department's areas. The exchange of information between the project team specialists allowed creating a "new imaginary NICU" on which to discuss and debate. The next step was to check the technical feasibility of the new "imaginary" department. Since there were few such experiences in Europe and Italy to draw inspiration, we had to investigate technical literature and market products effectively available to assess the feasibility of each suggested solution. Studying and scouting of potential suppliers of technological solutions required several months and was carried out in collaboration with medical and nurse team to which every possible alternative with relative strengths and defects have been explained. The most difficult problems to be addressed were data computerization process and implementation of remote control of each alarm from monitoring systems and from any connected medical device. Following the logistical and operational changes of the new department, a solution was sought in order to facilitate:

- remote management of data from medical device: monitors, ventilators, respirators, infusion pumps, incubators;
- integration of clinical application (electronic medical records, admission discharge transfer, LABs);
- internal communication among the staff;
- communication between parents and staff;
- intercom;
- phones;
- nurse call;
- pager.

All these requirements had to be balanced with the ease and simplicity of communication, minimizing the number of devices each user could have to

manage. All members of the department were involved in the transition process. Meetings were organized where the "new imaginary department" (at this point not so imaginative) was presented to all staff. These meetings helped each professional to visualize his new skills within the entire technology complex of the ward. Once the design phase was completed, production phase started. All suppliers were involved in the process of creating a comprehensive, integrated framework of various parts (servers, computers, mobiles, tablets, medical and institutional software), able to work within a single environment (**Fig. 1**). The primary chain was comprised of the multiparametric patient monitor and the central station (BeneVision CMS, Mindray). From monitors and central stations, data are sent to central servers (eGateway, Mindray; X-Port, Software Team) that, after appropriate checks, send the alarms to the connected handled devices (Smart Pager, Software Team), via a wireless local area network. Other medical devices (infusion pumps, respirators, other specific monitors, etc.) are connected to the network via a connector medical device that uniquely identifies the room and the patient inside. Data from all monitors and devices are also sent to the EMR (Metavision, iMDsoft) via a wired connection. Furthermore, mobile devices can be used as intercoms via uploaded voice communication apps. Both the network and smart pager are equipped with monitoring software that allows reporting any operational problems. The whole production phase was constantly monitored with a series of periodic progress meetings. Acting in this way allowed changes to be made, in a continuous process of refinement. Creating an on-site test room, where each vendor could implement and test the solutions agreed during the technical meeting, was crucial and enabled health personnel to carry out realistic and accurate tests. This strategy also reduced deployment time and improved system customization. In conclusion, the constant dialogue and teamwork with the clinical staff, with which every phase was shared, was the keystone of the project. Following along all phases of operation was the way to achieving solutions that creates certain usability in all its parts (technological and infrastructural). One last note: it is not to overlook the involvement of the staff, even during the designing phase, as it will be the final user. It's from it that come the tips that make the difference between a "project" and a "working project".

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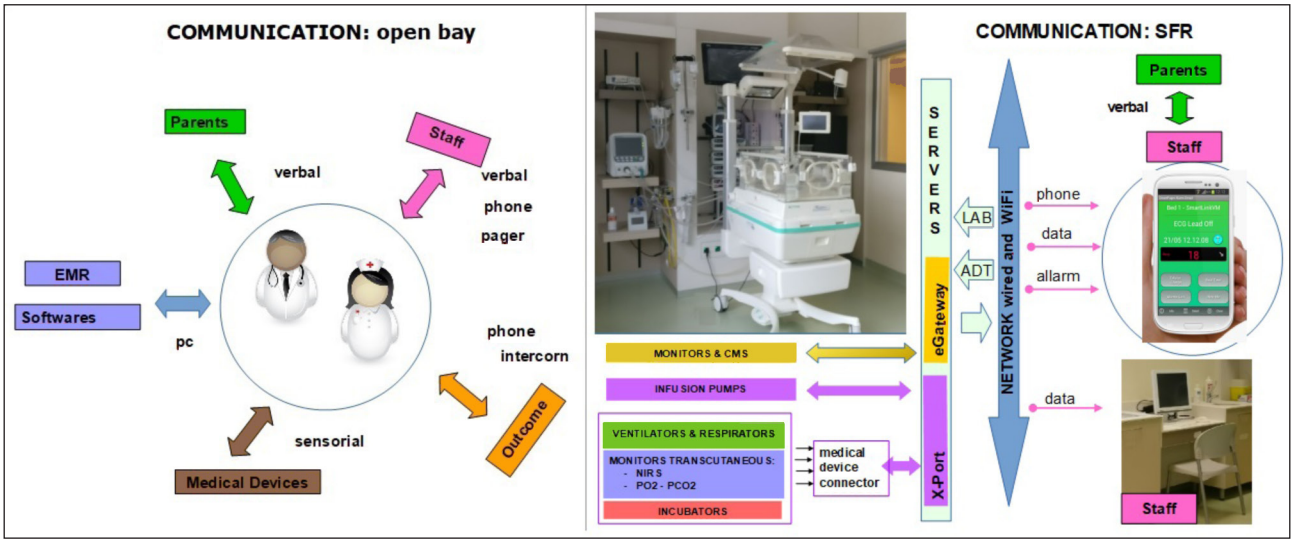

Figure 1 (LECT 20). NICU's communications: open bay versus Single Family Room (SFR).

LECT 21

BREAST MILK FOR THE PRETERM INFANT: THEORY & PRACTICE

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THE BENEFITS OF HUMAN MILK

Pediatric and Neonatology Societies recommend that all preterm infants should receive human milk due to the impressive well documented benefits that nutrition with human milk provides to this vulnerable population [1]. In fact, compared to premature infants receiving preterm formula, those receiving human milk and particularly mother's own milk show a decreased rates of late-onset sepsis, necrotizing enterocolitis (NEC), an improved neurodevelopmental outcomes, in addition to lower rates of metabolic syndrome and cardiovascular diseases. For many of these outcomes there appears to be a dose response effect of human milk feeding, possibly due to the special biological and immunological composition of human milk. For instance, a dose of mother's own milk higher than 50 ml/kg/d decreases the risk of late-onset sepsis and NEC compared to a dose < 50 ml/kg/d.

CHALLENGES TO PROMOTE THE USE OF HUMAN MILK

Unluckily, the use of mother's milk for the preterm infants is relatively limited, particularly in the intermediate birth weight category (1,500-2,499 g) [2] and much investment should still be spent in order to promote it [3]. Nevertheless, providing mother's own milk to the preterm infant may actually represent a challenge for the organization of the Neonatal Unit as well as for the mother-infant dyad [4]. First of all, the NICU should follow a policy of open doors for parents/family in order to facilitate mother-infant relationship, reduction of maternal stress and a timely start of kangaroo mother care [5]. In Italy, initiatives have been recently launched to facilitate the presence of parents in the NICUs. In fact, on May 12th 2016, the Task Force on Breastfeeding of the Ministry of Health (MOH), the Italian Society of Neonatology and "Vivere ONLUS", a NGO that represents parents of infants admitted to Italian NICUs, have co-signed a joint statement that call health professionals to action in order to allow an unlimited access of parents to Italian NICUs. Second, preterm infants have some characteristics that affect feeding and particularly direct feeding to the breast [6]. In fact, they show difficulties in latching, sucking, swallowing and maintaining temperature; moreover, they are drowsy and have more respiratory instability [3]. As a result, the great majority of preterm infants must be tube fed until they prove to be able to feed orally. Common experience and published literature demonstrate that feeding on demand is safe, suitable and feasible for healthy late preterm babies. Diagram for the application of semi-demand feeding also in less mature preterm infants is available, aiming to attain successful transition from tube to breastfeeding. To maximize milk supply, new mothers should pump shortly after delivery (within 6-12 hours of delivery) and should be encouraged to pump 8-12 times per day. Although preterm mothers may have a normal breast milk supply, the shorter duration of pregnancy (that implies a trunked maturation of the mammary gland) and the frequent delayed onset of lactation after childbirth (due to stress and/or medical conditions associated to the preterm delivery) account for a wide range of breast milk production. Third, the prolonged length of hospital stay of a tiny baby may interfere with the psychological wellness of her/his mother, possibly causing a decrease of breast milk production after an initial capability to fully cover her/his nutritional needs. Four, the skills of health professionals in breastfeeding support to preterm mothers and their attitude to value human milk at the top of a biological hierarchy in the nutrition of the preterm infant may be suboptimal [7]. Five, breast milk given to preterm infants with a birth weight under 1,500 g should be fortified to supplement key nutrients with particular emphasis on protein, calcium, and phosphorus. The need for fortification of human milk that leads to improved growth in weight, length and circumference does not cast a shadow on the superiority of mother's own milk, when compared to preterm formula and even to donor milk. Recently, a human milk fortifier formulated by concentrating pasteurized donor human milk has provided the opportunity of providing an "all-human diet" to premature infants, possibly more beneficial than a nutrition based on human milk plus a bovine derived fortifier.

CONCLUSIONS

The use of maternal/human milk and breastfeeding should be regarded as a medical priority among the high risk newborn infants admitted to NICUs, while the intervention required are well known and proven to be effective.

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LECT 22

INEQUALITIES AT BIRTH

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All the children of the world should be born equal, but this is not so: even in Italy striking differences are obvious already at birth. Every baby born in our country should have the opportunity to grow up and develop in an "optimal" way, get the best possible treatment in case of illness, get an education that allows them to develop their full intellectual and cognitive potential. In Italy, despite the high standards of national health care, many aspects of these rights are denied. One of the most accurate indexes to assess demographic wellbeing and quality of life of a population is neonatal mortality (defined as the number of deaths occurring in the first 28 days of life for every 1,000 live births) and infant mortality (number of deaths occurring in the first year of life for every 1,000 live births). In the last few years, there has been a significant decrease in infant mortality, equaling or even surpassing the rates recorded in the most developed Western countries [1]. The reasons underlying this progress are the improved socioeconomic and environmental conditions, the cultural development involving children's rights policies, and the scientific and medical progress. As mortality due to infectious diseases had significantly decreased, perinatal and congenital conditions now have a predominant role. Neonatal mortality, which represents 70% of infant mortality, has not decreased homogeneously: in Southern Italy it is about 30% higher than in the northern part of the country, with no significant changes to this regard in the last few decades [1]. There are several reasons for this disparity: in addition to the well-known differences in social and economic conditions, a decisive role is played by the inadequate organization of perinatal care and the number of small maternity units. Often units with less than 500 births per year have insufficient specialized resources and health care personnel without specific expertise to deal with emergencies involving the mother and/or the newborn. Despite the State-Regions Treaty signed in 2010, where a progressive rationalization/reduction of maternity units with less than 1,000 births/year was agreed upon, local administrations are having a hard time shutting down small units. An additional kind of inequality at birth involves babies born to immigrant women. In the last few years, the sharp increase in migration flow towards our country has changed the composition of the Italian population, with 8% being represented by foreigners. Recent studies have highlighted a greater risk of mortality and morbidity among children born to foreign women compared to Italian women [2-5]. The most recent data from the Italian Statistic Bureau (ISTAT), referring to the 2014 census, show higher neonatal (3.2 vs. 1.8/1,000) and childhood (4.7 vs 2.4/1,000) mortality rates among foreign children living in Italy compared to Italian children (Italian residents). This difference increased from 2011 to 2014, especially due to the perinatal health conditions of immigrant women during pregnancy. Social, economic, cultural disadvantages, heavier work conditions with scanty social security benefits, inadequate nutrition, poor hygienic living conditions, delayed and inadequate obstetric care of immigrant women during pregnancy are all causes of the increase in morbidity and mortality risk in the newborn. There are marked differences in infant health care among Italian regions, in terms of neonatal expanded screening, palliative care, vaccinations, and health care of babies born to migrants with irregular judicial status. It is of mandatory importance to make sure that health care is equal among all Italian regions, stopping all kind of disparities, and to ensure the right to the best possible health conditions for all, from the moment of birth. We must bear in mind that "everyone has the right to a standard of living adequate for the health and well-being" as stated in Universal Declaration of Human Rights of the United Nations (Art. 24) on the

rights of infancy and adolescence and in the Art. 32 of Italian Constitution. Infancy cannot be guaranteed by the mere fact that children themselves exist. There is therefore urgent need for a political and social plan unmistakably focusing on infancy, because children are our future.

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LECT 23

PHARMACOLOGICAL NEUROPROTECTION

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Hypoxic-Ischemic Encephalopathy (HIE), secondary to perinatal asphyxia is one of the most important causes of neonatal death and adverse neurological outcome [1]. Cerebral injury does not occur immediately after the event, but begins during hypoxic-ischemic insult and, in the most serious cases, continues in the following period ("reperfusion phase"), which can extend from 6 to 48 hours [2]. Therapeutic hypothermia (TH) is the standard of care for moderate-to-severe HIE, by reducing the combined outcome of mortality and long-term neurodevelopmental disability at 12-24 months of age [3-5]. Nevertheless, TH does not completely protect an injured brain. There is evidence that neonates with the most severe forms of HIE may not be able to be rescued [3-5]. In addition, its benefit in babies with encephalopathy during sepsis or in those born following chorioamnionitis is unclear [6]. Pathogenic mechanisms involved in neonatal hypoxia-ischemia recognize the brain injury extending into a tertiary phase, which lasts for weeks to years after the initial insult and opens up new possibilities for therapeutic strategies [2]. The rationale of adding neuroprotective drugs to TH would be the extension of therapeutic window or the provision of long-lasting additive/synergistic protection. On the other hand, it is important to consider that drugs administered during the neonatal period may be toxic to the immature brain. Furthermore TH has the potential to alter the pharmacokinetics (PK) and pharmacodynamics (PD) of many drugs routinely used in the care of critically ill neonates, leading to higher serum concentrations and risks for adverse effects through a decreased function of CYP450 and hemodynamic changes. Rewarming may also produce significant alteration in PK and PD [7-8]. Antiepileptic drugs (AED), frequently used to control seizures in HIE, may also have potentially neuroprotective properties, acting by reducing excitatory amino acid release and calcium overload in the ischemic cells. Topiramate has shown some synergistic effect with TH, if used immediately after hypoxia-ischemia [9]. Recently studies performed on melatonin, a naturally occurring hormone that regulates the circadian rhythm, have aroused considerable interest. Melatonin achieves powerful neuroprotective effect via anti-oxidant, anti-apoptotic and anti-inflammatory processes and by promoting neuronal and glial development. Its potent free radical-scavenging properties provide neuroprotection towards developing brain tissue [10, 11]. Erythropoietin (EPO) can also be considered in neuroprotection from neuronal damage. There are preliminary data on the biological role of recombinant EPO (r-EPO) in the developing nervous system, based on the expression of its specific receptor (EPO-R), located on neurons, glia and endothelial cells. EPO is a pleiotropic cytokine with multiple roles in addition to that of haemopoietic growth factor; it acts as anti-apoptotic, anti-oxidative and anti-inflammatory agent. In addition EPO plays a key role in neuronal repair resulting from cerebral damage, stimulating neurogenesis, oligodendrogenesis and angiogenesis [12, 13]. Endocannabinoids are emerging as substances with high potentially neuroprotective effects mediated by TH for HIE [14]. They represent an endogenous neuromodulatory system that can inhibit glutamate excitotoxicity, intracellular calcium buildup, activation of cell death pathways, microglia activation, neurovascular reactivity and infiltration of leukocytes circulating throughout the blood [15]. In combination with TH, neuroprotection by Xenon, a known potent anesthetic, has been tested in several experiments. Their mechanisms of action are inhibition of AMPA and Kainate receptors, reduction of neurotransmitter release and effect on ion channels [16]. Allopurinol, a xanthine oxidase inhibitor

that lowers uric acid concentrations, acts as a direct scavenger of hydroxyl radicals, suggesting a role in neuroprotection [17]. Other potentially useful drugs are N-acetyl-L-cysteine, the transcription factor kappa B (NFkB) and stem cell therapy [18, 19]. Possibilities for pharmacologic combination therapy, where each drug will be administered based on the optimal point of time in the cascade of destructive molecular reactions, may further reduce brain damage due to perinatal asphyxia. It is necessary to investigate the optimal dose of these agents, the optimal point of start and duration of pharmacological therapy in order to provide more effective neuroprotection. However, intensivists must be aware of the effects of TH on drug disposition, metabolism and response, in order to maximize the therapeutic efficacy of the agents used in conjunction with this therapy.

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LECT 24

WHEN AN INFANT DIES IN NEONATAL INTENSIVE CARE UNIT (NICU): EXPERIENCES BY NOVARA AND TURIN

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INTRODUCTION

This project was born inside the Complex Structures of Neonatology, Obstetrics and Gynaecology of the Hospital S. Anna of A.O.U. City of Health and Science of Turin and of Neonatal and Pediatric Intensive Therapy of A.O.U. Maggiore della Carità of Novara, Italy. The Unit of Neonatal and Pediatric Intensive Therapy is a space marked out by high technology, which is useful to support the premature babies growth or to restore the health of children who are seriously ill. Losing a baby/child is a huge psychic trauma, which creates a remarkable shock in parents' life, because it is actually a "multiple" loss: losing a child also means losing the parental liability. This situation gets often worse because of the absence of a team support and insufficient aid, which complicate the grief development process of the couple and produce an extra charge of emotions into the professional team. The emotional and psychological support of health workers could represent in this particular moment an added value,

due to the need of approaching the relationship in a "deeper understanding of parents' needs". Into these teams of intensive therapies, a context analysis has shown that very often the health care activities prevail on communication among professionals and the helping relationship through the family. The educational project has been thought because of the team's need of sharing feelings and defines the used and shared activities, to support the communication level relationship between professionals and families.

AIMS

To define an educational path for health workers to support family in the moment of losing a child.

SAMPLE

Participants were all the health workers of the NICUs (doctors, nurses, pediatric nurses).

MATERIAL AND METHODS

To create the educational event, the training programme follows the steps below:

1. debate with directors of the training programme;
2. needs analysis;
3. macro planning of the meeting;
4. micro planning of the meeting;
5. evaluation of the training speech.

RESULTS

Meetings with supervisors of training have focused as object of debate the following topics: sharing specific goals, choosing didactic methods and resources, and the chance of validate the educational path in Continuous Medical Education. After a research on literature and Italian reality, a questionnaire has been identified to evaluate the training need. The tool "Lucina survey 2012", elaborated and validated by "Ciaolapo Onlus association", examines procedure and certainties of health workers on prenatal grief during intensive therapies. Training part represents the core of the project; the most appropriate didactic method is the focus group. At the moment, the following resources have been identified: the presence of a representative of Psychology Department of A.O.U., who can engage experts or health workers who have already had a training on unexpected grief; the organization of meetings in small groups debating situations/experiences of grief and macro areas identified by data and literature analysis. Some of the topics of the meetings are: communication strategies in critical situations (true and complete information); communication availability with health workers; sharing therapeutic choices between professionals and parents; emotional expression and support by the team; preservation of integrity of the relationship between parents and child (the parents have to stay with the child during and after the death); trauma psychology and prenatal grief, and faith. After the realization of this educational event, participants evaluated its usefulness by filling a specific questionnaire form. The goal of the project is supporting families when losing a child. This is why it will be necessary to activate, engage and coordinate Hospital Departments in the management of life ending, creating a shared educational path.

LECT 25

THE NEONATAL NETWORK OF THE ITALIAN SOCIETY OF NEONATOLOGY

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A deep knowledge of the organization of perinatal care and the acquisition of accurate statistical data about births, pregnancies and their outcomes are important public health instruments for evaluating and improving efficiency and effectiveness of neonatal and women's care, both for single institutions and on a regional basis. To this effort, the Italian Society of Neonatology (SIN), which has the aim to promote any measure that can improve well-being of newborn and neonatal care, in the past years, developed and promoted the Neonatal Network of the Italian Society of Neonatology (NNSIN). The NNSIN is a free, collaborative, voluntary, on-line network aimed to collect, maintain and evaluate data of all preterm infants admitted by the Italian neonatal units participating. The NNSIN is the first Italian network that offers the possibility to collect reliable information on a population of preterm babies (including obstetric and neonatal history, short-term and long-term outcomes) and to conduct descriptive and analytical analyses also in the group of late preterm babies (from 34^{+0} to 36^{+6} weeks of gestational age), who are at greater risk of mortality and short-term morbidity than term babies. All Italian Neonatology Units, not only Neonatal Intensive Care Units, may have now their own database with no supplementary costs and this is a unique opportunity. Adherence to the NNSIN is free and is governed by a special contract between the center and the SIN. Database requires only an Internet connection and a password is provided at the time of enrollment.

Data entry is done on-line and no special skills or dedicated software is required. Once the data entry is complete, any center will have the following options: a) comparing data among different centers enrolled in the same region; b) comparing data with all Italian centers enrolled (so with the Network); c) comparing data of their own center longitudinally to assess what changed during the time and to evaluate temporal trends in practices and in neonatal outcomes. All data are available in electronic format (Excel®) with the possibility to make specific elaborations for their own purposes. A support team is always available at the email address nnsin@biomedia.net for scientific and technical support and there is also an expert on statistics for data analysis. NNSIN was born in 2014 and since then the number of participating centers has progressively increased. Nowadays, 111 units are enrolled. Seventeen Italian regions have at least one participating structure. Friuli-Venezia Giulia, Molise and Valle d'Aosta regions are the only regions not yet covered, at the moment. Distribution based on level of standard of care provided is: 56 level III centers, 37 level II centers and 18 level I centers. Data entry for the year 2016 ended on March 31, 2017. This data has been subjected to statistical processing. All network participants can view online the perinatal statistics as well as the outcome and perinatal care of their own preterm newborns. In 2016, the participating centers produced 4,889 newborns so distributed: 883 (18.0%) very preterm neonates; 808 (16.5%) moderate preterm neonates; 3,206 (65.5%) late preterm neonates. An adequate graphical representation allows visualizing, synthesizing and interpreting the variability of the parameters/characteristics of a study; therefore it has been created a report page equipped with two different types of dynamic charts: bar graphs and "caterpillar plot". It's possible to choose different hierarchical levels of geographic aggregation and to analyze data combining weight at birth, gestational age and the year of birth. All the variables included in the network can be graphically represented. "Caterpillar plot", in this context, will be used for the graphical representation of quartiles of the continuous variable that is selected in the interactive report pages. The resulting diagram will show the location of your own center (highlighted in red) compared to other network structures (highlighted in blue and unlabeled) and compared to both, regional (highlighted in gray) and total network (highlighted in black) (**Fig. 1**). Bar chart will be used to display percentage for each category of the nominal variable that is selected in the interactive report pages. With the improvement of the "Graphics" section on the report pages, we aim to create a new tool able to offer

Figure 1 (LECT 25). "Caterpillar plot" of weight at discharge (example). Year 2016.

to researchers, neonatologists and all the professional figures involved in perinatal care, the ability to perform effective, friendly and personalized data analysis in real time. This can represent a further help to better evaluate level of activities, outcomes and quality of care provided and suggest directions for future studies and for possible organizational changes aimed to increase quality and safety of care.

LECT 26

NEUROPHYSIOLOGICAL TESTS IN THE NEONATAL PERIOD

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Neurophysiological tests (NTs) are important tools for evaluation of nervous system function, with recognised diagnostic and prognostic utility in neurology [1]. NTs give useful informations that integrate clinical examination and neuroimaging. NTs can explore both Central (CNS) and Peripheral Nervous System (PNS). NTs that explore CNS are: conventional electroencephalography (EEG), video-EEG with polygraphy, automated EEG which includes amplitude integrated electroencephalography (aiEEG) or cerebral functioning monitor (CFM), evoked potentials (EPs) in the somatosensory (SEP), visual (VEP) or auditory modality (brainstem auditory evoked potentials – BAEP) and motor evoked potentials (MEP). Furthermore, the evoked potentials methodology can be also used to evaluate integrity of auditory and visual functions, by means respectively of BAEPs and VEPs. In the last decade NTs have been increasingly used in neonatal neurology particularly as prognostic tools in hypoxic ischemic encephalopathy, especially aiEEG, EEG and SEPs. Herein we will focus on these NTs techniques. The CFM, or aiEEG, is a technique for cerebral function monitoring that records, through 2-4 electrodes, changes in amplitude of the electroencephalogram and the impedance between the recording electrodes. It is broadly used for diagnosis of HIE and selection of newborns for therapeutic hypothermia [2]. EEG, but especially video-EEG with polygraphy, is considered the gold standard for diagnosis of neonatal seizures and it is a crucial tool for differential diagnosis with non epileptic paroxysmal motor events. Video-EEG with polygraphy consists in recording of multichannel cerebral activity (8 electrodes), muscular activity, electrooculography, heart rate, breath rate and abdominal movements while video recording the patient; it allows to correlate ictal events with clinical motor manifestations, to diagnose subclinical seizures or electrical seizures occurring because of electro-clinical dissociation [3]. Advantages of aiEEG over conventional EEG are easy use and interpretation, reduced number of electrodes, possibility of continuous monitoring; disvantages of aiEEG are occurrence of many artifacts, missing of short and low amplitude ictal events and the lack of neurophysiological information on all brain areas. The best practice includes a combination of CFM and conventional EEG and needs a good cooperation between neonatologists and neurophysiologists. EPs evaluate sensory pathways and their respective cortex activated by acoustic, visual and somatosensory stimuli; median and tibial nerves are usually used; they consist in variations of electric charge recorded close to the afferent volleys and on the scalp, as a sequence of waves with specific latency, amplitude and morphology depending on the different sensorial stimuli used. SEPs are generated in peripheral nerves, spinal cord and the brain following electrical nerve stimulation. They offer the unique possibility to test both peripheral and central somatosensory pathways. In the neonatal period they differ from adult responses because of somatosensory system immaturity. SEP technique in newborns is different from children and adults; in fact different frequency of electrical stimulation and filter settings are needed [4]. VEPs evaluate functional integrity of the visual system by recording bioelectric potential variations of occipital cortex after a visual stimulation; they are useful as integration to other NTs for CNS study. Trollmann et al. in their study demonstrate that SEPs are a valuable tool for early diagnosis of HIE, but they aren't prognostic of neurodevelopmental long-term outcome [4].

