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Lectures

Selected Lectures of the 2nd International Workshop "Intensive Care of the Newborn"

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LECT 1

RESUSCITATION OF EXTREMELY PREMATURE INFANTS: HOW TO IMPROVE EVEN FURTHER

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Managing a newly born apneic premature infant is complex. Ventilation strategies to optimize the establishment of functional residual capacity (FRC), judicious oxygen management and avoidance of moderate hypothermia are critical initial strategies to facilitate transition. Situational awareness and teamwork are essential to accomplish these goals. Situational awareness should include a pre-brief in the delivery room (DR) with consideration of at least some of the following elements: gestational age, antenatal corticosteroid administration, placental inflammation i.e. chorioamnionitis, intrauterine growth restriction and labor complications – e.g. FHRT abnormalities. Three important points to consider in the DR in this regard are: who is the team leader, use of checklists and teamwork. There are 7 basic concepts to consider when faced with a depressed baby: 1) assessing if the baby is in primary or secondary apnea; 2) effective ventilation is key to successful resuscitation; 3) heart rate (HR) is the best indicator of effective ventilation; 4) establishing FRC is key; 5) minimizing O_2 exposure; 6) maintaining temperature in a normal range; 7) delaying cord clamping (DCC). The first four will be briefly discussed. It is important to assess whether the depressed baby is in primary apnea (HR 70 to 100 BPM, quick response to stimulation and drying ± brief positive pressure ventilation [PPV]), secondary apnea (HR ≤ 60, slower or no response to stimulation invariably will require PPV ± intubation ± intensive resuscitation). HR is the best indicator of effective ventilation and should increase within 30 to 60 seconds. If not consider repositioning the mask, clearing the airway of potential secretions, increasing the inflation pressure, checking for leak and consideration of an alternative airway, LMA or intubation (so called MR. SOPA). What is the best way to determine HR in a depressed baby? Auscultation is superior to umbilical cord palpation. In a depressed baby, ECG is the gold standard and superior to pulse oximetry in the first postnatal minutes. Establishing FRC is key and can be difficult in a depressed baby. Studies have shown that an infant's own inspiratory effort is an important precursor to establishing FRC. An inconsistent response to ventilation in a depressed baby includes the infant's response to initial mechanical breaths. The most common is a rejection response with the production of high intrathoracic pressure, i.e. expiratory effort with no gas exchange. A second response is the called "heads" paradoxical reflex with production of high negative intra-esophageal pressure and a marked improvement in the mechanical characteristics of the lung and the establishment of a functional residual capacity. The third response is passive inflation with no change in esophageal pressure. In premature apneic babies, the "heads" paradoxical reflex is invariably absent and may contribute to difficulty in establishing FRC. Facemask leak and obstruction are very common when PPV is applied to a premature infant. In summary establishment of breathing patterns at the time of birth is dynamic complex and may involve numerous reflex patterns. The presence or absence of these reflexes and the type of induced reflex responses will modulate lung volume recruitment. Two strategies have been proposed to establish FRC in the apneic premature infant namely prolonging the inspiratory time and the use of positive end expiratory pressure. It was shown years ago that prolonging the inspiratory time from 1 to 3 seconds increases the mean volume change from 15 to 33 ml and the FRC from 1 to 16 ml. Experimental studies in lambs have shown that prolonging the inspiratory time coupled with PEEP and/or the use of PEEP alone enhances the ability to establish FRC. The desired initial oxygen concentration to use during resuscitation remains unclear. In the preterm infant the current recommendation is to initiate resuscitation with a FiO_2 concentration between air and 30%. However this remains unclear, as there are data to suggest that starting with air may be associated with increase of mortality. The importance of DCC in infants < 37 weeks gestation has been summarized in a recent meta-analysis. 18 RCTs compared delayed vs early cord clamping in 2,834 infants. Most infants allocated to DCC were assigned a delay of ≥ 60 seconds. DCC reduces hospital mortality

(RR 0.69, 95% CI 0.52 to 0.91, p = 0.009). In 996 infants ≤ 28 weeks gestation, DCC decreased hospital mortality (RR 0.70, 95% CI 0.51 to 0.95). Subgroup analyses showed no differences between randomized groups in Apgar scores, intubation for resuscitation, admission temperature, mechanical ventilation, IVH, brain injury, BPD, PDA, NEC, late-onset sepsis or ROP. DCC decreased the need for blood transfusion by 10% (95% CI 6 to 13%, p < 0.00001). In conclusion managing the VLBW apneic infant in the DR is complex and dynamic; it requires situational awareness and teamwork. Each patient should be treated on his/her merit.

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LECT 2

MAINTAINING NORMAL TEMPERATURE IN THE NEWLY BORN: NOT A TRIVIAL GAME

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The last 50 years have seen a significant increase in the published evidence regarding neonatal resuscitation and stabilization practices. Since 2000 the International Liaison Committee on Resuscitation (ILCOR) has reviewed available evidence regularly which has led to an increase in animal and human research upon which to base recommendations [1]. The World Health Organisation has also produced written recommendations for use in healthcare settings with varying levels of resources [2]. Recent ILCOR recommendations have referred to use of oxygen, airway management and ventilation, cord-clamping, circulatory stabilization, and neuroprotective measures such as therapeutic hypothermia for term infants [1, 3-5]. However, despite advances in these areas of neonatal resuscitation, maintaining the temperature of a newborn infant within the desired range remains a challenge in all settings. Guidance on thermoregulatory techniques, such as skin-to-skin contact and drying and wrapping, has been an initial and integral part of newborn life support algorithms since it was first produced even before guidance on airway management. However, infants continue to suffer cold stress in all health care systems [1]. This talk will summarise some past and some more recent evidence, which emphasises the vital importance for maintaining normothermia at birth in all but the most specialised of situations. Failure to do so increases mortality and morbidity at all gestations. Several recent quality improvement programmes in high resource settings and one randomised controlled trial have demonstrated that not only can admission temperatures be improved, but morbidity can be reduced. Historical studies and those in low resource settings have demonstrated reduced mortality with improved maintenance of temperature after birth. The best approaches to achieving normothermia will also be summarised as well as the continuing gaps in knowledge. Continuing to ignore this universal problem leaves infants at significantly higher risk of both mortality and morbidity.

