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Memorial Session Memorial Seminar for the late Prof. Akira Yamamoto

SL1-01 Remembrance of Dr. Akira Yamamoto

Mariko Harada-Shiba

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I met Dr. Akira Yamamoto for the first time when I was a graduate student. He was wearing a tremendous aura from being at the leading edge in the world at that time, after the First-in-Human Study of a statin and the development of lipoprotein apheresis. I became a postdoctoral fellow of the National Cardiovascular Center Research Institute, and started clinical and basic research on FH under Dr. Yamamoto. I was really surprised that Dr. Yamamoto gave us huge freedom in selecting research themes and how to proceed. For example, there was no check or rehearsal before any presentations at conferences. At one time, after I gave a presentation at a meeting, Dr. Yamamoto came to me and said, "You are working on an interesting theme!" I do not know any other boss who gives such huge freedom to the researchers. He has contributed to the establishment of the Japan Apheresis Society, the International Apheresis Society, and the Asian-Pacific Society of Atherosclerosis and Vascular Disease, and he was committed to the development of academic and medical sciences not only in Japan but also throughout the world. His First-in Human Study of a statin was the starting point, and statins have been shown to be effective in preventing atherosclerotic cardiovascular disease and have played a major role in public health worldwide. Patients with FH received tremendous benefit from statins improving their prognosis dramatically. Dr. Yamamoto's development of lipoprotein apheresis enabled selective removal of LDL for the treatment of homozygous FH. The therapeutic indication of lipoprotein apheresis is expanding to arteriosclerosis obliterans and focal glomerulosclerosis. The number of patients receiving benefits has been also increasing dramatically. Having learnt a lot under Dr. Akira Yamamoto, I will proudly continue to work on FH medical care. Dr. Akira Yamamoto, thank you very much.

SL1-02 In Memory of Prof. Akira Yamamoto

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Prof. Akira Yamamoto passed away on 7th January 2019. We were deeply shocked because the news of his death came so suddenly. He looked very well when we met him in October 2018, at the Annual Meeting of Japanese Society for Apheresis in Okayama. It became the last that we met him.

Prof. Yamamoto played a leading role in promoting the establishment of International Society for Apheresis.

Apheresis treatments had been globally and conventionally regarded as the topic in blood collection for transfusion, which had been mainly focusing on Donor Apheresis.

On the other hand, in Japan, the clinical studies and researches of the Therapeutic Apheresis had become popular because the late Prof. Yukihiko Nose and the late Dr. Noboru Inoue applied Membrane Separation into Apheresis treatments. Dr. Inoue had been leading Apheresis study in Tokyo, and Prof. Yamamoto had been developing Kansai Apheresis Society in Osaka at that



time. According to the effort of Dr. Inoue, et al from Tokyo, and Prof. Yamamoto, et al from Osaka, Japanese Society for Therapeutic Plasmapheresis was found in 1981.

It became the predecessor of current Japanese Society for Apheresis (found in 1992).

Moreover Prof. Nose proposed the necessity of the foundation of international society which aimed to spread and develop Therapeutic Apheresis, and started to promote it. In the way of the process, however, Dr. Inoue passed away. Prof. Yamamoto and Prof. Masashi Kodama succeeded this promotion as the leaders from Japan. They organized International Conference for Apheresis (ICFA) at Kyoto in 1996, and successfully achieved the establishment of International Society for Apheresis at that time. Prof. Yamamoto had served as the first President of International Society for Apheresis until 2001.

These are the photos from the 2nd World Congress of International Society for Apheresis in Saarbrücken in 1999. One, Prof. Yamamoto standing at the Opening ceremony. Another one, at the party. We can see Prof. Nose and Mrs. Nose, Prof. Yamamoto. We can also see the late Dr. Thomas Bosch at the table behind them, who came to study at Prof. Yamamoto's institution and became the 3rd President of ISFA.

This is the history that ISFA has been developing steadily since its establishment as the global society consist of the individual members.

We can remember his engaging gestures when he started to talk. He always started his talking with his shoulders shrugging and his head tilting. He got gentle and open-minded attitudes toward anyone. As soon as it came to his studies, however, he strictly faced to them with great emotion.

He made the outstanding achievement at the dawn of LDL Apheresis. Many junior researchers were encouraged by his instructions and his respectful attitude as well.

The scene still stays in our heart, that he always placed himself in the front row at the congress hall and evolved himself in passionate discussions even after he withdrew from the forefront of critical studies.

We believe that he is watching over us from the Heaven as ever and expecting ISFA to make a development as ever ...

Thank you so much for your long and great contribution. We all are proud of you. Rest in peace.

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Symposium 1 Current State of CAR-T Therapies in the World

SY1-01 Current Status of CAR-T Therapy in the United States

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Background: Harnessing the immune system to combat cancer, infectious disease, and other disorders has long been a dream. Advances in genetic engineering and cell manufacturing have made that dream a reality, at least in a subset of disease states. Specifically, cellular therapy utilizing chimeric antigen receptor-expressing T cells (CAR-Ts) have shown unprecedented success in treating certain CD19-expressing lymphoid malignancies. This presentation will discuss the mechanisms of action of CAR-T cells and current and future indications for use.

Methods: The design of first, second, and third generation CAR-T cell will be discussed. The landmark trials that led to approval by the Food and Drug Administration (FDA), as well as novel CAR-T studies will be highlighted. Finally, toxicities, specifically cytokine release syndrome and immune effector cell-associated neurotoxicity will be addressed.

Results: CAR-T cells are currently FDA-approved to treat pediatric and young adult B-cell precursor ALL, and relapsed or refractory large B-cell lymphoma. However, there are currently over 300 active CAR-T clinical trials listed on clinicaltrials.gov. Multiple myeloma appears closest to approval, though several targets for solid tumors are being investigated and may prove promising in the near future.

Conclusions: CAR-T therapy is an exciting advance in immunotherapy. However, challenges exist in the translation from bench to bedside. Despite these challenges, early clinical successes have proven that CAR-T technology can play an important in cancer therapy. Current and future investigations identifying targets beyond CD19 may provide opportunities to expand therapy to non-hematological malignancies.

SY1-03 Basic and clinical studies of CAR-T cell therapy in Japan

Keiya Ozawa, Ryosuke Uchibori, Ken Ohmine

Division of Immuno-Gene & Cell Therapy (Takara Bio.) Jichi Medical University, Tochigi, Japan

Adoptive immunotherapy with CAR (chimeric antigen receptor)-T cells is a promising cell-based anticancer therapy for hematological malignancies. Our group in Jichi Medical University conducted a clinical study of CD19-CAR-T cell therapy for malignant B-cell lymphoma in collaboration with Takara Bio, Inc. For the preparation of CAR-T cells, we utilized RetroNectin, a recombinant human fibronectin fragment, that consists of three functional domains (a cell-binding C-domain, a heparin-binding H-domain, and a CS-1 site), in place of a beads method using anti-CD3/anti-CD28 antibodies. RetroNectin-mediated activation (anti-CD3 antibody/RetroNectin) may be superior in an expansion of naive-like T cells (CD45RA+CCR7+), compared to anti-CD28 antibody-mediated activation. Clinical trials of CD19-CAR-T cell therapy are being conducted by several companies and a Nagoya University group. KYMRIAH (tisagenlecleucel) of Novartis Pharmaceuticals Co. was approved in Japan in March, 2019. Nagoya Univ group is utilizing a piggyBac transposon system in place of retroviral/lentiviral vector systems to suppress the cost for CAR-T cell preparation.



As for the basic study, we have developed an inducible promoter driven by activation signals from a CAR. Transgene expression in T cells transduced with the CD19-targeted CAR and inducible promoter-linked reporter genes (CAR-T/iReporter) was only induced by co-culture with CD19-positive target cells. This system also worked well in vivo using tumor-bearing mice. Our study indicated that the inducible promoter was selectively driven by activation signals from the CAR. This inducible gene system permits visualization and quantification of the activation status in CAR-T cells. This system will be valuable when additional genetic modification is needed to enhance the efficacy of CAR-T cells.

Symposium 2 LDL Registry

SY2-01 North American Lipoprotein Apheresis Registry (NALAR): Data collection design and rationale

Patrick M. Moriarty, Lauryn K. Gorby

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Objective: Develop a registry of patients undergoing lipoprotein apheresis (LA) in North America to promote awareness of LA treatment.

Background: Due to accessibility and insurance coverage, LA is not widely used in the United States, relative to other countries. Currently, it is unclear how many patients are receiving LA throughout the US and Canada. The development of a registry is critical to enable a comparison of patient outcomes in the US and Canada relative to other countries, to promote further coverage of LA for patients in the US and Canada.

Methods: The North American Lipoprotein Apheresis Registry (NALAR) is a multi-national, multi-center initiative that will track treatment regimen and clinical outcomes over a five-year period. This registry will use a prospective enrollment design with bi-annual follow-up. Patients will be identified by individual site providers based on receipt of LA therapy. General site data, excluding any PHI information will be collected separately to analyze the site utilization of LA therapy.

Conclusion: Currently pharmacotherapy does not always achieve goal lipid levels in patients. LA therapy can acutely reduce specific lipoproteins as well as other inflammatory markers and blood viscosity, when traditional pharmacotherapy has failed. For familial hypercholesterolemia (FH) patients, LA has been shown to significantly reduce Lp(a) and LDL-C levels by up to 70% and 67.5%, respectively, resulting in a reduction in CV events. Despite these findings, LA is underutilized in the U.S. and likely in other parts of the world. It is estimated, approximately 15,000 people in the U.S are maximally treated with pharmacotherapy and are at risk for premature CVD. Data collected will be used to determine the frequency of major cardiac events before and after initiation of LA. The goal of this registry is to develop a sustainable, extramurally funded registry of patients undergoing LA.

SY2-02 Registry of homozygous familial hypercholesterolemia

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Familial hypercholesterolemia (FH) is a genetic disease caused by pathogenic mutations in

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genes related to LDL receptor pathway such as LDL receptor, PCSK9 and apolipoprotein B. FH is characterized by high LDL-C levels from the childhood, cutaneous and tendon xanthomas and coronary artery disease caused by premature atherosclerosis. In order to prevent atherosclerosis in FH, early diagnosis and accurate treatment are mandatory. In most of the homozygous FH (HoFH), lipid lowering drugs are not effective because statins, ezetimibe and PCSK9 inhibitors reduce LDL-C levels via increase of LDL receptor activity. Therefore, in HoFH patients, lipoprotein apheresis has been the main treatment. In October 2009, HoFH was designated as a specified disease in the Specified Disease Treatment Research Program. Patient's data submitted for the application was obtained from the Ministry of Health and Welfare and analyzed. One hundred thirty HoFH patients' data was available including 65 males and 65 females. Cutaneous xanthoma was seen in 63%, tendon xanthoma 74%. 33.6% had aortic valve disease and 65.2% had coronary artery disease. PCI was performed in 36.5% and CABG was performed in 23% of the patients. Aortic aneurysm was prominent in 8.5% of the patients. Mean pretreatment levels of LDL-C were 450 ± 262 mg/dL. After drug treatment, LDL-C levels were reduced to 222 ± 100 mg/dL. By lipoprotein apheresis, LDL-C levels were decreased from 212 ± 108 to 52 ± 30 mg/dL. Statins and ezetimibe were used in 88% and 54% of the patients, respectively. Probucol, resin and fibrates were used in 28%, 20% 1.5% of the patients, respectively. Aspirin, ticlopidine hydrochloride and warfarin were prescribed in 35%, 8.5% and 6.9% of the patients, respectively. Japanese HoFH data shows that HoFH shows very severe phenotype and needs earlier diagnosis and treatment.

SA2-03 Current insights into the German Lipoprotein Apheresis Registry (GLAR,) more than 7 years on.