NTs in neonatology are very useful in neonates with HIE; in these patients SEPs positive predictive value for short-term outcome was 73-100% [1-5]. Suppiej demonstrated that combination of VEPs and SEPs is a good choice for neurodevelopmental prognostication [5]. In conclusion NTs are very

useful tools for neonatologists; it is important to integrate various NTs both for diagnosis and management of CNS pathologies.

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LECT 27

VENTILATION STRATEGIES FOR CRITICALLY ILL NEONATES WITH BRONCHIOLITIS

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Medical assistance of infants with bronchiolitis comprises symptomatic and supportive treatments but some infants may need respiratory support. These patients have severe obstructive airway disease with increased respiratory resistance, air trapping and decreased dynamic compliance with higher risks of respiratory failure. Until 1980s the usual treatment for respiratory failure has been invasive mechanical ventilation (MV); its application requires sedation and even neuromuscular blockade and is associated with significant airway adverse events: MV often exacerbates the inflammatory lung effect of the virus by inducing lung ventilator injury, ventilatory acquired pneumonia (VAP) and co-infection [1]. Non-invasive ventilation (NIV) has been used in children with bronchiolitis since the nineties and its use has rapidly spread. Increasing number of studies have reported experiences on NIV in bronchiolitis and relevant data confirmed that NIV is a valid alternative to MV for bronchiolitis: continuous positive airway pressure (CPAP), bi-level continuous positive airway pressure and non invasive positive pressure ventilation, applied through different interfaces, have been documented as successful techniques of NIV; in particular CPAP has been proposed as the first modality of respiratory support in bronchiolitis [2]. Although two recent systematic reviews [3, 4] identified a lack of large randomized prospective studies and concluded that the effect of NIV in bronchiolitis is uncertain, clinical practice has clearly moved towards NIV in this setting and numerous non-randomized studies supported the use of CPAP as gold standard treatment for severe bronchiolitis. This ventilatory strategy was associated with a decrease in respiratory distress symptoms by unloading respiratory muscles and improving breathing pattern, gas exchange and clinical outcome [5, 6]. NIV implementation allowed a decrease in need for MV [2,7], a lower rate of VAP and co-infection and a shorter duration of respiratory support [1, 8]. Furthermore, there is evidence that an early use of nasal CPAP is associated with significant reduction in the economic burden of severe bronchiolitis [2]. A recent new modality of non-invasive respiratory support for the management of respiratory distress due to bronchiolitis is high flow nasal cannula (HFNC) oxygen delivery. HFNC provides high heated and humidified gas flow with an oxygen concentration between 21% and 100%. Its mechanism of action comprises: washout of nasopharyngeal dead space, reduced work of breathing, increased pulmonary compliance, reduced metabolic cost for gas conditioning and some degree of CPAP [9]. Its use has been increasing implemented in clinical practice both in general pediatric wards and intensive care settings despite lack of strong evidence on its effectiveness [10]: it is considered less invasive than CPAP, better tolerated and easy to be set up and administered by the staff [11]. There is lack of international guidelines regarding flow rates and the optimal maximal flow for HFNC is not known: flow rates up to 1.5-2 L/kg/min (max flow 10 L/min) are being used in infants. In conventional nasal CPAP the pressure is controlled via a valve providing an escape route while in HFNC there is no equivalent control valve and the only escape routes are the leak at the nares-prong interface and via the mouth. The pressure applied to the airway is difficult to be determined or regulated and this fact perhaps could be related with few cases of pneumothorax reported in literature [12]. Retrospective and prospective observational studies have suggested encouraging results on both physiological [13, 14] and clinical variables. Main clinical effects reported a reduction

in respiratory rate (RR), improvement of blood gas parameters and a reduction in need for intubation [15, 16]; predictors of HFNC failure were lower pH, higher pCO_2, lower RR before commencing treatment and lack of change in RR after initiation of HFNC [17]. Currently, CPAP and HFNC represent the most diffuse NIV modalities for respiratory support in bronchiolitis, but data from studies comparing the two techniques are limited and no study has yet provided a direct demonstration of HFNC efficacy and safety compared with CPAP [18, 19]. A recent prospective multicenter randomized controlled trial (RCT) suggested that CPAP may be more effective than HFNC for initial respiratory support in young infants hospitalized in a Pediatric Intensive Care Unit for moderate to severe bronchiolitis [20]. High-quality RCTs using standardized methodology should be conducted to identify whether HFNC and CPAP do confer benefits on important clinical outcomes for infants with bronchiolitis. Until this evidence is available, HFNC may be used as a form of respiratory support but still with a critical approach regarding clinical effect and safety, particularly when operating outside of an intensive care unit.

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LECT 28

UTILIZATION OF ECHOCARDIOGRAPHY AND MANAGEMENT OF PATENT DUCTUS ARTERIOSUS: TWO SURVEYS IN ITALIAN NEONATAL INTENSIVE CARE UNITS

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In the neonatal intensive care unit (NICU) echocardiography has acquired a new role over the last few years. In past years, echocardiography has been performed only by pediatric cardiologists to diagnose and monitor congenital heart diseases. More recently, echocardiography has increasingly been used by neonatologists as an adjunct in the clinical assessment of the hemodynamic status in neonates [1]. The term "functional echocardiography" has been introduced to describe the use of echocardiography performed by neonatologist for cardiovascular assessment [2, 3]. There is a growing evidence that functional echocardiography is a useful clinical tool in the identification of hemodynamic instability and in guiding treatment [4, 5]. In 2011 the American Society of Echocardiography (ASE), the European Association of Echocardiography (EAE) and the Association for European Paediatric Cardiology (AEPC) published practice guidelines and recommendations for training in Targeted Neonatal Echocardiography (TNE), also called functional echocardiography [6]. More recently, a working group of the European Society for Paediatric Research (ESPR) and the European Society for Neonatology (ESN) wrote a consensus statement on functional echocardiography, taking into account the previous TNE recommendations [7]. In the past ten years, the increasing availability of echocardiography in the neonatal units together with the consistent lack of demonstrable improvement in neonatal and neurodevelopmental outcomes, following non-selective PDA treatment, allowed for more conservative management of PDA and for selection with early screening echocardiography of neonates requiring PDA treatment [8, 9]. However, controversy still remains on the optimal management of PDA and there is no robust evidence from randomized clinical trials that helps neonatologists to understand which patient to treat, when and with which drug [10]. Data on utilization of echocardiography and management of PDA were previously reported, but, to the best of our knowledge, no data are available from Italy [11-14]. Aim of our study is to investigate the utilization of functional echocardiography and the management of PDA in the Italian NICUs. We designed two surveys, the first on the utilization of functional echocardiography and the second on PDA management, in order to understand current clinical practice in Italy. A structured questionnaire was emailed with an online hyperlink to both directors and consultant neonatologists with an interest on neonatal hemodynamics, working in neonatal units in Italy. The survey was started in June 2017 and it will end in September 2017.

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LECT 29

CRANIAL ULTRASOUND IN LATE PRETERM INFANTS

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Late preterm infants (born at 34⁄0-7 through 36⁄6-7 weeks gestation) are the most represented premature infants in the developed countries, accounting for about 72% of preterm births [1]. Late preterms are physiologically immature compared to term infants and they are more likely to develop diseases in the early neonatal period (temperature instability, respiratory distress syndrome, excessive weight loss and dehydration requiring intravenous infusion, sepsis, hypoglycemia and jaundice requiring phototherapy) [2, 3]. Brain vulnerability has been documented and attributed to both intrinsic (brain immaturity) and extrinsic factors (postnatal morbidities). The weight of the fetal brain at 34 weeks gestation is about 65% of the term brain weight and the cortical volume is only 53% of the term volume [4]; in addition, the volume of myelinated white matter increases dramatically as term is approached, with a five-fold increase between 35 and 41 weeks [5]. Rapid cellular and structural changes occur during the late preterm period making the developing brain vulnerable to extrinsic insults [6]. Late preterm infants are exposed to a wide spectrum of perinatal brain lesions common to both term and more premature babies, including germinal matrix-intraventricular hemorrhage (GMH-IVH), cystic periventricular leukomalacia (cPVL), arterial/venous stroke [7], lesions related to hypoxic-ischemic (hypoxic-ischemic encephalopathy, HIE) [8] or hypoglycaemic insults. However, specific gestational age dependent characteristics of these lesions have been described: different patterns of brain involvement and different risk factors (twin-to-twin transfusion syndrome, fetal heart rate abnormality and hypoglycemia) have been demonstrated in preterm infants, including late preterms, with arterial ischemic stroke compared to term babies [7]; similarly, different injuries patterns, including white matter lesions, have been observed in a preterm cohort, predominantly represented by the late preterm group, suffering HIE [8]. Cranial ultrasound (cUS) scans allow the identification of most of these perinatal brain lesions in particular those correlated with adverse long-term motor prognosis although some lesions (arterial ischemic stroke, HIE) may become more obvious at cUS over a few days after birth suggesting that sequential cUS may be necessary for early diagnosis of brain injury. However, neuroimaging examinations are not routinely performed in late preterm infants due to the magnitude of this low-risk population requiring high resource utilization and medical costs [3]. According to a hospital-based cUS screening program, the risk for late preterms to develop an abnormal cUS is inversely related to gestational age at birth and it doubles for every week gestation moving from 36 to 34 weeks [9]. Gestational age and the occurrence of neonatal morbidities, in particular respiratory distress syndrome, seem to be the most important risk factors for developing an abnormal cUS in this population [9]. Similar results have been reported by Ballardini et al. in preterm infants with gestational age 33-36 weeks: babies born at 33-34 weeks gestation are four times more likely to show abnormal cUS compared to those born at 35-36 weeks [10]. In infants with abnormal cUS, a significant association was found between abnormal cUS and need for ventilation, use of surfactant and low Apgar index at 5 min while no significant association was observed with being small for gestational age [10]; the presence of at least one of these risk factors increased the probability of brain abnormalities detected by cUS of 4.76 times [10]. The effect of twin birth has also been investigated but no association

with US detected cerebral injury [11] has been documented. The occurrence of brain abnormalities in late preterm infants may contribute to explain the increased risk of impaired neurobehavioral outcome in late preterm compared to term infants reported in the literature (poor school performance, early intervention services, special education needs) [12-16]. However, the occurrence of these brain lesions may be underestimated as they are usually clinically silent and neuroimaging examinations (cUS) are not routinely performed. Considering the magnitude of the late preterm population, a universal cUS screening program would result in a heavy economic burden on caregivers; therefore, specific protocols tailored on perinatal risk factors should be developed in order to early detect those late preterm infants developing brain injuries who may benefit from early intervention programs.

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LECT 30

CAN REGISTRIES AND HEALTH ADMINISTRATIVE DATA HELP IMPROVE QUALITY OF CARE?

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QUALITY IMPROVEMENT AND DATA

"In God we trust. All others please bring data". These famous words are attributed to W. Deming, the father of quality improvement (QI) and of the Plan-Do-Study-Act (PDSA) cycle. It succinctly shows the importance given to data, and to decisions based on data, by the QI world. QI is an enterprise characterized by a dual nature: scientific and executive. Based on knowledge of the current state of a system and of the target state to which one wishes to arrive, it applies an intervention that builds on a variety of measures often taken from corporate culture to achieve the desired change. Though in medicine QI initiatives usually partake of the paradigm of evidence-base medicine, the instruments of change are not plainly "scientific". For instance, the interventional arms of QI initiatives are often not randomized, in contrast to what happens with purely scientific enterprises. In QI, typically one looks at a problem in a pragmatic, quantitative way (through one or more indicators) and defines steps that can be measured, quantitatively analyzed, and changed. After applying an intervention, the measurement is run again; changes in outcome and intermediate steps are recorded, new interventions are devised and carried out, and the cycle is repeated again. The measurement of an adequate indicator is a typical example of observational research, and both health administrative data and registries are instrumental to this purpose.

HEALTH ADMINISTRATIVE DATA

Ideally, a routine collection of data should require little effort, and include indicators that are robust, easy to collect, accurate, and reliable. The idea of routinely collecting data to rate the performance of hospital units is at the base of the "*Programma Nazionale Esiti*" ("National Program about Outcomes"), which uses data from Hospital Discharge Forms (*Schede di Dimissione Ospedaliera* – SDO). However, it distinctly lacks neonatal indicators. While the idea of using data routinely collected for administrative purposes is very appealing because apparently it does not require any extra effort, in reality it has a number of drawbacks. The first is probably the fact that access to these data and analysis requires permissions and are in general limited to governmental bodies (e.g., the State, or Regions or regional health agencies), and are not permitted to single hospitals or researchers. This obviously limits its usefulness, practical use and impact. The second problem is that several databases must be linked to obtain meaningful QI projects. In neonatology, the Birth Certificate (*Certificato di Assistenza al Parto*, CeDAP) is a useful starting point because it contains several important features of the mother and the baby, but is limited to the first hours or days after birth, and other databases must be linked to get information on outcome (e.g., death certificates, hospital admission and discharge data, etc.). Moreover, especially for extremely preterm babies, the CeDAP often contains errors and the linkage to other registries is not complete. A third drawback is the low granularity of health administrative data. As an example in neonatology, many evidence-based interventions are not recorded in CeDAP or in SDO, or lumped together without sufficient detail. In short, while health administrative data have the advantage of making large dataset available on entire populations, and their use for descriptive data and even scientific projects are countless, using for QI is much more limited, and examples are few.

REGISTRIES AND NETWORKS

In neonatology, registries are frequently used in QI. They are generally voluntary registries, created (and often run) by clinicians with a bottom-up effort, with strong clinical characterization and interests. Instead of "registries", they are usually called "Networks". They are often non-governmental but run by scientific societies and groups of hospitals. Their focus – for QI initiatives – is on the single hospital. Probably the first, and still the bigger and most known, is the Vermont-Oxford Network (VON). It started in 1988 with the collaboration of 34 units, collecting data on very low birth weight infants (VLBWI), and subsequently also on infants < 30 weeks. With more than 1,000 hospitals now participating, it has become a "standard", which has influenced several other networks and projects: the philosophy of these networks is to collect a limited number of carefully selected items, easily interpretable, with standard operative definitions so that there is little variation in data collection between hospitals. The mission of VON is to "improve the quality and safety of medical care for newborn infants and their families through a coordinated program of research, education, and quality improvement projects". To do this, it "offers data-driven, action-oriented learning for improving outcomes and increasing the quality, safety, and value of newborn care". A very important feature of these networks is the involvement of participants, including nurses, midwives and doctors. The aim is to create a community of practice that together applies evidence-based medicine, decreases variation of practice between places, and improves quality of care, where data collection is only a step in the process. In Italy, a rich history of networks and QI initiatives exists.

LECT 31

POSTNATAL MANAGEMENT OF URINARY TRACT DILATION DETECTED DURING PREGNANCY

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Urinary tract dilations (UTDs), a frequent occurrence in the ultrasound screening of congenital malformations, are reported in 1-2% of all fetuses; these represent the epiphenomenon of a wide spectrum of situations which can be pathological and physiological, influenced by the degree of bladder filling, by the state of hydration, and by the patient's position (in many cases the posterior anterior diameter of the pelvis [APRPD] is reduced if measured in the prone position). The most frequently reported cases during pregnancy involve mild dilatation of renal pelvis in fetuses that do not present associated malformations and that have normal kidneys by number, shape, position and echogenicity (often still called with the cacophonic term of pyelectasis). These mild dilatations of the

renal pelvis tend to have a progressive spontaneous resolution, do not predispose to urinary infections (UTIs), and do not cause long-term alterations in renal function. For these newborns, who would not benefit from invasive diagnostic investigations, communication with families must be reassuring and follow-up does not have to be too exhausting. More rarely, uterine UTDs reveal complex clinical situations: these are the cases where the pelvis dilation is associated with calyceal dilation (central: major calyces or peripheral: minor calyces), or with ureteral dilation or bladder abnormalities (increased wall thickness, presence of ureterocele, dilated posterior urethra), or with alterations of parenchymal appearance (reduction of the parenchymal thickness, increased echogenicity, reduction of normal corticomedullary differentiation, presence of cortical cysts). These rare, but more complex, ultrasound findings reveal risky pathologies and require timely diagnostic evaluation, to prevent the occurrence of complications (infections or calculations) and to limit the progress of the damage to the renal function. The main goal of neonatologists and experts (nephrologists, radiologists and pediatric urologists) involved in the postnatal management of UTDs is to distinguish the frequent benign dilations from potentially dangerous congenital malformations. To achieve this goal, we must use a common language (the different terminology used until now hindered the comparison of clinical data), we need a unique method, shared and repeatable, for performing pre- and postnatal ultrasound examination; above all we need a classification system in which the UTDs are distinguished not only by the magnitude of the dilation, but also by the concomitance of associated pathological ultrasound findings, which imply a different level of risk, and thus a different diagnostic, therapeutic, and follow-up program. A significant contribution to the achievement of these goals is due to the recent publication *Multidisciplinary consensus on the classification of prenatal and postnatal urinary tract dilation*, result of the collaboration of all the most authoritative international scientific societies. This consensus proposes to standardize the language of the professionals involved in the management of these pathologies, clearing the field from the use of non-specific and confusing terms such as hydronephrosis, pyelectasis, pelviectasis, uronephrosis, which are not recommended and should be avoided, while the use and dissemination of the only term "urinary tract dilation" (UTD) is recommended. A great merit of the same consensus is to point out the correct method of execution of the ultrasound exam: for example it specifies that the pelvis must be measured in its maximum intrarenal diameter, on the transverse plane, at the level of the hilum, with the patient in the prone position. Finally, the expert panel recommends abandoning the different grading systems currently used: descriptive (mild to moderate, moderate, severe), quantitative (based on numeric value of APRPD), or semi-quantitative, and proposes a unique classification system for pre- and postnatal ultrasound reliefs, that can reduce ambiguities in the exchange of information between gynecologists and pediatricians. The proposed classification is based on both quantitative parameters (APRPD and parenchyma thickness) and qualitative (calyceal dilation, making a distinction between central and peripheral location, parenchymal appearance), and includes evaluation of associated abnormalities of ureter and bladder. A different category of risk is associated with every type of UTD classified, and for each category a management program is proposed. Precisely this last point, certainly the most important, but also the most complex, highlights all the unresolved issues and all the limitations of our current knowledge, because the panel of experts recognizes that the importance of early diagnosis of vesicoureteral reflux and the effectiveness of antibiotic prophylaxis in preventing kidney damage is still controversial, and leaves the clinician with the burden of choosing to perform invasive diagnostics (voiding cystourethrography) and/or use of prophylactic antibiotics.

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LECT 32

ITALIAN RECOMMENDATIONS FOR THE MANAGEMENT OF CORD CLAMPING IN TERM AND PRETERM NEWBORN

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Delayed umbilical cord clamping (DCC) and cord milking (CM) are placental transfusion strategies that produce higher hemoglobin levels and iron stores in term newborns and better hemodynamic conditions, decreased rates of intraventricular hemorrhage, sepsis, necrotizing enterocolitis and transfusion in premature newborns. Recent evidences from the literature showed that cord clamping before the onset of ventilation determines the reduction of right ventricular preload that, combined with the increased afterload, decreases the left cardiac output. Lung aeration reduces pulmonary vascular resistance and triggers an increase in pulmonary blood flow, guaranteeing the left ventricle preload; hence, the hemodynamic stabilization obtained by DCC after the onset of spontaneous breathing is a potential strategy to preserve germinal matrix vasculature and reduce the risk of intraventricular hemorrhage. The interruption of umbilical blood flow before the onset of spontaneous breathing has been demonstrated to adversely affect cerebral perfusion during the transition from fetal to neonatal life and augment the risk of death or hospitalization. DCC is now recommended by many scientific societies for both term and preterm newborns not requiring resuscitation. In term newborns, DCC for at least 1 minute is recommended; however, to improve ferritin at 4-6 months of age; a 3 minutes delay seems to be preferable. In preterm newborns not requiring immediate resuscitation, a 30-60 seconds delay before clamping the cord is suggested. World Health Organization recommends delaying 1 to 3 minutes the clamping of the cord in term newborns and suggests stimulating not-breathing newborns before clamping the cord. A recent Italian survey showed a low application rate for both DCC and CM, especially at the lowest gestational ages; only 10% of the responders reported to perform DCC below 29 weeks of gestational age. The implementation of placental transfusion strategies in Italy is currently limited by problems of organization and pragmatic difficulties in clinical practice. The survey demonstrated a significant correlation between the implementation of DCC and CM and the knowledge of related benefits, the availability of obstetric-neonatal guidelines and the engagement across professions within the delivery-team. In order to improve the uptake of placental transfusion strategies and homogenize the management of the umbilical cord nationwide, an Italian Task Force for the Management of Umbilical Cord Clamping, composed by neonatologists, gynecologists and obstetricians, has been constituted in order to draft national recommendations for the management of cord clamping in term and preterm newborns. After identification and prioritization of the questions to be addressed, using the PICO (population, intervention, comparator, outcomes format), the task force performed a detailed systematic review using the methodological approach proposed by the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) Working Group. GRADE is a consensus process that rates quality of evidence and strength of recommendations along with values and preferences. The quality of the evidence is categorized as high (high confidence in the estimate of effect), moderate (moderate confidence, but there may be differences from a further elucidated truth), low (low confidence in the estimate of the effect that may be different from the true effect), or very low (it is possible that the estimate of the effect is substantially different from the true effect). A recommendation is defined as "strong" when there is a clear expectation for adherence to the recommendation and "weak" when there is a lesser insistence for adherence. The direction of effect may be in favor of or against

the recommendation. The document analyses all clinical scenarios that operators could deal with in the delivery room. Specifically, the panel intended to promote a more physiological and individualized approach to cord clamping, specifically for the most preterm newborn, when DCC is less implemented. A feasible option to implement DCC in very preterm deliveries is to move the neonatologist to the mother's bedside in order to safely guarantee the first steps of stabilization (provide warmth, ensure open airways, dry, and stimulate) before clamping the cord; this could allow at least a 30 second of DCC for all preterm newborns, without delaying resuscitation (see flow-chart). The task force suggests to milk the cord when DCC is not feasible. In vaginal delivered newborns, DCC for 3 minutes is suggested for term and late preterm newborns with spontaneous breathing. For those who do not breath spontaneously at birth, the cord must be clamped if the newborn continues to be apneic after stimulation. The evidence for the optimal time to clamp the cord during cesarean delivery in order to ensure greater amount of iron stores in infancy is weak; we suggest clamping the cord at 1 minute of life. Umbilical cord blood donation should not interfere with cord clamping and a delay between 1 and 2 minutes is recommended. Contra-indications to DCC are those situation that may endanger mother's health, placental abruption, umbilical cord prolapse, uterine rupture, monochorionic twins, birth asphyxia, shoulder dystocia, doubt about the integrity of umbilical cord, fetal hydrops. The project will end with a new Italian survey to be carried out in 2018 with the aim of evaluating the implementation of the recommendations.

LECT 33

NEONATAL ENDOCRINE EMERGENCIES

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Neonatal endocrine emergencies are uncommon, but may determine significant morbidity and mortality if a precocious diagnosis and treatment are not established. The transplacental passage of TSH receptor antibodies in mothers with current or previous autoimmune thyroid disease may determine a fetal/neonatal hyperthyroidism and/or hypothyroidism depending from the presence of stimulating and/or blocking antibodies. Although neonatal thyrotoxicosis is rare, it is associated with a high mortality (12-20%) if treatment is not started promptly. During pregnancy the maternal antithyroid drugs cross the placenta and are also the treatment for the fetal thyrotoxicosis but may render the fetus hypothyroid. During the first trimester of pregnancy the use of propylthiouracil is recommended because the use of methimazole is associated with congenital malformations. Signs and symptoms in the fetus are: tachycardia, arrhythmias, goiter on fetal ultrasound, IUGR, preterm delivery, death *in utero*. In the newborns, symptoms may be present at birth if the mother, with persisting thyroid stimulating antibodies, has been treated with surgery or radioiodine before pregnancy, or delayed for 4-5 days if the mother is on antithyroid treatment at time of delivery. FT4 and FT3 levels are elevated with suppressed TSH levels. Appropriate treatment with methimazole, Lugol's solution and propranolol should be started. Newborns with malformations of genitalia could be affected by life-threatening conditions and should be managed as a medical emergency as they can be associated with a salt-loss crisis. The right diagnosis should be defined as soon as possible in order to start the proper medical treatment and to take a decision about sex assignment. Careful pregnancy and familiar history and examination of external genitalia are of primary importance. To complete phenotype characterization, sonogram, MRI and genitogram are necessary. Hormonal tests must be performed with a precise temporal sequence. Genetic analysis should be considered after clinical evaluation and hormonal tests results. The more common cause is congenital adrenal hyperplasia, which can be related to different mutations of one of the enzymes involved in cortisol biosynthesis, that lead to increased ACTH feed-back secretion, with high blood cortisol precursors. The most frequent enzyme involved is 21-hydroxylase, which can be associated with a mild simple-virilizing form to a severe salt-losing form. Other forms can be associated with masculinization and hypertension (11β-hydroxylase deficiency) or with salt-loss and limited androgen secretion (3β-hydroxyl-steroid-dehydrogenase deficiency). Neonatal disorders of calcium metabolism are potentially life-threatening conditions. PTH, vitamin D, calcitonin, calcium-phosphate intake and serum magnesium levels are essential for the balance of serum calcium levels. Hypocalcemia (total serum calcium < 2.1 mmol/L

or ionized calcium < 1.1 mmol/L) can be associated with jitteriness, tetany, muscle jerking, generalized or focal seizures, stridor, wheezing, vomiting, prolonged QTc on ECG and impaired cardiac function. The abrupt cessation of placental transfer of calcium occurring after birth is regarded as a major factor in neonatal hypocalcemia but other possible causes are vitamin D insufficiency, increased calcitonin secretion, inappropriate PTH secretion or activating mutations of the *CASR* gene. For the diagnosis blood tests (calcium, phosphate, magnesium, ALP, albumin, pH, creatinine, electrolytes, PTH, vitamin D) and urinary tests (calcium, phosphate, creatinine, glucose, aminoacids and cAMP) must be done. Nevertheless, the knowledge of maternal calcium-phosphate state is necessary to a correct diagnosis. Acute treatment must be done with calcium gluconate 10% intravenously. If there is a concomitant hypomagnesaemia, magnesium sulphate should be administered too. Depending on the specific causes, other therapeutic options are alphacalcidiol and/or vitamin D. PTH and calcilytic treatments may offer new perspectives. Hypercalcemia (ionized calcium > 1.36 mmol/L or total calcium concentration > 2.75 mmol/L) is less common during neonatal period. It can be associated with anorexia, vomiting, constipation, lethargy or irritability, hypotonia, seizures, coma, hypertension, polyuria and dehydration, bradycardia and shortening of the QT interval on the ECG. It may be due to iatrogenic causes (TPN, excessive maternal intake of vitamin D), increased bone turnover, birth trauma, or excessive intestinal or renal absorption. It can be related also to inactivating mutations of the *CASR* gene. The management is above all based on hyperhydration with normal saline and administration of loop diuretics, limiting calcium and vitamin D intake.

