**Advances in Intestinal Failure in Children** – Creating a European Network
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**Summary**
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During the initial meeting of the ten leading paediatric intestinal transplant centers in Europe in March 2012 in Venice the participants had agreed to form a European network. Now, representatives of the ESPGHAN working group for intestinal failure and transplantation (F. Lacaille, L. D’Antiga, G. Gupte) invited together with A. Busch and E. Sturm (local organizers Tübingen) to an expert meeting to initiate networking of European centers and to drive the cooperation and to support advances in management of intestinal failure in children.

Within the ESPGHAN Working Group two different models of a web-based communication systems were presented by J. Hind (London) and E. Sturm (Tübingen). Both are based on a closed secure web-based communication platform resembling features of frequently used social media to facilitate communication between patients and health system professionals but also to offer a platform for expert communication in case discussions, data exchange, and to provide patient care tools. The members decided to establish the CAREON-Trustner platform for the needs of expert exchange within the working group. F. Lacaille (Paris) discussed the protocol for immunosuppression in presensitized patients (HLA donor - specific antibodies, DSA) for intestinal transplantation (ITx) based on treatment which antithymocyte globulin (ATG) for the high risk patients. Feasibility of a common European protocol on the background of scarce evidence in this field were discussed. G. Gupte (Birmingham) gave an overview of past and future tasks of the working group, concluding that increased collaboration between centers, countries and various expert individuals should be reached by creating a inclusive working group reaching out to members of other disciplines (e.g., pediatric and transplant surgeons) and to medical associates (nutritionists and nurse specialists) - It was emphasized that intestinal rehabilitation plays an increasingly important role in management of intestinal failure. Key targets in this area should be: 1. TPN optimization, 2. short bowel non-transplant surgery and 3. new concepts of enteral nutrition. In the field of ITx main topics are Tx surgery and common immunosuppression protocols. It was generally agreed upon that specific experts within the working group should be responsible for a specific topic (e.g. immunosuppression). Next steps and decisions will be taken in the next meeting of the working group in June during the ESPGHAN Congress in Jerusalem.

Presentations in the session on ‘Immunology in intestinal transplantation’ addressed approaches to induce tolerance in the context of intestinal transplantation such as selective tolerogenic immune-suppression, haploidentical stem cell and combined solid organ transplantation as well as tolerogenic cell therapy.
J. Pirenne (Leuven) reported on their tolerogenic protocol in ten patients using donor specific blood transfusion, low steroids and low tacrolimus levels. Thirty percent of patients experienced acute rejection within the first 18 months and a survival rate of 90% after 5 years with low infectious complications in the long term was achieved. D. Hartl (Tübingen) explained proven and potential effects of MDSC (neutrophilic myeloid-derived suppressor cells), which are able to suppress T cell proliferation and Th1 and Th17 response. MDSC can significantly alleviate immunologic activation in GvHD. R. Handgretinger (Tübingen) reported the experience with new tolerogenic strategies in Tübingen using combined haploidentical stem cell transplantation in combination with kidney and liver from identical living donors leading to complete tolerance and significantly improved quality of life as immunosuppressants became superfluous. Another new model for tolerance induction in solid organ living-donor transplantation could be the treatment with cyclophosphamide 3 days after transplantation in combination with other immunosuppressive agents (in vivo depletion) after a pre-transplant treatment which is only immunoablative. The risk-benefit relation of these new approaches was discussed extensively.

A comprehensive overview on the recent strategies to treat GVH disease in intestinal transplantation was given by M. Lopez-Santamaria (Madrid). The therapeutic approaches including steroids, monoclonal and polyclonal antibodies as well as fusion proteins, tyrosine-kinase inhibitors, mTOR-inhibitors, mesenchymal stem cells and extracorporal photopheresis were discussed. Future concepts are focused on targeted interventions like inhibition of IL 21, histone deacetylase and glycogen synthase kinase. Better biomarkers and prognostic tools need to be identified.

In the session on ‘Special aspects of paediatric transplantation’ D. Mirza (Birmingham) presented current surgical strategies to manage donor-recipient size and age mismatch in the very young child with intestinal failure which are still challenging. He discussed approaches such as use of skin expanders, delayed abdominal closure, graft reduction and meshed split skin grafts. He contrasted his description on improvements in surgical techniques by pointing to declining numbers of intestinal transplants especially in young children worldwide due to better intestinal rehabilitation and supported by lower incidence of IFALD. Criteria for transplant indications should be reviewed critically especially in the very young children.

To deal with decreasing numbers of intestinal donors S. Nadalin (Tübingen) analyzed attempts to establish an organ exchange collaboration between the Eurotransplant (ET) member states and other European countries, i.e. Great Britain, Italy and others. He explained differences in organ supply, need for donor organs (e.g., lower as expected in ET), waiting time (longer in ET compared to other organ sharing organizations), allocation systems and priorities. He concluded that in order to decrease waiting time and optimize use of scarce donor organs suitable for young children throughout Europe, further advances in organ sharing should be made. However, participating organizations have to overcome logistical challenges, to streamline communication and to find common quality standards (i.e., for organ explantation procedures).
M. Gäbel (Gothenburg) specified characteristics of renal failure prior and after intestinal transplantation. Renal failure pre (up to 50%) and after (more than 60%) pediatric ITx is a common problem although understanding of pathogenesis is still lacking. Etiology seems to be multifactorial including factors like chronic dehydration. Post transplant renal failure is correlated with general outcome and risk factors like age and type of graft and tacrolimus dosage.

