

Progress and challenges in the care and outcome of very preterm infants

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Dear participants,

Welcome to this lesson of our RECAP preterm Summer School.

For those of you, who are not neonatologists and are not familiar with the postnatal intensive care of very preterm infants, I would like to give a short overview on the progress and challenges in the care and outcome of these infants over the last decades.

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Normal human gestation lasts 40 weeks from the first day of the last menstruation, with a biological range from 37 to 42 weeks.

However, every 10th baby is born preterm, what means before 37 weeks of gestation.

Preterm infants can be categorized according to their gestational age or their birthweight, both of which are closely correlated.

Very preterm birth is defined as birth before 32 weeks of gestation and affects about 1 – 2 % of all newborns.

Extremely preterm birth means birth before 28 weeks of gestation.

Very low birthweight infants are those with birthweights below 1,500 g and extremely low birthweight infants those with birthweights below 1,000 g.

Initially, most preterm infants are not sick, but immaturity is a risk factor for death, severe acute morbidity and long-term problems.

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Prematurity is the single most frequent cause of infant mortality in developed countries.

Better understanding of the physiology of premature babies and improvements in neonatal intensive care have led to markedly decreased mortality during the last decades.

This figure shows the critical birthweight for 50 % survival from 1938 – 2001 in the United States decreasing from about 1,800 g to about 600 g.

This trend is very similar in other developed countries, like in Europe.

The graph reveals 3 important aspects:

1. Survival of newborn infants depends on birthweight and accordingly on gestational age, as both are closely correlated.
2. Survival of low birthweight infants has continuously decreased over the last decades.
3. Flattening of the curve at the end indicates that there seems to be a natural lower limit of birthweight and gestational age compatible with survival.

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The most important progress in the care of very preterm infants occurred in the 1990ies with the introduction of exogenous Surfactant substitution.

Surfactant lowers the surface tension of the lung and keeps it distended for breathing.

Absence of Surfactant on the other hand leads to a collapse of the lung and precludes ventilation and gas exchange.

As maturation of the endogenous surfactant system usually needs up to about 34 weeks of gestation, the lung of infants born earlier is not functioning adequately, leading to the typical respiratory distress syndrome of the premature infant.

This X-ray of a premature baby taken shortly after birth shows a so called white lung which indicates surfactant deficiency compromising ventilation and gas exchange.

One hour after application of exogenous Surfactant the lung looks dark as a sign of good ventilation.

I remember well when I gave Surfactant to a preterm infant for the first time:

It was like a miracle, when the baby's color promptly changed from blue to pink and the respiratory distress symptoms disappeared within minutes.

Since introduction of surfactant therapy short-term and long-term outcome of very preterm infants have markedly increased compared with the period before.

This must be considered when comparing cohorts of preterm infants born before or after introduction of surfactant therapy.

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With decreasing mortality of preterm infants the question arises how survivors will develop in later life.

In contrast to mortality and short-term morbidities long-term outcome is much more difficult to be assessed.

Acquisition of reliable data depends on a series of confounding factors:

The selection of the baseline population must be considered, defined for example by birthweight or gestational age, inclusion of all live births or only of babies admitted to the intensive care unit.

Also, the year of birth plays a major role as shown in context with the introduction of Surfactant therapy.

Attrition in follow up studies increases over time and confounds the results.

Commonly accepted assessment tools which have been validated and standardized for different populations in different countries are still very rare.

Rating of long-term outcome depends on the age at assessment and can change with increasing age.

The targets to be assessed often differ between follow up studies:

Targets can include motor skills, cognition, intellectual abilities, language, behaviour, and social life.

All these influencing factors lead to variable and sometimes contradictory results in the literature demonstrating the need for harmonization of data collection and for more accurate and standardized reporting of neurodevelopmental outcomes in very preterm children.

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Surviving preterm children face greater risks of health problems and impairment compared to children born at term.

Consequences of very preterm birth include visual and auditory deficits, poor respiratory outcomes, impaired motor and cognitive ability, learning difficulties, poor educational outcomes, psychiatric disorders and difficulties in social integration and relationships.

There is a wide variation in the rates of moderate to severe neurodevelopmental impairment among very preterm cohorts.

A meta-analysis of 30 follow up studies up to 6 years of life identified almost 17 % of very preterm or very low birthweight infants with cognitive delay and about 20 % with motor delay. Whereas this percentage remained nearly unchanged during the past decade, cerebral palsy showed a decrease in several studies.