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LECT 3

PRESENT AND FUTURE OF SURFACTANT ADMINISTRATION IN PRETERM INFANTS WITH RESPIRATORY DISTRESS SYNDROME (RDS)

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Surfactant replacement therapy (SRT) is a major therapeutic principle in the therapy of preterm infants with respiratory distress syndrome (RDS). When introduced into the therapy in the early 1990, most preterm infants with RDS were on mechanical ventilation due to severe respiratory insufficiency. Thus, surfactant was administered via the endotracheal tube during positive pressure ventilation. Nowadays preterm infants are more often born in better condition and have received an antenatal course of steroids. Therefore they also can be managed with noninvasive respiratory support and have not inevitably to be intubated. Recently it was even shown that the use of nasal continuous positive airway pressure (nCPAP) alone as primary respiratory support results in similar outcome as intubation, mechanical ventilation and surfactant application. However nCPAP can fail and nCPAP failure is related to worse outcome with severe complications like pneumothorax, IVH and even death [1]. Therefore there remains the idea that combination of nCPAP and SRT might be the combination of two highly effective principles and that this combination may have the impact to improve outcome of preterm infants with RDS. Until now different ways were reported to combine surfactant with nCPAP. These are the application into the pharynx, the nebulization of surfactant, the administration via a laryngeal mask and the administration via a thin endotracheal catheter. Nebulization on the one hand seems to be the most attractive way to administer surfactant as it is really non invasive, but on the other hand it raises a lot of technical problems that are not yet sufficiently solved [2-5]. In contrast application of surfactant into the pharynx is an old idea [6] and is technically easy to perform. Recently Lamberska et al. reported the results of an observational study including extremely preterm infants with a gestational age < 25 weeks [7]. In this study significant fewer infants in the study period required mechanical ventilation than in the before and thereafter period. So this approach is promising especially for extremely preterm infants. An also promising approach is the application via a laryngeal mask. This method has its technical limitation in the smallest infants and is more likely to be a mode of application for the less immature preterm infants. Several studies demonstrated that application of surfactant application via a laryngeal mask is feasible and safe [8-12] and one recent study demonstrated that it may have the potential to reduce the need of mechanical ventilation [13]. Surfactant application via a thin endotracheal catheter is the most studied mode of less invasive surfactant application (LISA). Several modifications of the procedure have been described. The common of all the reported modifications is that a small catheter is placed into the trachea after visualization of the vocal cords by laryngoscopy. Several observational and also some prospective randomized controlled trials demonstrated that the approach is feasible and safe. Furthermore it is related to a reduced need for mechanical ventilation and a lower rate of neonatal complications especially in extremely preterm infants [14-26]. In a network meta-analysis LISA was shown to be the method with the highest potential to reduce the need of mechanical ventilation and the rate of neonatal complications [27]. However the evidence is weak because the studies included in the meta-analyses had some methodical weaknesses. First of all they were not blinded. It will be the task of the following years to create clear evidence by performing well designed large randomized controlled trials and to answer the question about which mode of surfactant administration is the best mode for which patients.

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LECT 4

CONTINUOUS POSITIVE AIRWAY PRESSURE (CPAP), SURFACTANT, OR BOTH? A DILEMMA STILL WAITING TO BE SOLVED

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If surfactant has represented a cornerstone of neonatal critical care, the correct and early use of continuous positive airway pressure (CPAP) has changed the paradigm even more. Surfactant has dramatically changed the outcomes of preterm neonates, but the understanding of respiratory physiology leading to the correct use of CPAP has avoided intubation and surfactant administration when not really needed.

This has impacted even more on clinical outcomes. How to combine the two things may be a matter of debate, but surely both therapeutics must be integrated to optimise the care of preterm infants, as described by European and American guidelines on the topic. We will review the basic physiology data and the evidence available about this combination of therapies trying to highlight still open problems and future research steps.

LECT 5

NON-INVASIVE RESPIRATORY SUPPORT AND RESPIRATORY DISTRESS SYNDROME (RDS): IS NASAL CONTINUOUS POSITIVE AIRWAY PRESSURE (nCPAP) ALWAYS ENOUGH?