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Since 2005 an interdisciplinary German apheresis working group has been established by members of both German Societies of Nephrology. In 2009 the working group implemented the indication for lipoprotein apheresis (LA) as scientific basis of the registry including current cardiological dyslipidemia guidelines and current pathophysiological knowledge. In recent years the Federal Joint Committee (G-BA), a paramount decision-making body of the German health care system, required a reassessment of the approval of chronic lipoprotein apheresis therapy for regular reimbursement. In 2011 the German Lipoprotein Apheresis Registry (GLAR) was launched. All data were collected and analyzed during the time period 2012-2018. Over this time interval, 81 German apheresis centers collected retrospective and prospective observational data of 1,771 patients undergoing regular lipoprotein apheresis (LA) treatment due severe hypercholesterolemia and/or lipoprotein(a) (Lp(a))-hyperlipoproteinemia suffering from progressive cardiovascular disease (CVD). A total of 33,934 LA sessions were documented. All patients treated by LA exhibited a median LDL-C reduction rate of 68.4%, and a median Lp(a) reduction rate of 70.4%. In analogy to the Pro(a)LiFe study



results, patient data were analyzed and compared with respect to the incidence rate of major adverse coronary events (MACE) 2 years before the start of LA treatment (y-2) and prospectively five years on LA treatment (y+5). During the first years of LA treatment a MACE reduction of more than 78% was observed. In the years considered, LA treatment side effects occurred at a low rate (less than 3.0%) and mainly comprised vascular access problems. For the first time long-term real-world data generated by the GLAR show that LA lowers the incidence rate of cardiovascular events in patients with high LDL-C and/or high Lp(a) levels, progressive CVD and maximally tolerated lipid lowering medication. In addition, LA was found to be safe, exhibiting a low rate of side effects.

SY2-04 LDL apheresis in Heterozygous Familial Hypercholesterolemia : data from the French Registry of Familial hypercholesterolemia (REFERCHOL)

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Lipoprotein apheresis (LA) reduces concentrations of atherogenic lipoproteins and is commonly regarded as the final option for severe familial hypercholesterolemia (FH). In France, the indications for LA in heterozygous FH (HeFH) are low-density lipoprotein cholesterol (LDL-C) >200 mg/dL in primary prevention and >300 mg/dl in secondary prevention despite maximum-tolerated lipid-lowering treatment (LLT). The aim of the study was to evaluate if HeFH patients with LA indications were indeed treated with lipoprotein apheresis. The French Registry of FH gathers clinical and biological data from patients with HoFH or HeFH enrolled at 18 centers specialized in the management of FH. Among 1897 patients with HeFH enrolled retrospectively or prospectively from November 2015 to September 2018 who had attended a clinic visit within the previous 3 years, we identified 227 who fulfilled the criteria for lipoprotein apheresis. Of the 227 patients eligible to LA, 117 (51.5%) were men, median age was 56.0 years, and 128 (56.4%) were in secondary prevention; 119 (52.4%) patients were not receiving any LLT. Among the 227 patients, seventy-seven (33.9%) were receiving regular LA at their latest clinic visit.

Among patients with severe HeFH who are eligible for LA, two-thirds are not undergoing LA.

Symposium 3 Apheresis therapy for inflammatory bowel disease -Past, Present, Future-1

SY3-01 Leukocytapheresis as an Adjunct to Medication for Inflammatory Bowel Disease

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Inflammatory bowel disease: IBD is characterized by clinical remission and relapse due to severe intestinal inflammation and symptoms such as diarrhea, bloody stool, fever, and cramp. Efficacies of drugs therapies decrease with chronic use and sometimes have unpleasant side effects, and further, paradoxical reactions of bio-products are seen. This can represent a major

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difficulty in the long term management of this disease. In active IBD, leukocytes are elevated with activation behaviour, increased survival time and mucosal neutrophil level parallels the severity of intestinal inflammation and predicts relapse. Leukocyte-derived inflammatory cytokines are suspected to be major factors in the initiation and perpetuation of IBD. Accordingly, leukocytes should be appropriate targets for the therapy. To reduce peripheral leukocytes, centrifugation has been used to deplete them. However, it cannot remove enough. To overcome the limitations of centrifugation, membrane filters like the Cellsorba column and leukocyte adsorbing beads column like Adacolumn have been developed which are direct blood perfusion systems for removing activated leukocytes. In initial independent clinical studies, these two models have produced striking clinical efficacy, safety and a marked reduction in the dose of corticosteroids used to induce remission of active IBD. Leukocytapheresis has been associated with a significant decrease in the amount of several pro-inflammatory cytokines produced by leukocytes. Clinical data suggest that leukocytapheresis might be an effective adjunct to therapy of IBD, to promote remission, taper conventional drug dosage, recover from their secondly ineffectiveness of Bio-products, and remove their paradoxical reaction too, therefore potentially should reduce the number of patients who require colectomy. The results should be confirmed by further clinical studies and be understood the pathogenesis of IBD.

SY3-02 Granulomonocytapheresis as therapeutic option of IBD in Europe

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Ulcerative colitis (UC) and Crohn's disease (CD) are major phenotypes of the chronic inflammatory bowel disease (IBD), which afflicts millions of individuals throughout the world with debilitating symptoms. The chronic nature of IBD means that patients require life-long medications, and this may lead to drug dependency, loss of response together with adverse side effects as additional morbidity factors. The efficacy of antitumour necrosis factor (TNF)- α biologics has validated the role of inflammatory cytokines notably TNF- α in the exacerbation and perpetuation of IBD. However, cytokines are released by myeloid lineage leukocytes like the CD14+ CD16+ monocyte phenotype. Additionally in IBD, myeloid leukocytes are elevated with activation behavior, while lymphocytes are compromised. Therefore, patients' leukocytes appear logical targets of therapy. Adsorptive granulomonocytapheresis (GMA) with an Adacolumn uses carriers, which interact with the Fc γ receptor expressing leukocytes and deplete the elevated myeloid leukocytes, while the neutrophils, which re-enter the circulation via the Adacolumn outflow ($\geq 40\%$) are phagocytosed by CD19 B-cells to become interleukin (IL)-10 producing Bregs or CD19high CD1Dhigh B-cells. IL-10 is an anti-inflammatory cytokine. GMA has been applied to treat patients with IBD. The efficacy outcomes have been impressive as well as disappointing, the clinical response to GMA defines the patients' disease course and severity at entry. Efficacy outcomes in patients with deep ulcers together with extensive loss of the mucosal tissue are not encouraging, while patients without these features respond well and attain a favorable long-term disease course. Accordingly, for responder patients, GMA fulfills a desire to be treated without drugs.



SY3-03 **Adsorptive Granulocyte and Monocyte Apheresis in the Treatment of Inflammatory Bowel disease : The First Multicenter Study In China**

Yamin Lai

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Background/Aims: Patients with active ulcerative colitis (UC) have elevated levels of activated myeloid-derived leukocytes as a source of inflammatory cytokines. The selective depletion of these leukocytes by adsorptive granulocyte/monocyte apheresis (GMA) with an Adacolumn should alleviate inflammation, promote remission and enhance drug efficacy. However, studies have reported contrasting efficacy out- comes based on patients' baseline demographic variables. This study was undertaken to understand the demographic features of GMA responders and non-responders.

Methods: This was a multicenter study in China involving four institutions and 34 patients with active UC. Baseline conventional medications were continued without changing the dosage. The treatment efficacy was evaluated based on the endoscopic activity index and the Mayo score.

Results: Thirty of the 34 patients completed all 10 GMA treatment sessions. The overall efficacy rate was 70.59%. The receiver operating characteristic analysis showed that the area under the curve was approximately 0.766 for a Mayo score of ≤ 5.5 with 0.273 specificity and 0.857 sensitivity (Youden index, 0.584) for GMA responders. No GMA-related serious adverse events were observed.

Conclusions: The overall efficacy of GMA in patients with active UC who were taking first-line medications or were corticosteroid refractory was encouraging. Addition- ally, GMA was well tolerated and had a good safety profile.

SY3-04 **Real-world experiences of cytapheresis therapy for ulcerative colitis; results from large-scale multicenter observational studies**

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There are two types of extracorporeal therapy for treating active ulcerative colitis (UC), granulocyte and monocyte adsorption (GMA) and leukocytapheresis (LCAP). Although Sawada et al reported the efficacy of LCAP by the randomized controlled trial (Sawada K et al. *Am J Gastroenterol* 2005), the larger sham-controlled multicenter trial of GMA failed to prove its efficacy (Sands BE et al. *Gastroenterol* 2008). Therefore, evidence to show their efficacy relies more on the real-world data, including the post-marketing surveillance (PMS). The large-scale PMS for LCAP was named as REFINE study, involving 847 patients from 116 medical facilities in Japan (Yokoyama Y, Kobayashi T et al. *J Crohn Colitis* 2014). Adverse events were seen only in 10.3% and the vast majority were mild. The overall clinical remission rate was 68.9%, and the mucosal healing rate was 62.5%. These results were very consistent with the results from

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PMS of 697 patients treated with GMA, which also demonstrated its real-world effectiveness and safety (Hibi T et al. *Dig Liver Dis* 2008). In addition, a retrospective observational study aimed to evaluate the clinical outcome at 1 year and identify risk factors for relapse after LCAP was recently conducted among patients who had achieved remission in the PMS (Kobayashi T et al. *J Gastroenterol* 2018). The 1-year cumulative relapse free rate was 63.6%. Following LCAP, a high clinical activity and a high leukocyte count were associated with a greater risk of relapse. Intensive LCAP was associated with favorable long-term outcomes in corticosteroid-refractory patients. The response rate of re-treatment upon relapse was as high as 85%. These results on the risks of relapse as well as effectiveness of re-treatment may help to overcome the weakness of cytapheresis therapy in maintaining remission. Results from the clinical trial evaluating the clinical efficacy of intermittent maintenance cytapheresis therapy are also warranted.

SY3-05 Factors affecting clinical remission in patients with ulcerative colitis treated with cytapheresis therapy

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Backgrounds: Cytapheresis therapy is a treatment of choice among patients with ulcerative colitis (UC). We retrospectively investigated patients with UC treated with cytapheresis therapy to elucidate the prognostic factors suggesting clinical remission.

Methods: Total 52 sessions (41 cases) were enrolled from July 2010. The clinical activity of UC is assessed by using Mayo score. Clinical remission was defined as partial Mayo score 2 or less with each subscore 1 or less when ending a session of cytapheresis therapy. The endoscopic severity at the start of cytapheresis therapy was assessed by using Mayo endoscopic subscore and ulcerative colitis endoscopic index of severity (UCEIS).

Results: Forty one of 52 sessions were started with intensive schedule. Average number of apheresis therapy in one session is 8. Clinical remission was obtained in 24 sessions (46%). Concomitant prednisolone (more than or equal to 20 mg/day), partial Mayo score at the start 6 or less, full Mayo score at the start 10 or less, UCEIS 6 or less were indicative factors of clinical remission.

Conclusion: Our results indicate that the cytapheresis therapy should be selected among patients with relatively mild disease and endoscopic activity with concomitant prednisolone more than or equal to 20 mg/day.

Symposium 4 Apheresis therapy for inflammatory bowel disease -Past, Present, Future-2

SY4-01 A novel leucoyte apheresis adsorption system in refractory active ulcerative colitis

Wolfgang Kruis

Evangelisches Krankenhaus Köln Kalk (Formerly active as chief physician), Germany

Background and aims: In active ulcerative colitis (UC) refractory to mesalazine (Mes) escalation to either steroids or immunosuppression is common practice. Both treatments confer



considerable risks and side effects. We have studied the efficacy and safety of an alternative escalation therapy with a newly developed leucocyte apheresis device.

Patients and Methods: This was a prospective, randomized, controlled multicentric pilot study to compare a novel leucocyte apheresis device (Immunopure™) with prednisolone in active UC (DAI ≥ 4 and ≤ 8) refractory (3g/d for at least 2 weeks) or intolerant to Mes. Additional inclusion criteria were MAYO endoscopic score ≥ 1 , histologic score (Riley) ≥ 2 , peripheral venous access allowing apheresis. Group A received weekly leucocyte apheresis over 5 consecutive weeks. Group P received oral prednisolone 40 mg/d which was tried to taper to 0 mg at week 6. The Mes dose at start was continued throughout the whole study period. Other concomitant treatments were not allowed. The primary endpoint was steroid-free clinical remission (DAI ≤ 2) at week 12. Clinical response (DAI ≥ 1) and numerous other second endpoints were analysed. Statistical analyses were performed using t-tests after testing for normal distribution.

Results: A total of 24 patients were enrolled, 13 of which were randomized into group A (apheresis), and 11 into group P (prednisolone). Three patients were not started for missing inclusion criteria, resulting in 21 patients for intent-to treat (ITT) analysis. Both groups matched very well for biographic and clinical characteristics.

In clinical remission and without steroids at week 12 were 3/12 patients (25.0%) with apheresis and 2/10 (20.0%) in the prednisolone group ($p=1.0$). Response rate after 12 weeks was 75.0% in group A and 50.0% in group P ($p=0.3$). The mean DAI scores improved in both treatment groups significantly ($p=0.008$) over the study period. In group A it decreased from 7.6 ± 1.1 at baseline to 4.2 ± 2.6 at week 12, while in group P it decreased from 7.6 ± 1.9 to 4.7 ± 3.0 .