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LECT 34

NEONATAL NASAL INTERMITTENT POSITIVE PRESSURE VENTILATION (NIPPV)

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INTRODUCTION

Nasal CPAP reduces the need for mechanical ventilation (MV) and decreases the combined outcome of death or BPD among preterm infants [1]. Nevertheless, literature data show that up to 50-60% of infants treated with NCPAP alone, and 30-40% of infants treated with NCPAP and surfactant (INSURE or LISA techniques) may fail and require MV. These high failure rates inversely correlate to the infants' GA. Many clinicians are therefore interested in alternative strategies that, providing a greater respiratory support than NCPAP, may prevent intubation in a larger fraction of neonates.

PHYSIOLOGIC PRINCIPLES AND TECHNICAL CONSIDERATIONS

Among non-invasive techniques, NIPPV offers main physiological advantages over NCPAP. A peak inspiratory pressure above PEEP may improve flow delivery and airway patency either by activation of dilator muscles or by passive splinting. Moreover, the intermittent inflation of the hypopharynx may stimulate the respiratory drive, improving the respiratory rhythm. Finally, a higher MAP may enhance alveolar recruitment and FRC. The physiologic benefits of NIPPV may also depend on whether mechanical breaths are synchronized (SNIPPV) or not with spontaneous breathing. Studies in preterm infants indicate that, in comparison with NCPAP, SNIPPV decreases the WOB, improves thoracoabdominal asynchrony, increases tidal volumes and minute ventilation, and decreases CO_2 [2-4]. These results suggest the relevance of synchronizing NIPPV. Synchronization is not easy to obtain during non-invasive ventilation. Three triggering devices have been developed. The Graseby capsule which detects the increase of the abdominal pressure due to the diaphragmatic contraction, at the beginning of inspiration. This device is no longer approved for use in the US because its accuracy is too strongly dependent on position and fixation [1]. The neurally adjusted ventilator assist (NAVA), a sophisticated system that detects the electrical activity of the diaphragm to trigger the ventilator. The NAVA use is limited by technical issues and costs. Finally the flow trigger that synchronizes mechanical breaths on infant's spontaneous inspiratory flow. This device, which is the only one able to use the flow-signal to trigger the ventilator during non-invasive ventilation, has been implemented by our group in recent years in order to perform flow-SNIPPV [5, 6]. Using a non-invasive technique, the interface of choice may deeply affect the efficacy of the system by influencing the pressure transmission to the lung. Intermittent breaths are generally delivered through short binasal prongs, although masks and nasopharyngeal tubes have been used. With the aim of improving both infants' comfort and efficiency of flow-SNIPPV, we are now implementing the development of very light and comfortable dedicated nasal prongs with an integrated flow sensor. The shape of the device is similar to the high flow nasal-cannula (HFNC) while the efficacy of the pressure transmission to the lungs is similar to short binasal prongs (personal data).

CLINICAL STUDIES

Two recent *Cochrane*'s reviews summarise the effects of NIPPV/SNIPPV, compared with NCPAP, in treating RDS as primary mode [7] or after extubation [8]. As primary mode, the 2016 review [7] included 10 RCTs (1,062 infants), in 2 of which SNIPPV was used. Results show a reduced need for intubation among infants treated with early NIPPV (< 6 h of life) compared with early NCPAP (RR 0.78 [0.64,0.94]), but no reduction in the risk of CLD. Considering flow-SNIPPV, we evaluated in a retrospective study whether this technique, coupled with the INSURE method, was effective in further reducing the need for MV when compared to the conventional INSURE/NCPAP treatment [9]. Data showed that more infants in the NCPAP group failed the INSURE approach and underwent MV (35.5% vs 6.1%; p = 0.004). Recently, flow-SNIPPV has been successfully used as a rescue therapy for infants failing on NCPAP [10]. After extubation, the 2017 review [8] included 10 RCTs (1,431 infants), in 5 of which SNIPPV was used. A significant reduction in the risk of extubation failure within 48 h to 7 d for infants treated with NIPPV vs NCPAP was reported (RR 0.70 [0.60, 0.80], NNT = 8), but no significant reduction in the rates of CLD, NEC or death. Clinical observation also suggested that synchronization is important in delivering effective NIPPV. Finally, when NIPPV was used to

treat apnoea of prematurity (AOP), 2 studies showed some advantages over NCPAP [11, 12]. Also flow-SNIPPV has been successfully applied to treat AOP. Nineteen infants suffering from AOP with a mean GA of 30 wks at study entry were enrolled in a RCT with a crossover design [13]. They received flow-SNIPPV, NIPPV and NCPAP for 4 h each. Cardiorespiratory recordings showed a significantly lower incidence of desaturations, bradycardias and central apnea episodes in preterm infants during flow-SNIPPV compared with NCPAP or NIPPV, while these events did not differ between NCPAP and NIPPV.

CONCLUSIONS

Clinical studies suggest that NIPPV may be an effective alternative to NCPAP and may offer some advantages over NCPAP. Synchronization improves the efficacy of the technique. Further and larger studies are needed to confirm these observations.

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LECT 35

FAMILY PAEDIATRICIAN'S ROLE IN SUPPORTING BREASTFEEDING

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The goal that focalizes the efforts and energies of both the hospital and the primary care paediatric systems is ensuring that every newborn can be fed with the formula specifically designed for him: human breast milk. Early breastfeeding and maternal contact is facilitated in the hospital and instructions on how to proceed to ensure proper nutrition are provided. Once mother and newborn are back home, who takes care to ensure that there will be no bugs that compromise physiological breastfeeding is the family pediatrician. Family pediatrician will try an opportune care of the newborn and his/her family, ensuring a first contact within a few days of hospital discharge. It is in those early days (7-10) that more often you may experience problems or anxieties that may compromise proper breastfeeding. The anxiety of not having enough milk, that the weight increase is not regular or that the mother's milk is not adequate are among the most common reasons for introducing formula to a healthy baby's nutrition. The presence of mastitis or other maternal diseases are further common situation that bring to the use of formula. These are easily resolved issues with proper maternal counseling during the first visit. At the same time, Mom will meet her pediatrician and the clinic's organization (which is more and

more likely to include nursing staff to support mother) and will receive all the information needed to continue with proper nutrition. Pediatrician will be able to evaluate if there will be any organic, maternal or neonatal reason that may compromise breastfeeding and will be able to intercept the first signs of maternal depression. If everything goes well, the newborn will be re-evaluated one month later. All the instructions needed, to contact the pediatrician and the nursing staff when necessary, are to be provided to the mother. Despite these efforts, however, in a survey conducted in 2013 in the province of Bergamo in 8.85% of cases there was a break in breastfeeding in the first month of life for personal or maternal problems, while in the same age of life just under 80% of mothers had introduced at least one meal with formula. A strategy that also involves social support interventions could further improve breastfeeding percentages up to the sixth month of life.

LECT 36

PAIN IN NEWBORN AND HOW TO MANAGE IT

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Pain in the newborn is now well recognized and healthcare providers are well aware of this, though a gap persists between knowledge and practice. Newborn infants, especially those born preterm, are particularly vulnerable to procedural stress and pain early in their life, at a time of rapid and complex brain development. Concern has long been expressed about the effects of neonatal pain on brain development, and the impact of opioids and other medication used worldwide to treat pain in the newborn. Painful and stressful procedures are routinely performed on the newborn, particularly at the NICU but also in the nursery. Reports show that the newborn may undergo from 7 to 17 painful procedures a day, the most common involving skin breaking (heel lancing, venipuncture, peripheral venous catheter insertion), and nasal or tracheal suctioning [1]. Carbajal et al. recently conducted a European prospective cohort study on analgesia and sedation (A/S) management and pain assessment at 243 NICUs, which enrolled 6,680 neonates in 18 countries, including Italy. It found that 34% of newborn admitted to the NICU, and 82% of those tracheally ventilated (TV) were given some form of A/S [2]. Much the same results emerged when the Italian data collected for the same study were analyzed separately (35% of newborn admitted to the NICU, and 86% of those on TV were given A/S) [3] (**Fig. 1**). However, the type of A/S and the frequency and mode of its administration varied considerably across centers and countries. Pain assessment (PA) practices also differed from one unit to another, and were recorded for only 32% of newborn admitted to NICUs, and for 46%, 35% and

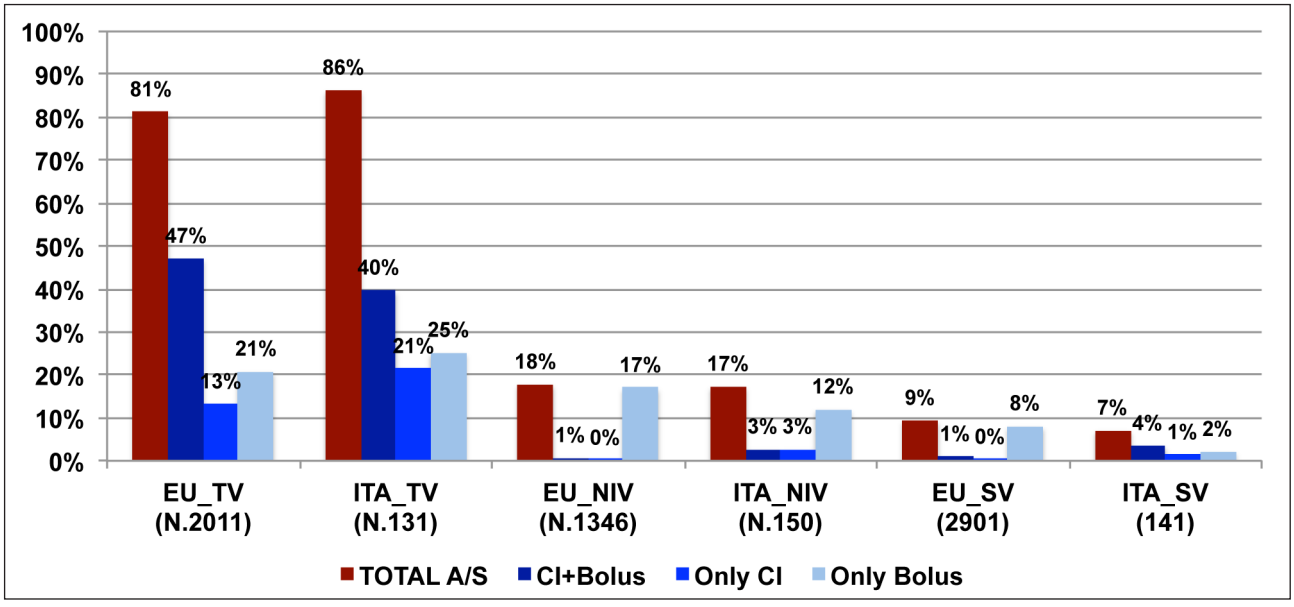

Figure 1 (LECT 36). Use of analgesia and sedation (A/S) and mode of drug administration at NICUs in Europe and in Italy alone.
TV: tracheal ventilation; NIV: non-invasive ventilation; SV: spontaneous ventilation; A/S: analgesia and sedation; CI: continuous infusion.

20% of neonates on TV, non-invasive ventilation (NIV), and spontaneous ventilation (SV), respectively ($p < 0.001$) [4]. Italy's PA performance was slightly better (documented in 67% of all in-NICU newborns, in 86% on TV, 67% on NIV, and 51% on SV [$p = 0.001$]) [3]. However, PA should be used routinely, as the fifth vital sign to monitor during daily care, because it enables the prompt identification of pain and affords a clear idea, at the bedside, of the efficacy and appropriateness of ongoing pain treatment. To understand the impact of early pain and stress on the newborn, we need to be aware of the characteristics of the developing brain and neuronal connections at this age. An imbalance between ascending excitatory pathways and descending inhibitory pathways explains why the newborn, especially those born preterm, are particularly vulnerable to pain. The nociceptive, emotional and cognitive dimensions of pain develop very early in life. The early onset of nociceptive transmissions through the spinal cord, brainstem and subcortical midbrain regions enables reflex behaviors as well as autonomic and hormonal responses to pain, while maturation of the thalamocortical projections to the somatosensory cortex, anterior cingulate cortex insula, and premotor cortex (complete by 24-25 weeks of postmenstrual age) defines the development of a comprehensive perception and awareness of pain. Even the extremely preterm newborn can perceive, feel, and possibly recall pain by the end of the second trimester of pregnancy. The newborn's brain also features a great plasticity, which contributes to anatomical and functional changes following early and repetitive skin breaking procedures. Neonatal exposure to procedural pain and stress has been found significantly associated with specific changes in brain development seen in individuals born prematurely, irrespective of other factors associated with prematurity [5]. International and national recommendations emphasize the need to adopt strategies to minimize the number of painful and stressful procedures conducted in the newborn. Environmental strategies to reduce light and noise, excessive handling, and other harmful stimuli should be adopted at all neonatal wards, and appropriate (less traumatic and painful) devices should be used for skin breaking procedures, e.g. automatic, arch-cut heel lancets, spinal needles with atraumatic tips). Pharmacological and non-pharmacological interventions should routinely be adapted to each newborn patient before every single invasive procedure. An adequate control of pain – be it procedural or illness-related (i.e. NEC, bone fracture, etc.), short-lived or prolonged – can only be achieved by constantly monitoring pain levels with appropriate, validated scales. Written guidelines should be available at every unit caring for the newborn, and all healthcare providers should be familiar with them. Training on how to measure and manage pain should be provided by medical schools and pediatric residency and fellowship programs. Finally, at every unit providing care for the newborn there should be a pain team of doctor(s) and/or nurse(s) responsible for implementing quality improvement schemes and ensuring compliance with evidence-based guidelines [6, 7].

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LECT 37

DELIVERY ROOM MANAGEMENT OF NEWLY BORN INFANT: WHAT TO DO AND NOT TO DO

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There is wide consensus among neonatologists about the importance of the delivery room (DR) management, especially regarding premature birth. In fact, the proper management of unstable babies in the DR can influence lifelong outcomes [1]. The most recent ILCOR guidelines on neonatal resuscitation [2] underline the importance of the first minutes of life, confirming the relevant role of the more well-known "golden minutes".

CORD CLAMPING AND CORD MILKING

There has been a great debate on the best timing for cord clamping and the population of infants who would most benefit from this procedure. Since no negative maternal effects of delayed cord clamping (DCC) have been demonstrated [3], it is now widely recommended [2]. However, the optimal time for this procedure is still controversial. Under specific circumstances (e.g. severe respiratory failure, asphyxia) an alternative manoeuver called "cord milking" (CD) has been proposed. It can be performed in few seconds and provides a substantial amount of blood promoting stabilization. Despite the paucity of data, CD seems to be as effective as DCC.

SUCTIONING

Suctioning the baby's nose and oropharynx as a routine care procedure is not recommended, for its effect on oxygen saturation (SpO_2) and heart rate (HR) [4]. Meconium aspiration either is no longer absolute criteria for suctioning, if the baby is vigorous. Moreover, wiping has been shown to be as effective as suctioning with no adverse effects in babies > 35 weeks' gestation [5].

TEMPERATURE

Even if maintenance of adequate body temperature is one of the most supportive therapies during neonatal transition, the achievement of this goal is still challenging. Hypothermia at birth has been associated with increased morbidity and mortality in preterm infants and this is why careful interventions are needed [6]. First, the DR temperature should be maintained at minimum 26°C when a very preterm (< 28 weeks' GA) infant is going to be delivered. Moreover, all babies < 28 weeks' GA or < 1,500 g birth weight should be wrapped in polyethylene or polyurethane bags up to their necks without being dried, to reduce heat loss and keep adequate humidity. Nevertheless, babies' temperature should be carefully checked, especially from 10 minutes after birth on the risk of hyperthermia increases when radiant heaters are used.

RESPIRATORY SUPPORT

Immediately after birth the neonate must aerate the lungs and establish a functional residual capacity (FRC) to initiate an effective gas exchange. The role of sustained inflation in achieving an early and effective FRC limiting the lung damage is under investigation [7, 8]. The aim of the neonatologist in the DR is to perform the gentlest ventilation able to favor fetal neonatal transition whilst reducing both baro- and volutrauma. Recently, using a Respiratory Function Monitor (RFM) it is possible to monitor the pressure and volume delivered during the resuscitation, in order to minimize pulmonary injuries and to support and identify spontaneous breathing [9, 10]. We hypothesize that in the next future, RFM could become essential in deciding whether to intubate or not the baby in the DR, beyond considering only HR and SpO_2 values. In infants whose GA is low or whose respiratory effort is not effective for other reasons (maternal sedation, complications during delivery) pressure ventilation and oxygen supplementation are mandatory. The most recent ERC guidelines advocate the use of controlled positive pressure ventilation with a T-piece resuscitator if available, with initial PEEP of about 5-6 cmH_2O [2]. Caffeine administration in the DR is under investigation to enhance spontaneous breathing [11]. Regarding surfactant therapy, less invasive techniques are gaining popularity as they are proved to be as effective as standard administration [12, 13] and are recommended in the first hours of severe RDS.

OXYGENATION

If clinical conditions suggest need for any kind of support, pulse oximetry should be put on the right hand or wrist as soon as possible. Regardless of the respiratory support provided, the resuscitation team should carefully follow HR and SpO_2. The best SpO_2 starting level is still under investigation; however, commencing with 0.21-0.30 seems to be a reasonable choice [14]. FiO_2 should be titrated according to the infant's response. The blender should be adjusted aiming to keep SpO_2 within a safety range between 10^{th}-25^{th} and 50^{th}-75^{th} centiles. The Dawson nomogram should be ideally made visible for the resuscitation team [15].

NOT TO RESUSCITATE

There are specific clinical situations in which resuscitation is not recommended or should be interrupted within a certain period of time. Neonatologists should consider not to start resuscitation in case of babies < 23 weeks GA, < 400 g, with lethal congenital malformation and/or proven genetic syndrome at high risk of premature death or severe disability. In case of no response (persistent asystole) to resuscitation maneuvers

after 10 minutes, resuscitation should not be prolonged further.

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LECT 38

ECMO IN NEONATAL TRANSPORT: EXPERIENCE FROM A NORTH EASTERN ITALIAN CENTER

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INTRODUCTION

Extra corporeal membrane oxygenation (ECMO) is a rescue method for extracorporeal support of cardiopulmonary function in patients with primary cardiac or respiratory failure. One of the advantages of ECMO is the opportunity of a safe temporal window for the healing of pulmonary lesions, if it is possible, or for providing a bridge before organ transplantation. ECMO is a consolidated resource for the treatment of severe meconium aspiration syndrome in newborn, with rate of survival higher than 94% of treated patients [1]. Exclusion criteria are: lethal chromosomal disorder, irreversible brain damage, uncontrolled bleeding, massive intraventricular hemorrhage (IVH), irreversible organ damage, bodyweight less than 2,000 g, gestational age less than 34 weeks, mechanical ventilation for more than 10-14 days. In Italy availability of ECMO is limited to a restricted number of third level centers, moreover the neonatal transport unit equipped for this procedure are limited in number over the country. Multidisciplinary team includes cardiac surgeons (consultants and residents fellows), perfusionists, nurses and neonatologists. All the members of the transport team have to be trained for ECMO. The nurse is a key personnel position for ensuring the best care of the patient and for the prevention of potential complications; in light of this, the ECMO hub centers have to provide a specific training for nurses who will be part of the ECMO team. Before the activation of the neonatal transport, the parents have to be informed by physicians about the conditions of the baby. A clear communication including a description of the

procedures, the risks and benefits is necessary for creating a therapeutic alliance between the care team and the family. ECMO implant and its management exposes the patient to a large number of potential severe complications that are reviewed with parents before obtaining informed consent to the procedure. The University Hospital of Padua, in North Eastern Italy, in 2009 started a program of ECMO transport named "Hub and Spoke" for adult patients, and since 2014 our center has activated an ECMO transport program dedicated to pediatric patients (including neonates) [2]. Since that, we have conducted 8 transports for neonates (6) and pediatric (2) patients to our hub hospital. One of the most common cases is meconium aspiration syndrome (MAS): 4/6 had grave respiratory complication caused by MAS. Here we report the pediatric experience of the Hub and Spoke program for the neonatal age, describing the role of the resident nurse in the ECMO team.

AIMS

To evaluate the performance of ECMO transportation in neonates with MAS.

METHODS

We retrospectively reviewed the clinical records of all the neonates who were treated with venous-arteriosus ECMO at University Hospital of Padua after a Hub and Spoke transportation in ECMO from peripheral centers of North Eastern Italy.

RESULTS

From May 2014 to December 2016, six patients were treated with Hub and Spoke ECMO. Two patients have been excluded by the data analysis due to unfavorable vascular anatomy. One patient presented ventricular fibrillation after the administration of the priming. Our experience hasn't got a history of adverse events like removal and dislocation of cannulas or hemorrhage during transport. After cannulation and before transport the nurse checks the dresses on the cannulas insertion, the temperature of the incubator, the position of the patient to guarantee adequate flow, the vascular access for infusions and the drugs that could be required during the transport. ECMO cannulas have been placed, in all the patients, trough right carotid and jugular without complications. During transportation we did not record any event affecting the ECMO performance or clinical outcome. After the ECMO implant at the peripheral hospital, our team transferred patients to the University Hospital of Padua (Hub) where the time in ECMO was 2.75 ± 1 days. The follow-up duration of this cohort is 15.5 ± 12.7 months, all the subjects have survived after the procedures reporting growth and neurological performance within normal limits per age.

CONCLUSIONS

MAS is a life-threatening condition that may be safely treated with ECMO support. ECMO requires a multidisciplinary team that can operate out of the hub center placing the extracorporeal circulation and transporting the patients to the hub hospital. Technical competencies and a good assistance are both important for the results of ECMO treatment.