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Respiratory distress syndrome (RDS) is one of the most challenging problem neonatologists have to deal with when approaching premature birth. Although mechanical ventilation (MV) has extensively shown to be a life-saving treatment and several improvements have been made to optimize ventilators' performances, subsequent bronchopulmonary dysplasia (BPD) is still a serious problem. For this reason, finding an alternative method to support preterm infants has become a priority for clinicians. The best-known and most largely utilized mode of non-invasive respiratory support (NRS) worldwide is nasal continuous positive airway pressure (nCPAP). It has been tested in different clinical settings and both as a first line treatment and as a post-extubation respiratory support. The physiologic mechanism through which nCPAP acts is not fully understood, however many studies have described its benefits in stabilizing chest wall and upper airways, reducing apneas and work of breathing (WOB), improving oxygenation and tidal volume (Vt) and promoting the achievement and maintenance of an adequate functional residual capacity (FRC). The most common scenario where nCPAP is used, regardless of the level of care provided by the neonatal unit, is in the delivery room (DR). In preterm infants, the achievement of an adequate FRC is a crucial point for the following NRS success [1]. To facilitate this achievement, nCPAP has been advocated as the optimal strategy for the initiation of respiratory support [2]. Other additional interventions can be performed in the DR to enhance nCPAP success, including early surfactant and caffeine administration [3]. This last has shown to be effective in increasing spontaneous breathing and minute ventilation. The use of nCPAP was first described in early 1970s, and to date continuous distending pressure (CDP) can be delivered through several different techniques, none of which has demonstrated to be the best. nCPAP is now usually delivered via the nose, since older interfaces have been replaced by nasopharyngeal prongs, nasal mask and bi-nasal prongs. Great attention needs to be paid in the nursing care of babies undergoing nCPAP, regardless of the interface in use, to avoid nasal septal injuries. In some clinical situations, nCPAP alone is not sufficient to support the preterm infant and nasal bilevel CPAP, otherwise known as biphasic CPAP or BiPAP, is a variant of NRS. This modality combines CPAP and additional pressure increases alternating two pressure levels while the infant breathes independently resulting in higher mean airway pressure. However, uncertainty remains regarding benefit of BiPAP compared with standard CPAP in preterm infants. Another strategy is nasal intermittent positive pressure ventilation (NIPPV) which combines two pressure levels (PEEP and PIP) with inflation rate and inspiratory time that can be adjusted [4]. NIPPV could be synchronized with the patient's spontaneous breathing. There are several techniques to add synchronization to NIPPV: flow or pressure sensor, pneumatic signal generated by an abdominal capsule and neurally adjusted ventilator assist (NAVA). In most studies comparing NIPPV with CPAP (especially when synchronized) there was evidence of reduced WOB in infants undergoing NIPPV compared to those on CPAP. Moreover, NIPPV improves extubation success and reduces the risk of BPD. The nasal application of high frequency oscillatory ventilation (nHFOV) has been introduced, but limited experience has been reported and further large-scale trials are needed. One of the most recent mode to provide NRS is nasal high flow therapy (nHFT), which deliver heated, humidified gas via single or binasal cannulae, usually in the range of 4-8 L/min. Its mechanism of action is not entirely known, but several studies have shown that nHFT can decrease the WOB, improve gas exchange and lung mechanics, reduce dead space making minute ventilation more efficient, provide mild CDP and eliminate the metabolic work related to gas conditioning [5]. Despite initial concerns regarding the lack of evidence about the efficacy

and safety of nHFT in very preterm babies, mainly in respect to uncontrolled and unmeasured airway pressure delivered, its ease in handling and its perception as a better tolerated form of NRS are driving physicians and nurses to familiarize with it. nHFT is currently used in neonatal units as a form of weaning from CPAP or as an alternative to this mode of ventilation. To date, there are no data available supporting the choice of nHFT as primary respiratory support in very preterm infants, although there are encouraging data regarding its use in late preterm infants. However, the use of nHFT in the post-extubation period in preterm infants has been sufficiently investigated, concluding that nHFT and nCPAP have the same efficacy for post-extubation support and nasal traumas were significantly lower in patients on nHFT. Some concerns remain about its use in the smallest infants after extubation and as a primary support after birth.

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LECT 6

NEURALLY ADJUSTED VENTILATORY ASSIST (NAVA) IN THE NEWBORN: A NEW STANDARD OF CARE?

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Neurally Adjusted Ventilatory Assist (NAVA) is a mode of ventilatory support in which both the timing and degree of ventilatory assist are controlled by the patient using a neural signal based on the electrical activity of the diaphragm (Edi). This Edi signal is obtained from a specialized indwelling nasogastric feeding tube with embedded sensing electrodes (NAVA catheter). NAVA improves patient-ventilator interaction and synchrony for breath initiation, size and termination even in the presence of large air leaks and therefore offers an optimal option for non-invasive ventilation (NIV-NAVA). Understanding the specialized settings for NAVA allows the practitioner to give patients control when breathing and adequately support them when apneic. Specifically, the following parameters must be set: 1) positive end expiratory pressure (PEEP); 2) FIO_2; 3) the assist or NAVA level, which determines the proportionality between the Edi and the ventilator pressure; 4) the apnea time, which is the time the infant can be apneic before going into backup and determines the minimum rate; 5) the peak pressure limit which must be set high enough to allow recruiting breaths to prevent atelectasis. The Edi trigger is adjustable, but the default setting of 0.5 uV is suitable for most neonates. The cycling-off criteria are fixed at 70% of the peak Edi. With respect to safety, back-up ventilation is provided in the case of no Edi (central apnea or accidental catheter removal). Careful attention needs to be given to the back-up settings, as the infant may decompensate if appropriate support is not provided during these episodes. NAVA provides patients, including premature neonates, the ability to use physiological feedback to control their ventilation by synchronizing the delivery of ventilatory support on a breath-by-breath basis. It uses all aspects of physiologic respiratory control to provide the ideal ventilation based on the patient's ever-changing needs. The Edi signal provides the caregiver the ability to access information and details about the central respiratory drive that were not available previously. This signal is a valuable respiratory vital sign for weaning and diagnostics, providing the clinician direction to the patient's respiratory status both with timing and depth of his breathing pattern. An increasing body of literature demonstrates that NAVA and NIV-NAVA work well, even in very preterm neonates and in the face of large air leaks. Clinical experience combined with recent studies suggests that NIV-NAVA is a viable mode that can be used as option in the neonatologist's non-invasive ventilation resource. NIV-NAVA may be used as a primary mode to prevent intubation, to facilitate extubation or as a rescue therapy for babies failing CPAP or other forms of NIV. The NICU at ProMedica Toledo Children's Hospital

treated 129 of 216 (60%) neonates 23-28 weeks GA from 7/1/2010 to 12/31/2014 with NIV-NAVA at some point during their NICU stay. 92% of those treated with NIV-NAVA were initially intubated, treated with surfactant and then extubated to NIV-NAVA; 74% of those were successful extubations and were maintained on NIV-NAVA a median of 8 days until they were transitioned to CPAP. 8% of the neonates were never intubated, and treated with NIV-NAVA only. Many of these neonates were also on conventional modes for varying amounts of time so outcomes specifically attributed to NIV-NAVA could not be determined. Of importance, no adverse outcomes (including pneumothorax, feeding intolerance, IVH or pulmonary hemorrhage) attributable to NIV-NAVA were noted. Studies with multi-center, randomized, adequately powered trials are currently underway to determine if NIV-NAVA is more effective than other modes of non-invasive ventilation in preventing intubation, facilitating extubation with enhanced post extubation support, decreasing time of ventilation, reducing the incidence of chronic lung disease, decreasing length of stay or improving overall long term outcome in preterm neonates.