CRP decreased from 6.0 ± 5.3 mg/l to 3.8 ± 3.7 mg/l at 12 weeks in group A and increased from 5.2 ± 6.0 mg/ml to 6.3 ± 7.9 mg/ml in group P (all differences $p > 0.05$).

Both treatments were well tolerated. No unexpected serious adverse events were seen in group A. During apheresis transient decreases of leucocytes and platelets were observed. In group P one symptomatic infection with *C. difficile* was diagnosed.

Conclusions: In patients with active UC in need for treatment escalation after failing Mes the novel leucocyte apheresis is a promising option. A comparison with standard prednisolone revealed similar therapeutic effectivity of apheresis, excellent safety and the chance to treat without the unwanted side effects of systemic steroids.

SY4-02 Safety and efficacy of single needle leucocyte apheresis for ulcerative colitis: A retrospective analysis

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Introduction: Leucocyte apheresis (LCAP) is an effective treatment strategy for active ulcerative colitis (UC) in Japan. The single needle (SN) apheresis reduces the needle puncture pain for the patients because it has one puncture site. We examined the safety of SN apheresis in order to reduce the patient burden.

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Method: We performed a retrospective study of active UC patients who were treated with either SN apheresis or conventional double-needle (DN) apheresis at the Kurume university hospital from February 2014 to March 2018. All the patients treated with LCAP (Cellsorba EX; Asahi Kasei Medical Co., Tokyo, Japan) after September 2016 underwent SN apheresis. We retrospectively compared the safety and efficacy between SN- and DN apheresis.

Result: Twelve patients underwent SN apheresis, and 12 underwent DN apheresis. The average time to the start of apheresis was significantly reduced to 19.4 minutes for DN apheresis and 10 minutes for SN apheresis. In addition, the number of difficult punctures was significantly reduced with SN apheresis. There were no differences in the adverse events between SN- and DN apheresis. There were similar trends for treatment benefits to remission rate and disease activity between the SN- and DN apheresis.

Conclusion: SN apheresis showed no difference in the number of blood clotting episodes; it reduced both the time to treatment initiation and pain during puncture. Although further comparative studies are needed, SN apheresis may be a safe alternative for patients to reduce the strain of treatment.

SY4-03 The efficacy of combination therapy of intensive GMA with biologics or a JAK inhibitor for refractory inflammatory bowel disease

Satoshi Tanida

Department of Gastroenterology and Metabolism, Japan

Background and Aim: A monotherapy with intensive GMA, biologics or a JAK inhibitor are limited in patients with intractable Crohn's disease (CD) or ulcerative colitis (UC). We retrospectively evaluated the 10- and 52-week efficacy and safety of combination therapy of intensive GMA with biologics or a JAK inhibitor for intractable UC or CD.

Method: A combination of intensive GMA (2 sessions a week, total 10 times) with tofacitinib (TOF) for active UC was performed and that of intensive GMA with ustekinumab (UST) for active CD was done.

Results: Of 6 consecutive UC patients receiving a combination therapy of TOF (20 mg daily for 8 weeks as induction therapy and subsequently 10 mg daily) plus intensive GMA for moderately-to-severely active UC and loss of response to corticosteroids, azathioprine, and/or biologic therapies, 67% (4 cases) displayed clinical remission according to Mayo score and 100% displayed mucosal healing at 10 weeks. A temporary increase in CPK were seen. Of 5 consecutive CD patients receiving a combination therapy of ustekinumab (every 8 weeks) plus intensive GMA for moderately-to-severely active CD and loss of response to corticosteroids, azathioprine, and/or biologic therapies, 75% displayed cumulative steroid-free clinical remission at 10 weeks and did such remission over 52 weeks under subsequent maintenance monotherapy of UST. The mean CDAI at baseline were 257. Its values at 10 and 52 weeks after the combination therapy with UST plus intensive GMA were 48 and 68, respectively. One case showed mucosal healing at 52 weeks according to SES-CD. No adverse events were observed.

Conclusions: Combination therapy of intensive GMA with biologics or a JAK inhibitor appeared to be effective and safe for refractory UC or CD.



SY4-04 Efficacy apheresis as maintenance therapy for patients with ulcerative colitis in a prospective multicentre randomised controlled trial

Makoto Naganuma

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Background/Aim: Apheresis therapy involves the selective removal of leukocytes and is used to induce remission in patients with ulcerative colitis (UC). The aim of this study was to demonstrate the efficacy and safety of apheresis therapy for maintaining UC remission.

Methods: We conducted a multicentre, prospective, randomised-control trial of patients with remitting UC induced by granulocyte or monocyte adsorption apheresis or leukocytapheresis. Patients were randomly assigned to the apheresis group (receiving apheresis treatment, twice per month, for 12 months) or the control group (without apheresis treatment), using a 1:1 allocation ratio. The primary end-point was the rate of cumulative clinical remission (Mayo score of 0-2) at 12 months. The secondary end-points were the rate of clinical remission, endoscopic remission (MES of 0-1), and complete endoscopic remission (MES=0) at 12 months.

Results: Between March 2013 and March 2017, 164 patients were enrolled. The cumulative remission rate at 12 months was 51.3% and 42.0% in the apheresis and control group, respectively ($p=0.1621$), and the rates of endoscopic remission of 42.5% and 25.9%, respectively ($p=0.0480$) at 12 months were significantly higher in the apheresis than the control group. Multiple logistic regression analysis confirmed a positive association between apheresis and clinical remission (Hazard ratio (HR): 0.45 (95% confidence interval (CI) 0.20-0.98)), endoscopic remission (HR 0.45 (95%CI 0.20-0.99)), and complete endoscopic remission (HR 0.38 (95%CI 0.15-0.96)) at 12 months. No severe adverse events were observed.

Conclusion: This is the first randomised controlled trial to evaluate the efficacy of apheresis therapy for maintaining clinical and endoscopic remissions. Apheresis was well tolerated as maintenance therapy for UC and provided beneficial effects to maintain clinical and endoscopic remission. Apheresis may be useful for maintaining remission in patients at high risk of infections, including elderly patients.

Symposium 5 Advancement of Apheresis in Dermatology

SY5-01 Granulocyte and monocyte adsorption apheresis for generalized pustular psoriasis

Mariko Seishima

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Generalized pustular psoriasis (GPP) is a rare inflammatory skin disorder characterized by a fever, edema, and generalized erythema with neutrophilic pustules. It sometimes occurs in the course of psoriasis vulgaris, or develops suddenly without any history of psoriasis. Mutations of the *IL36RN* (deficiency of interleukin thirty-six receptor antagonist: DITRA), *CARD14* and *APIS3* genes underlie monogenic auto-inflammatory disorders causing GPP. GPP patients are usually treated with oral administration of etretinate, cyclosporine, and methotrexate, biologics including TNF α inhibitors, antibodies to IL-17, IL-17 receptor, and IL-23 p19, and

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granulocyte and monocyte adsorption apheresis (GMA). Cyclosporine, TNF α inhibitors, and GMA are used for GPP in pediatric, pregnant, or lactating patients. GMA is an extracorporeal apheresis that removes activated granulocytes and monocytes using a column packed with cellulose acetate beads. Multicenter study was performed to assess efficacy of selectively depleting the myeloid lineage leukocytes in GPP patients. Fifteen patients with persistent moderate to severe GPP despite conventional therapy were included. Based on the GPP severity scores relative to entry, the overall scores improved, and the area of erythroderma, pustules, and edema decreased. Likewise, Dermatology Life Quality Index (DLQI) improved, reflecting better daily function and quality of life. Twelve out of 14 patients were judged as responders (85.7%), and 10 out of 12 patients maintained the clinical response for 10 weeks after the last GMA session without any change in medication. Thus, GMA is estimated to be safe and effective, suggesting a major role of granulocytes/ monocytes in the immunopathogenesis of GPP. Recent study showed that GMA was effective for 100% of DITRA patients and for 64.7% of the patients with IL36RN mutation-negative GPP. Thus, GMA is effective therapy for both DITRA and non-DITRA GPP patients. GMA may be a useful therapy for all GPP patients.

SY5-02 Granulocyte and monocyte adsorption apheresis for psoriatic arthritis

Takuro Kanekura

Department of Dermatology, Kagoshima University, Kagoshima, Japan

Adsorptive granulocyte and monocyte apheresis (GMA) with the Adacolumn is an extracorporeal treatment, which uses cellulose acetate (CA) beads as adsorptive leucocytapheresis carriers designed to remove elevated and potentially activated myeloid lineage leukocytes. Case series studies on the clinical effectiveness of GMA on skin diseases and associated arthropathy attributable to activated myeloid lineage leukocytes returned remarkable outcome without any serious adverse events. Psoriatic arthritis (PsA) is a chronic inflammatory arthropathy associated with psoriasis. PsA is an intractable immune disorder and refractory to pharmacological intervention. Efficacy of selective depletion of myeloid lineage leukocytes in patients with PsA was assessed in a multicenter setting. A total of 20 patients with moderate to severe PsA refractory to conventional and biological disease-modifying anti-rheumatic drugs were enrolled. Each patient received 5 sessions of GMA once a week. The primary efficacy outcome was 20% or more decrease in the American College of Rheumatology score 20 (ACR20). Partial responders received an additional 5 GMA sessions. Of 20 patients, 2 did not complete the study, 9 responded to 5 GMA sessions and 9 received 10 sessions. At the first evaluation 2 weeks after the last GMA session, 13 of the 20 (65.0%) patients achieved ACR20. ACR20 was maintained in 7 of 10 (70%) and 5 of 10 (50%) patients at the follow-up evaluation points 8 and 20 weeks after the last GMA session, respectively. GMA was well tolerated without any safety concern. This multicenter study demonstrated that GMA was effective with good safety profile in patients with PsA refractory to pharmacologicals. In this presentation, I will present the results of this study and mode of action of GMA.

SY5-03 Extracorporeal Photopheresis Treatment for Dermatological Diseases

Chisa Yamada

Transfusion Medicine, Department of Pathology, University of Michigan, Ann Arbor, Michigan, USA

Background: The first extracorporeal photopheresis (ECP) treatment on patients with



cutaneous T-cell lymphoma (CTCL) was published in 1987 and the procedure was approved by the FDA in 1988. Since then, trials with ECP treatment have been conducted for many other diseases and it has now been performed over 2 million procedures at more than 300 centers worldwide. This presentation will discuss the mechanisms of action of ECP and the ECP treatments for dermatological diseases.

Methods: Dermatological diseases for which an efficacy of ECP treatment was evaluated in new ASFA guidelines published in 2019 will be discussed. In addition, several reports of ECP treatments on dermatological diseases will be reviewed briefly.

Results: Dendritic cells (DCs) are taking important roles in bidirectional effects created by ECP treatment; immunity and tolerance. Good example of active immune response leading to anti-tumor effect by ECP for dermatological diseases is CTCL, and tolerance effect is graft-versus-host disease (GVHD). The majority of reports for ECP treatments are performed for those two conditions. Several other dermatological conditions, such as psoriasis, scleroderma, atopic dermatitis, pemphigus vulgaris, epidermolysis bullosa acquisita, lichen planus, and others have been treated by ECP with variable outcomes. The numbers of available literatures for these are limited however.

Conclusions: ECP treatment can create bidirectional effects on the immune system and DCs are important to explain the mechanisms of action of ECP. ECP treatments are applied for CTCL and GVHD in majority of the reports available. Although the number of reports is limited, several other dermatological diseases have been treated with ECP with variable outcomes.

SY5-04 Autologous Hematopoietic Stem Cell Transplantation for Treatment of Severe Systemic Sclerosis

Mark Wener

University of Washington, Department of Laboratory Medicine & Division of Rheumatology, USA

Background: Systemic sclerosis (SSc, also known as scleroderma) is an autoimmune disease with hallmark features of vascular abnormalities such as Raynaud's phenomenon, localized and systemic inflammation, and fibrosis in affected organs. Internal organ involvement can include interstitial pulmonary fibrosis, myocarditis, hypertension with severe rapidly progressive renal failure, and significant gastrointestinal disease with malabsorption. When severe, these manifestations are life-threatening and unresponsive to conventional treatments.

Methods: Data from 3 randomized controlled trials (RCTs) of autologous hematopoietic stem cell transplantation (aHSCT) will be reviewed and presented. Methods of harvesting and preparation of the transplanted cells will be reviewed, including use of CD34 cell selection in 2 of the 3 studies.