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LECT 39

DYSPHAGIA IN THE PRETERM INFANT

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A significant proportion of preterm infants need hospital stay in the neonatal intensive care unit (NICU) for the first weeks or months of life. Many developmental milestones must be attained during NICU stay. The mastery of oral feeding, either breast- or bottle-feeding, is a major developmental task, recognized by the American Academy of Pediatrics as an essential criterion for discharge home from the NICU [1]. The inability to safely and efficiently master the oral feeding skill is a frequent cause of delayed discharge. However, no evidence-based guidelines are currently available for the management of feeding problems in the NICU. Dysphagia has been defined as a disruption in the ability to move food or liquid from the mouth through the pharynx and esophagus into the stomach safely and efficiently. This condition has been reported to occur in a substantial proportion of preterm infants (up to 26%) in whom it doubles the incidence in the general population (13%) [2]. Specific difficulties have prevented researchers from fully understanding the mechanisms of dysphagia in preterm infants. Moreover, it is difficult to disentangle the beneficial role of specific medical interventions to prevent or treat the condition from the progressive acquisition

of skills related to infant's growth and maturation. Skills required for efficient and safe feeding include sucking ability, coordination of breathing with sucking, and swallowing. Altogether, the process involves the functional interaction of multiple organs and structures, including lips, jaw, tongue, palate, pharynx, larynx, and esophagus. Swallowing functions begin as early as in the fetal period. During intrauterine life, the first function to appear is non-nutritive sucking, starting at 15 weeks' gestational age (GA). More complex swallowing is observed later on during pregnancy (at 22-24 weeks' GA). Coordinated sucking and swallowing starts at 32-34 weeks' GA; coordinated sucking, swallowing and breathing are acquired by 37 weeks' GA. More specifically, the coordination of sucking, swallowing, and breathing undergoes maturation starting at 32 weeks' GA, while rhythmic breathing is acquired between 34 and 36 weeks' GA [3]. Thus, oral feeding is usually not initiated in preterm infants before 32 weeks' GA. In neonates and young infants, rhythmic sequences of breathing, sucking and swallowing are followed by sequential esophageal contractions and relaxations of the upper and lower esophageal sphincters. Protection against gastro-esophageal reflux is achieved through pharyngeal, esophageal and upper airway motilities that allow managing and clearing the retrograde flow from the stomach. While the ability of sucking and swallowing is usually attained by 34 weeks, coordination with breathing is still immature at this stage. Primary and secondary esophageal peristalsis is induced by swallowing and distention, respectively, and represents the main mechanisms of bolus progression between 26 and 32 weeks GA [4]. Dysphagia often occurs in association with life-threatening neonatal diseases, including extremely preterm birth (< 28 weeks' GA at birth), cardiopulmonary diseases, and neurological disorders. The increase in the incidence of dysphagia is probably related to the increased survival rates among extremely preterm infants and infants suffering from life-threatening conditions. Invasive medical interventions, including intubation, placement of nasogastric tubes, and frequent airway aspiration, may slow down the developmental process of sucking and swallowing [5]. The coordination of suction, swallowing and breathing depends on the appropriate functional maturation and synchronization of the muscles that are implicated in each of these functions. For example, sequential contraction of the muscles from the perioral area (generation of sucking pressure), of the jaw (opening and closing), and of the tongue (bolus formation and transfer to the pharynx) requires a complex regulation. Pharyngeal musculatures are implicated in the oropharyngeal swallowing. Dysphagia occurs when any of these constituents is compromised. The correct coordination of sucking, swallowing and respiration functions are thought to be achieved through central nervous system control activity, called "central pattern generators" (CPGs). The anatomical location for CPGs that coordinate sucking, swallowing, and respiration has been described in the medulla. Distinct pools of motor neurons are thought to be involved in the achievement of the sequential and rhythmic activation of the individual functions. The fine-tuned regulation of these activities is obtained through feedback from intact sensory afferents signaling. This fundamental regulation may change depending on different environmental and physiological conditions, which include feedback from respiratory gas (oxygen and carbon dioxide). In preterm infants respiratory problems involving oxygen and carbon dioxide exchange are frequent and are main contributors to altered sucking, swallowing and breathing coordination [6, 7]. In conclusion, readiness to oral feed is a fundamental developmental milestone with profound clinical implications. More work is needed to identify the standard criteria to define such readiness. In current clinical practice, oral feeding is progressively introduced by using a "trial-and-error" approach at 32-34 weeks' GA, and adverse events are often treated with interventions not always supported by evidence-based information [8]. While scales to assess "readiness to oral feed" have been developed, they have not been universally adopted. Further development and adoption in the NICU of evidence-based scales taking into account the developmental stages of sucking-swallowing-breathing-esophageal peristalsis is a future goal in the field of nutrition of the preterm infant.

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LECT 40

CARDIAC EMERGENCIES IN NEONATES AFTER HOSPITAL DISCHARGE

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INTRODUCTION

Early recognition and management of neonatal cardiac emergencies is essential to ensure lifesaving treatment and prevent comorbidities. As a consequence of the decreasing length of hospital stay after birth, conditions that previously were detected during nursery hospitalization can now appear at home as emergencies. Congenital heart disease (CHD) is the main cause, but also dysrhythmia should be considered. CHD: even though prenatal ultrasounds and pulse oximetry screening produced a significant progress in the diagnosis of CHD, some defects can remain undiagnosed and become clinically significant days or weeks after discharge. Difficulties in the prenatal diagnosis of some CHDs (e.g. coarctation of the aorta [CoA] and total anomalous pulmonary venous return [TAPVR]) and the persistence of fetal shunts during the first days of life can contribute to diagnostic problems. CHD presentation is various and age dependent (**Tab. 1**). Defects that depend on the ductus arteriosus patency, for pulmonary or systemic circulation, usually present suddenly with cyanosis or shock in the first days or week of life, as the ductus closes. Lesions resulting in increased pulmonary blood flow (PBF) and congestive heart failure (CHF), first of all large ventricular septal defect (VSD), become gradually symptomatic from the third-fourth week of life, when pulmonary vascular resistance (PVR) falls and the left-to-right shunt increases. CHD presenting with cyanosis usually can be detected early, because of clinical appearance or low O_2 saturation; on the contrary left obstructive lesions are more difficult to suspect. The signs of low cardiac output are frequently to sepsis or metabolic diseases, but CoA is not infrequent and it is essential to check brachial and femoral pulses, to obtain blood pressure and O_2 saturation on both right arm and one leg. In the clinical assessment of

Table 1 (LECT 40). Clinical and time of presentation of congenital heart disease (CHD).

Clinical presentation	CHD		Timing of presentation: Birth	1st week	2nd week	1-2 months
Cyanosis (central cyanosis, hypoxia not improved by O_2)	TGA		→			
	Tetralogy of Fallot		—	—	—	----
	Tricuspid atresia		→			
	Pulmonary atresia		→			
	Truncus arteriosus		→	→		
	TAPVR – obstructed		→			
Shock (poor feeding, lethargy, tachycardia, pallor/pale grey skin, weak peripheral pulses, ↑ capillary refill, hypotension/decreased blood pressure in lower extremities)	Left obstructive lesions:	• Hypoplastic left heart syndrome	→	→	→	
		• Critical aortic stenosis	→	→	→	
		• CoA		→	→	
	ALCAPA myocardial infarction		→			
CHF (feeding difficulties, sweating, failure to thrive, difficulty breathing, tachypnea, rales, hepatomegaly)	VSD			—	—	----
	Patent ductus arteriosus			→	→	→
	Atrioventricular canal			—	—	----
	TAPVR – not obstructed			—	—	----
	ALCAPA – recurrent ischemia			—	—	----

CHF: congestive heart failure; CHD: congenital heart disease; TGA: transposition of great arteries; TAPVR: total anomalous pulmonary venous return; CoA: coarctation of the aorta; ALCAPA: anomalous left coronary artery from pulmonary artery; VSD: ventricular septal defect.

patients in poor general conditions due to cardiac lesions presenting with CHF, the chest X-ray defines cardiomegaly, the signs of increased PBF and sometimes a diagnostic cardiac shape. A particular form of CHD with increased PBF is TAPVR: in the presence of obstruction pulmonary venous hypertension, cyanosis and CHF appear quickly, while symptoms of CHF develop days or weeks after birth in TAPVR not obstructed. Also anomalous left coronary artery from pulmonary artery (ALCAPA) can present in different ways: early myocardial infarction or an insidious presentation due to recurrent ischemia. Indeed, the progressive fall of PVR results in a drop of the left coronary artery perfusion pressure ("coronary steal") that leads to left ventricular dilatation, mitral regurgitation and impaired cardiac function. Episodes of angina could manifest as irritability, diaphoresis during feeding, pallor and respiratory distress. The ECG typically shows abnormal Q waves with T waves inversion in leads I, aVL and V4-V6.

ARRHYTHMIAS

Tachycardias (TC) and bradycardias (BC) are relatively common in infants and the physiological properties of neonatal myocardium make it more vulnerable to dysrhythmias. TC and BC occur commonly without serious consequences but sustained forms can lead to CHF or shock and must be considered in the differential diagnosis of a critically ill infant. Arrhythmias generally occur in structurally normal heart but they can also be associated with CHD (Ebstein anomaly, corrected transposition of great arteries [TGA], single ventricle). The ECG of supraventricular tachycardia (SVT) shows a rapid regular rhythm (220-300 bpm) without variation, with narrow QRS and no discernable P wave before the QRS complex. Atrioventricular reentrant tachycardia, with a reentry circuit involving the AV node and an accessory connection is the most common mechanism of SVT in neonatal period. Atrial ectopic TC and permanent junctional reciprocating TC occur less frequently. If episodes of SVT remain unrecognized for hours or days because of nonspecific signs (fatigue, lethargy, poor feeding, irritability), they can lead to CHF or shock. Differential diagnosis from reactive sinus TC is possible with the ECG. In unstable patients, synchronized cardioversion is required. Treatment of stable patients includes vagal maneuvers, such as application of ice to the patient's face and/or intravenous adenosine. Atrial flutter (AF), caused by reentry within the atrium, with high degree AV block and near normal ventricular rate can be well tolerated. In the neonate, the atrial rate is usually around 400 bpm with 2:1 AV conduction. AF is easily resolved by synchronized cardioversion and typically does not recur. Ventricular TC, rare in neonates, can be caused by myocarditis, electrolyte and metabolic abnormalities, drug toxicity, rare cardiac tumors (hamartomas and rhabdomyomas), and cardiac channelopathies (long QT and Brugada syndromes). The ECG shows wide QRS and AV dissociation and the main differential diagnosis is SVT with anterograde conduction through an accessory pathway. Adenosine, generally not useful to treat VT, is helpful in the differential diagnosis. Neonates of mother with lupus erythematosus are known to be at risk for congenital complete heart block. Furthermore, infants with corrected TGA are also at risk for complete heart block. Management of these cases depends on the presentation and the hemodynamic status.

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LECT 41

ROLE OF OSTEOPATHY IN NEONATOLOGY

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Complementary and alternative medicines are generally utilized for premature babies. Osteopathy is based on a manual approach to diagnose and treat "somatic dysfunctions". The latter refers to bodily areas that show altered tissue texture, tenderness, asymmetry and restriction of range of motion. Even though osteopathy has been used in health care, and in particularly in musculoskeletal disorders, osteopathic trials investigating the impact and role of osteopathic manipulative treatment (OMT) in the care of preterm infants are still lacking. In 2011, a first trial showed a significant reduction of the risk of Length of Stay (LOS) longer than 28 days (OR = 0.22; 95% CI 0.09 to 0.51) in newborns who underwent OMT. Another RCT reported a positive effect of OMT compared to usual medical care in reducing LOS (-5.906; -7.944 to -3.869) and costs (-2.725; -3.492 to -1.958). A further multicentre RCT, enrolling 695 newborns randomly allocated to either the OMT study group (n = 352) or the usual care control group (n = 343), showed a statistical significant difference between the two groups for the LOS (13.8 vs 17.5 days: study vs control, $p < 0.001$, effect size: 0.31). Using a multivariate analysis, the authors reported a reduction of LOS of 3.9 days (95% CI -5.5 to -2.3, $p < 0.001$). Moreover, a significant reduction of cost was estimated in the OMT group (1,586.01€; 1,087.18 to 6,277.28; $p < 0.001$). Interestingly, no complications were reported in the study group. Other studies have been conducted aiming at exploring the effect of OMT on other outcomes. A recent trial showed the safety of OMT in extreme preterm infants, although no clinically significant findings were found in relation to general movements. Two recent systematic reviews on neonatology were published showing that OMT seems to be effective in reducing the days of hospitalization, despite the small sample sizes of trials included. In addition to that, both reviews concluded that osteopathy is a safe approach, which could be included in neonatology routine care. Conversely, a 2013 pediatric review concluded that the effectiveness of OMT for pediatric conditions is still unclear, mainly due to the lack of quality of studies conducted. The authors concluded that, despite the positive results, more research is necessary to affirm the efficacy of OMT and other touch-based therapies in perinatal care. Indeed, the literature showed high heterogeneity regarding duration, frequency of intervention, and type of touch used. In order to clarify the potential effectiveness of such interventions in premature babies, hypothesis-driven protocols are strictly necessary. This might help to understand better the neurobiological compounds underlying any efficacy. Indeed additional discussions and research are required, about the physiological effects of OMT on preterms. In adults, some studies showed a modulation of autonomic nervous system (ANS) functions and were shown to reduce pro-inflammatory cytokines. In addition, OMT was associated to a reduction of pro-inflammatory substances also *in vitro*, indicating an anti-inflammatory role, partially confirmed by recent clinical-based research. Preliminary laboratory-based evidence demonstrated the results of specific osteopathic techniques on the increase of the lymphatic and immune system function improving the interleukin-8 (IL-8) levels and leukocyte counts. These results were confirmed both by more recent human research which reported significant differences in the immune molecules levels, including IL-8, between OMT and sham light-touch control, and from more basic animal research where massage-like stroking of mice with a hand (but not a brush) was shown to boost the immune system. Taken together, these findings would argue that OMT could possibly decrease the

number of cytokines released and the activity of the sympathetic system, creating a chain of physiological and neurobiological events, which regulates the inflammation, the ANS mechanisms and the immunological profile. As far as possible impacts on health care system are considered, the studies published could be considered a successful example of integrated medicine. Indeed the WHO has been encouraging cross-disciplinary collaborations to improve quality of practice. This led to include some traditional, complementary and alternative medicines within health care services. In the context of NICU, team working was tested since the 90s in order to enhance clinical procedures and deliver better practices. Notwithstanding this, a complete integration of disciplines is still limited. Based on these premises, a multicentre nation-wide clinical project (ne-O project) was established to create a multidisciplinary network for improving quality of life and clinical outcomes in preterm babies. Therefore the ne-O project aims to fulfill these objectives and produce compelling evidence regarding the short-, medium-, and long-term biological, neurological and health-related effects of osteopathic treatment on preterm infants. Thereby, it aims to produce data to explore the extent in which osteopathy can play a role in improving disabilities following neonatal conditions and the economical value of an osteopathic approach. Within the worldwide framework and long-term health care goals, alternative and complementary approaches aiming to improve health conditions in preterm infants, the ne-O project could give rise to further discussions informing government policy-makers, regulators, researchers and health-care practitioners seeking to implement evidence-based multidisciplinary practices.

LECT 42

MANAGEMENT OF THE NEWBORN INFANT WITH CONGENITAL ANOMALIES

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Congenital anomalies, also referred to as birth defects or congenital malformations, occur in 2-3% of all newborn infants. 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. In approximately 50% of the cases, an etiologic diagnosis cannot be established, thus complicating the clinical management. The early and accurate diagnosis is crucial to avoid long and unnecessary diagnostic workouts, may provide the rationale for using specific treatments and preventing late-onset co-morbidities, and is a prerequisite for the genetic counseling. Altogether, the molecular characterization of congenital anomalies results in an improved management of the patient.

How to get to the right diagnosis? The familial, prenatal and maternal histories may guide the diagnostic process and help in the initial differentiation of likely genetic from non-genetic conditions. The family history should include at least three-generation pedigree, and contain information on spontaneous abortion, stillbirth, birth defects, geographical origin, and consanguinity. The maternal history should include information on chronic maternal diseases, exposure to drugs, alcohol, radiation, and infection during current pregnancy. The prenatal history may provide information on the timing of onset of the condition, e.g. during early intrauterine life or in the perinatal period. Of note, some findings at prenatal screenings that are usually associated with chromosomal abnormalities (e.g. size of nuchal fold, levels of specific proteins in the maternal serum) may be observed in the absence of any chromosomal abnormalities. In such cases, copy number variations (CNVs) in specific genomic regions or monogenic disorders may explain the clinical phenotype. One common example is the increase in the size of the nuchal fold in infants with Noonan syndrome, caused by single-gene defects. Additional pre- and perinatal information should include the timing of onset and pattern of fetal activity, gestational age at birth, mode of delivery, the fetal and biometric parameters (ultrasound measurements and fetal growth curves), and neonatal adaptation. The physical examination should be as accurate as possible, and should be focused on detecting both major anomalies and minor dysmorphisms. Detailed neonatal biometric parameters should be compared to the reference charts for the specific ethnic group of the patient. These should include birth weight, length and cranial circumference at birth, and some more specific measurements including the intercanthal distance, the length of the pinna of the ear, the inter-mammary distance, the length of fingers, hands, feet, and other measurements. A systematic description of all the anomalies by type, site and size should be recorded. Each clinical sign suspected to

be a birth defect should be also searched in other family members in order to ascertain its relevance to the proband disease. Two modes of diagnostic approach are possible: a subjective approach, where the observation of the patient as a whole allows the immediate recognition of a specific and well known phenotype (e.g. Down syndrome) and a more analytic approach based on differential diagnosis, in which the recorded signs and anomalies, imaging, and blood tests are studied for matching to the constellation of findings in known syndromes. Given the extreme rarity of some individual conditions that can be sometimes observed by the clinical geneticist, several software applications have been developed as an aid to the physician. These include the recently developed machine learning-based software that uses the facial recognition technology to assign the phenotype of the patient to the most likely disease. When a specific condition is suspected (e.g. Down syndrome), the genetic laboratory may confirm the initial hypothesis. When a more generic hypothesis is proposed (e.g. suspected chromosomal abnormality), the laboratory should address the question and provide information on the specific genetic findings (e.g. presence or absence of chromosomal abnormalities, and type). In some cases, the clinical information and the differential diagnosis are not sufficient to restrict the suspect to one or few conditions. In such cases, the diagnostic workout should include imaging and laboratory tests in order to be as accurate as possible in the definition of the clinical phenotype. A strict interaction with the geneticist may help to further investigate the condition. Depending on the phenotype and on available information, highly selective genetic tests, tests to study CNVs or whole-exome/whole-genome sequencing may be the most appropriate approach to address the clinical question. Currently available technologies allowed the obtainment of very high diagnostic success rates in some studies, with an efficiency that was not even predictable only a few years ago.

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LECT 43

UNIVERSAL NEWBORN HEARING SCREENING: RECOMMENDATIONS AND CRITICISMS

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Permanent hearing impairment (PHI) is the most common sensory defect in childhood. A significant degree of PHI occurs in about one to three per 1,000 live births in industrialized countries. Its prevalence might double by age at school entry and increase by three to ten times in at-risk pediatric population such as infants admitted in the Neonatal Intensive Care Unit (NICU) [1]. Sensory deprivation during periods of maximal receptiveness leads to language learning impairment, language-based learning disabilities and psychosocial difficulties [2]. In the

last 20 years, the remarkable progress in scientific, clinical and medical technology allowed early diagnosis and adequate treatment of PHI at almost any degree. Universal newborn hearing screening (UNHS) is the first and main step of the program for early intervention in childhood PHI. In the last few decades, several regions have implemented local policies aiming at infant PHI detection, based on UNHS and surveillance programs. Most of these programs have shown excellent results in term of coverage and reduced age of PHI identification [3-5]. A recent analysis of systematical nationwide surveys, which was promoted by the Italian Institute of Social Medicine, reveals that screening coverage increased progressively from 29.3% in 2003 to 78.3% in 2011 even if there are still considerable differences among different geographic areas of our country [6]. In 2016, UNHS has been officially included in the so-called Essential Levels of Assistance (LEA) and its final approval by the Ministry of Health is forthcoming. Nevertheless, many criticisms remain to be solved. In 2013, a multicenter/multidisciplinary study group tried to develop an integrated regionally based public healthcare model for identification, diagnosis and intervention in childhood deafness, under appointment of the Italian Ministry of Health [7]. This work and many other studies describe and analyze strengths and weaknesses of the Italian reality [6, 8, 9]. The first obstacle in these studies is the great variability in reporting UNHS performance data [9]. Lack in standardization in describing experiences hinders to calculate the complete set of UNHS quality indicators and main benchmarks (i.e. universality, timely detection and over referral). Many criticisms have been identified in evaluating and comparing UNHS programs: heterogeneity in criteria for identifying hearing loss (bilateral or unilateral, pass/fail level) and for defining high-risk neonates, in the selection of the adopted screening tests, in personnel performing tests and, in addition, in the environment in which tests were carried out. Deficiencies, which are commonly found in communication between the birth center and the Audiology/ENT unit, cause a difficult management of the 2nd and 3rd diagnostic level appointment and an increase of the "drop out" phenomena [6, 8-10]. The latter is one of the main causes of the alarming percentage of newborns who failed the initial test and does not approach further evaluation [9, 11]. A recent survey [12] reveals that only 62% of all newborns with "refer" result at hearing screening completed diagnostic evaluation, and that among these newborns, only 52% were evaluated at 3 month as recommended by the most quoted UNHS guidelines [13]. One of the most important points of weakness of UNHS programs is the difficulty to correctly identify false negative cases. This correct identification requires an efficient cooperation between health services and professionals and, in the presence of a late diagnosis of hearing loss, it consists in the correct differentiation between true false negative (i.e. omitted by the screening) and acquired, late onset or progressive hearing losses. Large cohort follow-up studies conducted in UK [14, 15] revealed that less than 60% of children with a moderate or worse bilateral deafness diagnosed in the initial years of their primary education have been identified neonatally, even in the presence of an established and sensitive newborn hearing screening. Either risk factors for late onset hearing loss (e.g. Cytomegalovirus infection, culture positive postnatal infections, children who have received extracorporeal membrane oxygenation etc.) or caregiver concern regarding hearing, speech, language or developmental delay should always be taken in account [16, 13]. True false negative cases may be due to inadequate screening techniques: babies at risk for "auditory neuropathy spectrum disorders" (e.g. admission to NICU, familiar history of neurodegenerative disorders, etc.) should be tested by auditory brainstem response as they may result negative at oto-acoustic emissions recording [13]. Aiming to resolve the above mentioned problems of false negative cases and of delayed hearing loss, the American Academy of Pediatrics and the Joint Committee on Infant Hearing, averred that UNHS program should include a surveillance phase in which infants up to 30 months of age undergo monitoring for auditory skills, middle ear status and developmental milestones [13]. The Sense Organs Study group of the Italian Neonatology Society has draft recommendations on UNHS practice in order to achieve a uniform nationwide protocol overcoming the above-mentioned critical issues. Based on the international UNHS guidelines, on Italian regional programs (e.g. Campania and Friuli Venezia Giulia regional protocols) and on the most recent reviews, recommendations define algorithms for hearing screening in newborn populations with and without audiological risk factors including their follow-up. Moreover, they describe rules and responsibilities of levels of healthcare assistance stressing the fundamental aspect of their coordination. Last but not least, these recommendations stress the importance of information and dissemination of

knowledge for hospital operators, families and family pediatrician to grant an effective infant care network.

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LECT 44

ALARM MANAGEMENT: A NURSE CHALLENGE IN A SINGLE FAMILY ROOM DESIGNED NEONATAL INTENSIVE CARE UNIT

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The new single family room (SFR) neonatal intensive care unit (NICU) in Monza opened its doors in April 2017. It's organized in two units, one of them for 12 tertiary intensive beds, the other one for 16 step-down beds. Every unit has a central staff workstation, a meeting room, many support areas and it's separated from the other unit by a central area. Every SFR is equipped with a multiparameter monitor (BeneVision N19, BeneWiew T1, Mindray) and infusion pumps (Guardrails Plus, Guardrails VP Plus, Alaris), both directly connected with NICU's information technology (IT) network. When clinically needed, additional devices could be interfaced with the network, such as incubators (Incu I, Atom), ventilators (Fabian Acutronic, Leoni Heinen-Lowestein, Florian Acutronic), transcutaneous gas monitors (SenTec V-Sign™ System, Sentec) and near infrared monitors (NIRS, Nonin Medicals). Medical devices' data and alarms could be sent to the central workstation monitor, to other patient monitors (bed to bed communication) and to handheld devices (smart pager). The nursing ratio varies by the two units between 1:6 (step-down unit) to 1:3 (intensive unit). Every nurse has her own patients in charge (caregiver nurse). From planimetric analysis and from an on-site evaluation, it was immediately clear that nurses could not maintain a contemporary visual control on three patients, even with a logistic bed cluster selection. This meant that all alarms must reach the nurse through the IT path. At this point, the nurse task force for implementing alarm system faced the challenge of balancing the need not to miss a true alarm with the risk of having too many false alerts, condition also known as alarm fatigue. This term refers to the "tendency for caregivers to miss true alarms because the frequency of false alarms is overwhelming and dwarfs the number of true alarms" [1-8]. The three key points seemed to be: choosing the right signals, setting the right limits and tracking the right path. Even if some other NICUs are adopting SFR room design, it's very difficult to find publications about alarms management in the SFR environment. One of the few was the van Pul's *Alarm management in a single-patient room in intensive care unit* [9], which resulted to be inspirational and useful to us. Unfortunately, even if some similarities are

present, like the framework of the IT solution, Pul's experience was not completely exportable in our unit. In particular, room design and the nurse organization model were completely different. In van Pul's description, intensive care nurses were responsible for no more than two babies placed in contiguous rooms, separated by a glass window. Despite those differences, our work's inspiring topics were the analysis of alarm's different feature and the security range setting. Analyzing every signal coming from devices, our team identified a list of serious alarms (red) and a list of secondary alarms or pre-alarms (yellow). Red alarms, potentially life-threatening events, are immediately sent to the central monitoring station, to the inter-bed communication system, and to the caregiver nurse. The yellow alarms were not life-threatening but, differently from van Pul's experience, are sent not only to the control unit and to inter-bed communication system, but also to the caregiver nurse. In order to filter false alarms and other brief but self-limited events, we added a time criteria to the threshold criteria and the alarms are sent to the nurses only after parameter's value remains out of the preset security range more than 15 seconds [2]. To be more accurate and, consequently, causing less alerts, we set nine different configurations, contributing to minimize the noise stress related risk. Every alarm produced by any online device causes an alert that can be sent to a remote receiver. To receive those alerts, every nurse and doctor on shift are provided with smartphone (G389 Galaxy Xcover, Samsung), acting as pager, to which every alert is addressed (**Fig. 1**). At the beginning of the shift, a nominal access leads the nurse caregiver to be the first to receive alerts from patients in charge. If the caregiver is not able to respond to, the alarms are re-directed to other nurses within 30 seconds. The caregiver has also the option to activate for a specific alarm the colleagues with a simple touch of the screen (we call it "Escalation"). It's also possible to activate a blue code, for every ongoing emergency event. Furthermore, using the smartphone, nurses and the doctors have the opportunity to check the status of online parameters for every connected bed in NICU from every place in the unit, all covered by Wi-Fi signal. The new system complexity and the radical changes in the everyday working routine due to moving from an open bay to an SFR designed NICU, required a proper training. At first the team organized meetings on the new system architecture, then we organized training courses using both

Figure 1 (LECT 44). Nurse in the Monza single family room (SFR) managing alarms with the smartpager.

frontal lessons and practicing. The four-hour training was leaded by one from the team supported by providers and took place in the new NICU. Every member of the unit attending newborn care was involved in order to share the knowledge on the alarm management in our SFR designed NICU.