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LECT 7

HIGH-FREQUENCY, MULTI-FREQUENCY OSCILLATION, JET VENTILATION: WHERE ARE WE?

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The first clinical trials of high-frequency ventilation (HFV) in newborn infants were commenced over thirty years ago. Twenty trials of high-frequency oscillatory ventilation (HFOV) and three trials of high-frequency jet ventilation (HFJV) are now complete. Despite theoretical benefits for reduced ventilator induced lung injury, systematic reviews consistently show that use of elective HFOV in infants with respiratory distress only slightly reduces the severity of chronic lung disease or the composite outcome of chronic lung disease or death prior to hospital discharge. These benefits of HFOV are likely offset by an increased incidence of air leak. The interpretation of these trials is complicated by high variability in outcomes between trials, suggesting that additional factors such as treatment strategies, clinician expertise and equipment selection may impact on infant outcomes. The observed benefit in reduced incidence of bronchopulmonary dysplasia is more pronounced in the systematic review of clinical trials using HFJV, however the overall number of infants recruited to these trials remain low, and concerns persist about the potential for neurological harm if low-volume clinical strategies are used. Recent research and further development of ventilator technology over the last decade highlight new areas for further refinement of clinical strategy in application of high-frequency ventilation. Increased awareness of the potential for barotrauma when HFV is used in the non-compliant lung has focused attention on the identification and maintenance of an optimal distending lung volume. Further, we now understand clearly that ventilation and oxygenation are both influenced by the mechanical properties of the lung, and the risk of volutrauma in the setting of rapid changes in lung compliance or barotrauma in the setting of changing resistance. New hybrid ventilators that provide volume targeting during HFOV provide a major advance in reducing the variability in clinical application of high-frequency ventilatory modalities, and need to be subjected to clinical trial against similarly protective volume-targeted, synchronized ventilation. Increased understanding of clinical monitoring tools that enhance bedside understanding of ventilator-patient interactions and consequences, and the difference between use of classical HFOV and the newer volume-targeted HFOV is vital prior to conduct of any new RCT. HFOV to date has principally been delivered selecting a single primary frequency for ventilation. However, variability in biological signals is widely acknowledged to offer biological benefit. Variable respiratory frequency in both conventional and high-frequency ventilation enhances gas exchange and volume recruitment, and improves surfactant

production. Multi-frequency oscillatory ventilation may overcome some of the inherent issues associated with monotonous delivery of very small tidal volumes to surfactant-deficient neonatal lungs. Further research is required to improve the safety and efficacy of high-frequency ventilation. We also need to understand more about which approach (HFOV or HFJV) is optimal in which clinical setting. It is incumbent on every clinician using HFV to understand the underlying physiological principles, to utilize these modalities safely and to gain maximum advantage for the newborn infant.

LECT 8

SURVIVAL AND NEURODEVELOPMENTAL OUTCOME IN PERIVIABLE INFANTS

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Periviable birth is broadly defined as birth occurring between $20^{0/7}$ to $25^{6/7}$ weeks of gestation [1]. The likelihood of infant survival at the margins of this interval range from 0% at the lower end to over 75% at the upper end, but outcomes are less certain for infants born between 22-24 weeks of gestation [2, 3]. Approximately half or more of surviving infants have favorable neurologic and developmental outcomes, but the rates of mortality and adverse neurodevelopmental outcomes remain high [4]. Consequently, decisions surrounding the approach to treatment of these infants represent a major challenge for clinicians and families. The rates of survival and the neurodevelopmental outcomes of surviving infants vary widely between centers, regions, and countries [2-5]. A considerable proportion of this variation is attributable to differences in rates of active infant treatment in the delivery room [5]. Proactive perinatal care and antenatal steroids are additional modifiable treatment factors that are related to survival and neurodevelopmental outcomes. A number of recent studies have demonstrated temporal increases in the rates of survival among infants born in the periviable period, raising concerns about the neurodevelopmental outcomes of surviving infants [3]. In a recent study of 4,274 infants born at 22-24 weeks of gestation within US academic centers in the Eunice Kennedy Shriver National Institute of Child and Human Development (NICHD) Neonatal Research Network (NRN), survival increased from 30% in 2000-2003 to 36% in 2008-2011. The proportion of infants who survived without moderate or severe neurodevelopmental impairment (NDI) increased across these time periods from 16% to 20% ($p = 0.001$), while the proportion of infants who survived without NDI did not change significantly (15% to 16%, $p = 0.29$). Recent studies and national guidelines continue to emphasize the need for shared decision-making with families anticipating preterm birth in the periviable period.