Results: Three randomized controlled trials (ASTIS multi-center European randomized controlled trial, SCOT multicenter US RCT, and ASSIST single-center U.S RCT) of aHSCT have been published, and each has demonstrated significant improvement in patients treated with aHSCT, in comparison with cyclophosphamide. Published metanalysis of those 3 RCTs (supplemented by data from an Italian retrospective analysis series) reported that the 143 patients treated with aHSCT had lower overall mortality (risk ratio 0.5) and improved pulmonary function, skin score, and quality of life. Long-term followup has demonstrated clinically significant and sustained improvement. However, the treatment is expensive, and has the potential for substantial morbidity. Some example cases the presenter has personally cared for will be presented.

Conclusions: Hematopoietic stem cell transplant, either with or without CD34 selection, has

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been proven to be more effective than cyclophosphamide in selected patients with severe systemic sclerosis.

Symposium 6 PDF SESSION I

SY6-01 The improvement of acute kidney injury by plasmadiafiltration on sepsis animal model

Jianda Lu¹⁾, Mingxin Li¹⁾, Junfeng Liu¹⁾, Wei Wang¹⁾, Peng Sun²⁾,
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Objective: To investigate whether the plasmadiafiltration (PDF) improve the renal function of sepsis.

Methods: All 20 sepsis models were made by cecum ligation perforation (CLP). They were divided into PDF (group A) and the common CVVHD (group B). The group A received 8 hours of PDF everyday. While the group B received 24 hours CVVHD everyday. The inflammatory mediator concentration of TNF-a, HMGB1 and IL-6 in the blood were detected at the 0, 4, 8, 16, 24, hours from the start of blood purification.

Results: Circulating inflammatory mediators concentration of group A was lower than group B. The odds ration of cytokines decrease by PDF in TNF-a, HMGB1 and IL-6 was 1.97(1.64-2.51 95%CI, p=0.012), 1.97(1.67-2.46 95%CI, p=0.007) and 1.70(1.33-2.70 95%CI, p=0.047), respectively. There was a linear relationship between the urine volume changes and IL-6 by Cox regression analysis (p=0.045). The result also found that each increase unit of IL-6 was associated with a 0.348 ml/kg/h urine volume decrease under the fixed level of cytokine. And the Cox regression showed that the kidney end point event risk of group A was 0.197 times of group B (p=0.029). And the median end point time in PDF group and the CVVH group was 31 and 25 hours, meanwhile the mean end point time in PDF group and the CVVH group was 31.4 and 25.7 hours, respectively (P=0.005 by Log-rank test).

Conclusions: The PDF Treatment effectively removed macromolecular plasma inflammatory mediators, and thus protected the sepsis animal kidney function.

SY6-02 Plasma adiponectin levels in acute liver failure patients treated with plasma filtration with dialysis and plasma exchange

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3) Department of Surgery, Konan Hospital, Japan

4) Department of Critical and Intensive Care Medicine, Shiga University of Medical Science, Japan

Background: Adiponectin (APN), which is an adipose tissue-derived hormone, is known as an anti-inflammatory cytokine. The effects of APN on the production of inflammatory mediators and hepatic injury during polymicrobial sepsis were evaluated using APN-knockout mice. Plasma filtration with dialysis (PDF) is a blood purification therapy in which simple plasma exchange (PE) is performed using a selective membrane plasma separator while the dialysate



flows outside of the hollow fibers. Improvement of hypoalbuminemia is considered to be a useful therapeutic approach for ameliorating fatal conditions including cardio-metabolic and infectious disease.

Material and Methods: We investigated the effects of PDF in comparison to PE in terms of plasma adiponectin (APN) changes in patients with acute liver failure (ALF). Seventeen patients with liver failure were studied. PDF was performed 55 times and PE 14 times. Blood samples for assay of plasma APN were collected at the start and immediately after each plasmapheresis session into endotoxin-free heparinized blood-specimen tubes.

Results: Plasma APN levels increased significantly after PDF, while decreasing significantly after PE. In pre-treatment levels before PDF, no significant difference was observed between plasma APN levels in survivors and those in non-survivors. Plasma APN levels in survivors increased significantly after treatment.

Conclusion: PDF appears to be useful blood purification therapy for ALF in terms of increasing plasma APN levels.

SY6-03 PDF procedure induce IL-10; a case report

Yutaka Eguchi

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Introduction; We have previously reported on the effectiveness of plasma filtration with dialysis (PDF) in patients with acute liver failure (ALF) (Ther Apher Dial. 14(5);444-50, 2010), presented that PDF procedure decreased cytokines, and discussed that PDF may be the useful blood purification therapies in terms of the removal of low- or intermediate-molecular-weight substance, such as water-soluble and albumin-bound toxins. Haptoglobin (MW;100kDa) is produced in the liver, secreted into the circulation bound as an extracellular high mobility group box 1 (HMGB-1)(MW;30kDa) isolating acute phase protein via CD163. Recently, HMGB-1-haptoglobin β complexes were found to be anti-inflammatory effects induced through the CD163-mediated L-10 (MW;35-40kDa) release in a mouse model (J Intern Med 2017;282:76-93).

Case Report; A 49-year-old man was admitted to a hospital, then several day after, he was transferred to our ICU. He showed sepsis-induced ALF, therefore, PDF was immediately performed for 3 session. He regained liver function. He was diagnosed with amyloidosis, then died of heart failure on the 7th hospital day. We measured IL-6, IL-8 and IL-10 before and every after PDF procedure. The serum levels of IL-6 and IL-8 decreased continuously, however, those of IL-10 increased conversely.

Discussion; We measured haptoglobin and cytokines obtained from a patient (n=28) with sepsis within 24 hours after admission in 2017. All of the patients over the haptoglobin level 120 mg/dl has survived for 28 days after entering ICU (SHOCK 51, supplement1;48, 2019). These findings suggest that low level of haptoglobin may produce freedom HMGB-1 that deteriorate prognosis in patients with sepsis.

Conclusion; PDF procedure may be efficacious, especially for the patients with low level of haptoglobin, because supplementaion of FFP add haptoglobin, and the Evacure EC-2A plasma separator preserve HMGB-1-haptoglobin β complexes that induce IL-10, and remove freedom HMGB-1. Further study is required.

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SY6-04 Utility of the novel artificial liver support combination therapy, PDF with high flow-volume CHDF

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Manabu Kakinoana

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Liver transplantation is one of the prominent therapeutic option but it is limited. We should choose some artificial liver support systems and carry out these. However there are no complete artificial liver support systems. The important point is how to replace the liver functions, “detoxification” and “synthesis”. Novel artificial liver support system, plasma filtration with dialysis (PDF) is established in Japan. The plasma separator made of ethylene vinyl alcohol (Evacure2A) is chosen for PDF system. Usually some amount of fresh frozen plasma (1800ml) is necessary at one PDF session. We spent eight hours in a session. The PDF can maintain own fibrinogen in patients. And the PDF can remove a certain amount of albumin and small molecule that is the cause of hepatic encephalopathy. High flow-volume continuous hemodiafiltration has established a firm position about artificial liver support systems to manage hepatic encephalopathy. However high flow-volume continuous hemodiafiltration cannot replenish the clotting factors. For the reason simple plasma exchange (PE) therapy and/or FFP infusion therapy are simultaneously used with high flow-volume continuous hemodiafiltration (CHDF). These combinations, PE+CHDF often lost their clotting status adjustment. Combination therapy of PDF and high flow-volume continuous hemodiafiltration are quite effective treatment. Because high flow-volume CHDF can remove the hepatic encephalopathic molecule. In the meantime the PDF can replenish the clotting factors especially fibrinogen. The therapeutic systems are simple and less fresh frozen plasma volume at one session. We can recommend the novel combination therapy, PDF and high flow-volume CHDF in terms of the utility and the patient safety.

SY6-05 High flow-volume plasma filtration with dialysis and plasma exchange with dialysis

Hajime Nakae, Kasumi Satoh, Yasuhito Irie, Tomoki Furuya, Manabu Okuyama

Department of Emergency and Critical Care Medicine, Akita University Graduate School of Medicine, Japan

Selective plasma exchange (SePE) with dialysis (PED) is an apheresis by which simple plasma exchange is performed by using a selective membrane plasma separator (Evacure EC-2A with an albumin-sieving coefficient of 0.3) while the dialysate flows out of the hollow fibers. Our two experimental studies showed that PED therapy using EC-4A with an albumin-sieving coefficient of 0.4 was found to be equivalent or superior to direct hemoperfusion and SePE for the removal of phenobarbital and lithium, and that the removal rates of the substances in PED using EC-4A was higher compared with those in plasma filtration with dialysis (PDF) using EC-2A, while maintaining the serum albumin concentration. PED with EC-4A may be applied to acute poisoning and severe acute pancreatitis, as well as acute liver failure and septic shock.



SY6-06 Continuous plasmfiltration with dialysis (CPDF)

Takumi Taniguchi

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Plasma Filtration with Dialysis (PDF) is the blood purification therapy in which simple plasma exchange is performed using a selective membrane plasma separator while the dialysate flows outside the hollow fibers. Several studies demonstrated that PDF therapy is one of the most useful blood purification therapies for use in cases of acute liver failure or severe sepsis. However, PDF therapy is very difficult to undergo in septic shock and/or hypovolemic shock patients with acute liver failure because of unstable hemodynamics. Moreover, it is likely to deteriorate in acute liver failure immediately after PDF or Plasma Exchange therapy. We have experienced that new method which is known as continuous PDF (CPDF) therapy can undergo in unstable patients with acute liver failure. Presenter explains the indications, methods, and problems of CPDF and reports two cases that underwent CPDF because of acute liver failure.

Symposium 7 PDF Session II

SY7-01 Comparison of selective plasma exchange, plasma diafiltration, MARS and Prometheus systems in treatment of liver failure

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Currently clinicians have a new type of membrane devices - Evaclio plasma separators (Kawasumi Laboratories, Japan). In this study we compared clinical and laboratory effects of selective plasma exchange (SPE) on Evaclio 2C20, 3C20, 4C20, plasma diafiltration (PDF) on Evaclio 2C10 and MARS and Prometheus systems (FPSA) in patients with hepatic insufficiency.

Materials and methods: In each case 15 extracorporeal procedures were performed. Concentrations of direct and indirect bilirubin, albumin, creatinine, urea were determined before and after the session, the next morning state was evaluated by MELD score.

Results and discussion: Direct bilirubin was best reduced by SPE on Evaclio 3C20 - 44%, on Evaclio 4C20 - 36%, FPSA - 39%; indirect bilirubin - by SPE on Evaclio 3C20 - 42%; creatinine and urea by PDF - 45 and 41%, respectively, and FPSA - 43 and 41%, respectively. The concentration of albumin decreased by SPE on Evaclio 4C20 - 10%, FPSA - 8%, by SPE on Evaclio 2C20 it increased - 25%. The next morning state on the MELD score decreased with FPSA - 8.6%, PDF - 9.5%, SPF on Evaclio 4C20 - 8.3% and when using MARS - by 7.2%. Significant differences in the changes in the concentration of indicators were absent, with the exception of the increase in the concentration of albumin in the SPE at 2C20.

Conclusions:

1. SPE with Evaclio 2C20, 3C20, 4C20, PDF with Evaclio 2C10 are generally comparable

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with liver failure treatment by MARS and Prometheus system at the significantly lower cost despite minor's differences.

2. When using FPSA and PDF LMW substances - urea and creatinine - are removed better.
3. The least amount of albumin solutions and FFP is necessary with Prometheus system, the highest - with SPE's on Evaclio 4C20, 3C20. When using MARS, Evaclio 2C20 and Evaclio 2C10, the number of required albumin solutions and FFP is comparable.

SY7-02 Safety Management in Plasma Diafiltration

Maki Kagitani

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There are various unexpected issues with introducing a new mode of the Plasma filtration with dialysis (PDF) therapy. In PDF, a plasma exchange using a selective membrane plasma separator is performed with dialysis. PDF is effective for acute liver failure and other critical diseases. Recently, several improved PDF modes have been developed, and we expect that PDF will be used more widely in intensive care units (ICUs) or critical care units (CCUs). When a new medication mode like as PDF is introduced, recognizing and preparing for possible side effects, limitations due to the equipment and expected problems really need for each facility and staffs. In this report, we discuss the problems we encountered and other potential issues, in particular, the difference of machines, detailed apheresis modes, replacement fluid and the scheduling issue, providing a kick-off guide to those medical facilities which are newly starting the PDF therapy.