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LECT 45

APPARENT LIFE-THREATENING EVENTS AND SUDDEN INFANT DEATH SYNDROME

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The term "Apparent Life-Threatening Events" (ALTE) was introduced in 1986 to replace the term "near-miss Sudden Infant Death Syndrome" (SIDS). The definition of ALTE is any event that is "frightening to the observer and is characterized by a combination of apnoea (central or occasionally obstructive), colour change (usually cyanotic or pallid but occasionally erythematous or plethoric), a marked change in muscle tone (usually marked limpness), and choking or gagging". Although an "apparent life-threatening event" can effectively put the child's life at risk, SIDS and ALTE should be considered as two separate phenomena because ALTE cannot be understood as a precursor of SIDS. The reasons for keeping these events separated can be summed up as follows: a) the dramatic drop in the incidence of SIDS that occurred following the risk reduction campaign was not matched by an equal decrease in the incidence of ALTE; b) the temporal distribution of the two phenomena is not superimposable (2-4 months for SIDS, 1-3 months for ALTE); c) only a small percentage of ALTE seem to turn into SIDS (< 1%); d) the risk factors for ALTE and SIDS are different, with the exception of smoking, male gender, very low birth weight and low gestational age. Recently, the American Academy of Pediatrics decided to replace the acronym ALTE with the term "Brief Resolved Unexplained Events" (BRUE) to indicate events "occurring in an infant of less than 1 year when the observer reports a sudden, brief, and now resolved episode of more than 1 of the following: cyanosis or pallor; absent, decreased, or irregular breathing; marked change in tone (hyper- or hypotonia), and an altered level of responsiveness". In our opinion, the term BRUE should refer to mild idiopathic cases while the acronym ALTE should be used to describe severe idiopathic cases that remain unexplainable after first and second level examinations. SIDS is the sudden death of an infant under the age of 1 year that remains unexplained even after a complete investigation that must include an autopsy and a thorough review of the death scene and the complete family and medical histories. Therefore, the diagnosis of SIDS should be considered an exclusion diagnosis which, in order to be properly formulated, must necessarily follow the above-mentioned steps. Consequently, every sudden unexpected death occurring during the first year of life should initially be defined as a "Sudden and Unexpected Infant Death" (SUID). Only after performing the complete diagnostic steps can the case be classified either as SIDS or "unexplained" if not attributable to SIDS (e.g. if the death did not occur during sleep) or any other known pathology. SIDS represents the third cause of death between the first month and the first year of life in industrialized countries, with an incidence of < 0.5‰ live born per annum. The etiopathogenetic model internationally adopted

is the so-called triple risk model, which includes three interdependent factors to explain the death: 1) biological vulnerability; 2) critical development period (vulnerability window); 3) triggering external factors (risk factors). According to this conceptual model, at the age of maximum risk, ranging between 2 and 4 months of life, the combined action of environmental risk factors (e.g. prone position during sleep) in infants presenting weak auto-resuscitation mechanisms (biological vulnerability) during sleep (arousal and gasping) can lead to a sudden and unexpected death. It thus emerges that the role of prevention is crucial. Indeed, thanks to the back to sleep campaigns, the incidence of SIDS in the countries adopting the "reduce the risk" message has progressively decreased by more than 50%. Twenty years after being launched, the "back to sleep" campaigns have been renamed "safe to sleep" campaigns to underline how SIDS risk reduction measures have a wider impact as they also help reduce deaths from accidental causes. In the Tuscany region a risk reduction campaign has been actively carried out since 2002, while the aspects regarding the correct diagnosis and reception of affected families are contained in a regional resolution in force since 2009. The back to sleep campaign involved the AOU Meyer SIDS Centre, the Department of Health Law and Solidarity Policies of the Tuscany Region, the Prosecutor's Office, family pediatricians, emergency services (118 and First Aid), midwives and neonatologists, and the Parental Association for SIDS. The two main results observed were a gradual increase in the supine sleep position, which rose from 55% in 2002 to 72% in 2010, and a drop in SUID mortality below 0.25‰, only 50% of which were true SIDS. These mortality data are found at the lowest international levels, but at the same time they correspond to a general trend that has shown a plateau over recent years. From a global perspective, careful case selection and the creation of international biobanks could lead to the acquisition of new scientific knowledge aimed at permanently eradicating this tragic event.

LECT 46

VIRAL INFECTIONS: DIAGNOSIS AND THERAPY

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INTRODUCTION

Fetuses and infants, due to developmental immaturity of cellular and humoral immune response, are particularly prone to develop infections and viruses are the most frequent microorganisms causing disease in neonates. Chronic viral diseases affecting pregnant women (HIV, HCV, HBV), as well as acute maternal viral infections acquired during pregnancy (parvovirus B19, rubella, VZV, CMV, enteroviruses), can affect babies through vertical transmission occurring at different times during gestation, labor, delivery, or after birth through breast milk (HIV, CMV). Horizontal transmission of viruses from family members and/or caregivers by means of contaminated hands and droplets may occur as well; in fact, enteroviruses, adenovirus, rotavirus, norovirus and respiratory syncytial virus have all been reported as possible causes of viral outbreaks in neonatal nurseries. Further, viruses, when compared to bacteria, are by far prevalent in infants less than 3 months of age who are hospitalized for suspected sepsis [1].

DIAGNOSIS

Diagnostic virology evolves continuously looking for more reliable, easy to use and rapid diagnostic tools. Molecular diagnosis, in this light, has represented a huge step forward in the last twenty years. Nowadays, techniques employing nucleic acid amplification by means of polymerase chain reaction (commonly known as PCR) have replaced, often completely, culture assays and play a fundamental role in viral detection and quantification. Culture assay, when compared to PCR based assay, generally yields lower sensitivity and turnaround time and, particularly for neurological viral infections such as HSV, CMV, VZV and enteroviruses, PCR is now the methodology of choice [2]. Quantitative real-time PCR, in which the results are detected while amplification occurs, is currently the mainstay of viral diagnosis [3]. Molecular diagnosis of viral diseases has a deep impact in neonatology. The risk of vertical transmission of viral diseases like HIV, HCV and HBV is correlated to maternal viral load during pregnancy and maternal therapy, in order to prevent vertical transmission, and is practiced according to viral load values (HIV, HBV). Neonatal prophylaxis for HIV varies depending on maternal viral load at delivery [4]. The diagnosis of neonatal viral diseases such HIV, HBV, CMV and HCV, due to the bias of maternal IgG antibodies, deeply rely on molecular diagnosis; repeated PCR testing in the first months of life are necessary to rule in/out vertical transmission of infection. Quantitative

methods are also necessary to evaluate the efficacy of antiviral therapies in HIV and CMV congenitally infected infants. In recent years, the development of multiplex PCR based assays, in which numerous pathogens may be detected in a single reaction, have encouraged the so-called "syndromic" approach to diagnosis. In this kind of approach multiplex assays are designed to detect different microorganisms (not only viruses but also bacteria, fungi and parasites) that cause the same type of diseases and a number of panels (for meningitis, respiratory and gastrointestinal diseases) have been developed [3].

THERAPY

According to medical literature, antiviral drugs have proved effective for the treatment of some neonatal viral disease but, to date, only few of these drugs have been licensed for neonatal treatment. Intravenous acyclovir for 14-21 days is the therapy of choice for neonatal HSV infections and it is highly effective in reducing morbidity and mortality [5]. Oral acyclovir suppression for six months after neonatal herpes further improves the neurodevelopmental outcome [6]. Acyclovir is also indicated for VZV infection in neonates but little data are available about the use of acyclovir in this disease. Six months of valganciclovir, when compared with six weeks of treatment, appear to improve hearing and neurodevelopmental outcomes in the longer term in congenitally infected symptomatic infants [7]. Both acyclovir and valganciclovir use is associated with an increased risk of neutropenia and their use require careful monitoring of the bone marrow function. Neonates are at high risk for influenza complications and antiviral drugs (oseltamivir is the only FDA-approved drug for the treatment of infants > 2 weeks) reduce the duration and severity of the disease [8]. A recent randomized, double-blind, placebo-controlled trial of pleconaril for the treatment of neonates with enterovirus sepsis demonstrated shorter times to culture and PCR negativity and greater survival among pleconaril recipients [9]. For perinatal HIV infection, current guidelines suggest to initiate a combination of antiretroviral therapy with zidovudine and lamivudine (two nucleoside reverse transcriptase inhibitors [NRTIs]) plus nevirapine (a non nucleoside reverse transcriptase inhibitor [NNRTI]) or lopinavir/ritonavir (a protease inhibitor [PI]). HIV infected neonates should be managed by pediatric HIV specialists [4].

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LECT 47

PRETERM NEWBORNS: CARE AND PARENTAL INVOLVEMENT

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Thanks to advances in medicine and technology, the survival rates and quality of life of premature infants, including infants born at the borderline of viability, have improved significantly over the past 20 years [1, 2]. Yet, prematurity remains a growing problem for public health systems, due to its potential consequences in terms of short- and long-term morbidity. The brain damage that can occur in preterm infants is due to the combined effects of different pathways (e.g. ischemic and inflammatory), leading not only to tissue loss but also to disturbances in subsequent brain development [3]. Moreover, exposure to different risk or protective factors, modulated by genetics and environmental factors, can improve the resilience or increase the vulnerability of the central nervous system. Continuous advances in obstetric techniques and intensive and neonatal care have the potential to increase the proportion of preterm newborns surviving without serious cerebral damage, however it seems that the most promising strategy available is actually to compensate for their weaknesses and to enhance their growth potential, exploiting their environment through early intervention programmes. In this context, it is important to bear in mind that parental well-being, too, is an important focus of care. Indeed, preterm birth *per se* can impact on maternal parenting [4], and is considered a distressing event for parents for many reasons: an unexpected preterm birth interrupts prematurely the antenatal process of maternal bonding with the infant and leaves the mother feeling weak and helpless [5, 6]. Parents of preterm infants experience high level of psychological distress linked to the trauma of the birth, apprehension about the child's survival, and worry over his/her fragility [7]. The physical environment of the neonatal intensive care unit is another possible source of stress for parents. About 50% of mothers of preterm infants [8, 9] report critical levels of anxiety, depressive symptoms and/or stress [10]. These are greater than the levels observed in mothers of full-term infants, as our recent experience confirms. Mothers with significant psychological distress may have feelings of detachment and helplessness, and consequently be less able to take care of a premature baby [11]. This clinical evidence has implications with regard to parental competence and mother-infant interaction; problematic mother-infant interaction has been shown to correlate with neurodevelopmental impairment, and also to have direct and indirect effects on the child later in life. Against this background, we developed a protocol of early intervention aimed at preterm infants and their mothers, to be implemented during the child's hospital stay and in the first weeks post-discharge. A study was planned involving 40 high risk preterm babies (gestational age ≤ 32 weeks and/or birth weight ≤ 1,500 g) and their mothers divided into two groups of equal size to evaluate the feasibility, applicability and efficacy of our new protocol, which is easily applicable in clinical practice. After the recruitment phase and during the hospital stay, the mothers were invited to take part in two meetings, conducted in small groups, to share information and discuss the typical characteristics of preterm babies and their special care needs. Moreover, each mother had at least three individual meetings with the neurodevelopmental therapist at baby's crib, during which mother and therapist observed, together, the baby, his/her attitude, behaviour, temperament, and ability to call for help and accept external intervention, as well as his/her ways of showing stress, and of coping. After discharge, once the children reached term and then 3 months of corrected age, each mother had an individual meeting with the pediatric neuropsychiatrist and the neurodevelopmental therapist, to evaluate the changes in the baby and in her own attitude. Our protocol is geared at reducing maternal stress and improving newborn behaviour and mother-child interaction. The approach adopted in the physician and therapist meetings was inspired by Boukydis's [12] model of "Collaborative Consultation with Parents and Infants" which consists of observing the baby together with parents, developing active listening skills to help parents understand and "read" their baby and to increase their sense of connection with him/her. We are convinced that helping mothers to better understand their infants and supporting the parental role in the difficult weeks after a preterm birth could modify parents' attitudes and their relationships with their baby. Enriching the environment, adapting it to the special needs of a preterm infant, may help with this process; it may also favor modification of neuronal

plasticity, thereby improving development of high-risk preterm babies.

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LECT 48

POSTDISCHARGE MANAGEMENT OF IRON DEFICIENCY ANEMIA IN PRETERM NEWBORNS

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Preterm newborns are at high risk to develop anemia [1, 2] due to: blood sampling loss during stay in hospital, low erythropoietin levels, reduced half-life of erythrocytes, incomplete trans-placental transfer of iron stocks [3], fast growth rate [4]. Furthermore, prenatal risk factors such as maternal iron deficiency, maternal hypertension, diabetes in pregnancy, maternal exposure to smoking, lack of intrauterine growth contribute to anemia in the first few months of life [4]. Iron deficiency anemia (IDA) is typically a late sign of iron deficiency (ID) in preterm infants. Iron is essential for the proper growth since the fetal period [5]. Effects of ID are: reduced growth rate, arising of gastrointestinal disturbs, thyroid dysfunction, infection predisposition [6], body temperature instability, and worsened neurodevelopmental outcome. Iron supplementation is effective in decreasing the risk of the development of IDA. However, despite its relevance for neonatal health, it is noteworthy that iron is a double-edged sword. Iron at high concentrations, and when it is not tied to transport and storage proteins, can become toxic. Free iron, in the presence of oxygen, undergoes the Fenton reaction and generates hydroxyl radicals, which are the most potent oxidizing agent of a biological system [7, 8]. The toxicity is exacerbated by the absence of specific excretion mechanisms, which can facilitate its accumulation [4]. There are no worldwide accepted guidelines about dose, start and duration of iron supplementation in low birth weight infants; however, enteral iron supplementation is recommended between 2 weeks and 2 months of life [4]. Early supplementation, at 2 weeks of life, would offer benefits in terms of transfusion performance and neurocognitive development compared to late introduction [9]. Iron supplement at a dose of 1 to 2 mg/kg/day up to 6 months reduces the risk of IDA without significant side effects [4, 10]. In very low birth weight infants the iron dose should be adjusted to the levels of ferritin: 2-3 mg/kg/day in case of ferritin level higher than 60 μg/L; 3-6 mg/kg/day if ferritin level is lower than 60 μg/L. Additionally, in cases where ferritin values are higher than 300 μg/L, (e.g. in multiple transfusions), supplementation [11] should be delayed. Oral iron supplementation is often poorly tolerated. The strengthening of milk formulas between 0.3 to 1.3 mg of iron per 100 Kcal, provides adequate mineral quotas [10]. It is

noteworthy to point out that commercially available iron preparations are supplements for which it is difficult to attribute therapeutic indications. Their use is indicated for prevention. Among them, prolonged release formulations (liposomal iron) allow for better absorption of trivalent iron (ferric pyrophosphate). Otherwise, bivalent iron is more readily absorbed than the trivalent one and therefore ferrous compounds (phosphate salts, gluconate, iron phosphate) are actually the most common. Moreover, glycinated components, whose chelating amino acid coating is digested in the gut, would seem to optimize intestinal absorption [12]. Complete blood count (CBC), ferritin, transferrin and transferrin saturation (Tfs) are useful parameters for assessment of iron status, but they are unable to provide a faithful image of early therapeutic response to iron treatment due to their association with metabolic and inflammatory conditions. Emerging biomarkers are presented. Reticulocyte count indicates the response of bone marrow [13]. Reticulocyte production index (RPI) describes the correct reticulocyte count for the severity of the anemia [14]. Soluble transferrin receptor (sTfR) is not influenced by functional ID, such as chronic inflammatory diseases [14, 15]. Content of reticulocyte hemoglobin (CHr) is the most reliable ID (cut-off 27.5) and IDA (cut-off 26.0) indicator [14, 16]. Zinc protoporphyrin (ZPP) is produced under poor iron availability condition, representing an indirect indicator of iron stock at marrow bone level. It is not affected by chronic illness or inflammatory conditions, although there may be false negatives in case of zinc deficiency [14]. Hypocromic red blood cell percentage (%HYPO) has a high positive predictive value for the diagnosis of IDA [14, 17]. A biomarkers panel consisting of ferritin, CBC, reticulocyte count, tranferrin, Tfs is useful to early identify newborns with ID at high risk of IDA. Additional measurements of sTfR, ZPP, %HYPO, RPI and CHr appear to be useful for management of infants with ID and/or IDA. Local policies regarding iron supplementation in preterm newborns are encouraged to reach the objective to effectively prevent IDA in the first months of life [18-20]. A proposal of clinical protocol for IDA prevention is reported in **Fig. 1**.

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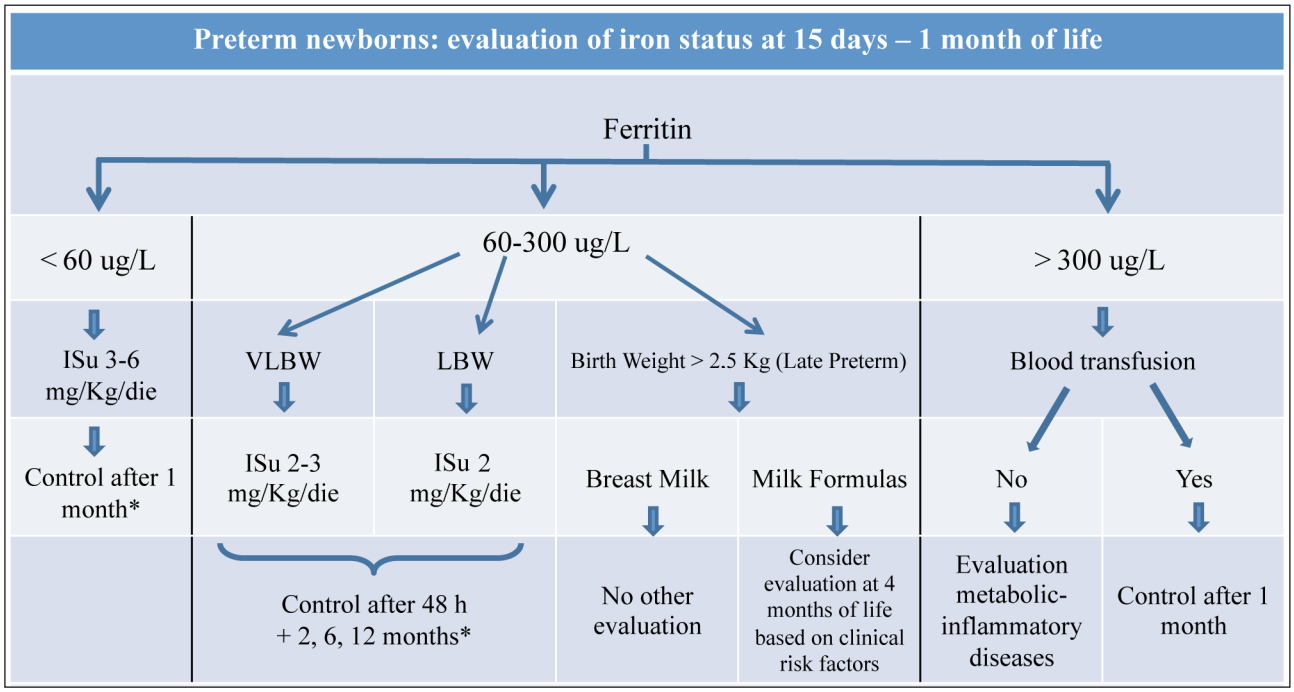

Figure 1 (LECT 48). Proposal of clinical protocol for prevention of iron deficiency (ID) and iron deficiency anemia (IDA).
VLBW: very low birth weight; LBW: low birth weight; ISu: iron supplementation.
*Lab test = complete blood count, reticulocyte count, content hemoglobin of reticulocyte, ferritin, transferrin, transferrin saturation, C-reactive protein.

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LECT 49

PAIN ASSESSMENT IN NEONATAL INTENSIVE CARE UNIT USING THE EDIN SCALE ADMINISTERED BY INFANTS' PARENTS

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INTRODUCTION

All the infants admitted to neonatal intensive care unit (NICU) are daily submitted to numerous stressful and painful procedures. Painful experience may lead newborn infants, especially preterms, to a major incidence of negative outcomes because of the repeated painful stimulations that could alter the development of the newborn. The main goals of neonatal pain management include identifying a potentially painful condition for the infant, to quantify the level of pain through a correct assessment and to estimate a program of intervention for the prevention of pain with parents' involvement. Pain is one of the factors that mostly worry parents in NICU, increasing their level of stress up to the moment of the discharge of their own child. Purpose of this project is to encourage the empowerment of parents in pain assessment of their own child, making them able to prevent and manage it. This is to improve infants' positive outcomes and reduce the tied up stress of parents during the hospitalization in NICU, increasing their role in infants' care. To achieve this goal the collaboration among nursing staff and family in the infants' care will be implemented, according to the principle that parents are the primary caregivers of their children: they have an active role in their infant's care, facilitating stability, relaxation and comfort.

MATERIALS AND METHODS

This is a study with a prospective design lead in the NICU of "Infermi Hospital" in Rimini (Italy), where NIDCAP methods are daily applied. The aim of the study is to compare the relieve of the chronic pain through the application of EDIN scale performed by mother and performed by the

nursing staff. Recipients of the study are parents (mother) of infants admitted to NICU with the following criteria: 1) intubated newborns or in other forms of respiratory assistance; 2) newborns carring drainage or major wounds; 3) newborns with continuous analgesia; 4) newborns in the first 72 hours of the post-surgical phase; 5) newborns out of the aforesaid criteria that are not submitted to painful procedures (a scale for the acute pain is not applied). Exclusion criteria include mother not able to understand the Italian language and mother who cannot be present in NICU for at least 4 hours during morning or afternoon or night. A scientifically significant result can be obtained with the analysis of at least 285 EDIN scales, collected by mothers.

PROCEDURES

The study will be conducted through the following steps: 1) mother's training to measure the pain of her own child through the EDIN scale. The EDIN scale is an unidimensional scale proposed by Debillon in the 2001 to measure the infants' long-lasting pain including the evaluation of five behavioral parameters. The application of this scale doesn't require a specific training because it codifies behaviors normally observed during the nursing care. For mother's training multimedia materials will be used, like written text, videos and images (draft by nursing staff of NICU) that described in detail the signals of stress and pain coming from the baby, as well as tools to ensure his/her comfort and care. The materials will be delivered and illustrated to mothers at least 72 hours from the admission to NICU, previous explanation of the study goals by the medical personnel and obtainment of the informed consent; 2) comparison of EDIN scores obtained, contemporarily and blindly, by mothers and nurses; 3) measurement of the maternal stress before the discharge, compiled by the referent psychologist of NICU. Currently the first step has been completed, with the implementation of the multimedia materials validated from a group of parents of children discharged from NICU. The study has obtained the favorable opinion of the Ethical Committee in September 2016 and it actually started on February 13th 2017.

CONCLUSIONS

The ultimate goal of the project is to verify the real possibility of parents to be the voice of their children for what concerns the relief of pain. It will also be appreciated if parents' involvement in pain management may favor acquiring a safer parental role with a positive impact on the infant's development or may increase parents' stress related to admission to NICU.

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LECT 50

APPROACH TO THE DYSMORPHIC NEWBORN

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Congenital anomalies are present in at least 10% of all neonatal intensive care unit admissions, of whom many have an underlying genetic condition [1, 2]. Neonatologists are often the first physicians to evaluate these infants and consequently need to be familiar with various physical differences in order to pursue further screening for occult malformations, perform diagnostic testing and appropriately counsel families [2]. On the basis of etiological criteria, it is possible to distinguish primary malformations, secondary malformations (disruptions) and deformations. They may be isolated and single or multiple and they may be caused by genetic and/or environmental factors, acting singly or in combination [3]. New

cytogenetic and molecular techniques (i.e. CGH array, next generation sequencing, etc.) may be useful to identify etiology, genotype-phenotype correlation, natural history and follow-up of each patient [4]. Furthermore, these new diagnostic tools have allowed prior undefined identification of the underlying causes. For example only in recent years, by the application of the genomic comparative hybridization in the diagnostic arena, several genomic rearrangements had been outlined as autonomous nosological diseases and, due to disruption of one or more dosage-sensitive genes whose loci are harbored within, new autosomic disorders had been discovered so far. Moreover, at the molecular level, the baton has now been handed over to next generation sequencing analyses (whole genome, exome and target sequencing), which replaced the "gene by gene" diagnostic strategy with panels of genes that are known to act in network due to common pathogenetic pathways which account also for their own genetic and clinical heterogeneity. All these technologies, taken together, constitute a promising methodological solution for somatic mosaicism disorders whose incidence is still underestimated as their genotypes in the mosaic ratio, especially in the low-grade ones [5]. This widens the scope for new non-invasive diagnostic procedures based on various tissue samples tested (oral mucosa, saliva, etc.), which will allow for an earlier diagnosis as well as for a better genotype-phenotype correlation, management and follow-up. Also set to greatly change the practice of genetic medicine is the introduction of non-invasive prenatal testing (NIPT) for a greater range of chromosomal and single gene disorders and the application of so-called liquid biopsies [6, 7]. Although NIPT analysis for the detection of trisomies 21, 13 and 18 is rather straightforward, it is reasonable to suppose that a new scenario due to single-cell genome analyses may overcome rapidly those conventional tests such as celocentesis, villocentesis and amniocentesis as well. Furthermore, recent genome-wide studies on single cells have delivered new insights into the nature and frequency of DNA mutations occurring during human gametogenesis, embryogenesis and neurogenesis [8] even though, at the same time, several major bioethical issues have arisen concerning a generic approach to the preimplantation of genetic diagnosed human cleavage-stage embryos [9]. Finally, in the forthcoming years, the challenge will be focused on the disorders that are thought to embrace complexity and presumably remain multifactorial resulting from a very complex interaction between genetic, epigenetic and/or environmental factors. To overcome several hypotheses and because metabolites both influence and are influenced by genetics, proteins and microbiomes, metabolomics studies will be conducted in conjunction with other "-omics" studies to integrate complex and big data sets in order to create the so-called "exposome", which is the most complete understanding of a whole biological system with translatable results [10]. These could lead us to the identification of a new scenario where common and rare variations combine to produce a diagnosis and, possibly, common variations (such as genetic or familial background) contribute to define the specific associated phenotypes, enhancing at the bottom-line the potential for novel therapeutic windows.