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LECT 9

PATHOPHYSIOLOGY AND TREATMENT OF SEPTIC SHOCK IN NEONATES

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Sepsis within the first four weeks of life kills more than 1 million newborns globally every year. Traditionally, neonatal sepsis is categorized as either early onset (< 72 hours of age) or late onset (> 72 hours of age). Each category differs to some extent with respect to etiology and clinical course. Pathogens most commonly associated with early onset sepsis include *S. agalactiae*, *E. coli*, and *L. monocytogenes*. These can also cause late onset sepsis, but other pathogens become more prevalent, particularly among hospitalized neonates. The possibility of Herpes virus infection should always be considered in neonates with suspected sepsis. Some of the risk factors associated with neonatal sepsis include low Apgar score, poor prenatal care, low birth weight, maternal infection, and meconium staining. A definitive diagnosis is predicated on positive microbiological cultures from a normally sterile site, but a very low proportion of neonates with suspected sepsis have positive cultures. Diagnosis is therefore typically based on non-specific clinical and laboratory signs, and clinical context. This likely leads to overtreatment of a substantial number of neonates without sepsis, but the risks of overtreatment are weighed against the potentially devastating consequences of untreated neonatal sepsis. Neonates with sepsis may progress to septic shock, exemplified by cardiovascular dysfunction. A subset of patients progress to multiple organ failure, the common final pathway to death. Although mortality is a focus of many studies, survivors of neonatal sepsis are at substantial risk for long-term morbidity. For some patients, the manifestations of septic shock reflect uncontrolled infection. In others, the manifestations reflect a dysregulated inflammatory response causing injury to host tissues. Many patients reside along a spectrum between these two extremes. Multiple molecules and pathways, related to both innate and adaptive immunity, contribute to dysregulated inflammation. They include cytokines, chemokines, oxygen radicals, adhesion molecules, the coagulation cascade, endothelial cells, and the complement cascade. Despite decades of quality research, there are no approved therapies for septic shock that directly target any of these molecules and pathways. The mainstays of therapy are early initiation of antibiotic therapy, infection source control when indicated, and organ support. Early antibiotic therapy is absolutely critical as delays in antibiotic administration are associated with poor outcomes. Support of the cardiovascular system typically entails fluid resuscitation, plus inotropic or vasoactive support. Much recent attention has been given to the association between "fluid overload" and poor outcomes among critically ill patients. But there remains the fundamental physiological principle that septic shock, particularly in the early stages, is characterized by increased fluid needs due to a combination of decreased fluid intake, increased insensible fluid losses, third spacing of fluid, and increased vascular capacitance. Therefore, aggressive fluid resuscitation with isotonic fluids remains a mainstay of therapy. Inotropic and vasopressor support is predicated on the cardiovascular physiology of a given patient. Those with low cardiac output require inotropic support, while those with low vascular resistance require vasoactive support. In the absence of invasive monitoring, it can be difficult to accurately assess these parameters in the neonate. Therapeutic endpoints for cardiovascular support include restoration of adequate end organ perfusion based on physical exam, normalization of mixed venous saturation, and/or lactate clearance. Recent adult studies do not support targeting of mixed venous saturations as a singular endpoint. It is unknown whether this also applies to neonatal septic shock. The most common form of other organ support during neonatal septic shock entails respiratory support via mechanical ventilation. This reflects concomitant primary respiratory failure (e.g. pneumonia), or secondary respiratory failure due to severe cardiovascular shock. Renal failure can be managed medically or with renal replacement therapies if necessary. The role of adjunctive corticosteroids for septic shock remains controversial. Septic shock is a heterogeneous syndrome, rather than a distinct disease. This heterogeneity significantly impedes clinical care and research, but resolving it would improve our understanding of disease pathogenesis, guide the development of more effective therapies, and help identify which patients are most likely to benefit from which therapies. Current research efforts seek to develop clinical tools to stratify patients based on outcome risk and underlying pathophysiology. These approaches highlight the relatively unique biology inherent to the neonate with sepsis, and hold the potential to bring precision medicine to the bedside of critically ill neonates.

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LECT 10

CLINICAL METABOLOMICS IN NEONATAL SEPSIS

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INTRODUCTION

In the last years we have observed relevant improvements in understanding the physiopathology of sepsis, including neonatal sepsis. The increasing importance of the microbiome in human health and the widespread of "omics application" in the field of infections have underlined the potential role of metabolites for the early diagnosis and prediction of sepsis [1]. The ambitions of metabolomics in this topic are extremely high, including the diagnosis of the etiology, the severity and the progression of the infection, as well as the response to therapy, the organ toxicity and the role of microbiome in early (attack of pathobionts to the organism) and late (collapse of the microbiome) phases of sepsis. The resilience of the microbiome is important. The aim of this paper is to focus the attention on the last news on the application of metabolomics, namely in neonatal infections.

METABOLOMICS: A CUTTING-EDGE RESEARCH ON SEPSIS

Metabolomics is one of the -omics sciences, which allows studying the instantaneous modifications of metabolism of an individual, both in health and disease, through the analysis of metabolites in biological fluids such as blood, saliva, feces and urine [1]. What we have learnt from metabolomics experimental studies is that it is possible to predict the death of infected animals (rats) with an accuracy ranging from 94 to 100%, to underline interindividual differences of treated animals and to demonstrate the metabolic targets, the efficacy and the toxicities of the therapeutics agents, such as antibiotics or erythropoietin. Considering clinical studies in all ages (adults, children, neonates), about 2,000 patients with sepsis or SIRS have been evaluated with metabolomics until today. Different biofluids have been studied (serum, plasma, blood, urine, BALF) with different techniques (NMR, GC-MS, LC). The results are really impressive with the possibility to predict the fate (including death) of adult and pediatric patients with the analysis of metabolites on admission. In some cases (like the sepsis-induced acute lung injury) some metabolic markers have been proposed as indicators of oxidative stress (increase of total glutathione), loss of ATP homeostasis (increase of adenosine), apoptosis (increase of phosphatidylserine) and disruption of endothelial barrier function (increase of sphingomyelin).

METABOLOMICS IN NEONATAL SEPSIS

It seems that metabolomics could represent a new tool for the neonatologist [2].