SY7-03 Artificial liver support for liver transplant recipients during perioperative period

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The combined evolution of artificial liver support (ALS) and liver transplantation (LT) has substantially affected the treatment of liver failure and changed the perioperative therapeutic strategy of LT. Irreversible hepatic encephalopathy must be prevented and infectious complications must be avoided, because such complications are contraindications to LT. Therefore, preparation of patients for LT (registration of patients on the waiting list for deceased-donor LT and exploration of the possibility of living-donor LT) using effective ALS to prevent encephalopathy is important under adequate collaboration with the transplant team. We introduce plasma diafiltration (PDF) for perioperative ALS from 2009. Plasmapheresis, including PDF were safely introduced in perioperative period of LT. Also, PDF had certain therapeutic effects as ALS in postoperative periods of LT for coagulopathy and jaundice. On the contrary, the prognosis of the LT cases, which need prolonged ALS was still poor. ALS including PDF is effective as 'bridging therapy' for LT recipients, until re-transplantation or graft regeneration. Although, in the situation of donor shortage, evolution of ALS could not directly improve prognosis of LT recipients, who need ALS. For end stage liver disease patients, evolution of liver transplantation and ALS are both indispensable to improve prognosis.



SY7-04 Multicenter Study of Plasma filtration with dialysis (PDF) in Patients with Acute Liver Failure

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We previously reported the 28 and 90-day survival rates were 70.0% and 16.7% in patients with acute liver failure (ALF), respectively (Ther Apher Dial. 14(5):444-50, 2010). A nationwide survey of ALF in Japan based on the new criteria has been proposed that patients showing prothrombin time (PT) values of 40% or less of PT-INR of 1.5 or more caused by severe liver damage within 8 days of onset are diagnosed as having ALF, and classified into two types in which no hepatic coma and grade II or more hepatic coma develops within 10 days (Hepatol Res. 41(9):805-12,2011). Therefore, according to these criteria, we carried out a plasma filtration with dialysis (PDF) from Oct. 2012 to Jan. 2014 in various centers for 59 without coma and 5 patients with coma of ALF, expect for cases of liver transplantation. The survival rate at 28 days was the primary endpoint of the study. We evaluated 28 days survival rate with the use of PDF according to the level of severity as measured by the Model for End-Stage Liver Disease (MELD) score. The MELD score was categorized into three grades: 20-29, 30-39, and 40 or higher. The 28 day and hospital survival rates in patients without coma and with coma were 68%(40/59), 32%(19/59) and 20%(1/5), 0%(0/5), respectively. The 28-day survival rate at a MELD score between 20 and 29 was 59% (13/22), and that at a MELD score was between 30 and 39 was 75%(6/8). In conclusion, PDF appears to be useful blood purification therapy for use in cases of acute liver failure without hepatic coma.

Symposium 8 Critical Care Medicine

SY8-01 Dose of CRRT in AKI: The Other Way Around

Bin Du

Medical ICU, Peking Union Medical College Hospital, China

Continuous renal replacement therapy (CRRT) has become standard of care in patients with severe acute kidney injury (AKI). However, optimal dose of CRRT remains controversial, due to negative results of multiple randomized controlled trials. While discussing about potential reasons of these negative trials, clinical parameters to assess the dose of CRRT merit cautious interpretation. In general, dose of CRRT has been routinely assessed by solute clearance, defined as the volume of blood cleared of a solute over a given period of time. This approach neglects the volume of solute distribution, which has been incorporated in Kt/V, a commonly used parameter to evaluate the adequacy of dialysis dose. Moreover, evaluation of treatment adequacy should also consider solute production. A similar scenario is the assessment of CO₂ removal by mechanical ventilation. Alveolar minute ventilation only represents rate of removal, whereas PaCO₂ is the balance between CO₂ production and clearance. In many patients, if not all, the indication of CRRT is fluid overload, rather than azotemia, or decreased clearance of other solutes. In these patients, the dose of CRRT should be evaluated by solvent clearance (negative fluid balance) rather than solute clearance. In conclusion, as the indication of CRRT may be different in different patients, dose should be evaluated by different criteria, rather than the current solute clearance.

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SY8-02 Apheresis for Sepsis

Takeshi Moriguchi, Kenichi Matsuda, Norikazu Harii, Junko Goto

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Apheresis for sepsis aiming at the removal of cytokines with various settings could not show a survival advantage in RCTs. However, apheresis, such as PMX-DHP (direct hemoperfusion with polymyxin B-immobilized fiber column) and CHDF (continuous hemodiafiltration) are performed in the patients with sepsis to remove endotoxin and cytokines as a treatment covered with Japanese public health care insurance. In our institution, we perform CHDF on the ICU patients not only as a renal replacement therapy but also as a remover of cytokines especially in the patients with sepsis or septic shock. When we perform CHDF for the removal of cytokines, a polymethylmethacrylate hemofilter (CH1.8W™, Toray, Japan) or a polyacrylonitrile hemofilter (SepXiris™, Baxter Japan, Japan) are used to adsorb excessive cytokines from the blood stream. Most critically ill patients cannot tolerate the conventional intermittent hemodialysis, which vigorously removes waste substances and excess water, because of the hemodynamical instability. On the other hand, critically ill patients including children tolerate CHDF. Our previous study shows that the CHDF using polymethylmethacrylate hemofilter (PMMA-CHDF) can remove excessive cytokine such as IL-6 from the blood stream and has clinical benefits such as the increased blood pressure and urine output leading to the improved survival compared to the CHDF using a hemofilter made of polyacrylonitrile membrane (PAN-CHDF), which does not adsorb the cytokines. We can assure that the improvement on the septic patients is the result of the removal of the cytokines because that improvements were not seen in the patients with low output syndrome who treated with PMMA-CHDF. In this presentation, I will introduce the technique, safety and efficacy of CHDF in the clinically ill as much detail as possible.

SY8-03 The application of the column adsorbing LAP positive cells to therapy of sepsis-induced immune paralysis

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Immune paralysis causes delayed deaths after surviving sepsis. Therefore we attempted to treat sepsis model rats by hemoperfusion with the column adsorbing LAP (latency associated peptide)-positive cells. LAP positive and IL-10 producing cells decreased by the hemoperfusion, and the treated rats were survived, although all control rats were died.

SY8-04 Early Prediction of Acute Kidney Injury in ICU

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Acute kidney injury (AKI) is a severe disease and, the incidence of AKI in critically ill patients is around 57%, and the more severity, the high mortality. The KDIGO criteria used in clinical settings is based on urine output and serum creatinine, however, deterioration of urine output and serum creatinine is posterior to kidney injury, and urine output and serum creatinine are



always influenced by some factors(eg. blood volume, medicine, operation and stress and others), therefore, diagnosis depend on urine output and serum creatinine tends to delay the assessment of AKI. Accurate clinical indicators and biomarkers are needed to enable early and accurate diagnosis of AKI.

Biomarkers have the advantages in prediction of AKI. There are three classifications, the first one is inflammation markers, which include neutrophil gelatinase-associated lipocalin(NGAL), IL-6 and IL-8 and others; the second one is cell injury markers, include KIM-1, L-FABP and others; the third one is cell cycle markers, include TIMP-2 and IGFBP-7 and others. In our multicenter study, 588 patients were enrolled and 70 patients developed AKI, the AUC of [TIMP-2]•[IGFBP-7] of prediction incidence of AKI within 12 hours after enrollment was 0.64($p < 0.001$), [TIMP-2]•[IGFBP-7] levels of critical ill patients could be used to detect early incidence and deterioration of AKI .

Not only biomarkers, but some new indicators are used to predict AKI. Multivariate panel of physiological measurements, circulating miRNA signature (miR-24-3p, miR-23a-3p, miR-145-5p) that can potentially early detect AKI in high risk patients.

In conclusions, AKI need early recognition, and biomarkers, multivariate panel of physiological measurements, circulating miRNA signature could help to early detect incidence and deterioration of AKI .

Symposium 9 Update report, PMX on sepsis

SY9-01 Impact of timing of polymyxin B immobilized fiber column direct hemoperfusion on outcome in patients with septic shock

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Polymyxin B immobilized fiber column direct hemoperfusion (PMX-DHP) can selectively adsorb endotoxin and theoretically prevent the progression or halt the sepsis cascade and decrease inflammatory humoral mediators. The efficacy of PMX-DHP has been evaluated in many studies, including EUPHAS, ABDOMIX and EUPHRATES trial, which nevertheless reported varying levels of efficacy in septic shock. We suggest that these variations could be explained by the timing of PMX-DHP initiation and/or infection site. We performed the retrospective observational study to investigate the effect of PMX-DHP on outcome in septic shock patients depending on initiation time and infection site (intra- or extra-abdominal infection (IAI/EAI)). The patient cohort was divided into four groups based on the quartile time from catecholamine treatment to PMX-DHP initiation, and the IAI and EAI groups into two subgroups by median time from catecholamine treatment to PMX-DHP initiation, and we compared the outcomes of each groups. Among the final eligible 49 patients, the median interval from catecholamine treatment to PMX-DHP initiation was 9 h (interquartile range, 6-29 h). Therefore, 49 patients were divided in four groups: group 1; within 6 h, groups 2 ; 6-9 h, group 3; 9-29 h, group 4; after 29 h. 90-day mortality in group 1 at 8.3% was significantly lower than in groups 2 (46.1%), 3 (58.3%) and 4 (75.0%) ($p = 0.021$). Among the 29 patients with IAI, 90-day mortality was significantly lower in the early (within 9 h) than the late group (after 9 h) (13.3% versus 64.2%; $p = 0.003$). However, there was no significant intergroup difference among the 20 patients with EAI (within 9 h; 50.0% versus after 9 h; 70.0%; $p = 0.564$). Our

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results suggest that early PMX-DHP initiation (within 9 h after catecholamine treatment) reduces mortality from septic shock, especially in IAI patients.

SY9-02 Blood purification for septic shock patients

Toshiaki Ikeda, Hidenobu Kamohara, Shingo Suda, Takeo Nagura

Division of Critical Care Medicine Tokyo Medical University, Hachioji Medical Center, Japan

We measured the levels of endotoxin activity(EA) and multiple biomarkers in a patient blood obtained within 24h after ICU admission and analyzed(1) Whether there were associations between these markers, and (2) the usefulness of each biomarker in detecting infection and predicting patient outcomes. A total of 142 patients diagnosed with sepsis or suspected sepsis were included. After excluding the 13 patients missing EA data,129 were analyzed. We found that the EA levels highly correlated with the presence or absence of infection, but there was no difference in the EA levels between Gram-negative and positive bacterial infection. We speculate that endotoxin in the blood may rise regardless of infecting bacterial species due to bacterial translocation associated with the failure of the intestinal barrier that occurs under critical conditions. In fact, EA levels are reported to increase in polytrauma and post-cardiac arrest patients in parallel with the damage of intestinal barrier. PMX-DHP is a blood purification which removes circulating endotoxins from patient blood. In the latest clinical study evaluating this, the EUPHRATES trial evaluating the effectiveness of PMX-DHP, which removes endotoxin by extracorporeal circulation, EA was used as part of the entry criteria. In the EUPHRATES trial, patients with an EA level of 0.6 or higher were included, however, our results showed that patients with intermediate EA l(0.4-0.6) were also critically ill and had a mortality equivalent to that of patients in the high EA level(0.6-0.9). Whether the distribution of EA levels of sepsis patients also differs by race or region is unknown, but our results suggest that there is a possibility that Japanese patients exhibit lower EA levels than Westerners when the disease severities are similar. We speculate that, at least in Japan, patients with EA levels between 0.4 and 0.6 may also be suitable subjects for PMX-DHP.

SY9-03 Role of Rescue therapy using Polymyxin B Hemoperfusion in immunocompromised hosts with refractory septic shock

Sang-Bum Hong

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Current survival sepsis guideline more focus on early managements of septic shock. Generally mortality of Septic shock is decreasing now. However still quite portions of septic shock, so called refractory septic shock patients, show high mortality, so we need other treatment options. Among one of options could be polymyxin B hemoperfusion (PMXB). Total 74 patients with 77 sessions of PMXB were done. Total 28d mortality was 51.3% (38/74), among them 21 patients died first day of septic shock (55%, 21/38) and through day 2 - 28 mortality was 45% (17/38). If excluding day1 death, among total patients 53, 28d mortality rate was32% (17/53). We also measured EAA level and prospectively included patients with sepsis or septic shock between December 2017 and .September 2018. The EAA levels were measured within 24 hours after ICU admission. Patients were classified into low-EAA (EAA<0.6, n=34) and high-EAA (EAA≥0.6, n=55) groups and were compared to each other. The baseline sepsis related organ failure assessment (SOFA) score was significantly higher in high-EAA group than low-EAA



group (9.5 ± 3.1 in low-EAA group vs. 11.2 ± 3.1 in high-EAA group, $p=0.022$). The EAA level was significantly correlated with the SOFA score ($r=0.331$ and $p=0.002$). However, the 28-day ICU mortality rates were not significantly different between the EAA groups (22% in low-EAA group and 13% in high-EAA group). Rescue therapy using Polymyxin B Hemoperfusion in immunocompromised hosts with refractory septic shock might be useful and EAA level correlates with severity of organ dysfunctions.