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LECT 51

ORGANIC MILK

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The demand of organic products has increased rapidly over the past 20 years. Milk products account for 15% of total organic products in US and > 30% in some European countries. Italy is the fifth producer in the world of organic products and organic milk represents about 2.7% of all milk. The reason for this significant increase is the perception by consumers that organic products are healthier and safer compared with conventional ones, not contaminated by pesticides, antibiotics and hormones. Preservation of the environment and the welfare of animals represent other important reasons. Organic milk is obtained from a production regulated by specific legislation covering all stages of production, preparation, storage, processing and distribution with specific EU logo (EC Regulation No. 834/2007). This legislation promotes and regulates a sustainable agriculture management system that respects the plant and animal systems, soil and water and contributes to biological diversity, ultimately to obtain high quality products that promote human health and respect of the environment. Organically produced milk must come from native bovine breeds that best fit local environmental conditions with good resistance to disease, free access to pasture. Cows must be fed with organic food (fresh forage and high-quality feed) produced for the most part by the same farm and no GMOs should be used. The use of fertilizers, herbicides and pesticides is forbidden. The use of antibiotics or allopathic veterinary medicinal products, hormones and other growth factors is prohibited and use of phytotherapeutic and homeopathic products is foreseen [1]. The breeding process includes: proper staging of the stables, room treatments, adequate animal density, adequate distribution of food and drinking water, health interventions and cleaning. The milking process must be carried out in a place built in such a way as to avoid contamination risks and to ensure effective cleaning and disinfection. Milk collection must take place within 36 hours after milking, collection tanks are subject to inspection checks and the milk temperature must never exceed 6°C. Before discharge of the inlet milk analyses and a first heat treatment of pasteurization are performed. Milk transport takes place in chilled, washed and sanitized tanks with sealed and plunged nozzles. Biological baby milk is produced from cow's milk through a series of processes and after adding various components (eg. vegetable oils). The finished product goes to microbiological, chemical and organoleptic controls. The difference between organic and conventional milk must be evaluated in terms of nutritional, hygienic, sanitary, organoleptic and technological characteristics. From a nutritional point of view, although studies have shown that there is a wide variability within organic production systems that makes the results often conflicting, there is no substantial difference between organic and conventional milk in terms of protein content, fat, vitamins and minerals. The nutrients present in the two types of milk actually depend very much on the type of cattle breed and the type of feeding offered to animals (fresh forage in organic farms, conventional feed crops) rather than by the production method. Several studies have shown, however, that in organic milk there is a higher content of polyunsaturated fatty acids (PUFA: alpha linolenic acid [ALA], omega-3 fatty acids, conjugated linolenic acid [CLA], eicosapentaenoic acid [EPA], docosahexaenoic acid [DHA]) as well as a better relationship between omega-3 and omega-6. Organic milk generally also contains a higher antioxidant content, especially α-tocopherol, as well as iron. Iodine and selenium concentrations are lower than in conventional milk [2-6]. Polyunsaturated fatty acids have positive effects in regulating the blood level of cholesterol and triglycerides, cardiac and cerebral function, and in regulating blood pressure. Regarding health quality, biological milk has the advantage of not containing hormone residues (GH, sex hormones), pesticides, antibiotics, and nitrates. These last, long-lived and generally non-degradable substances can act as endocrine disruptors; pesticides are neurotoxic and teratogenic substances [1, 7]. Environmental quality is a factor in favor of organic: the lack of chemical fertilizers, herbicides and pesticides has a positive effect on the ecosystem, reducing contamination of soil and water with the protection of flora and fauna. The environmental weakness of the biological system is that it requires more soil extension to produce the same amount of product as the conventional method. The cost of organic products is generally higher than the conventional one for higher production costs and staffing for lower profitability. Finally, there is not clear evidence that organic food can have a positive impact on individual health and the greatest advantage of this method could be above all the greater eco-compatibility [8-10].

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LECT 52

ANALGESIA AND POST-OPERATIVE SEDATION

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The administration of analgesic drugs in the post-operative period aims to control pain, reduce neuroendocrine and metabolic reaction to surgical stress, improve respiratory and overall outcome functionality. Analgesic coverage is therefore strongly recommended. Therapeutic choices should be based on the type of intervention, on the difficulty and invasiveness of the surgical system, on the type of anesthesia and on the duration. It is also important to keep in mind the general condition of the infant, whether the infant is incubated or not, or if there are risk factors for the use of opioids or non-steroidal anti-inflammatory drugs (NSAIDs). Therapy should provide an analgesic coverage for at least 48-72 hours. In the ventilated infant, the choice of the drug to be used should probably fall on the opioids, while, for the newborn not ventilated, the choice of the drug depends on clinical conditions, the presence of peridural catheter and the evaluation of the newborn's antalgic state. The use of NSAIDs at the time of infancy and especially in preterms is generally not recommended. Ketorolac is the analgesic most commonly found in literature in the infant. Tramadol does not have the same efficacy as in the pediatric age for the immaturity of the serotoninergic systems. Sedatives medicine such as midazolam should be used in this context with great caution with the aim of saving on the dose of opioid because they may mask the pain and because there is insufficient data to promote use in preterms, due to the effects adversity to neurological outcomes. The efficacy of the treatment should be evaluated with validated algometric scale in order to identify as much as possible the treatment. In summary, post-operative analgesia is strongly recommended in the infant, but in the choice of pharmacological options the available evidence of low or very low levels of evidence does not allow precise information on therapeutic options. It is suggested, especially after major surgery, the use of opioid associated with paracetamol with a total dose saving effect of 48-72 hours, monitoring algebraic score. In selected cases, the use of NSAIDs, such as ketorolac, may be recommended, with careful monitoring of renal and coagulation function.

POST-OPERATIVE ANALGESIA BY PERIDURAL CATHETER

Peridural anesthesia is increasingly used to control post-operative pain in the infant. This method requires a specific experience from the operator, but in our Intensive Care Units it is possible to follow newborn infants in the post-operative position by continuing catheterization. Continuous peridural

analgesia, like other loco-regional anesthesia techniques, is extremely beneficial to the surgical infant since it allows savings of general anesthetics during surgery, systemic analgesics both in the intra- and in the postoperative, reduces the significance and the incidence of paralytic lameness and the duration of mechanical ventilation after surgery, and offers the best possible protection against surgical stress. Post-operative management of continuous infusions of local anesthetics is not free from risk and requires adequate staffing and training to be able to recognize both the complications of the method and the signs of overdose of the anesthetics used. Performing continuous anesthesia requires that general anesthesia or deep sedation be first induced. By means of a peridural catheter, left in place, at the end of the surgery, it is possible to continue the control of post-operative pain. Currently, there are three anesthetics used to control post-operative pain by continuing catheterization; however, the only local anesthetic recorded for epidural continuous infusion in the newborn and the baby is ropivacaine. It is possible to enhance the effect of the local anesthetic by adding to the low dosage solutions of an opiate, more often fentanil. The association with an opiate requires frequent monitoring of respiratory rate, level of consciousness and oxygen saturation as well as of the state of anxiety. However, it should be borne in mind that, although the concentrations of these drugs appear to be non-neurotoxic at the moment, the neonate's spinal cord is developing and studies of the potential neurotoxic effects of such anesthetics still have no significance. In summary, despite continuous anesthesia is an effective technique that saves on the total dose of systemic analgesics needed in post-operative and wider recovery, its use is documented in early-born babies with low or very low evidence quality. Adverse events are poorly reported and consequently its use should be cautiously advised, as it is not possible at present knowledge to make an accurate risk-benefit balance.

LECT 53

PAIN TREATMENT IN RESPIRATORY DISEASES OF THE NEWBORN. GUIDELINES FOR INTUBATION, MECHANICAL AND NON INVASIVE VENTILATION

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TRACHEAL INTUBATION

Tracheal intubation is a stressful, painful and potentially dangerous procedure because of the possible changes in vital parameters and airway trauma as well. Literature shows how the procedure and the conditions of intubation in the newborn can be improved by the premedication. In the same way, the premedication can reduce the pain, stress and procedure related changes in heart rate, arterial pressure, oxygen saturation and endocranial pressure. Premedication for tracheal intubation has several goals: decrease in pain, in stress and decrease of procedure related side effects, procedure facilitation, short-lasting effects of the sedation (e.g. surfactant administration for intubation, surfactant, extubation method [INSURE]). The following recommendations (processed using the GRADE method) regard the goals as a whole: premedication for intubation in the newborn is strongly recommended. In order to get a safer, faster, less painful and less dangerous procedure, use: a) atropine + fentanyl + succinylcholine or rocuronium. Neuromuscolar blockers can be avoided in the newborn unable to oppose the procedure (e.g. newborn with severe asphyxia, muscular dystrophy or other neuromuscular pathologies); b) in > 32 weeks gestational age (GA) newborn, if hemodynamically stable, use as well: atropine + fentanyl + midazolam; c) in > 1 day old newborn, if hemodynamically stable, use as well: atropine + propofol; d) for INSURE you can use: atropine + remifentanil/fentanyl + succinylcholine (after the procedure, eventually use naloxone for a faster respiratory recovery); e) in the hemodynamically unstable newborn you can use ketamine, paying particular attention to the extreme premature. However, it is important to choose the proper drugs considering both the pharmacological features and patient status.

MECHANICAL VENTILATION

During mechanical ventilation (MV), all the care procedures and the non-pharmacological analgesia should be performed in order to reduce the newborn's stress. Systemic pharmacological interventions should be considered as well. There are two different approaches according to the following situations: expected short-term MV and MV in the patient with severe respiratory failure. In case of expected short-term MV (mainly in the premature with respiratory distress syndrome), in order to reduce and prevent acute pain, evaluated by scales, intermittent doses of opioids (fentanyl, remifentanil or morphine) are advised. The use of "BOLI as required" results in decreased cumulative drug amount and side effects.

The dose has to be evaluated according to gestational age, postnatal age and MV in patients with severe respiratory failure (surgical or neurological diseases, malformations, severe sepsis, pulmonary hypertension). A more continuous analgesic therapy might be required to keep the proper level of sedation. This can be achieved by continuous opioid infusion (fentanyl or morphine). Prefer fentanyl (1-2 mcg/kg in 30' + infusion of 0.5-3 mcg/kg/h) if there is risk of hypotension, if GA is < 27 weeks, and if there are disorders in gastrointestinal motility or kidney failure. Currently there is no evidence demonstrating that continuative analgesia in the premature in MV can improve short-term neurological outcomes (severe intraventricular haemorrhage and periventricular leukomalacia) and prevent death in the first month of life. The dose-related opioid side effects are: longer-lasting MV, delayed full-enteral feeding, hypotension (mostly morphine) and possible long-term neurological side effects. If a stronger sedative effect is required (e.g. pulmonary hypertension, severe air-leak, after major surgery), a short-lasting benzodiazepine (e.g. midazolam) can be given in late preterm newborns without hypotension, in addition to the opioids. Doses should be individualized according to gestational age and the therapy should not last longer than a few days. The association with the opioids saves the opioid dose itself. For particular situations, as when every other analgesic/sedative therapy does not seem to work anymore, the use of dexmedetomidine has recently been approved. Anyway, a judicious use of the latter is recommended because of the little available evidence.

NON-INVASIVE VENTILATION

There are no RCTs in literature on this subject. It is suggested: a) to prefer non-pharmacological analgesia techniques; b) to monitor pain through validated scales; c) to use opioids before invasive procedures, at minimum doses recommended, in neonates > 27 weeks GA; d) to assess the chance of sedation/analgesia, with midazolam or low dose opioids, in term newborns. In the newborn in CPAP/bilevel/nasal ventilation, the opioid discontinuation is not necessary: respiratory depression is among the first side effects to disappear during opioid treatment. In the transition from invasive ventilation to non invasive ventilation, use validated neonatal pain scales to reduce opioid doses.

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LECT 54

ABDOMINAL ULTRASOUND IN THE NEWBORN

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Ultrasound is the most commonly used method in the pediatric population, including the neonatal period, to investigate suspected abdominal diseases as it does not require radiation or iodine contrast or anesthesia, and it is easily performed at bed side. Though it is a highly sensitive and easily accessible imaging mode, errors in abdominal ultrasound investigation result from many factors, including the knowledge of anatomic and pathophysiological differences, as well as of clinical symptoms and pathology at each stage of child development. In addition, when a single ultrasound examination is performed in infants and children, it may be necessary to apply a wide range of different sensors for the most appropriate applications. All these considerations entail responsibilities in the execution, in the iconography and in the report of the investigation. The course aims to introduce the principal ultrasound features of some of the most frequently encountered diseases and some of the rarer entities in the neonatal age. In addition to the knowledge of the ultrasound patterns of each disease, including the hepatobiliary and pancreatic ones, it is important to understand the normal appearance and variations to avoid interpretation errors. Abdominal ultrasound can play a role both in the diagnostic and interventional process, and both in neonatal intensive care unit for pathologies that most typically involve premature infants and in a first level birth point. For many years a direct abdomen radiography has been considered the technique of choice to investigate patients, certain or suspected, with necrotizing enterocolitis. The latest literature data show that the role of intestinal ultrasound may be equal or greater than X-ray. The advantages of ultrasound imaging include direct visualization of intraperitoneal fluid, including its ecogenicity characteristics, as well as intestinal wall visualization that allows us to investigate ecostructure, thickness, peristalsis and perfusion. In case of neonatal abdominal and pelvic masses, distinct sonographic findings can help to establish the right cause considering a wide differential diagnosis, and can guide proper diagnostic and therapeutic management. Finally, abdominal ul-

trasound is needed to verify, in the postnatal age, anomalies identified by the prenatal diagnosis of the second and third trimesters, among which one of the most common is the dilation of the renal collector system (with a frequency of about 1-4.5%). The diagnosis of these anomalies allows a correct follow-up and to establish medical and/or surgical treatments to reduce or eliminate any complications (pyelonephritis, pain, kidney stones, hypertension, and kidney failure). On the other hand, taking into account that approximately 64-94% of prenatal hydronephroses do not correlate with urological anomalies, a correct ultrasound diagnostic iter is needed in the timing and execution modes, to avoid the medicalization of normal conditions.

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LECT 55

NEONATAL OSTOMY: GOALS AND PRIORITIES

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INTRODUCTION

Several pathological conditions, mostly congenital, typically present in the neonatal period of life and require procedures that result in ostomy. Depending on the underlying causes, ostomies can involve any part of the digestive tract and are associated with morbidity and mortality. Therefore, nurse care of a neonatal ostomy is critical to prevent potential severe complications and it has a significant impact on the survival rate of the newborns affected by complex malformations.

OBJECTIVE

To evaluate the quality of the pre- and post-operative nurse interventions in newborns affected by pathological conditions requiring ostomy.

METHODS

The newborns enrolled in the study were identified by the registry database of all the infants who required assistance at our NICU in the 6-year period from 2010 to 2015. Medical and nurse records of all the neonates undergoing digestive ostomy were reviewed and analyzed. Data regarding gestational age, underlying pathological conditions, need of parenteral nutrition, central venous catheter and mechanical ventilation were considered for the study.

RESULTS

In the 6-year period studied, among a total of 2,281 newborns who received assistance at our NICU, 13 (0.57%) newborns underwent ostomy surgical procedure, among whom 9 (69%) were at term and 4 (31%) preterm infants (M = 8, 61.5%). The ostomies were 1 jejunostomy, 5 ileostomies and 7 colostomies. Of the preterms, 2 underwent emergency enterostomy creation for necrotizing enterocolitis, 1 had jejunostomy for jejunal atresia and 1 colostomy for anal atresia. Of the born at term infants, 3 had ileostomy for meconium ileus (as early manifestation of cystic fibrosis in 2), 4 had colostomy for congenital anorectal malformations, 1 had colostomy for Hirschsprung disease and 1 for intestinal duplication. All received parenteral nutrition, all but two central venous catheter, half of them needed mechanical ventilation. The number of days at the NICU ranged from 18 to 98; one infant deceased (**Tab. 1**). The nursing care consisted in both pre- and post-surgery assistance. Nursing efforts were aimed to guarantee optimal vital parameters before, during and after surgery, along with caring also for the psychophysical status of each newborn. After surgery, care was mainly aimed to apply therapy protocols with continuous monitoring of vital signs, bowel functioning and hydration. Proper care of the ostomy helped to prevent the occurrence of skin problems such as injuries and infections. At any time the stool pouch was changed or removed, the nurse took care of it by gently shifting it from a higher to a lower level, also ensuring moist skin. After removing the stool pouch, the nurse cleaned the skin by warm

Table 1 (LECT 55). Main characteristics of our newborn series.

Type of ostomy	No.	GA (range)	TPN	CVC	Mechanical ventilation	Days at NICU (range)
Jejuno	1	34	100%	100%	100%	33
Ileum	5	28-40	100%	90%	90%	17-65
Colon	7	28-38	100%	100%	90%	14-110

water only, avoiding the use of any detergent or soap, and dried it by gently applying soft paper press. These procedures allowed the prevention of any skin injuries around the ostomy. As part of the nurse role was also parents' educational training for the home care of the stool pouch. Another important role of the nurse was in helping the transition toward breast feedings by following the recommendations and guidelines suggested by WHO/UNICEF, including, for example, the use of a teaspoon until the baby was able to suckling directly from the breast.

CONCLUSIONS

The present study highlights how the assistance of newborns with malformations that require ostomy is an articulate process, which the nurse has to accomplish through two distinct but equally complex phases of the pre- and post-surgery nurse care. During the pre-surgery, the nurse care should guarantee both adequate respiratory function of the neonate by the proper use of the respiratory machines, and nutrition by ensuring adequate calories intake by total parenteral nutrition and/or by promoting breast milk feeding. Moreover, the nurse care must include techniques to favor sufficient rest and sleep hours to all the newborns at the NICU. During the post-surgery, the nurse must take care of all the measures needed for preventing the occurrence of serious complications, by accurately applying therapeutic protocols for proper ostomy care, including parents' education and autonomy. In conclusion, proper nursing care of newborns affected by conditions that require ostomy is fundamental in order to ensure optimal and complication-free outcomes, at both short and long terms. The care of the newborns with ostomy regards not only the pre- and the post-surgery periods but it must also include parental education and training for the proper care of newborn with ostomy at home.

LECT 56

ACUTE SCROTUM

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Acute scrotum is a pathological condition characterized by the sudden appearance of scrotal pain accompanied by skin reddening, edema, scrotal swelling and often requiring urgent surgery to prevent the loss of the testicle. Testicular torsion is the most severe cause of acute scrotum and requires prompt diagnosis. It may be intravaginal (torsion of the testis itself, more frequent in prepubertal age, determined by a faster growth of the gonad compared to the mesorchium, its fixation system) or extravaginal (torsion of the spermatic chord, more frequent in the neonatal or early age, often associated with an undescended testis and favored by a contraction of the cremaster muscle that determines the rotation of the chord on its major axis). In the newborn, it is common to detect the prenatal torsion of the gonad, characterized by the appearance of a dark, blackish scrotum. Conditions such as a retractile testicle may also predispose to the onset of testicular torsion or recurrent testicular pain. Testicular appendages, present in the 90% of males, may twist around their vascular pedicle. Orchiepididymitis is an acute or chronic process involving the testicle and epididymis. The etiology can be bacterial (*E. coli*, *Proteus spp*., *Klebsiella spp*., *Chlamydia spp.*) or viral. It is often associated with urinary tract infection; in 30% of cases it may follow a parotitis. Idiopathic scrotal edema is supposed to have an allergic or hyperergic etiology. The incidence of the different causes of acute scrotum varies according to age and has a bimodal presentation for testicular torsion: between 0 and 2 years and between 12 and 14 years testicular pain is most frequently caused by a torsion of the gonad. The incidence of torsion of epididymal appendages is prevalent in patients aged between 7 and 12 years; symptomatic varicocele and orchiepididymitis are more frequent in pubertal patients, generally older than 13 years. However, orchiepididymitis may occur at an earlier age in patients with urinary tract malformations (ectopic ureter, double moiety, vesico-ureteric reflux and deferential reflux; persistence of Müllerian remnants, genital abnormalities).

Testicular torsion: sudden onset of pain, often accompanied by nausea and vomiting, spread to the lower abdomen and the inguinal region, hyperemic, edematous and tense scrotum, lack of cremasteric reflex, swollen testicle, increased in volume, ascended, intensely painful on palpation. Torsion of testicular appendages: the pain is more gradual but worsening, the cremasteric reflexes are usually preserved; the scrotum, however, is swollen and red and painful on palpation especially in the upper testicular pole; the blue-dot sign (bluish area visible in transparency or translucency) can be detected; associated symptoms are rare. Orchiepididymitis: the onset is usually slow and the pain is not very intense, in contrast with the presence of an intensely swollen, reddish and edematous scrotum. A recent history of urinary symptoms is frequent. Idiopathic scrotal edema: presence of significant scrotal swelling and erythema, spread to the base of the penile shaft and modest or no subjective symptoms. Diagnosis of acute scrotum is predominantly clinical, based on the physical examination and the history. Laboratory tests are often unspecific; in case of orchiepididymitis there may be leukocyturia or pyuria. Testicular ultrasound associated with Doppler can provide useful data, but it is not always a reliable test, and in some cases it may even be misleading. It may highlight an increased blood flow in case of orchiepididymitis, a reduction in flow with parenchymal alteration in case of torsion, it may identify twisted testicular appendages, or define parenchymal damage as a result of a trauma. Testicular ultrasound can be associated with renal and bladder ultrasound in order to exclude urinary abnormalities.

Therapy of acute scrotum is always surgical as long as a testicular torsion cannot be safely excluded. Considering that testicular necrosis develops after 4-6 hours after torsion, this should be regarded as a not deferrable urgency. The procedure is performed through an inguinal access in the neonate with a twisted chord and through a scrotal access in the testicular torsion of the pubertal patient; it consists in derotating the twisted testicle, waiting for and evaluating its reperfusion before replacing it back into the scrotum and fixing it in order to prevent future torsions. In case of severe ischemic damage of the testis, orchiectomy may be necessary. The fixation of the contralateral testicle is controversial, although always indicated after orchiectomy and generally preferable; it must be associated with the section of the cremaster muscle to avoid the risk of axial rotation favored by cremaster contraction. In case of acute scrotum caused by torsion of testicular appendages, a remission of symptomatology can be obtained with conservative treatment. If symptoms persist, however, surgery is indicated to evacuate the hydrocele and remove the twisted appendix. Orchiepididymitis is managed medically with anti-inflammatory and antibiotic therapy.

LECT 57

PALLIATIVE CARE PRACTICE IN NEONATOLOGY

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INTRODUCTION

In the last years the problem of the limits of viability has been faced by neonatologists focusing their attention on two critical aspects: firstly, to resuscitate or not to resuscitate in the delivery room; secondly, whether or when to withdraw intensive care in newborn infants with little chance of survival. Several recommendations and guidelines have been elaborated by several institutions in many countries, but the unanimous consent has never been met being the decision making process based on the gestational age as well on the poor prognosis [1-5]. Our hospital does not allow the voluntary termination of a pregnancy and we are not involved in the decision to resuscitate or not, but we faced the therapeutic futility in our neonatal intensive care unit (NICU) [6-9]. Our study aims to identify the limit between proportionate and futile interventions in the NICU.

MATERIALS AND METHODS

The study includes two steps. In the first step we reviewed the previous five years of our database in order to identify the causes of death of newborn infants admitted to our NICU. Sixty-five of the 727 patients admitted to the NICU died and we identified six situations related to death and which we will call "terminal conditions": 1) cardiac arrest unresponsive to cardiac and respiratory resuscitation for at least 15 minutes; 2) pulmonary hypertension in maximal respiratory support (Maximum Inspiratory Pressure > 35 cmH_2O, FiO_2 1, Mean Airway Pressure > 15 cmH_2O) with acidosis (pH < 7.00 for more than 12 hours), not

responsive to treatment with inhaled nitric oxide plus sildenafil plus prostacyclins; 3) acute respiratory distress or severe chronic lung disease in maximal respiratory support and pharmacological therapy; 4) renal failure associated with persistent anuria for over 72 hours, in absence of possibility for dialysis or kidney transplantation; 5) septic shock with sclerema, unresponsive to antibiotic therapy, cardiac, circulatory, and anti-inflammatory support; 6) seizures not controlled by maximal sedative therapy (more than two anticonvulsant drugs) or deep coma for at least 12 hours, in association with massive intracranial and intracerebral hemorrhage or with asphyxia-induced multi-organ failure. All babies affected by one of these "terminal conditions" eventually died, and all implemented therapies have proven their futility. In the second step of the study (from June 2013 to December 2014) we prospectively evaluated all the newborn infants who reached "terminal conditions" in order to verify if they were inevitably destined to die. The assessment of "terminal condition" was done by at least two neonatologists and a nurse responsible for the childcare. In this step, treatments were managed without changing our policy to verify the final fate of these babies.