In a previous study of ours, the metabolome of both term and preterm newborns was altered from 48 to 72 hours before the onset of signs and symptoms of sepsis ('not looking well, not feeding well, not breathing well'). Metabolomics led to identifying the molecules responsible for the differences in the metabolic profiles, among which glucose, lactate and acetate, the urine content of which had increased in septic neonates compared to controls, while THBA, ribitol, ribonic acid and citrate had decreased [3]. These results agree with recent works published in the literature [4]. In particular, in our study the presence of ketone bodies in the urine of the septic group suggests a compensatory reaction to a reduced level of ATP. In another study of ours, it was possible to follow, in an individualized way, the urinary metabolome of a VLBW newborn with a fungal infection towards clinical resolution. At the end of the antifungal therapy the metabolome

was far from normal values [5]. Moreover metabolomics has been studied in neonates born by mother affected by chorioamnionitis [6] and in necrotizing enterocolitis [7]. Interestingly, in the last 2 conditions gluconic acid is strongly involved. In the first case (neonates born by mother affected by chorioamnionitis) among the first 40 metabolites involved, gluconic acid is the only up regulated. In the second case (necrotizing enterocolitis) gluconic acid is one of the 3 major involved metabolites [7]. Generally, it is representative of overgrowth of some bacterial species like *St. faecalis*, *Pseudomonas spp.*, *E. coli* due to the activation of a specific bacterial pathway (Entner-Doudoroff) in aggressive bacterial species, as expression of microbiota disorder [7]. With metabolomics, it is possible to distinguish metabolites of human and bacterial origin: it could therefore be defined as the 'Rosetta Stone' of microbiomics [1]. Considering the whole literature, the main pathways involved in neonatal sepsis, according to metabolomics studies include: 1) inflammation, hypoxia, oxidative stress; 2) energy problem: reduced level of ATP and compensatory reaction to a major oxidation of fatty acids; 3) increase in glucose turnover through glycolysis; 4) redistribution of glucose consumption from the mitochondrial oxidative phosphorylation to other metabolic pathways, such as the production of lactate and the pentose phosphate pathway. Finally, monitoring the efficacy and toxicity of drugs, namely antibiotics, could be reasonable goals for metabolomics in the next future [9-13].

CONCLUSIONS

The predictive power of metabolomics in sepsis seems impressive [13]. Big data make it possible to predict the mortality of patients in the short or medium term with the current protocols [1]. They also allow assigning some patients to more aggressive treatment, and others to less aggressive treatment, based on the severity of the disease and/or their fragility/resilience [1]. Timing of beginning of treatment is crucial in newborns: an earlier diagnosis and an individualized therapy (precision neonatology) [1, 14] can allow a reduction in mortality rate, changing the fate of patients.

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LECT 11

OPTIMIZING EARLY NUTRITION SUPPORT IN VERY LOW BIRTH WEIGHT (VLBW) INFANTS

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Optimizing early nutrition in very low birth weight (VLBW) infants mainly depends on parenteral nutrition (PN) support. For many years, a considerable number of authors have worked on defining nutritional requirements of premature infants and European guidelines for PN in children

– including premature infants – have been updated recently [1]. Current evidence suggests that PN need to be started as soon as possible after birth in order to prevent any catabolic state and to provide minimal energy requirement [1, 2]. A minimum of 45 kcal/kg and 1.5 g/kg of amino acids need to be provided on the first day of life targeting 45-55 kcal/kg and 2-2.5 g/kg of amino acids [1, 2]. Afterwards, nutritional supply should be increased rapidly allowing premature infants to grow similarly to the intrauterine fetuses up to theoretical term taking into account the dramatic change in the infants' environment and the associated specific needs [1, 2]. To meet such needs, a PN supply of at least 90 kcal/kg per day with at least 2.5 g/kg/d of amino acids is necessary within a few days after birth [1, 2] in complement to the initiation of enteral nutrition [3, 4]. The first challenge in VLBW infants PN support is to have an adequate PN solution available soon after birth in order to initiate rapidly PN supply [5, 6]. By providing sufficient amount of nutrients from birth and rapidly increasing PN intakes, it is feasible to significantly reduce and rapidly abolish the frequent cumulative nutritional deficit that occurs in VLBW infants, especially in extremely premature infants born before 28 weeks of gestation [7]. Another challenge is to provide each nutrient in the adequate proportion to meet infants' demand and to maintain adequate blood homeostasis [1, 2, 8]. In particular, allowing adequate fluid and electrolytes homeostasis is very challenging during the first days of life when insensible water losses are very high [7]. In addition, allowing for anabolism with sufficient macronutrient intakes implies increased electrolyte and mineral supplies to avoid inadequate and sometimes iatrogenic biological disturbances [1, 2, 8]. In particular, sodium, potassium and phosphorus supply needs to be increased in VLBW infants compared to what was frequently performed in the past [1, 2, 8].

Optimizing early PN support is not really evident in clinical practice and many studies have showed that significant cumulative nutritional deficits, biological instabilities, and postnatal growth restriction are still frequently described during in-hospital stay of premature infants, especially VLBW infants [4]. Unfortunately, such difficulties have been associated with poor long-term outcomes and require significant attention for improving neonatal care [4]. Hopefully, some recent studies have demonstrated that some optimization may be reached by using a well-balanced standardized PN solution from birth onwards [4-8]. The early provision of such PN regimen with a rapid increase of intakes in addition to an optimized enteral feeding approach has led to improved growth, improved biological homeostasis and improved feeding tolerance [3, 4].

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LECT 12

LONG-TERM ADVERSE EFFECTS OF EARLY GROWTH ACCELERATION OR CATCH-UP GROWTH

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The idea that early nutrition and patterns of growth may influence, or programme, the long-term health of infants has been strongly supported by several decades of research starting from the early 1980's. At the time, it was recognised that a high protein