The session on ‘Intestinal failure’ started with a critical overview of J. Frick (Tübingen) about diagnostic and therapeutic aspects of the microbiome in short bowel syndrome and small bowel bacterial overgrowth (SBO). By summarizing evidence from animal models Dr. Frick demonstrated that an association of the microbiome with pathophysiology of intestinal failure is likely. In humans, detailed pathogenesis and association of clinical scenarios with host-microbe interactions are not fully understood yet and are subject to further research. A potential target for therapy is the specific modulation of the microbiota composition, however, the use of probiotics in short-bowel syndrome (SBS) has not shown any significant beneficial effect.

Current status of medical and nutritional therapy for improving gut function in SBS was reported by S. Kolaèek (Zagreb) focussing on the relevance of enteral nutrition to induce bowel adaptation. The type of formula nutrition seems to be irrelevant for the effects. She critically analyzed the potential effects of mucosal trophic hormones like GLP-2 which requires further study in children. Use of trophic substances such as orally administered insulin to stimulate mucosal growth are promising but need further evaluation. Evidence is accumulating that the application of different medical treatments is most beneficial if introduced and followed as an integral part of an intestinal rehabilitation programme.

S. Biskup (Tübingen) presented the currently available spectrum of genomic tools and their potential use in children with intestinal failure. These tools may be helpful in diagnosis of the underlying disease, e.g., in patients presenting with chronic pseudoobstruction (CIPD) due to an inborn metabolic or intestinal disease. Today, methods of Next-Generation-Sequencing (e.g., sequencing of whole exome or genome) deliver relevant information for management of intestinal failure in children in a much improved time-frame and cost efficiency. Once relevant genes are known specific gene panels can be created for even faster screening.

An update of conventional and novel non-transplant surgery procedures for children with SBS was given by S. Warmann (Tübingen). He focused on relevance and efficacy of these procedures in the treatment algorithm of children with intestinal failure. He pointed to difficulties comparing and evaluating outcome of lengthening procedures (Bianchi and Serial Transverse Enterotomy Procedure) Preoperative bowel length is still the only prognostic and independent factor influencing outcome. In SBS patients surgery for strictures, adhesions and obstructions as well as the complex aspects of stoma surgery are still challenging. New methods such as temporary insertion of a hydraulic bowel extender in a separated bowel segment are promising procedures
that have been analyzed in clinical trials. All surgical methods are most beneficial when integrated in a treatment algorithm in the setting of a multidisciplinary intestinal rehabilitation programme.

One of the major problems in children with intestinal failure is growth failure. J. Pichler (Vienna) explained the complex pathophysiology of metabolic bone disease (MBD) in intestinal failure which is multifactorial and poorly understood. Main factors influencing MBD are metabolic acidosis, vitamin D deficiency, negative calcium balance, aluminium toxicity, chronic inflammation and side effects of heparin. Regular screening for MBD is essential using established diagnostic tools (e.g., calcium and phosphate excretion in 24 hour urine samples) and novel markers of bone metabolism, i.e., osteocalcin and C-telepeptid.

Starting the session on intestinal failure associated liver disease (IFALD), L. D’Antiga (Bergamo) gave a detailed update on the spectrum of risk factors for IFALD. Apart from well-known factors like prematurity, reduced bile flow and impaired bile acid recirculation the influence of excessive amounts of metabolic substrates such as methionine, manganese, aluminium and glucose have to be considered. Deficiencies of taurine, carnitine and glutamine may drive IFALD as well as exclusively continuous parenteral nutrition (PN) instead of cyclic PN. Clear definitions of IFALD are still missing especially to distinguish the complex features of IFALD from PN-associated cholestasis (PNAC).

Pointing out the role of intravenous lipid emulsions (ILE) in pathogenesis of IFALD R. Shamir (Tel Aviv) focused on adverse effects of phytosterols from soy bean lipid emulsions and potential reasons of the anti-inflammatory impact of fish oil based ILE. Long term studies are lacking to prove the beneficial effects of Soy-MCT-Olive-Fish oil based ILE (SMOF). Recommendations for the use of ILE in prevention and in pre-existing IFALD need to be clarified.

Liver fibrosis not always resolves after weaning from PN. This finding was reported by A. Mutanen (Helsinki). She presented data from her recent study comparing the extent of fibrosis pre and post weaning. Despite resolution of cholestasis and portal inflammation, significant liver fibrosis and steatosis may persist after weaning off PN. Age-adjusted small bowel length, portal inflammation and absence of ileocecal valve were predictive for the degree of fibrosis. These results emphasize the necessity for long term investigations on outcome and progression of IFALD and clearer criteria and definitions for this type of liver disease.

In summary, the ESPGHAN NITE symposium on „Advances in Intestinal Failure In Children“ brought together experts from leading European Centers to discuss new strategies in management of this condition. As a spin-off of this meeting a platform for communication between experts will be established, new roles for established therapies were defined and the potential contributions of novel diagnostic tools and therapies were discussed. As the format of this meeting has been evaluated positively by its attendants a follow-up meeting will be organized in Geneva in 2016.