RESULTS

From June 2013 and December 2014, 998 newborn infants were admitted in our NICU, of which 93 died. Thirteen infants died so suddenly that the evaluation of terminal condition was not possible. Eighty neonates, 42 males and 38 females, were considered for perspective evaluation if "terminal conditions" were satisfied. **Tab. 1** shows the clinical data of the 80 infants included in the study. Perspective evaluation was performed at a mean age of 10 ± 26 days (range 1 to 140). The evaluation of "terminal conditions" was made by two physicians not involved in the clinical management of the newborn, while the neonatologists involved in the active care were unaware of the evaluation. Seventy infants who met the terminal criteria died at a mean age of 14 ± 28 days (range 1 to 160), while 10 neonates who did not meet terminal criteria were discharged alive from the NICU. Forty infants reached the "terminal conditions" in the first 96 hours of life, 26 infants between the 5th and the 28th day of life, and 4 infants after the 28th day of life.

Table 1 (LECT 57). Table shows the clinical data of the 80 infants included in the study.

GA 23 weeks	5
Not viable congenital anomalies	9
Trisomy 18	3
Multiple malformations	2
Renal aplasia	2
Hydrops	1
Osteocondrodysplasia	1
Malformations	15
Congenital diaphragmatic hernia	7
Artero-venous malformation (2 Galeno, hepatic)	3
Hydronephrosis	2
Sacral teratoma	1
Myelomeningocele + Hydrocephalus	1
Cerebral hypoplasia	1
Severe neonatal asphyxia	5
IVH + Cerebral tamponade + Seizures	7
Persistent pulmonary neonatal hypertension	17
Septic shock	20
Severe bronchopulmonary dysplasia	2
Total	80

DISCUSSION

Neonatologists are often involved in end-of-life decisions, dealing with withholding or withdrawing intensive treatments, but they are reluctant to accept the idea of not resuscitating in the delivery room, so they tend not to resuscitate only infants with no chances of survival at all [1-7]. Active end-of-life decision practice is not legal in Italy, and every neonate receive the maximum amount of intensive care regardless of the future quality of life, the burdens imposed to neonates, and the cost-benefit ratio. For these reasons we focused our attention on the withdrawing intensive treatment in the NICU, with the aim to help neonatologists to take the right decision without violating the law and basing on their religious beliefs [8, 9]. The results obtained by our study seem to confirm that our "terminal conditions" can identify all neonates without any chance of survival, and can be used to avoid aggressive but futile treatments.

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LECT 58

NURSES AND NEAR INFRARED SPECTROSCOPY (NIRS): THE ROLE OF NIRS IN NEONATAL INTENSIVE CARE UNIT

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BACKGROUND

The consistent progress in the intensive care of newborn has led to a significant increase of the survival even in the extremely preterm newborns; unfortunately, these results are still darkened by a substantial increased rate of negative neurological outcomes. Considering these results, although continuous monitoring is guaranteed to all the newborns (heart activity, respiratory activity, peripheral oxygenation, arterial pressure and body temperature), it appears to be paradoxical that it lacks any form of continuous cerebral activity control besides the neuroimaging and the electroencephalography, which we can use for a relatively short time. The implementation in the continuous monitoring of the amplitude-integrated EEG and of the near infrared spectroscopy (NIRS) may overcome the problem, giving us direct judgment elements to improve the diagnostic/therapeutic management and consequently the short- and long-term prognosis. We report our experience regarding the use of NIRS in our unit, started more than five years ago, with the simultaneous measurement of the cerebral (cSO_2) and renal (rSO_2) oxygenation in all newborn admitted to our NICU during the first 72 hours and, if necessary, for longer time. This technology relies on the transparence of human tissue to light in the near-infrared region, on the absorption of the light travelling the tissue by pigmented compounds (chromophores) and on the different light absorption of compounds, such as hemoglobin, pending on their oxygenation status. Despite the different technical approaches of the now available NIRS devices, they give an absolute value reflecting the mixed oxygen saturation in the arteries (± 25%), capillaries (± 5%) and veins (± 70%).

METHODS

We use the Somanetics 5100 Invos™ device (Covidien), employing the CNN/SNN sensors applied over the forehead for cSO_2 and over the right or left posterior lateral flank for rSO_2 [1].

OBJECTIVES

Besides the knowledge of the absolute values of the regional saturations, the calculation of the extraction fraction of the O_2 (FTOE) ($SaO_2 – rSO_2/SaO_2$) allows the assessment of the relationship between supply and consumption of oxygen in a district and evaluating its changes in every condition lived by the critical newborn.

RESULTS

The contemporary measurement of the cerebral and renal saturations gives much information regarding the hemodynamic of related diseases (such as the heart diseases, the hypoxic-ischemic manifestation, the anemia and the sepsis) estimating also the impact of nursing measures on the single subject. The measurement of oxygenation variations in different districts allows to anticipate the clinical expressions and to research the cause underlying every cerebral troubles. In our experience, we consider as an alarm bell an $rSO_2 \leq 60$ or an rFTOE ≥ 30 and a difference between renal and cerebral saturation ≤ 0 (n.v. 9.0 ± 8.9) [2]. With these cut-offs, sensitivity and specificity reach 90% and 80%, respectively. The application of this protocol leads to consistent changes in the treatment of patent ductus in preterm newborns and in the decision about blood transfusion in anemic states. For example, we have modified our approach to PDA and left to right shunt, starting with dopamine as soon as the renal oxygenation decreases to 50% and/or its extraction fraction is more than 40%. The Cox-inhibitors are used both if the ductus is still open at or near the end of the first week, and are anticipated if signs of systemic and/or cerebral hypoperfusion appear

or persist. Moreover, in the anemic states, only the newborns who reached a determined threshold of hemoglobin and show an rSO_2 of 50 ± 5% and/or an rFTOE ≥ 40% underwent the blood transfusion [1]. The impact on the nursing measurements has led to consistent changes, which could help physicians in the maintenance of the newborn stabilization.

CONCLUSIONS

The NIRS appears to be a simple, non-invasive method of monitoring. However, this method could be also imperfect because of the high inter-patient and intra-patient variability of the results, which are related to the lack of precision. Thus, the consistent variations of the regional saturations, if are correctly used, give us more information about the potentially dangerous changes of the oxygenation and perfusion. In conclusion, considering our experience with the NIRS over the years, we believe that it should be available for all newborn in neonatal intensive care units.

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LECT 59

THE ITALIAN CLINICAL PATHWAY FOR THE MANAGEMENT OF UMBILICAL CORD CLAMPING IN TERM AND PRETERM NEWBORNS

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Delayed umbilical cord clamping (DCC) and cord milking (CM) are placental transfusion strategies that improve hemoglobin concentration and iron stores in term newborns and decrease the incidence of intraventricular hemorrhage, sepsis, necrotizing enterocolitis and transfusion in preterm newborns. DCC is recommended by many scientific societies for both term and preterm newborns not requiring resuscitation. Many authors consider milking the umbilical cord from the placenta to the newborn an adequate substitute, when DCC is not feasible. A recent Italian survey showed a low application rate for both DCC and CM especially at the lowest gestational ages; the study showed that the implementation of DCC and CM correlated with the knowledge of benefits deriving from these practices, the availability of local guidelines and the obstetrical-neonatological engagement in the delivery room. To improve the uptake of placental transfusion strategies in Italy and to homogenize the management of the umbilical cord nationwide, in 2017 the Italian Task Force for the Management of Umbilical Cord Clamping, composed by neonatologists, obstetricians, and midwives, drew up the first national recommendations for the management of umbilical cord clamping. The recommendations have been drawn using the methodological approach proposed by the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) Working Group. The course we have organized aims to implement the good clinical practice of DCC and CM in all clinical scenarios. After a first introductory part about state of the art, the course provides a framework for the physiology of the fetal placental unit, with particular attention to transitional cardio-circulatory aspects. Subsequently, recommendations on DCC and CM practices are presented in the various clinical contexts. In particular, it is considered the management of the umbilical cord clamping in the neonate born by vaginal delivery and cesarean section, twin pregnancy, the infant from the mother with congenital infection, the late preterm infant. The aspects related to DCC and CM in the extremely

premature infant and the role of the neonatologist to the mother's bedside is discussed, and an operative flow chart that includes international resuscitation guidelines is presented. The course also includes sections concerning the relationship between cord blood gas analysis and DCC and the management of cord clamping when parents want to donate cord blood. Lastly, a session will be presented to suggest a pathway to the implementation of these clinical practices at birth rooms. To achieve this goal, a local delivery team composed by neonatologists, obstetricians and midwifes should draft operating guidelines that consider local logistical and operational specificities. The key point to apply placental transfusion strategies is to decide before childbirth which approach to cord clamping is preferable, taking into account the possible need for neonatal resuscitation, mother's clinical conditions, and possible obstetric-related surgical problems. It is important to schedule regular divisional meetings and multidisciplinary simulations to promote the application of DCC and CM locally. Periodic audits are suggested to monitor the compliance of the delivery room team and to update local choices.

LECT 60

NEONATOLOGIST PERFORMED ECHOCARDIOGRAPHY (NPE): THE ITALIAN PROJECT

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Bedside echocardiography for hemodynamic assessment of sick infants is increasingly spreading in NICUs worldwide. Also known as functional echocardiography or targeted neonatal echocardiography, it aims to define normal structural anatomy of the heart and to identify cardiovascular compromise. It allows a better understanding of ongoing hemodynamic processes and supports clinical decision-making. In literature, there are three guidelines published on this topic so far [1-3]. These are expert consensus statements that provide recommendations for structured training program and accreditation in Neonatologist Performed Echocardiography (NPE). They highlight the need to ensure standardization of training in order to pursue quality assurance and patient safety. Close and continuous collaboration with paediatric cardiologist is consistently recommended. The *Consensus Statement endorsed by European Society for Paediatric Research (ESPR) and European Society for Neonatology (ESN)* identifies training standards applicable in Europe [2]. In Italy, interest in functional echocardiography has spread fast over the past years. Neonatologists with a particular interest in NPE developed themselves their own path to knowledge, skills and practice in the field, taking primary responsibility for choosing the means to achieve this, in the effort to fill the gap due to the fact that structured training in NPE is lacking in Italy, as it is across Europe. Surely, there is large variation in the use of echocardiography in clinical practice and level of expertise may vary, leaving room for improvement. In view of all these considerations, the current Italian Study Group on Neonatal Cardiology made the realization of structured training program and accreditation in NPE a priority. We aim to offer qualified learning opportunity to neonatologists approaching this practice, to ensure standardization of training and guarantee the safe dissemination of this practice. Few other European countries have established their own training system. Switzerland adopted the American Society of Echocardiography/European Association of Echocardiography/Association for European Paediatric Cardiology guidelines for Targeted Neonatal Echocardiography [4]. These guidelines recommend a core training period followed by an advanced period of training, each lasting 4-6 months; direct or indirect supervision and coordination by the

paediatric cardiologist is mandatory. This approach is difficult to realize in Europe where the proximity of neonatal units to paediatric cardiology centers may vary significantly. The Australasian Society for Ultrasound in Medicine provides a Certificate in Clinician Performed Ultrasound (CCPU) in Neonatal Ultrasound. It is designed to cover the theoretical and practical curriculum for imaging, not only the neonatal heart, but also brain, abdominal organs and central line localization. It comprises two separated courses: basic and advanced. Holders of the CCPU in Neonatal Ultrasound are expected to consult and request appropriate advice by a paediatric cardiologist in situations where suspicion of congenital heart disease (CHD) is high, such as those circumstances where primary clinical concern is the possibility of CHD, specific treatment is being instituted for CHD based on a clinician performed ultrasound (CPU), the clinical findings or course are not consistent with the CPU findings, transfer to a paediatric cardiology unit is being planned based on a CPU, the baby is no longer in an NICU setting (e.g. after discharge) [5]. The European *Consensus Statement* on NPE remarked that this program does not require establishing structural normality of heart and includes other organ scans. They pointed out that it requires modification to allow integration in clinical practice and develop a system that is fit for practice across Europe, where emphasis is on confirming structural normality [2]. The Italian Study Group of Neonatal Cardiology decided in agreement with the Italian Society of Neonatology Board to follow the recommendations for NPE suggested in the *Consensus Statement endorsed by European Society for Paediatric Research (ESPR) and European Society for Neonatology (ESN)* [2]. The working group on *Consensus Statement* advocates that training should be coordinated, directed, and conducted by qualified neonatologists, emphasizing the need of close and solid collaboration with paediatric cardiology services [2]. Referral should be made to a paediatric cardiologist for any infant with clinical or echocardiographic suspicion of CHD. Tertiary/Quaternary Neonatal Intensive Care Units, Paediatric Cardiology Centers and Trainers are identified in order to guarantee proper training conditions. The training program should cover both basic and advanced skills in echocardiography. Training program and accreditation in NPE have been submitted to the Italian Pediatric Cardiology Society (SICP) Board, establishing close collaboration. SICP offered its support and endorsed this project.

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LECT 61

ROLE OF CEREBRAL ULTRASOUND IN PERINATAL STROKE

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Neonatal stroke, also known as perinatal stroke, is a damage of a brain tissue area resulting either from disruption of cerebral blood flow in one of the main cerebral arteries from thrombosis or embolism (perinatal arterial ischemic stroke, PAIS) or from thrombosis of major cerebral veins (cerebral sinus venous thrombosis, CSVT). Time of onset is between the 20th week of fetal life and 28 days of postnatal age. The diagnosis must be confirmed with neuroimaging or neuropathological studies. Physiopathology and clinical presentation are similar for both ischemic arterial stroke and venous thrombosis, but they considerably differ for site and kind of lesions. Currently, sinus venous thrombosis is in most

cases hemorrhagic. Incidence of arterial stroke is reported as 1:2,300-4,000 deliveries; instead, incidence of cerebral sinus venous thrombosis is 1-2.6:100,000 newborns. Etiology of perinatal stroke is overall unknown; nevertheless, arterial ischemic stroke is presumed, but seldom proven, to result from emboli from the placenta passing through the patent foramen ovale. Left middle cerebral artery is the most frequently involved in embolism. Cerebral sinus venous thrombosis is supposed to be promoted by prothrombotic factors, although, despite many infants show one or more prothrombotic factors, further ischemic and/or thrombotic events rarely occur beyond the neonatal period. Therefore, the role of genetic prothrombotic factors is currently not well defined. Perinatal stroke occurs close to delivery and birth and this fact suggests that stroke is related to peripartum factors more than genetic prothrombotic factors. In most cases, infants with arterial ischemic stroke do not need cardiopulmonary resuscitation at birth, although labour and delivery are often complicated. They are usually managed as healthy infants but they become symptomatic (generally with seizures) within the third day of life. Instead, complicated birth is common among infants affected by sinus venous thrombosis, who become symptomatic within 48 h of delivery in approximately 50% of cases. Neuroimaging is essential for the diagnosis of perinatal stroke. Computed tomography is rarely used because of poor detection rates for parenchymal lesions and high radiation dosage. Magnetic resonance imaging (MRI) is the most sensitive technique for diagnosis of perinatal stroke. Diffusion-weighted imaging allows diagnosis of perinatal stroke in the first 24 hours of life. Typical MRI imaging in T1 and T2 allows exact diagnosis of brain area involved and the extent of the lesions. Furthermore, very small lesions or damage in deep area, such as brainstem, can be well identified with MRI. The role of head ultrasound is very debated in literature, because doubts have been arisen about its poor sensitivity in early diagnosis of brain damage induced by perinatal stroke. Head ultrasound offers undisputed advantages over other neuroimaging techniques: it is easily available in every neonatal intensive care unit (NICU). Furthermore, cerebral ultrasound (CUS) can be simply and quickly performed bedside, so that it is not necessary to move the patient from intensive care unit. Unfortunately, this methodic shows poor sensitivity, which is equal to about 68% within the first 3 days of delivery and reaches 87% in the following days up to the tenth day of postnatal age. Ultrasound shows very different images depending on whether it is arterial ischemic stroke or cerebral sinus venous thrombosis. Moreover, in the case of arterial stroke, focal lesions may be observed, more or less extensive, attributable to partial or total occlusion of a specific artery and non-specific lesions not explained by the occlusion of a cerebral vessel. Contrary to what considered in the past, CUS allows detecting 2/3 of the ischemic stroke injuries immediately after the onset of symptoms to reach a very high sensitivity (87%) after the fourth day of the clinical onset. This method can identify most secondary lesions of arterial ischemic stroke, which cause hemiplegia. One can observe several abnormal scans with different shape, extent and localization of the echogenic area. The most frequent ultrasound image is that caused by the infarction of the primary branch of the middle cerebral artery. It looks like a wedge area with linear margins. Another relatively frequent lesion is characterized by less typical focal echogenicity with more rounded edges affecting only one hemisphere. Very typical are lesions that one can observe in brain imaging caused by ischemic events affecting the perforator arteries. The parasagittal plane is the most used scan for detecting perforator stroke. The ganglio-thalamic egg is best inspected in the parasagittal plane. In this typical scan we can better observe caudate, putamen and pallidus in front of the posterior limb of the internal capsule. The main perforator arteries involving in the perforator stroke are: the Heubner's artery that originates from the anterior cerebral artery (ACA), the anterior choroidal artery, which also originates from the ACA, lateral and medial striate arteries starting from the middle cerebral artery, thalamic arteries that originate from the posterior cerebral artery and hypothalamic arteries. Most perforator strokes are first diagnosed using CUS in 80% of cases, mainly in the first week of life. 40% are diagnosed after the first week of life and 5% with routine CUS after the 28 days. Right-sided lesions occur as frequently as left-sided lesions. Perforator strokes are usually first identified with CUS, probably because CUS is the first choice imaging modality in NICUs. The higher sensitivity of CUS at the tertiary referral centers suggests that probes and techniques used in performing CUS and the training of the physicians interpreting them play a role in determining the sensitivity for diagnosing

arterial stroke in general and perforator stroke in particular.

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LECT 62

FETAL ORIGINS OF HYPERTENSION AND CHRONIC KIDNEY DISEASE

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Non-communicable diseases (NCD) such as cardiovascular disease, hypertension, type 2 diabetes, and obesity have replaced communicable diseases as the predominant causes of mortality worldwide. Genetic and environmental factors contribute to the development of NCD, and fetal development is an important modulator of NCD risk. Chronic kidney disease (CKD) is a major cause of hypertension and a major risk multiplier of cardiovascular diseases. Since the first observations by Barker that adults who were born with low birth weight (LBW) were at higher risk of premature cardiovascular death, increasingly epidemiologic and experimental evidence has highlighted the "programming" impact of intrauterine stresses on organ development and long-term organ function. Subsequently, Brenner and colleagues hypothesized that developmental programming in the kidney might reduce nephron number, which in turn later in life could contribute to hypertension through limiting sodium excretion because of decreased filtration surface area, and could increase the risk of CKD if further nephrons are lost through age or other injuries. Nephrogenesis continues until 36 weeks of gestation and no new nephrons develop after birth in term newborn infants. Therefore a kidney with fewer nephrons, as in intrauterine growth-restricted (IUGR), preterm and LBW infants, could have a reduced renal functional reserve capacity and be less able to withstand additional renal injury. Many factors may impact fetal kidney development: quality and quantity of nutrition received during fetal life, maternal diabetes, preeclampsia, infection, exposure to nephrotoxic drugs, or toxic substances (alcohol, tobacco). Postnatal nutrition, exposure to nephrotoxic drugs and acute kidney injury (AKI) are also contributing factors to further nephron loss, enhancing susceptibility to CKD. To address the neglected issue of developmental programming of hypertension and kidney disease, a multidisciplinary working group, including international expert obstetricians, neonatologists and nephrologists, was convened at the Clinical Research Center of the Mario Negri Institute for Pharmacological Research, Bergamo, Italy. They identified the need to raise awareness on the role of developmental programming in renal disease and suggested locally adapted prevention strategies that could have long-term benefits on health and health cost-saving worldwide. The proposed consensus recommendations emphasize the cooperation of different specialists with the common purpose of improving mother and child health, related not only to medical risk factors, but also to lifestyle, education, socio-economic

status. Efforts should be made to improve maternal health before and during pregnancy, in order to improve fetal health. Maternal diabetes, obesity, hypertensive disorders, and preeclampsia should be screened and managed in accordance with available guidelines. Nutrition during pregnancy must ensure appropriate intake of macro- and micronutrients. Alcohol and tobacco should be avoided. Fetal growth must be monitored and in case of IUGR best time for delivery should be identified. Birth weight and gestational age at birth should be recorded, and IUGR, prematurity or LBW should become a prominent part of the person's medical record. In addition to the low nephron number, preterm infants are at increasing risk for multifactorial kidney injury due to hypoxia, thrombosis, bleeding, free radical injury, exposure to nephrotoxic drugs. Every effort to prevent AKI should be made through optimization of fluid management, preservation of blood pressure, minimizing and monitoring use of nephrotoxic drugs. Recommended feeding for children is exclusive breastfeeding for the first 6 months; other food sources should be introduced prudently, enabling regular and balanced growth, avoiding rapid catch-up growth to prevent obesity-associated exacerbation of renal risk. IUGR, preterm and LBW infants as well as those exposed to preeclampsia or maternal diabetes should undergo periodic controls of blood pressure and urinalysis during pediatric and adult age. Families should be educated about healthy lifestyle to minimize obesity and malnutrition. There are many remaining gaps that requires further research study in the field, including the establishment of registries for documenting LBW and prematurity, conduction of intervention trials and identification of new early biomarkers of risk.

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LECT 63

MOTHERS' KNOWLEDGE AND ATTITUDES TOWARD MEDICATIONS AND NATURAL PRODUCTS USE IN BREASTFEEDING: AN OBSERVATIONAL STUDY IN A TERTIARY CARE UNIVERSITY HOSPITAL OF NORTHERN ITALY

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BACKGROUND

World Health Organization (WHO) and UNICEF recommend early initiation of breastfeeding within 1 hour of birth, exclusive breastfeeding for the first 6 months of life and introduction of complementary foods together with continued breastfeeding up to 2 years of age and beyond [1, 2]. Breast milk is the gold standard of nutrition for infants and breastfeeding has many benefits for both children and their mothers, regardless of whether they live in high or low-income countries or in a rich or poor household [3]. There are many societal norms, values and beliefs that influence women in their choice of feeding methods. Among the factors that undermine the duration of breastfeeding, concern about the potential risk of infant exposure to maternal medications is often cited as a reason to stop breastfeeding [4]. In Italy 66% of postpartum women required at least one medicine during breastfeeding [5] and 1.1% of women stopped breastfeeding to avoid any potential risk for the infant [6]. Despite most of drugs pass through human milk in insignificant amounts and rarely cause serious adverse events in infants [7], almost 80% of drug leaflets contraindicates the use, mainly due to medico-legal aspects [8]. A significant lack of breastfeeding evidence-based knowledge among many health professionals means that women may receive inappropriate and often conflicting information leading to a premature weaning [9, 10].

OBJECTIVE

The purpose of this study is to evaluate mothers' knowledge and attitudes about the use of medications and natural products during breastfeeding in a tertiary care university hospital of Northern Italy and find out to which health professionals mothers can refer to get information.

METHODS

A survey was conducted from August to September 2016 using a 52-item questionnaire developed through adaptation of a similar instrument after the author's permission [8]. The questionnaire designed to be self-administered to the mother 24 hour after birth was divided in 3 sections: socio-demographic characteristics, women's opinions and breastfeeding and pharmacovigilance. All women admitted in the postnatal ward of a tertiary-care university hospital in Northern Italy (approximately 6,000 live births per year) were eligible for the study. The mothers were excluded from study if they were minor, unable to understand written Italian language and not present or unavailable in their room in more than two occasions. The data were processed by Epi Info™ 7.0 software, applying descriptive and bivariate analysis.

RESULTS

During the study period, 389 women were enrolled. Most of them were Italian and higher educated. 75.8% of women reported use of medications or natural treatments during pregnancy, mainly analgesics for headache or vitamin supplements. 2.6% of women stopped breastfeeding in a previous pregnancy due to medications. Many mothers thought that most of the drugs are not compatible with breastfeeding and 53.5% of women could stop breastfeeding while taking medications. 43.7% of mothers evaluated natural products safer than medications during breastfeeding. 28.3% of multiparous mothers took both drugs and natural products during previous breastfeeding. To receive information about the drug risk for infants, mothers think to ask mainly to a pediatrician for consultation, while to know the drug risk for themselves, they consider to contact the physician who prescribed the medication. In bivariate analysis, women with university degree or higher education (odds ratio [OR] = 1.7, 95% confidence interval [CI] = 1.1-2.5) and women who attended to childbirth class (OR = 1.8, 95% CI = 1.2-2.7) had higher probability to understand the potential risks of stopping breastfeeding.

CONCLUSIONS

Despite only a few medications are contraindicated during breastfeeding, most of the mothers think that maternal drug use is hazardous to a breastfeed infant [8]. This concern is one of the factors associated with premature weaning. Given the benefits of breastfeeding for infant, many mothers assume natural products instead of medications, considering them safer than drugs [8]. Furthermore, there is often inconsistent advice provided by the healthcare professionals to mothers about the safety of continuing to breastfeed when taking medications. Information and bibliographic references are available, but there is urgent training need about this topic for doctors and pharmacists as they represent the main source of information for mothers [9, 11]. Moreover, mothers should be informed about resources as LactMed, a free online database with information on drugs and lactation, and free national breastfeeding and drug helpline as that of the Poison Control Centre Hospital Papa Giovanni XXIII of Bergamo.