SY9-04 The case for using PMX in critically ill patients - Don't through out the baby with the bath water

Sean M. Bagshaw

Critical Care Medicine, University of Alberta, Canada

Septic shock is a life-threatening emergency. The hallmark of septic shock is profound circulatory, cellular and metabolic abnormalities culminating in high risk for mortality. Endotoxin levels are often elevated in selected patients with septic shock and facilitating reduction of endotoxin levels may improve patient outcomes. The PolymyxinB (PMX) hemoperfusion cartridge (Toraymyxin™) has been used clinically in thousands of patients and published literature is abundant. However, there remains considerable discordance in the literature regarding the effectiveness of hemoperfusion with (Toraymyxin™) in critically ill patients with septic shock. In 2018, the large multi-centre EUPHRATES trial was published and aimed to understand “Does Polymyxin B hemoperfusion improve survival in patients with septic shock and high levels of endotoxin in the blood?” While this trial did not meet the pre-specified primary endpoint of 28-day mortality, it did reveal new information in ad hoc analysis to guide further inquiry on the optimal application of Toraymyxin™ in critically ill patients with septic shock with EAA levels between 0.60-0.90 and at high risk of death. These recent findings, along with a new proposed FDA-approved trial (TIGRIS) to begin later this year, and the ongoing role of Toraymyxin™ in patients with septic shock and endotoxemia will be discussed.

Symposium 10 Lowering Lp(a)

SY10-01 Lipoprotein(a)-Risk Marker and Therapeutic Target

Reinhard Klingel

Apheresis Research Institute, Cologne and 1st Department of Internal Medicine, University of Mainz, Germany

Lipoprotein(a) (Lp(a)) consists of an LDL particle whose apolipoprotein B (apoB) is covalently bound to apolipoprotein(a). An increased Lp(a) concentration is a causal, independent risk factor for atherosclerotic cardiovascular disease (ASCVD) and a predictor of incident or recurrent cardiovascular events. Although Lp(a) was first described as early as 1963, only the more recent results of epidemiological, molecular, and genetic studies have led to this unequivocal conclusion. By the majority of existing investigations an association of Lp(a) concentration on total or cardiovascular mortality was demonstrated. More than 20% of Western populations have elevated Lp(a) values. Lp(a) concentrations should be always part of the lipid profile when ASCVD risk is assessed. However, presence of other risk factors, laboratory findings, medical history and family history must be considered to conclude on its clinical relevance in an individual patient. Early or progressive ASCVD or a familial predisposition are key findings

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which can be associated with elevated Lp(a). The cholesterol portion contained in Lp(a) is also included in the various methods of LDL-C measurement. To assess proximity to the cardiovascular risk adjusted target value for LDL-C, appropriate correction should be applied with high Lp(a) values to estimate the LDL-C that can actually be treated by lipid lowering drugs. LDL and Lp(a) particles exhibit a mutual effect modification on related ASCVD risk. Residual Lp(a)-associated risk remains after effective LDL-C lowering with statins or PCSK9-antibodies. Therefore, LDL-C levels and concomitant LDL-C lowering treatment must be considered. The German guideline for the indication of lipoprotein apheresis in patients with Lp(a)-HLP proved to be of value to identify patients at highest risk, using the composite of a Lp(a) threshold >60 mg/dl (>120 nmol/l) and clinical ASCVD progression despite effective LDL-C lowering therapy. Initial study data show that antisense oligonucleotides, which selectively decrease apolipoprotein(a), might become future treatment options.

SY10-03 Antisense and RNA interference drug therapy for the reduction of Lp(a) levels

Patrick M. Moriarty, Julie-Ann Dutton, Anne K. Nugent, Lauryn K. Gorby

University of Kansas Medical Center, USA

Background: Lipoprotein(a) (Lp(a)) is a genetically determined and independent cardiovascular disease (CVD) risk factor. Current data indicates that 20% of the world's population have an elevated Lp(a). Present therapy for the consistent reduction of Lp(a) with clinically significant event reduction is limited to lipid apheresis. The development of readily accessible therapies, which target the reduction of Lp(a) are imperative.

Objective: To review ongoing pharmacotherapy clinical trials targeting the reduction of Lp(a) levels.

Methods: Outline two new Lp(a) pharmacotherapy trials. First, a randomized, double-blind, placebo controlled (RDBPC), dose-ranging phase 2b study of ISIS 681257 (AKCEA-APO(a)-LRx) administered subcutaneously to patients with elevated Lp(a) and established CVD. Second, a phase 1, RDBPC, single ascending dose study in subjects with elevated plasma Lp(a) to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of AMG 890.

Results: AKCEA-APO(a)-Lrx is an antisense oligonucleotide (ASO) that mediates cleavage of apo(a) mRNA in hepatocytes through RNAaseH1 mechanism. The phase 2 clinical trial enrolled 286 patients at 30 centers. Patients were randomized 5:1 (treatment: placebo) to five dosing cohorts. The primary endpoint was the percent change of serum Lp(a) levels from baseline to week 25 or 27 (dependent on cohort). The results demonstrated a 35-80% reduction in Lp(a) with a favorable safety and tolerability profile. AMG 890 is a synthetic, small interfering RNA (siRNA) NAG-conjugated, liver-targeted therapy that inhibits apo(a) translation and Lp(a) production. AMG 890 targets the mRNA transcribed from LPA gene, which encodes apo(a) protein in liver cells. Pre-clinical data demonstrated AMG 890 can reduce Lp(a) by more than 80%. The phase 1 study is expected to randomize 64 participants with an estimated study completion date in June 2020.

Conclusion: The antisense (AKCEA-APO9a)-Lrx) and RNA interference (AMG 890) are two new promising therapies under investigation that may be effective in the treatment of elevated Lp(a) levels and CVD.



SY10-04 Effect of PCSK9i on Lp(a)

Atsushi Nohara

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Lp(a) has been one of residual risks in cardiovascular disease (CVD) in the era of statins. Only LDL-apheresis reduces Lp(a) efficiently as one of its pleiotropic effects. Ezetimibe or fibrates cannot reduce Lp(a) levels, and statins may increase Lp(a) further. Niacin showed moderate reduction in Lp(a) levels, but even extended-release of niacin could not show protective evidence in CVD.

Recently, Lp(a) has become a focus again. Newly developed PCSK9 inhibitors (PCSK9i) have triggered as they can reduce Lp(a) levels considerably. Intriguingly, response of LDL-C and Lp(a) to PCSK9 antibodies show discordance. Generally, response of Lp(a) to PCSK9i tended to be smaller and vary widely compared to that of LDL-C.

Mechanism how PCSK9i lower Lp(a) levels has not been fully understood. There are conflicting reports about the role of LDL-receptor for Lp(a) with in vivo and in vitro studies. Evolocumab was reported to decrease Lp(a) production in monotherapy and to increase Lp(a) catabolism in combination therapy with atorvastatin. Up-regulation of LDL-receptor may be involved in clearance of Lp(a) particle, but it is not clear about the discordance with the effect of statins. Lp(a) levels are higher in FH with LDLR mutations, and also in FH with PCSK9 gain-of-function mutation. On the other hand, PCSK9i lower Lp(a) even in receptor-negative homozygous FH patients without lowering LDL-C. PCSK9 was reported to enhance apo(a) secretion from hepatocytes, and alirocumab reported to decrease apo(a) production in nonhuman primates. Further studies are required for understanding the regulation of Lp(a) with PCSK9.

In a point of CVD risk reduction, benefit from Lp(a) lowering with PCSK9i should be established. FOURIER and ODYSSEY-Outcome trials seemed no incremental benefits over LDL-C reduction, but patients with higher Lp(a) showed more benefit. On-going Lp(a) antisense drug trial or study with apheresis may make clear the clinical benefits of Lp(a) reduction.

Symposium 11 Position of Lipoprotein Apheresis after Recent Development of Lipid Lowering Drugs

SY11-01 Treatment of FH in Japan

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- Department of Molecular Innovation in Lipidology, National Cerebral and Cardiovascular Center Research Institute, Japan*

Familial hypercholesterolemia (FH) is characterized by hypercholesterolemia, cutaneous and tendon xanthomas and premature atherosclerotic cardiovascular disease. Low-density lipoprotein (LDL) apheresis has been developed as the treatment for refractory FH. Currently, 3 procedures are available in Japan, including the plasma exchange, double-membrane filtration, and selective LDL adsorption. Selective LDL adsorption, which was developed in Japan, has been one of the most common treatment methods in the world. LDL apheresis enabled the prevention of atherosclerosis progression even in homozygous FH (HoFH) patients, because LDL adsorption has various antiatherosclerotic effects in addition to LDL

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removal. For example, we previously demonstrated that LDL apheresis removed ApoC3, proprotein convertase subtilisin/kexin type 9 (PCSK9), small dense LDL, etc. However, in our observational study, HoFH patients who started LDL apheresis in adulthood had a poorer prognosis than those who started in childhood. Therefore, HoFH patients need to start LDL apheresis as early as possible. Although the indication for LDL apheresis in heterozygous FH (HeFH) patients has been decreasing with the advent of strong statins, our observational study showed that HeFH patients who discontinued LDL apheresis had a poorer prognosis than patients who continued apheresis therapy. These results suggest that it is beneficial for very-high-risk HeFH patients to be treated by LDL apheresis even if their LDL-C is controlled well by lipid-lowering agents. Since launching a new class of lipid-lowering agents, PCSK9 antibody and microsomal triglyceride transfer protein (MTP) inhibitors, the indication for LDL apheresis in FH has been changing. However, even these new lipid-lowering agents have limited potency in HoFH. Therefore, despite the development of these drugs, LDL apheresis is still an option with a high therapeutic effect for FH patients with severe atherosclerotic cardiovascular disease.

SY11-02 Treatment of Familial Hypercholesterolemia in the United States

P. Barton Duell

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Familial hypercholesterolemia (FH) is a highly atherogenic genetic disorder that is most commonly caused by mutations in the LDL receptor and less commonly by mutations in apolipoprotein B, PCSK9, and the LDL receptor adaptor protein. A sizable proportion of individuals may have no identifiable mutations in any of these genes, but alternatively may have mutations in unknown genes or possibly polygenic hypercholesterolemia. In the untreated state, individuals with heterozygous FH (HeFH) may have an approximately 50% risk of ASCVD events by the age of 50 years in men and 60-65 years in women. The lifetime risk of ASCVD events may be about 85%. Homozygous FH (HoFH) is associated with severely accelerated development of ASCVD, resulting in ASCVD events starting as early as the first decade and leading to a mean age of mortality of about 18 years in the untreated state.

In light of the very high risk of ASCVD events among patients with FH, it is imperative to implement aggressive and effective LDL-C lowering starting at the age of 8-10 years in patients with HeFH and at the time of diagnosis in patients with HoFH. Among adults, high intensity statin treatment is recommended in combination with ezetimibe and other adjunctive medications, as needed, to achieve effective LDL-C lowering. Rarely, patients with heterozygous FH may be adequately treated with high intensity statin monotherapy, but most patients require multidrug therapy to achieve sufficient LDL-C lowering < 70-100 mg/dl in adults. It is estimated that 1-2% of patients with HeFH may require lipoprotein apheresis despite aggressive drug therapy, whereas 30-50% with HoFH may require lipoprotein apheresis. New drugs, such as PCSK9 inhibitors have reduced the need for lipoprotein apheresis, and experimental treatment with evinacumab may further reduce the need, but many patients still require lipoprotein apheresis, particularly those with HoFH.