intake was required in preterm infants to achieve a post-natal growth rate closer to the intra-uterine rate of growth of a normal fetus of the same post-conceptional age, a goal regarded optimal for short- and long-term health. Subsequently, long-term follow-up of preterm infants randomised to a high protein formula (for an average of only 4 weeks after birth) demonstrated beneficial effects up to 16 years later on brain structure and function including 10% greater volume of the caudate nucleus and higher IQ [1]. Since this early research, numerous observational studies have demonstrated an association between sub-optimal nutrition in the early post-natal period (as measured by faltering growth, poor growth in head circumference, and inadequate protein intake) and impaired long-term neuro-cognitive development [2], although more recent reviews and studies suggest that this concept remains unproven [3]. In contrast to the benefits for neurodevelopment, follow-up of the same preterm nutritional trials above suggested that faster post-natal weight gain, as a consequence of higher protein intake, increased later risk factors for cardiovascular disease. Infants randomised to a higher protein formula for the first 4 weeks had increased adiposity, insulin resistance, dyslipidemia, markers of inflammation and vascular endothelial dysfunction up to 16 years later [4]. In contrast, infants randomised to lower-nutrient, donor breast-milk, had long-term beneficial effects on risk factors for cardiovascular disease. These programming effects of faster infant growth termed the growth acceleration hypothesis [3] (i.e. upward centile crossing for weight or length) have now been demonstrated in both animal and human studies [3-5]. Of particular interest is the impact of catch-up growth (the higher than expected rate of growth seen following recovery from illness or starvation), a pattern of growth most commonly seen postnatally in infants with low birth weight, and a global problem affecting > 20 million newborns a year. However, whether catch-up growth should be actively promoted in such infants (e.g. by encouraging a higher plane of nutrition) is an area of considerable controversy and debate [5]. The long-term adverse effects of early growth acceleration have been confirmed in many epidemiological studies and for several cardio-metabolic outcomes such as risk of obesity, diabetes and cardiovascular disease [4, 5]. This effect is seen in infants born preterm [3] or at term, infants born appropriate weight or small for gestational age (SGA), and in developed and developing countries. Importantly, 6 randomized studies support a causal link between infant growth and later risk of metabolic disease. For instance, term SGA infants randomly assigned to nutrient-enriched formulas (that increased infant weight gain) had higher diastolic blood pressure at age 6-8 years and, in 2 trials, 18-38% greater fat mass at age 5-8 years than controls [5]. Interestingly, differences in fat mass or blood pressure between randomised groups in childhood were related to the rate of weight gain in infancy suggesting a "dose-response" association between early growth and later cardiovascular risk. Overall, these studies suggest a large effect size. For example, > 20% of later obesity risk may be explained by the rate of infant weight gain and the relative risk of later obesity associated with more rapid weight gain in infancy ranges from 1.2 to as high as 5.75. Based on the risks and benefits, the optimal pattern of post-natal growth is likely to differ in different populations. In infants born prematurely, faster post-natal growth predisposes to cardiovascular risk factors, but improves long-term cognitive function. So, on balance, the current policy is to promote faster growth by increasing nutrient intake (e.g. using higher-nutrient preterm formulas). Whether the same policy should apply to the larger preterm infant is currently unknown. Similarly, in infants from impoverished environments, the short-term benefits of faster post-natal growth may outweigh any long-term disadvantages. Whether similar considerations apply to low birthweight infants from countries in transition is uncertain. For term infants born SGA from developed countries, promoting catch-up growth by nutritional supplementation has few advantages for short- or long-term health [5]. The present review will consider the long-term adverse effects of early growth acceleration in preterm and term infants focusing on the biology, mechanisms involved and clinical impact.

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LECT 13

ROLE OF NEAR INFRARED SPECTROSCOPY DURING NEONATAL TRANSITION

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Adequate oxygenation during neonatal transition is a very important topic. We know that inadequate oxygenation increases mortality and cerebral morbidity significantly [1]. Nevertheless, it is difficult to aim for oxygenation targets. Routinely oxygenation is assessed with pulsoximetry, therefore there is an ongoing discussion about SpO_2 targeting during neonatal transition [2]. In the last years near-infrared spectroscopy (NIRS) was increasingly used to assess cerebral tissue oxygen saturation ($crSO_2$) during neonatal transition. As the brain is an important and vulnerable organ it seems appropriate to ensure adequate cerebral oxygenation in that phase. First, it has been shown that SpO_2 (pulsoximetry) and $crSO_2$ (NIRS) do not parallel each other during neonatal transition [3]. In the following step it was necessary to define percentiles for normal $crSO_2$ values in the same manner as it was done for SpO_2 for the transitional period. These were published in 2013 [4]. In observational studies we were able to show, that $crSO_2$ values below the 10th percentile were associated with an increased risk for severe intraventricular haemorrhage (IVH) [5]. Furthermore, we could show, that the burden of cerebral hypoxia was inversely correlated with quality of spontaneous body movements, a proxy for short-term neurological outcome [6]. To introduce NIRS into clinical work a Phase I/II Trial was designed, the COSGOD trial, where COSGOD stands for "Cerebral Oxygen Saturation to Guide Oxygen Delivery in preterm neonates for the immediate transition after birth". It showed that $crSO_2$ targeting was feasible on the resuscitation table, and that with $crSO_2$ targeting the burden of cerebral hypoxia was significantly reduced [6]. Recently the corresponding Phase III Multicenter RCT was started to investigate, whether this approach of using NIRS during neonatal transition will improve the outcome of preterm infants.

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LECT 14

HEART RATE CHARACTERISTICS AS PHYSIOMARKERS FOR DETECTION OF SEPSIS AND OTHER DISEASES

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Despite preventive efforts, late-onset sepsis (LOS) and necrotizing enterocolitis (NEC) affect about 15% and 8% of very low birthweight (VLBW) infants in the Neonatal Intensive Care Unit, with about 20% mortality and substantial morbidity including neurodevelopmental impairment. Early warning systems for LOS and NEC could lead to earlier treatment and improved outcomes. The first commercially available system for prediction and detection of infection in VLBW infants is the HeRO monitor which analyzes the bedside monitor electrocardiogram signal for abnormal heart rate characteristics (HRC) of decreased variability and superimposed transient decelerations. These patterns, similar to those seen in a distressed fetus, often occur in preterm infants during a systemic inflammatory response. Three components contributing to a rise in the HRC index are low heart rate (HR) variance, high sample asymmetry (skewing of a histogram of HR toward more decelerations and fewer accelerations), and low sample entropy.

