

## New Concepts in Neonatal Sepsis

### IS-013 NEONATAL SEPSIS, NEW PREVENTIVE STRATEGIES

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10.1136/archdischild-2014-307384.13

Severe infections represent the main cause of neonatal mortality, accounting for more than 1 million neonatal deaths worldwide every year.

Late-onset infections (occurring after the first 72 h of life) are thought to be caused by horizontally transmitted microorganisms, and may be 1) nosocomial, occurring during hospital stay in NICU, or 2) non-nosocomial, affecting home discharged, otherwise healthy full-term neonates.

1) Strategies to reduce the incidence of infection in NICU include

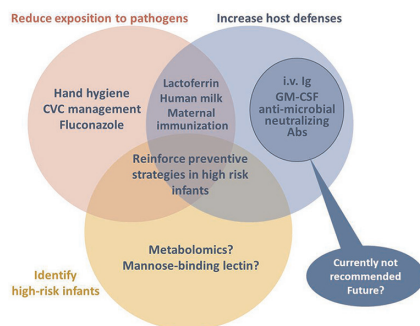
i) Reduction of the exposition of newborn infants to pathogens: hand hygiene practices; proper management of central lines; promotion of early enteral feeding with human milk; prophylaxis with lactoferrin and fluconazole;

ii) Improvement of neonatal defenses: lactoferrin and human milk. Cytokines/growth factors (e.g., GM-CSF), and other immune therapies (intravenous Ig, monoclonal anti-staphylococcal antibodies) are currently not recommended for neonates. Future strategies may include: the development of highly specific, broadly neutralising antibodies to be used in high risk infants; and maternal immunisation practices to prevent both late-onset infection and early-onset infection and/or infection-related preterm birth.

iii) Identification of high risk infants: this is a central point including, but not limited to, the use of metabolomics for risk stratification.

2) Strategies to prevent infections in otherwise healthy, home discharged full-term neonates

These infections are almost always unpredictable and often severe; future research should focus on the identification of high-risk infants, in order to implement preventive protocols; and on maternal immunisation against common pathogens as a general practice to reduce neonatal vulnerability.



**Abstract IS-013 Figure 1** A comprehensive view of the strategies for the prevention of neonatal infections

## Nosocomial Infections in the ICU

### IS-014 THREAT IN ICU: GRAM NEGATIVE BACTERIA RESISTANCE

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10.1136/archdischild-2014-307384.14

Threat in ICU in 2014; emerging resistance in Gram negatives.

Emerging antibiotic resistance mechanisms are emerging now worldwide at a high rate in particularly among nosocomial infections. The perspective of impossible-to-treat infections is raising due to lack of perspective of the development of effective novel antibiotics. This may cancel the developments of the modern medicine such as important surgery, transplantation and intensive care.

Multidrug resistance and pandrug resistant strains are increasingly identified in species such as *Klebsiella pneumoniae*; *Escherichia coli*, *Pseudomonas aeruginosa* and *Acinetobacter baumannii* which are the main Gram-negative pathogens in ICU. The most important resistant traits are the extended-spectrum  $\beta$ -lactamases and the carbapenemases that hydrolyse at least the expanded-spectrum cephalosporins and the carbapenems, respectively. Those resistance traits are mostly associated to resistance markers to fluoroquinolones and aminoglycosides which are the two other main antibiotic classes of broad spectrum activity. Those emerging resistance traits are mostly the results of overuse and misuse of antibiotics in developing countries in human medicine followed by transfer of multidrug resistant bacteria by humans themselves (travel, migration...). Screening of infected patients and carriers by using rapid diagnostic techniques is becoming mandatory for choosing the most appropriate first line antibiotherapy and preventing the development of outbreaks.

## Paediatric Cancer

### IS-015 TRANSLATIONAL RESEARCH IN PAEDIATRIC CANCER: FROM THE BENCH TO THE BEDSIDE

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10.1136/archdischild-2014-307384.15

Malignant tumours in children and adolescents are rare diseases with different prognosis and biologic behaviour. Prognosis of childhood cancer has improved considerably in recent decades and survival is approximately 70% in western countries. However, even with the current multimodal therapies, a considerable number of these patients still relapse and eventually die due to progressive or refractory tumours.

To improve the efficacy of anticancer therapies in children we have established a Translational Research Program in Paediatric Cancer consisting on:

1. Molecular characterisation of paediatric tumours.
2. Identification of new molecular targets.
3. Screening of new drugs in cell lines and in animal models.
4. Phase I-II clinical trials.

We start with the identification of genes and pathways candidates to be targeted using different platforms, followed by the validation of the identified targets in cell lines and primary tumours and the selection of appropriate candidates. The next

step consists on testing the effects of drugs *in vitro* in cell lines and *in vivo* in mouse xenografts.