SY11-04 Characterization of patients being treated with lipoprotein apheresis (LA) at the Dresden LA center

Ulrich A. Julius, Sergey Tselmin, Ulrike Schatz, Sabine Fischer,
Stefan R. Bornstein

Department of Internal Medicine III, University Hospital at the Technische Universität Dresden, Germany

Aim of Study: The Dresden LA center was founded in 1990. We characterize our patients being treated with regular LA at present with respect to the occurrence of cardiovascular events (CVE; means and range) per patient before the start and during LA therapy.

Materials & Methods: All patients were on maximal tolerated lipid-lowering drug therapy, including PCSK9 inhibitors. Patients who began the LA since 2018 have been evaluated separately. Actual data of LDL cholesterol (LDL-C) and lipoprotein(a) (Lp(a)) were measured before and after a recent LA session.

Results: In 60 (42 M / 18 F) patients no new CVE were seen during LA (mean age at start of LA: 55 (29 - 75) years; duration of LA: 5.1 (1.4 - 17.7) years; CVE before LA: 2.07 (1 - 9); in 2 patients no Lp(a) was detected). In 48 (28 M / 20 F) patients CVE developed during LA therapy (mean age at start of LA: 60 (41 - 75) years; duration of LA: 6.3 (1.4 - 26.4) years; CVE before start of LA: 3.44 (1 - 8); CVE during LA: 2.38 (1 - 6); in 9 patients no Lp(a) was detected). Measured LDL-C and Lp(a) levels were similar in these two groups, also the acute reduction rates (even when comparing the 6 different LA methods used). Since 2018 20 (11 M / 9 F) patients started LA (mean age: 59 (39 - 75) years; CVE before LA: 2.8 (1 - 10)). 2 more patients from high-risk families did not develop any CVE, two patients are treated after heart transplantation (Htx).

Conclusions: Patients who suffered from CVE during LA were older at the start of extracorporeal treatment and showed a tendency for a higher number of CVE before LA, but the time on LA (mostly weekly) and actual lipid levels were rather similar.

Symposium 12 CART, Its Current Status and Prospect for the Future Leaps 1

SY12-01 Verification of serum albumin elevating effect of cell-free and concentrated ascites reinfusion therapy for ascites patients

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Koji Hashimoto, Yuji Kamijo

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Cell-free and concentrated ascites reinfusion therapy (CART) is frequently used to treat refractory ascites in Japan. However, its efficacy remains unclear. This controlled cohort study verified the serum albumin elevating effect of CART by comparisons with simple paracentesis. Ascites patients receiving CART (N=88) or paracentesis (N=108) at our hospital were assessed for the primary outcome of change in serum albumin level within 3 days before and after treatment. A significantly larger volume of ascites was drained in the CART group. The change in serum albumin level was $+0.08 \pm 0.25$ g/dL in the CART group and -0.10 ± 0.30 g/dL in the paracentesis group ($P < 0.001$). The CART - paracentesis difference was $+0.26$ g/dL (95%CI

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+0.18 to +0.33, $P < 0.001$) after adjusting for potential confounders by multivariate analysis. The adjusted difference increased with drainage volume. In the CART group, serum total protein, dietary intake, urine volume, and body weight were significantly increased, while hemoglobin was significantly decreased, versus paracentesis. More frequent adverse events, particularly fever, were recorded for CART, although the period until re-drainage was significantly longer. This study is the first demonstrating that CART can significantly increase serum albumin level as compared with simple paracentesis. CART represents a useful strategy to manage patients requiring ascites drainage.

SY12-02 Characteristics and methods of the cell-free and concentrated ascites reinfusion therapy (CART) procedure in Japan

Atsushi Ohkubo¹⁾, Tomokazu Okado²⁾

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2) *Department of Nephrology, Tokyo Medical and Dental University, Japan*

Cell-free and concentrated ascites reinfusion therapy (CART) is a method for the treatment of refractory ascites. There are several variations in CART procedures regarding the direction of filtration and driving force. There are two types of the driving force to filter and concentrate ascites (pump or gravity). Although the pump-type requires a hemopurification machine, it can monitor a transmembrane pressure. On the other hand, although the drop-type using gravity as driving force does not need a hemopurification machine, it cannot monitor a transmembrane pressure. As for the driving force of CART, the pump was used in most of CART sessions in Japan. There are two types of the direction of filtration (inside-out and outside-in). Regarding the direction of filtration, inside-out filtration was used in most of CART sessions in Japan. There are the other processing conditions, such as filtration speed, concentration speed, and transmembrane pressure. In our data, the filtration-concentration speed may be desirably below 3000 mL/hour because the increase in body temperature tended to be high when the filtration-concentration speed was high. Moreover, the transmembrane pressure is desirably below 100mmHg because the blood ascites may cause hemolysis. In this symposium, the characteristics and methods of CART procedures in Japan will be explained.

SY12-03 Cell-free and Concentrated Ascites Reinfusion Therapy (CART) against malignancy-related ascites

Tetsuya Ito

Department of Palliative Care, Japanese Red Cross Medical Center, Tokyo, Japan

Ascites is commonly seen in patients with decompensated cirrhosis or malignancy. The mainstream of treatment option against ascites includes restriction of sodium intake and use of diuretics. However, there still remains ascites not reacting to these treatment options and causing variety of symptoms in those patients.

In Japan, Cell-free and Concentrated Ascites Reinfusion therapy (CART) has been applied widely against refractory ascites. CART is comprised of three steps. First, removed ascites is filtered to eliminate cell component. Second, the filtered ascites is concentrated to reduce its volume. Processed ascites including proteins such as albumin and globulin is finally reinfused intravenously.

Since established in 1970s, CART has been applied mainly against cirrhotic ascites. Efficacy



and safety of CART against malignancy-related ascites has been reported recently and it is now performed widely in patients with malignancy as well as decompensated cirrhosis. Increase of urine output after CART may reflect improved diuretic resistance often seen in patients with refractory ascites. Its favorable effects on performance status and oral intake are also reported. As for symptom management, CART is reported to improve variety of malignancy-related symptoms and ADL of the patients. It is remarkable that CART can also ameliorate fatigue which is the adverse event concerned in large volume paracentesis.

Although its mechanism still remains unclear, CART is now expected as one of the therapeutic options against malignancy-related ascites.

SY12-04 Safety and quality control for filtered and concentrated ascites reinfusion therapy

Taiju Utsugisawa, Yoshio Okamoto, Hitoshi Kanno

Department of Transfusion Medicine and Cell Processing, Tokyo Women's Medical University, Tokyo, Japan

Cell-free and concentrated ascites reinfusion therapy (CART) has been developed as a treatment method for patients with refractory ascites or pleural effusion. Reinfusion of filtered and concentrated ascites not only improves the patient's quality of life but also reduces the amount of albumin preparation used. Since concentrated ascites fluid contains many biological proteins as well as serum-derived albumin, adverse reactions may occur if the patient from whom ascites fluid is collected is not administered the concentrated ascites correctly. Recently, we discovered that anti-A and anti-B antibodies corresponding to the patient's ABO blood group exist in ascites fluid and are concentrated as well as other proteins. These antibodies may cause an immediate hemolytic reaction in patients with ABO major mismatch. Patients with ascites fluid retention may have infections or malignancies; thus, proteins such as endotoxin and cytokines in the ascites fluid that cause adverse reactions may also be concentrated. Moreover, if the free hemoglobin released from erythrocytes through hemolysis in ascites fluid is not removed using filtration via CART, it may cause acute kidney damage. Therefore, we measure the endotoxin concentration and the amount of free hemoglobin in the concentrated ascites fluid before delivery. At the same time, misadministration is prevented by using the same system for patient authentication as is used for the blood products. The number of patients with indications for CART is increasing, indicating that careful attention should be paid to quality control and prevention of patient confusion.

Symposium 13 Hemapheresis and cellular therapy-state of the art and clinical applications-1

SY13-01 Overview of Cellular Therapy and the Critical Role for Apheresis Professionals

Bruce Sachais

New York Blood Center, USA

Cellular therapies comprise a variety of treatments that use cells collected from patients or healthy allogenic donors that can be used to treat a variety of disorders including cancer and inherited disorders of hemoglobin. Many of these therapies require the collection of cells from the peripheral circulation, placing apheresis medicine front and center in the cell therapy

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revolution. This talk will provide an overview of cellular therapy and illustrate the importance of apheresis professionals in this rapidly expanding therapeutic area.

SY13-02 Cellular Collections for Immunotherapy, Perspective from a Large Academic Center

Nicole Aquí

Department of Pathology and Laboratory Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA

Background: In 2017, two chimeric antigen receptor (CAR) T cell therapies were approved by the Food and Drug Administration (FDA) - tisagenlecleucel (KYMRIAHA, Novartis) for the treatment of pediatric and young adult B-cell precursor ALL, and axicabtagene ciloleucel (YESCARTA, Kite) for adult patients with relapsed or refractory large B-cell lymphoma. Since that time, demand for mononuclear cell collections to provide starting material for commercial manufacturing has increased significantly. However, it is clear that manufacturing a cell-based product is very different from the synthesis of other pharmaceutical drugs. This presentation will focus on implementation of a cellular collection program for immunotherapy from the perspective of a large academic center.

Methods: Characterization of pre-collection and procedural variability and their effects on the cellular product and manufacturing will be discussed. Recommended components of a cellular program will be presented. Regulatory requirements for collection facilities will be addressed.

Results: Mononuclear cell products are a snapshot of the donor; therefore, there are many factors prior to and at collection that can affect downstream parameters. Sources of variation include patient demographics, clinical indication, and prior treatment. Variation mitigation strategies have been used with varying levels of success.

Conclusions: Before implementing a cellular therapy program, it is important for apheresis practitioners to have an understanding of the manufacturing process to best optimize the collection for individual patients. It is also vital to have knowledge of the regulatory requirements that govern the facility/manufacturer's country.

SY13-04 Recent advances in diagnosis and treatment of light-chain (AL) amyloidosis

Nobuhiro Tsukada

Department of Hematology, Japanese Red Cross Medical Center, Tokyo, Japan

The systemic amyloidoses comprise an increasing number of diseases characterized by multiorgan deposition of misfolded and aggregated autologous proteins as β -pleated sheet fibrils. Immunoglobulin light-chain (AL) amyloidosis is the most common and the most severe because it often targets the heart. Amyloid deposit involves vital organs, such as heart (75%), kidney (65%), soft tissues (15%), liver (15%), autonomic nervous system (10%), and gastrointestinal tract (5%), and clinical symptoms are various. Patients with cardiac involvement are characterized by ventricular diastolic dysfunction due to wall thickness and by arrhythmia. Patients with kidney involvement shows nephrotic syndrome. Hypotension caused by autonomic dysregulation is also frequently observed. The goal of therapy is to eliminate the clonal plasma cells producing this toxic light-chain to halt and reverse symptomatic organ damage. High-dose melphalan and stem cell transplantation (HDM/ASCT) is an effective



treatment modality, but eligible patients are limited. The rest of ineligible patients are treated with conservative treatment including melphalan plus dexamethasone (Mel/Dex). Sixty-six patients received HDM/ASCT in our institution between 2006 and 2017. Of those, 54 patients are alive after a median follow-up of 51 months, and the 8-year estimated overall survival rate was 78.6%. Five patient died within 100 days post-HDM/ASCT. Survival rate is significantly worse in patients with cardiac involvement. To maximize the benefit and minimize toxicity, careful patient selection and experienced management are important, especially for patients with cardiac involvement. Novel anti-plasma cell approaches borrowed from multiple myeloma are currently being considered for treating AL amyloidosis. In this presentation, evolution of HDM/ASCT and novel treatment strategies are discussed.

Symposium 14 Hemapheresis and cellular therapy-state of the art and clinical applications-2

SY14-01 Autotransplantation for POEMS syndrome

Masahiro Takeuchi

Department of Hematology, Chiba University Hospital, Chiba, Japan

POEMS syndrome is a rare plasma cell dyscrasia presenting with polyneuropathy, λ -type M protein, vascular endothelial growth factor elevation, and systemic manifestations. The standard treatment has not been established, but autologous stem cell transplantation (ASCT) has exhibited effectiveness in this syndrome.