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LECT 64

UNIVERSAL CONGENITAL CYTOMEGALOVIRUS INFECTION SCREENING USING SALIVA SAMPLES: A SINGLE CENTER EXPERIENCE

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Cytomegalovirus (CMV) is a member of the Herpesviridae family of viruses. It is a wide spread viral infection. In the developed countries it is the most common etiologic cause of congenital infection. In Italy the incidence of congenital CMV infection is 0.3-0.5% of births. About 500,000 neonates are born in Italy every year, therefore 2,500 probable CMV infected babies are likely to be expected. Data taken from screened populations' studies indicate that the majority (85-90%) of newborns infected *in utero* have no clinical signs at birth; however, a small number of these asymptomatic neonates (10-15%) will develop sequelae such as hearing loss, neurological delay, cognitive deficit and visual impairment during their early life. Sensorineural hearing loss (SNHL) is the most common late-onset CMV infection damage but only about half of this deafness is detectable by the audiological screenings. Since a normal hearing threshold is absolutely necessary to develop a normal speech and neurological functions, it becomes paramount the early identification of CMV infected newborns, in order to follow them during their early infancy. Since 2016 ubiquitous hearing screening is compulsory in Italy, but in some regions, such as Lombardy, it has started much earlier. At "Spedali Civili" Hospital in Brescia, the audiological screening started in 2008 for all the babies, either term or premature. Since 2011 all the babies not responding to transient-evoked oto-acoustic emissions testing (TEOAE), such as microcephalic and low birth weight ones, have been submitted to a "target screening" for CMV. It is well known from the literature that the CMV target screening fails to identify a number of infected neonates who are at risk of developing late-onset symptoms later in infancy. For this reason, the audiological screening has been supported in our Neonatal Unit with an all-inclusive CMV screening program. It has been performed since October 2015 both in the Nursery and in Neonatal Intensive Care Sections. The punctual identification of infected but asymptomatic neonates to be enrolled in a follow-up was the aim of our project, to promptly identify those babies who need special therapeutic and educational support. Saliva has been chosen as the biologic sample for the detection of cytomegalovirus because high titers of virus are shed in specimens, it is an easy and not invasive method of samples gathering. Saliva samples were obtained by rubbing a foam swab within one side of the infants' cheek, immediately after birth in babies admitted to NICU. For healthy neonates in the nursery department the collection of samples was done together with the dried blood spots collection after the 49th hour of life. All the screened infants were not fed for over two hours. Swabs were immediately eluted in transport medium and stored at -20°C. Screening was performed by the laboratory using the CMV-DNA rt-PCR assay and the positive samples were confirmed twice. Babies with a CMV positive screening were definitively assessed by the evaluation of urine CMV-DNA load. All the infected infants started a clinical, audiological and neurodevelopmental follow-up still proceeding nowadays. Between October 2015 and May 2017, 5,032 saliva samples were collected in our Unit. Twenty-one infants (0.41%) were found CMV-positive both at screening and confirmation tests. Eighteen newborns were from the nursery ward (85.7%) and three from intensive care unit (14.3%). Seven of CMV-positive infants were foreseen as their mothers had CMV seroconversion during pregnancy. Fourteen infants had no congenital CMV-related risk factors or fetal signs of infection. Among these, five mothers were CMV immune in pregnancy, eight ladies didn't evaluate CMV serology during pregnancy and only one mother was seronegative. Among the babies with prenatal diagnosis of congenital CMV infection, three showed clinical symptoms at birth. Two babies were preterm (one of them late preterm) with low weight at birth. Only one was also microcephalic with a pathologic brain fetal magnetic resonance. Among the newborns with an unexpected CMV infection, five showed symptoms at birth. A female baby experienced endovitreal lesions, three were late preterm and two of them were also small for gestational age. Four infants showed connatal cysts at cranial ultrasound, and non-cystic leukomalacia at magnetic resonance was found in one. One infant with a prenatal diagnosis left the follow-up because the parents chose a closer hospital. At follow-up a female baby with prenatal diagnosis of

microcephalia and polymicrogyria associated with congenital CMV developed a heavy psychomotor delay. All the remaining infants are healthy up to now. In the group of babies without prenatal diagnosis, none showed audiological problems (all of them passed TEOAE and AABR) or neurological deficits at birth, but only two infants developed a transient hearing loss at six and three months, respectively. Clinical follow-up is still ongoing.

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LECT 65

THE NURSING ROLE IN CLINICAL TRIALS AND PHARMACOLOGICAL RESEARCH

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BACKGROUND

It is of crucial importance to integrate the best evidence of research with clinical practice in the neonatal field and more and more it seems necessary to find new roles for the nursing figure, and an increase in status and social value in both clinical practice and as a researcher. Today, more than ever, the consolidation of autonomy and professional responsibility by nurses requires them to have a structured methodological, technical and relational knowledge to be used in the clinical and organizational context. It is therefore a matter of orienting professional practice towards the appropriateness, effectiveness and efficiency of performance. Organizing nursing care according to deeply integrated and multi-professional management models is important as the field of health cannot be considered as one single profession.

AIM

In Italy there isn't a "research nurse" figure. The solutions adopted to bridge this gap are varied and often inadequate because they are affected by the poor preparation inherent within the organization, such as research protocols and clinical and biological data collection. The aim is to investigate the possibilities of developing the role of nurse in the field of medical and clinical research, but above all as a protagonist in research projects in neonatology. In particular, we intend to investigate the role of nurse within the pharmacological clinical trial process, a crucial role for the development of the status and social value of the nurse. Finally, we will try to highlight the differences between the scope of the research nurse in Italy and its social and professional recognition as opposed to what is happening abroad.

RESULTS

Italy is less progressive than other European and International medical fields in the definition of the role and in awareness of the potential for nurses in certain areas of research, like neonatology. Current

Italian legislation has been analyzed to determine in which areas of the pharmacological clinical research the nurse can be employed. The nurse is described as the ideal person to monitor adverse effects because he is the professional figure in close contact with the patient. He can thus be made available to solve clinical and ethical problems with the family, get informed consent, and guarantee a free and independent outcome, with the possibility of leaving the study at any time without any negative consequences. This figure is more appropriate than others for his ability to listen and be closed to the caregivers. He is ally of the patient, ensures that the protocol is followed closely, shares the emotions and the psychological and cultural repercussions of the parent's choices. The nurse also has the potential to play an important role in data collection, dealing with all phases of data collection, analysis, management and quality. A nurse can, by virtue of his clinical background, be an ideal candidate, provided that he has adequate training in clinical methodology and data processing, such as the knowledge of statistical programs and the representation of elaborates.

CONCLUSIONS

Pharmacological research has recently introduced a new professional figure, defined by the Clinical Research Associate (CRA) Guidelines, an interesting figure also in the evolution of nursing. The specific task of the CRA, with respect to the above requirements, is to fully monitor clinical trials. This includes the final interface, alone with the auditor (for the final and independent verification of the requirements required for the process of research and proper management of the protocol). It develops in the following areas: firstly training, which includes how to conduct the study; secondly checks to verify that the procedures required by the study are performed properly and the Case Report Forms are reviewed; thirdly, explaining how to avoid errors and run procedures; next, liaison to keep in contact with the researcher and staff of the center; finally, acting as an interface so as to be "Project Ambassador". In general, the research nurse can cover the most general roles such as obtaining informed consent and educate/follow the caregiver of the patient during the research phases, while with the more advanced training the functions emerging from the analysis of Italian legislation can be covered: to inform about the protocols and procedures, the GCPs, the status of the study, goals and results. The nurse can also obtain information on the progress of the study; he can solve problems with respect to the procedures required, that is, more generally handle everything that concerns the protocol, approvals, and regulatory affairs. The potential of nurses needs to be highlighted through education, in order that they receive training to cover not only their clinical roles but also to encourage new discoveries and experiences by increasing their social status.

LECT 66

SUPPORTING PREMATURE BABIES AFTER CLINICAL STABILIZATION IN SINGLE FAMILY ROOMS 24/24H

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The development of the Central Nervous System (CNS) between the 22nd and 35th week of gestational age goes through a very delicate phase, which will allow the achievement of many higher-level brain function. This developmental period is characterized by a continuous interaction with the environment through the activation of immature sensorial channels. In the preterm baby this process takes place in the NICU, a destabilizing setting which can easily affect baby's vital signs, weight gain, oral feeding, hearing, vision and CNS development. Many researchers found a correlation between some anomalies in the differentiation of the cerebral cortex (with subsequent cognitive and behavioural dysfunctions) and the length of stay in the NICU. This is the reason why today supporting preterm babies means not only taking care of diseases and their clinical complications, but also checking the environmental factors potentially affecting the regular process of maturation of the CNS. The Neonatal Care, the whole complex of attentions given to a premature baby, aims to minimize "baby stress" by both limiting visual/hearing and pain stimulation and increasing sleeping time and early bonding with the mother. Neonatologists over time became more and more sensitive to these needs of care, usually not taken into account by the standard clinical approach. The Neonatal Care moved from the Open Bay approach in the '60s – many neonates in a big single room, in order to facilitate constant monitoring of their clinical status/vitals, communication and team-work – to the "Family Centered Care" in the late '70s, which took into consideration the physical as well as the emotional and psychological needs of both babies

and parents, promoting their bonding. In the '80s the "Developmental Care" took place: a model of personalized care emphasizing the importance of the parent-child bonding, while in the '90s a drastic change in some USA and North European centers (single bed rooms) led in 1992 to the creation of the first NICU with "Single Family Rooms" (SFR) at the Rainbow Hospital in Cleveland, Ohio. In 2006 the American Institute of Architecture drafted some recommendations in order to follow the SFR model when planning new NICUs – which means a place where newborn and family have their own personal room. In 2014 around 90 NICU supported the SFR model; in Italy the first NICU to move from the Open Bay to the SFR was Monza. In our NICU in Mirano on top of an Open Bay room we created three SFR, with a designated position for the baby with her crib/incubator close to a source of air and oxygen as well as to the bed of her parent, in order to offer good care to the baby and comfort to her caregiver. Vitals monitoring will be accomplished by connecting a central station, watched by nurses, to a peripheral one attached to the baby in her room. Exclusion criteria for the SFR are: need of ventilatory support, apneic spells needing stimulation/ventilation and mother's reluctance to stay with her baby 24/24 h or for most of the day. We can admit a newborn to the SFR if he/she needs incubator, oxygen, i.v. therapy, NG/OG tube. Following this model every mother will have the chance to talk to, stroke, console her baby and perform skin to skin or kangaroo care in a quiet and private setting, with secondary benefits for the newborn (stabilizing vital signs, improving bonding and breastfeeding). In addition to this, SFR promotes the alliance between caregivers and parents who end up being more involved in the care process and lowers the risk of neonatal infection.

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LECT 67

NEONATAL BACTERIAL INFECTIONS: DIAGNOSIS AND THERAPY

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Neonatal sepsis contributes substantially to neonatal mortality and morbidity. It is estimated, worldwide, that approximately 36% of neonatal deaths annually are due to invasive infections [1]. A recent report by Stoll et al. for the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network (NRN) review 20-year (1993-2012) trends in neonatal care, complications and mortality among infants born at 22-28 weeks gestation and with birth weight 401-1,500 g [2]. The authors show that an overall 2% and 32% of infants had early-onset (EOS) and late-onset sepsis (LOS), respectively. The percent of infants with EOS remained stable over the study period, while the percentage of infants with LOS decrease in the years 2005-2012. *Group B Streptococcus* (GBS) is the most common EOS pathogen with a mean incidence of 0.43/1,000 live births and a 12.1% of case fatality ratio [1]. While most studies report stable rates of EOS caused by non-GBS pathogens, epidemiological data from a recent study shows that for the first time in decades, most infants with EOS are very low birth weight (VLBW) infants instead of term infants and that *E. coli* replaced GBS as the most common pathogen isolated during EOS [3]. For what concerns LOS the predominant pathogens are coagulase-negative staphylococci, followed by Gram-negative bacilli and fungi. Remarkably empiric antibiotic treatments with broad-spectrum antibiotics, often inappropriately used, are the consequence of emerging and increasing incidence of multi-drug resistant bacterial strains. Dong et al. [4] report that multidrug-resistant Gram-negative bacteria account for approximately 20% of LOS cases. In a recent work Weissman et al. [5] found a high rate of ampicillin resistance among *E. coli* isolates from neonatal cases of EOS, highlighting the importance of continuing surveillance of antibiotic resistance to ensure that standard empiric regimens remain effective since the ampicillin is a recommended antibiotic for EOS. It is clear how antibiotic utilization practices in NICU influence the types of pathogen responsible for neonatal sepsis and their resistance patterns. Given the increasing of resistant microorganisms, several experts and institutional guidelines underline the importance of the development, in each hospital, of an antibiotic stewardship program specific for NICUs in order

to optimize antibiotic treatment [6]. The diagnosis of neonatal sepsis is extremely challenging due to the vague and non-specific clinical signs, frequently shared by non-infectious conditions especially in VLBW infants and to the difficulty to isolate a causative pathogen from a sterile site; therefore several laboratory diagnostic biomarkers are in use to improve identification and management of affected neonates. The recent development of "multi-omics" techniques holds particular promise for the discovery of novel biomarkers and unique signatures of mediators for early and rapid diagnosis of sepsis [7, 8]. On the other hand, several laboratories are working for the discovery of new antibacterial drugs. It is worth citing novel approaches for drug discovery such as using unexplored strains. Recently it has been shown that human nasal commensal bacteria produce a novel peptide antibiotic named lugdunin [9]; another recent example is teixobactin produced form a previously uncultured soil bacteria [10]. Rates of infection in NICU are stable or declined as demonstrated by the NRN [2]. The reduction of infection and the related mortality and morbidity is of primary importance in NICU. Optimal use of available biomarkers for identification and management of septic neonates and judicious antibiotic use is crucial in order to improve outcomes and limit the emergence of resistant strains.

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LECT 68

COST-EFFECTIVE COMPREHENSIVE NEONATAL CARE AT HOSPITAL LEVEL IN LOW-INCOME COUNTRIES

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2.9 million neonatal deaths occur worldwide every year [1], accounting for 45% of the total under 5 deaths [2]. Main causes include preterm birth complications (1 million), intrapartum conditions (700,000) and infections (600,000). In addition low weight at birth is the biggest underlying risk factor for more than 80% of neonatal deaths [1]. Sustainable Development Goals (SDGs) and the U.N. Secretary-General's Global Strategy for Women's, Children's and Adolescents' Health (2016-2030) commit international community to reduce neonatal death rate to 12 or less per 1,000 live births by 2030 [3]. U.N. Global Strategy priority interventions on neonatal health include: care in the facility for at least 24 hours after an uncomplicated vaginal birth, immediate drying and thermal care,

neonatal resuscitation with bag and mask, early initiation of breastfeeding, hygienic cord and skin care, prophylactic antiretroviral therapy for babies exposed to HIV, kangaroo mother care for small babies, extra support for feeding small babies, presumptive antibiotic therapy for newborns at risk of bacterial infection, CPAP to manage babies with respiratory distress syndrome, detection and case management of possible severe bacterial infection, management of newborns with jaundice and postnatal contact with a skilled provider, at home or in the health facility, around day 3, day 7 and at 6 weeks after birth. This approach is consistent with the vision of the 2014 third paper of the Lancet Every Newborn Series, especially where Bhutta et al. [4] give their answer to the question: can available interventions end preventable deaths in mothers, newborn babies, and stillbirths, and at what cost? This new alignment, beyond primary health care, implies a step forward essential care at hospital level in low-income countries, toward a definition and the implementation of comprehensive neonatal care, at least at provincial level hospitals. Obstetricians learnt this lesson long ago, defining and implementing essential or comprehensive emergency obstetric care at different level facilities. Full coverage of known interventions, including neonatal sub-intensive care within an in-country referral system, is the best chance to achieve the very ambitious neonatal death rate reduction before 2030. The way to get it goes through an aligned definition and implementation of neonatal comprehensive care at hospital level in terms of protocols and procedures; however, more importantly, a definition of the doctors and nurses' patient ratio and a list of drugs and equipment to effectively manage neonatal departments aiming to reduce neonatal death are still needed. This requires rigorous review, including systematic reviews and WHO-coordinated expert opinion. In the 2016, publishing *Towards a Grand Convergence for child survival and health*, Costello and Dalglish highlight that innovations (or known interventions not yet scaled up in low income countries) for technical guidelines are available, but a unified global advisory body of experts should assess the evidence before scale-up [5]. In fact there is no global multi-stakeholder scientific body to advise in a systematic way how and if innovations can be useful. This is even more true when discussing if interventions implemented in high income countries, but not yet scaled up in low income countries, can be adapted cost-effectively into guidelines and strategies delivered in neonatal departments of low income countries. Would a standing independent global external advisory committee be an effective mechanism to set standards for comprehensive neonatal care at hospital level in low-income countries? The Partnership for Maternal, Newborn and Child Health (PMNCH, www.pmnch.org), especially within the academic training and research constituency (ART), may represent an umbrella of institutions wide enough to start this process together with Ministries of Health of the countries with highest neonatal mortality rates. The SIN (Italian Society of Neonatology) working group on neonatal care in low-income countries, being member of the PMNCH within the ART constituency will actively advocate to achieve definition and implementation of cost-effective comprehensive neonatal care at hospital level in low income countries.

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LECT 69

THE NEONATOLOGIST AND SINGLE FAMILY ROOM: LIGHTS AND SHADOWS

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In the sixties of last century, at the dawn of modern Neonatology, when the only aim of the physical environment of the NICUs seemed to be supporting life, the "open bay" became the reference model

for neonatal intensive care design. It's a design solution based on the need to maintain visual and auditory control on patients, monitors and support devices [1]. Furthermore, the open environment facilitates communication and teamwork of the staff. When equipment and nursing plans were quite simple and family members were not allowed prolonged entry, noise and traffic were not a problem. With the advancement of technology, the multidisciplinary approach and the growing engagement of parents in newborn care [2], the NICUs have become larger, crowded and noisy [1]. Noise and crowding can have a negative impact on staff performance, by causing medical errors and lowering [2] the compliance with the rules for prevention of nosocomial infections [3]. Concentration of multiple beds into one area limits the privacy of family members and makes individualized developmental care plans difficult to apply. Observing the baby's behavior, responding to stress and pain signals, controlling acoustic and light stimuli by getting in tune with circadian rhythms can become unavoidable goals in an overcrowded environment. In the early nineties, a radical change began to take shape: in USA and in North European countries some NICUs implemented their wards with some private rooms, named Single Family Rooms (SFR), equipped with a family area. Initially SFR acted as pre-discharge rooms, allowing parents to experience home-like environment. In the following years, the number of NICU completely oriented toward SFR design increased. This choice was probably linked to the attractiveness of creating an intimate and private environment that would allow stimuli control and family involvement [4, 5]. Over the last fifteen years, the real effects of switching to the SFR model have been reported in many publications. Benefits include reduction of nosocomial sepsis [6-8], apnea events [7], moderate-to-severe bronchopulmonary dysplasia [8], total length of hospital stay [8, 9]. Nutrition also benefits from SFR: infants cared in SFR NICUs have an earlier transition to enteral feeding [7, 8], receive more human milk [7,10], have a greater rate of weight gain [11]. However, although more satisfied with the quality of the environment, parents and staff in the SFR report a bad quality interaction with team members or, even worse, a perception of isolation and stress [6, 12-15]. It can be assumed that the same isolation may also have the effect of sensory deprivation on newborns. Indeed, in a follow-up study [16], children who had experienced SFR in the neonatal period showed worse speech performance when compared to children from an "open bay". Too much silence can have the same effects as too much noise. But probably the problem is the quality of sounds, not only the intensity. Actually, in a recent study of the same authors [17], parent presence and engagement were related to greater language exposure. These studies draw attention to the need for identifying strategies that favor parents' stay. Otherwise, it has been outlined how infants with high maternal involvement or high exposure to parental talk in both NICUs (SFR or open bay) had greater cognitive and language scores than infants with low parent involvement [9, 18]. One of the strongest barriers to adopting the SFR model is the difficulty in maintaining visual control over patients. One solution may be the use of systems for remote alarming. These systems can collect signals from medical devices (monitors, infusion pumps, respirators) and send them to mobile devices (such as smart phones). However, these systems introduce other disruptive elements in staff communication models and work organization [19]. In 2016 the San Gerardo Hospital in Monza (Italy) completed the construction of a 1,600 m^2 SFR level III NICU (**Fig. 1**), to replace an older open-bay ward with only 500 m^2 floor space. Transition to the new SFR facility, which more than tripled the size of the old unit, was superintended and managed by the MBBM Foundation. The new department has 26 beds (like the old open bay) and it's the first Italy's SFR NICU. The space is organized in two units, one of them for 12 tertiary intensive beds, the other one for step-down beds. The process of designing and implementing the new department has been performed in collaboration between architects, engineers, neonatologists, nurses and parents [1, 8, 20]. The multidisciplinary team worked in a series of interactive meetings where ideas and solutions were discussed and tested with the help of simulated models (mock-ups). This methodology has also been useful in the development of the IT network, thus optimizing data flow coming from medical devices, labs, hospital applications and telephony. Managing this huge data stream, all directed to the staff, is one of the keys to running SFRs. The leading role of the neonatologist in a project of NICU SFR design renovation is to combine the information obtained from the critical reading of previous reported experiences with the knowledge of his own department workflow, the old one and the new one.

Figure 1 (LECT 69). Single Family Room (SFR) Monza Neonatal Intensive Care Unit. Planimetry.

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LECT 70

USEFULNESS OF FLEXIBLE FIBEROPTIC ENDOSCOPY IN THE NEONATAL AIRWAY

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In the last three decades we have witnessed major advances in the field of flexible airway endoscopy (FAE). In late seventies, Wood and Fink first reported the application of flexible laryngo-tracheo-bronchoscopy in young children [1]. Since then, FAE has been increasingly used at the bedside in critically ill paediatric and neonatal patients, even in those undergoing mechanical ventilation, resulting in a wide range of diagnostic and therapeutic applications [1-6]. In addition, the availability of ultra-thin endoscopes, with smaller calibres (down to 2.2 and 2.8 mm outer diameter) and inner operative channels, has much expanded the use of FAE for diagnostic and therapeutic purposes even in very small patients, including extremely preterm babies [7-9]. The purpose of this study is to give a short overview of the scope, indications and applicability of flexible airway endoscopy, with a special focus on term and preterm infants. More detailed information on indications and technical standards for performing FAE in children are available in a recent publication, endorsed both by the American Thoracic Society and the American Academy of Pediatrics [10]. The rationale for carrying out a diagnostic or therapeutic FAE in newborns depends on patient's characteristics as well as the clinical information which are needed, taking into account the risk/benefit ratio of the intervention. Appropriate equipment, safe environment and adequate providers' expertise are essential for the procedure to be safely and effectively performed. An accurate past medical history, followed by informed consent procedure, should always anticipate the manoeuvre, even in emergency conditions, if possible [9]. Sedation, analgesia and monitoring should be tailored to the single patient, according to his/her clinical status and the working diagnosis. An ongoing balance between comfort of the patient, maintenance of adequate gas exchange and stable hemodynamics should be pursued, at the same time optimizing conditions for getting proper diagnostic or therapeutic results by the endoscopic procedure. FAE is usually performed introducing the endoscope transnasally (often best option), transorally (the tongue may interfere), via endotracheal tube or tracheostomy cannula (size may be a limitation). In special situations, particularly in very small subjects or when the patient would not be able to tolerate the procedure without a respiratory support, use of a laryngeal or oral mask may be helpful [10]. Main indications of FAE in the neonatal intensive care unit include early detection of congenital or acquired airway anomalies (e.g. laryngomalacia, laryngeal cleft, subglottic tracheal stenosis, injuries), difficult airway management (e.g. bronchoscopic intubation), treatment of atelectasis and pulmonary bleeding, bronchoalveolar lavage (e.g. microbiologic samples in newborns at risk for ventilator-associated pneumonia) (**Tab. 1**) [7-9]. Notably, endoscopic airway evaluation in newborns implies additional inherent risks, if compared with older children. In fact, critically ill newborns may have severe gas exchange abnormalities, hemodynamic instability or significant co-morbidity such as congenital

Table 1 (LECT 70). Common indications for flexible airway endoscopy in newborn infants.

Diagnostic indications	Therapeutic indications	Special procedures
Unexplained or persistent stridor (e.g. laryngomalacia, vocal cord paralysis)	Therapeutic bronchial lavage (e.g. segmental or lobar atelectasis)	Bronchoscopic intubation (e.g. difficult airway)
Suspected anatomic airway anomalies (e.g. tracheo-esophageal fistula)	Bronchoalveolar lavage with sterile saline or diluted surfactant (e.g. meconium aspiration)	Monitoring of tracheostomy (e.g. granulomas, cannula tip position)
Suspected external compression of mainstay bronchi (e.g. vascular rings)	Control of pulmonary haemorrhage	Exogenous surfactant replacement (e.g. difficult airway)
Unexplained wheeze or weaning failure (e.g. bronchomalacia)		Dilation of a stenotic airway
Bronchoalveolar lavage (e.g. infections, protein surfactant abnormalities)		
Radiographic abnormality (e.g. lobar emphysema)		

heart disease or pulmonary hypertension, which may markedly limit the safety and feasibility of such procedure in these patients. Moreover, in intubated newborn infants, particularly in smaller ones, the inner diameter of the tracheal tube may not allow the procedure to be performed through the tube itself, exposing the baby to the need of an elective extubation and subsequent reintubation. In this situation, the use of a laryngeal mask may be convenient, giving the healthcare providers a tool for ensuring adequate gas exchange during the whole endoscopic intervention. Even though FAE is generally considered as a relatively safe procedure, often offering essential diagnostic and therapeutic yields for clinical management, some related adverse effects have been reported in the neonatal population, including episodes of severe oxygen desaturation, bradycardia, bleeding and air leaks [8]. A multidisciplinary team with specific competencies in neonatal FAE, scrupulous monitoring and correct indications may prevent or reduce the incidence of such complications. In summary, FAE has become an indispensable bedside procedure in advanced neonatal intensive care units, often offering key information and therapeutic options not easily replaceable by other means. Neonatologists involved in advanced critical care should incorporate FAE in their armamentarium.

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