To translate the results of this research into the clinical scenario the program includes the development of phase I-II trials. Considering that cancers in children are different from tumours of adults we need to test new drugs in early phase clinical trials specifically designed for children.

In summary, the promotion of early clinical research in children with cancer combined with a better knowledge of the tumour biology will allow a more effective introduction of new targeted therapies into the clinical practice.

## Pulmonology

### IS-016 ASTHMA DEATHS

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10.1136/archdischild-2014-307384.16

The UK has the highest Paediatric asthma mortality and morbidity in Western Europe. Data will be reported from a longstanding regional (East of England), and the National Review into Asthma Deaths (NRAD). These data clearly describe the risk factors in the UK for asthma death in childhood. Conversely and arguably the UK produces some of the best evidence based clinical guidance (BTS /SIGN, NICE) in the world, however it is clearly failing to deliver quality and safe care to its asthma populations. This contrast has initiated an NHS England quality improvement program; “Delivering improvements in childhood asthma outcomes; A collaborative approach”, to implement a national high impact change model to improve asthma outcomes for children and young people, using the skills, expertise and resources of the 12 NHS England Strategic Clinical Networks. This aims to nationally improve the education of health workers and the asthma population at large, encourage self-management, standardise materials, and review the commissioning of asthma services. Lastly, in a financially challenged health care economy, are such ideals achievable?

Pulmonology Symposium (Supported by and Unrestricted Educational Grant from Chiesi).

## Pulmonology Symposium (Supported By and Unrestricted Educational Grant from Chiesi)

### IS-017 PULMONARY VASCULAR RESISTANCE IN THE PRETERM INFANT – FROM PHYSIOLOGICAL TO PATHOLOGICAL

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10.1136/archdischild-2014-307384.17

Serial cardiac ultrasound has given us a window on circulatory transition, both normal and abnormal. Preterm birth is not physiological so physiology has to be assessed in well term babies. Pulmonary blood flow increases with the first breath as resistance falls and these balance each other so that the fall in pulmonary artery pressure (PAP) over the first 4–6 h of life is modest. So, early on, well babies will have PAPs close to systemic pressures confounding early assessment for pulmonary hypertension.

The ‘pulmonary ischaemia’ model of RDS originated from early studies when RDS was a different disease. PAP will fall more slowly in preterm babies ventilated with RDS but, in most

preterm babies, PAP is below systemic BP even in the early hours after birth. Thus the impact is too much blood in the pulmonary circulation due, not pulmonary ischaemia from high vascular resistance and blood bypassing the lungs.

There are exceptions to the above, particularly babies with severe RDS, congenital pneumonia or those born after prolonged oligohydramnios, in whom raised PAP is a consistent finding. Oligohydramnios babies are not common, so have been a difficult group to study systematically but several case series have described this as well as the responsiveness of this group to iNO.

There seems to be sub-clinical persistent raised pulmonary vascular resistance in many babies with chronic lung disease. The significance of this is uncertain but in the most severe cases, pulmonary hypertension can be an important component of the disease.

### IS-018 NEW THERAPIES FOR PULMONARY HYPERTENSION AND BPD – FROM BENCH TO BEDSIDE

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10.1136/archdischild-2014-307384.18

We have used mesenchymal stem cells in preclinical models of pulmonary hypertension (PH) and in the hyperoxia-induced neonatal murine model of bronchopulmonary dysplasia (BPD) to suppress inflammation and improve survival while attenuating alveolar injury and PH. The protective effect was predominantly mediated by paracrine mechanisms, since, cell-free MSC-conditioned media were even more efficacious than MSCs in preventing or reversing established disease. The active moieties that confer the therapeutic efficacy of MSCs remain elusive but likely include secreted proteins, nucleic acids, and membrane components, all potentially packaged in MSC-released microvesicles. We have shown that such particles, a class of which is represented by exosomes, convey the therapeutic efficacy of MSCs in the murine hypoxic model of PH. Exosome treatment was also able to abrogate early hypoxic macrophage influx and downregulate hypoxia-activated inflammatory pathways, thus recapitulating the well-characterised, anti-inflammatory properties of MSCs. The clinical use of MSCs in several on-going trials or the MSC secretome (e.g. exosomes) is a budding new field that represents an exciting and promising approach to therapeutic interventions for diseases of the lung.

## The Brain

### IS-019 THE EMERGENCE OF CONSCIOUSNESS

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10.1136/archdischild-2014-307384.19

The first breaths of air have since antique time been regarded as the ignition of life as indicated by the word spirits. The newborn becomes animated in this way – i.e. the emergence of consciousness. In modern time a bioethics committee<sup>1</sup> has stated that when the new-born encompasses the capacity to breathe either independently, or with the support of a ventilator is the moral and legal point when human life must be preserved independent of gestational age. Awakening at birth is crucial for being conscious. This is triggered by the stress of being born i.e. mobilisation of catecholamines, cooling due to evaporation of the amniotic fluid