The HRC index is a number from 0 to 7 and is the fold increased risk the infant will have a clinical deterioration consistent with sepsis in the next 24 hours. The continuously displayed HRC index is updated every hour and represents HRC over the previous 12 hours. A rise in the HRC index over the prior baseline indicates a change in physiology that should prompt clinicians to consider whether the infant may be in the early stages of an infection or inflammatory process. Like any physiologic risk score, it should not be the sole factor determining whether or not to work up and treat for infection. The HRC index should be considered in the context of demographic variables, clinical signs, and laboratory studies. Major clinical risks for infection include low gestational and postmenstrual age and presence of one or more invasive devices such as a vascular catheter or endotracheal tube. Signs of sepsis or NEC may include increased apnea, respiratory distress, lethargy, and poor perfusion. Laboratory indicators might include low or high leukocyte count, increased immature neutrophils or elevated C-reactive protein. A radiograph or ultrasound might show signs of NEC. Clinicians have the challenging task of interpreting clinical risks, clinical signs, laboratory and imaging tests, and the HRC index in concert. An infant with significant clinical signs or with a large, otherwise unexplained rise in the HRC index should be considered for antibiotics and other supportive care pending results of cultures and screening tests. On the other hand, an infant with an equivocal clinical picture or HRC index might be better off with a "watchful waiting" approach, especially in the face of reassuring laboratory and imaging results. In any case, clinical vigilance is key to early detection and timely treatment of early stage LOS and NEC, increasing the chance of a favorable outcome. There are several important caveats for use of the HRC index monitor. Some infants with severe intraventricular hemorrhage have frequent spikes in their HRC index in the first month after birth, in absence of infection, possibly representing autonomic nervous system dysfunction. Infants with severe lung disease may also have a chronically elevated index due to chronic systemic inflammation or effects of hypoxia and acidosis on HR variability. Most medications do not seem to significantly impact the HRC index, notable exceptions being dexamethasone, which increases HR variability and lowers the index and atropine, which does the opposite. Improved early warning systems for LOS and NEC are under investigation. Adding respiratory parameters to HRC makes intuitive sense since many preterm infants develop increased apnea or exaggerated periodic breathing early in the course of a systemic inflammatory response. This increase in immature breathing patterns is due, at least in part, to release of endogenous prostaglandins and inflammatory cytokines. HR decelerations coupled with oxygen desaturations ("brady-desats") can be analyzed as a surrogate marker of central apnea, as can be increased cross-correlation of HR-SpO_2, a mathematical function representing co-trending of these two signals allowing for a specified time delay. Combining cardiorespiratory analysis with demographic and clinical variables may substantially improve the sensitivity and other diagnostic utility parameters. Finally, adding spot checks of biomarkers such as cytokines in cases where clinical and physiomarker signs are equivocal might enhance clinicians' ability to rule in or rule out sepsis and NEC. Two competing goals of earlier treatment of these life-threatening illnesses and avoiding unnecessary antibiotic exposure must be balanced to optimize outcomes of preterm infants.

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LECT 15

ENHANCED CARDIORESPIRATORY MONITORING OF THE PRETERM INFANT DURING STABILIZATION IN THE DELIVERY ROOM

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"Not all that is measurable is of value, and not all that is of value can be measured".

Preterm adaptation represents a unique physiological time period. Monitoring adaptation has primarily focused on clinical evaluation consisting of observation and auscultation, both with their own inherent limitations. In recent decades, there has been a significant increase in the number of monitoring options available for clinicians caring for newborn infants in the NICU setting and by extension the delivery room (DR). Examples include pulse oximetry, electrocardiography (ECG), echocardiography and non-invasive cardiac output monitoring techniques. Respiratory assessment includes incorporation of capnography, capnometry and the use of respiratory function monitoring devices to assess end tidal CO_2, respiratory rate and tidal volume. Neurological monitoring consisting of electroencephalography and near-infrared spectroscopy are also available. However, at present, routine monitoring of preterm in the DR remains relatively limited, primarily with clinical assessment and pulse oximetry. The relative lack of monitoring options in the DR is a reflection of the difficulties in acquiring the information, interpreting this data for decision making in real time and initiating proven interventions [1]. As adjuncts to clinical monitoring during initial infant stabilisation in the DR, the recent 2015 ILCOR recommendations advise the use of two objective assessment tools as routine for preterm deliveries where advanced stabilisation measures are expected: 1) pulse oximetry (with or without ECG) to regulate oxygen delivery, and 2) exhaled carbon dioxide (CO_2) detectors for confirmation of correct endotracheal (ET) tube placement. These two devices generate real-time accurate physiological data and document changing observations over time. The information provided assists in clinical decision-making in real time and has the potential to improve both short- and long-term outcomes for preterm infants. Video recording provide objective measures of DR performance in the stabilisation of preterm infants, and can be utilized for education, research and audits of performance. Fifteen years ago, Carbine and colleagues reported that video recordings in the DR are feasible quality assurance tools [2]. Video recordings can help assess neonatal teamwork in the DR, facilitate debriefings, and improve performance [3]. Video analysis of newborn resuscitation and stabilisation has shown that the availability of real-time information is less than optimal when compared with recommended guidelines [2, 4]. In one study, less than 50% of high-risk infants had a pulse oximeter reading 60 seconds after transfer to the resuscitation table [4]. These findings are important, as they emphasize the need to maintain clinical skills given that the availability of real-time physiological data from monitors can be delayed. The majority of the monitoring techniques have focused on cardiorespiratory adaptation. Assessing brain health in the immediate newborn period has not been prioritized historically, nor in current international guidelines for monitoring newborn infants [5]. The current methods under investigation for assessing brain health in the immediate newborn period, particularly cerebral oximetry, will be described. Introducing new monitoring devices into clinical care remains challenging. Feasibility studies are required to assess whether new devices can be applied safely. Human factors need to be considered and evaluated prior to introduction into the clinical environment. Ideally, both short- and long-term benefits should be evaluated by randomized controlled trials prior to the introduction of a new device into routine clinical care. In this presentation we will review the different modalities available for cardiorespiratory and neuromonitoring in the DR, and assess the current evidence based on their feasibility, strengths and limitations during preterm stabilisation.

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