The rates of developmental problems increased with decreasing gestational age or birthweight, respectively.

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Five decades ago, the primary goal in the intensive care of very preterm infants was reduction of mortality.

The limiting organ leading to death was the immature lung.

After introduction of surfactant therapy, the survival rate has reached more than 90 % in infants with birthweights below 1,500 g.

With this success, morbidity and long-term outcome of very preterm infants has come to the fore:

Problems in development, behaviour and social life need to be solved.

The focus in the care of very preterm infants has changed from the lung to the brain and from survival to quality of life.

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Although overall survival has increased, there are still large differences among countries and regions even in Europe.

In the European MOSAIC Project done in 10 representative European regions in 2003 mortality in very preterm infants differed between around 7 % and around 21 % among regions.

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Also severe neurological morbidity, defined as intraventricular hemorrhage (IVH) grades III and IV or cystic periventricular leukomalacia (cPVL) differed markedly among regions from around 3 % to up to around 16 %.

These differences emerge the questions, which factors influence survival and neurological outcome in very preterm infants and how the prognosis of these infants can be equalized and further improved.

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To answer research questions and to gain new knowledge, two major scientific approaches are available:

Randomized controlled intervention trials and prospective cohort studies.

Both approaches have strengths and limitations and their application depends on the research question.

While in RCTs the population is highly selected and exposed to one particular intervention, cohort studies reflect the „real life“ in a „normal“ population exposed to many complex influencing factors.

Whereas RCTs are important to show effectiveness and safety of a specific intervention, cohort studies help to identify risk and influencing factors, like the socio-economic background, and the reaction of people to their typical environment.

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Both types of research design, randomized intervention trials as well as cohort studies can complement each other to gather and increase knowledge.

However, the question arises, how new knowledge can be translated into clinical routine and how this transfer influences the clinical outcome.

This was a pivotal question of the European EPICE Project, when 19 regions from 11 European countries recruited a large birth cohort of very preterm infants in 2011/12.

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To investigate the implementation of evidence based interventions into clinical routine and their impact on mortality and morbidity of very preterm infants, we analyzed the combined use of four evidence based practices using an "all or none" approach:

Delivery in a maternity unit with appropriate level of neonatal care; administration of antenatal corticosteroids; prevention of hypothermia; surfactant use within two hours of birth or early nasal continuous positive airway pressure.

All of these practices had been confirmed in RCTs before and were now evaluated in a large observational project, the EPICE cohort

We found, that only 58 % of infants received all four highly evidence based practices for which they were eligible.

Infants with low gestational age, growth restriction, low Apgar scores, and who were born on the day of maternal admission to hospital were less likely to receive complete evidence based care.

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After adjustment for gestational age, sex, small for gestational age, multiple pregnancy, pregnancy complications, type of delivery, Apgar score and region, receiving evidence based

care was associated with lower in-hospital mortality, lower severe neonatal morbidity, or a combination of both.

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Assuming that all four evidence based interventions would have been provided to all infants, mortality could have been reduced by almost 18 %, severe neonatal morbidity by almost 10 % and the combination of both by about 11%.

Thus, the EPICE cohort revealed that evidence based medicine is translated into clinical routine only in part and that more comprehensive use of evidence based practices in perinatal medicine could increase survival without severe morbidity in very preterm infants.

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In summary:

Survival of very preterm infants has markedly increased over the last decades.

However, developmental problems and delays are still relevant in this population.

Mortality and neonatal morbidity differ markedly among countries and units.

What I have not shown, but what is known: Social risk factors interfere with medical care.

Translation of evidence based practices into clinical routine needs time and is not sufficient.

Many open questions remain with the care of very preterm infants to be answered by RCTs and epidemiological studies like the RECAP preterm project.

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These open questions include:

How to further reduce mortality and neonatal morbidity like intraventricular hemorrhage, necrotizing enterocolitis, retinopathy of prematurity and bronchopulmonary dysplasia?

How to intensify and fasten the translation of knowledge into clinical routine?

How to identify children needing special support?

How to improve short-term and long-term outcome?

How to involve and support parents of very preterm infants?

How to coordinate research for humans born very preterm?

For all these open questions concerted action is required.

Combining several cohort studies can help to answer these questions.

The RECAP Platform is a helpful tool for this goal.

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This slide shows some references for further reading.

Thank you very much for your attention.