SY14-02 Update on granulocyte transfusions, including granulocytapheresis and clinical effectiveness

Satoshi Yoshihara

Department of Transfusion Medicine and Cellular Therapy, Japan

Bacterial and fungal infections during the neutropenic period remain one of the most important causes of mortality in patients with aplastic anemia or in those who undergo chemotherapy or stem cell transplantation. Previous studies have confirmed that the transfusion of granulocyte concentrates, which are collected from healthy donors after mobilization with granulocyte colony-stimulating factor, result in a substantial increase in the patient's absolute neutrophil count. However, granulocyte transfusions (GT) have several controversial issues, including the use of high-molecular-weight hydroxyethyl starch (HMW-HES) during granulocytapheresis, and more importantly, GT's clinical effectiveness. HMW-HES accelerate RBC sedimentation, thus improve granulocyte collection efficiency and reduce the contamination of red blood cells and platelets. However, several studies have highlighted the toxicity of HMW-HES, including a study that showed the use of HMW-HES in critically ill patients was associated with decreased survival. Although the amount of HMW-HES applied to healthy donors during granulocytapheresis and patients receiving GT is remarkably small, several studies have explored the feasibility of non-HMW-HES granulocytapheresis to avoid the possible risk. Although numerous case reports and case series have suggested the efficacy of GT, two randomized controlled studies (RCTs) have failed to corroborate this. This may highlight the difficulty of designing and accomplishing RCTs for GT. The low accrual, which decreased the statistical power for detecting differences in these two studies, may come from physicians' concerns about the ethical feasibility of randomization of potentially life-saving treatment for patients with severe infections.

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SY14-03 Plasmapheresis for the treatment of acquired thrombotic thrombocytopenic purpura

Yasunori Ueda

Department of Hematology / Oncology, Transfusion and Hemapheresis Center Kurashiki Central Hospital Okayama, Japan

Thrombotic thrombocytopenic purpura (TTP) is the most representative disease of thrombotic microangiopathies. Deficiency of cleaving protease of von Willebrand factor (VWF)-a disintegrinlike and metalloprotease with thrombospondin type 1 motif 13 (ADAMTS13)-induce circulation of unusually large VWF multimers (ULVWFM) secreted from vascular endothelium and then generate VWF platelet thrombi in arterioles with high shear stress. Reduced activity of ADAMTS13 below 10% has been accepted internationally as a diagnostic criterion for TTP. Except congenital TTP, cardinal pathogenesis of acquired TTP is generation of autoantibodies against ADAMTS13. Plasma exchange (PEX) applying fresh frozen plasma (FFP) is the mainstay of the treatment of acquired TTP (aTTP) with autoantibodies. The purpose of PEX are removal of autoantibodies, infusion of ADAMTS13, removal of ULVWFM and infusion of VWF of normal size. Autoantibodies of ADAMTS13 usually consist of IgG. Immunosuppressive treatments including administration of glucocorticoid is required to prevent continuation of autoantibodies generation. About 40 % of IgG is distributed in circulation and one plasma volume(PV)PEX can remove two third, 1.5 PV PEX can remove 75% of circulatory substances. About one half of pathological IgG can be removed by successive PEX of 2 days. Successive PEX until platelet recovery is theoretically important . PEX with FFP for TTP is paradoxical treatment because PEX can remove ADAMTS13 autoantibodies but also stimulate generation of ADAMTS 13 autoantibodies from B lymphocyte lineage. We often experience inhibitor boosting during PEX and administration of more intensive immunosuppressive agent for example rituximab is required. Daily changes of ADAMTS13 activity and antibody titer during inhibitor boosting will be shown from our experience. In near future anti-vWF nanobody caplacizumab have possibility to change treatment strategy for aTTP.

SY14-04 Atypical hemolytic uremic syndrome

Akira Ashida

Department of Pediatrics, Osaka Medical College, Japan

Hemolytic uremic syndrome (HUS) is characterized by microangiopathic hemolytic anemia, acute kidney injury, and thrombocytopenia. Typical HUS, the most common form of thrombotic microangiopathy in children is Shiga toxin-producing *Escherichia coli* infection associated HUS (STEC-HUS), whereas one of the most frequent forms in adults is thrombotic thrombocytopenic purpura (TTP). Historically, the term “atypical HUS” has been used to describe any form of HUS other than STEC-HUS or TTP. Therefore, the term atypical HUS encompasses both the primary form - mainly complement-mediated HUS - and secondary atypical HUS caused by factors, such as drugs, malignancy, pregnancy, and transplantation. However, various clinical and experimental studies have clarified that 50 to 60% of cases of atypical HUS are attributable to inherited and/or acquired complement dysregulation in the alternative pathway. Therefore, the term “atypical HUS” is now only synonymous with complement-mediated HUS. Until recently, regular plasma exchange was recommended for atypical HUS in order to replace complement regulator protein and remove autoantibodies against it. Responses to plasma exchange are variable and depend on the underlying complement abnormality. On the other hand, observational studies and prospective multicenter trials have demonstrated the efficacy and



safety of eculizumab, a humanized monoclonal antibody against complement C5 that prevents the formation of C5b-9, the membrane attack complex of the terminal complement pathway. Therefore, eculizumab has become a first-line therapy for patients with a definite diagnosis of complement-mediated HUS in order to avoid the risk of complication associated with plasma exchange and central venous catheterization, such as plasma hypersensitivity, hemorrhage, thrombosis, and infections. Here we discuss in detail the indications, clinical practice, efficacy, and complications of plasma exchange therapy for patients with atypical HUS.

Symposium 15 Apheresis for kidney disease

SY15-01 Therapeutic Apheresis in the Field of Nephrology - Future Direction and Missions of Nephrologists

Norio Hanafusa

Department of Blood Purification, Tokyo Women's Medical University, Tokyo, Japan

Therapeutic apheresis is applied for wide varieties of conditions in the field of kidney diseases. These conditions include anti-neutrophil antibody (ANCA) associated rapid progressive glomerulonephritis (RPGN), anti-glomerular basement membrane (GBM) antibody-associated RPGN, desensitization before kidney transplantation, focal segmental glomerulosclerosis, and dialysis-related amyloidosis. The listed diseases are what the health insurance system in Japan reimburses. Moreover, other conditions such as diabetic nephropathy, and cholesterol crystal embolism (CCE) are now under investigation for the efficacy of low-density lipoprotein apheresis as a form of advanced medical care.

The American Society for Apheresis (ASFA) guideline recommends therapeutic apheresis as Category. The diseases covered by Japanese health insurance are categorized as I or II in most of the conditions. However, the evidence levels of the recommendations are not high in all the diseases. The scope of therapeutic apheresis is rare and acute conditions. Therefore, a clinical trial is difficult to be performed.

Refractory diabetic nephropathy and CCE are now investigated for the efficacy of therapeutic apheresis. The challenge of such an investigation is the recruit of the patients. However, the accumulation of the evidence is awaited for regarding the efficacy and safety of therapeutic apheresis in the conditions where the therapy has not been tried. Nephrologists are familiar with blood purification therapy because the volume of hemodialysis therapy is quite large. Therefore, we, nephrologists, can apply apheresis therapy on new diseases with the use of their knowledge and skills of blood purification. Such efforts will lead to the development and improvement of apheresis technology.

SY15-02 Apheresis for nephrotic syndrome

Kengo Furuichi, Hitoshi Yokoyama

Department of Nephrology, Kanazawa Medical University, Uchinada, Japan

Low density lipoprotein (LDL)-apheresis for refractory focal segmental glomerulonephritis was clinically valuable and established. Although several possibilities of apheresis for kidney diseases were speculated in animal experiments or human studies, clinical applications were limited thus far. Here, we try to show the possibility of LDL apheresis for diabetic nephropathy and leukocyte apheresis (LCAP) for refractory nephrotic syndrome. Diabetic nephropathy

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is a leading cause of end-stage kidney disease in the world. Diabetic patients with massive proteinuria show poor prognosis. Renin angiotensin system inhibitors are insufficient for suppressing urinary protein, and there is almost no other good treatment for diabetic patient with massive urinary protein. In these condition, LDL apheresis for patients with nephrotic syndrome caused by diabetic nephropathy were reported. To confirm the efficacy and safety of LDL apheresis for patients with diabetic nephropathy with massive urinary protein accompanying refractory hypercholesterolemia, clinical trial was conducted, recently. In minimal change nephrotic syndrome (MCNS), various lymphocyte dysfunctions and possible lymphocyte-derived permeability factors have been speculated. Activation of lymphocytes and accompanying immune abnormality in MCNS are presumed to be involved in the onset of this disease. These findings indicated that MCNS would be good target for LCAP. Actually, it was reported LCAP was effective in some refractory cases of MCNS or focal segmental glomerulosclerosis. In this symposium, we summarized the effectiveness of apheresis therapy for diabetic nephropathy and refractory cases of nephrotic syndrome. Importance of apheresis therapy for kidney disease is not only clinical effectiveness but also scientific valuable chance to find out causative factors for the diseases.

SY15-03 Apheresis for Focal Segmental Glomerulosclerosis

Andre A. Kaplan

University of Connecticut Health Center, Farmington, CT, USA

Focal segmental glomerulosclerosis (FSGS) is a glomerular disease associated with nephrotic syndrome and progressive loss of renal function. FSGS has been associated with varied etiologies including infection, toxins, medications, obesity, genetic abnormalities and decreased functional renal mass. A rapidly progressive form of FSGS can occur post renal transplant. Experimental studies suggest that there is a “glomerular permeability factor” which can cause rapid onset of glomerular protein leak and subsequent loss of transplant function in some patients whose original renal failure was associated with FSGS pathology. Published experience has demonstrated that plasmapheresis and protein absorption can improve outcomes in some of these patients, presumably by removal of the permeability factor. There are also data that suggest that primary FSGS may also benefit from lipid apheresis. The currently available data supporting the use of apheresis techniques for the treatment of transplanted and native kidneys with FSGS will be reviewed in this presentation.

SY15-04 Current status of Apheresis in the practice of Rapidly Progressive Glomerulonephritis in Japan

Shuzo Kaneko, Kunihiro Yamagata

The department of Nephrology, University of Tsukuba, Ibaraki, Japan

Rapidly progressive glomerulonephritis (RPGN) is a clinical syndrome from severe glomerulonephritis forming necrotizing crescentic lesions, which progresses to irreversible end-stage renal disease in a short period. Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) and anti-glomerular basement membrane (GBM) antibody disease are the major and serious causes of RPGN, and 60-70% of the causes of RPGN in Japan are these two diseases. In recent years, for anti-GBM -RPGN and AAV-RPGN, plasmapheresis (i.e., plasma exchange and double filtration plasmapheresis) treatment is approved in Japanese health insurance system from 2016 and 2018, respectively. RPGN from these diseases could become to be recognized as a pathological condition that apheresis is effective, even among non-

nephrologist. In this symposium, overviewing the evidence of apheresis for severe renal damage from AAV or anti-GBM diseases in the world, we focus on apheresis for RPGN in Japan and discuss about future prospect.

SY15-05 Efficacy of selective plasma exchange at pre-transplant desensitization of ABO-incompatible kidney transplantation

Toshihide Naganuma¹⁾, Ako Hanaoka²⁾, Yoshiaki Takemoto¹⁾, Junji Uchida¹⁾, Tatsuya Nakatani¹⁾

1) Department of Urology, Osaka City University, Osaka, Japan

2) Department of Medical Devices, Osaka City University, Osaka, Japan

Background: Selective plasma exchange (SePE) is a new simple plasma exchange (PE) modality that enables removal of small and medium-sized molecules without removing larger substances such as coagulation factors. We have performed selective plasma exchange (SePE) as apheresis before ABO-incompatible kidney transplantation since 2015. In this study, we investigated the efficacy of SePE.

Materials and Methods: In this study, we divided the SePE sessions into two groups, those using albumin alone (Group A) and those partially using fresh frozen plasma (FFP) (Group F), and compared their clinical efficacies. A total of 58 sessions of SePE (Group A: n=41, Group F: n=17) were performed in 30 recipients of ABOi kidney transplantation during the study period and the decrease in isoagglutinin titers, changes in the levels of serum IgG and IgM as well as coagulation factors (fibrinogen, factor XIII), and incidence of side effects were retrospectively compared.

Results: The median decrease in IgG isoagglutinin titer was by 2 [0, 1] fold in Group A and 4 [1, 2] fold in Group F, and there was a more significant decrease in Group F ($p < 0.0001$). The median decrease in IgM isoagglutinin titer was by 2 [0, 1] fold in Group A and 2 [1, 2] fold in Group F, and there was a more significant decrease in Group F ($p = 0.0044$). Immunoglobulins and coagulants were replenished in Group F. Meanwhile, the incidence of side effects was significantly higher in Group F. After their transplants, all patients have made satisfactory progress without incident of AMR.

Conclusion: SePE using FFP, which can effectively decrease isoagglutinins titers and replenish immunoglobulin and coagulation factors, may be a beneficial treatment modality as apheresis before ABO-incompatible kidney transplantation, in spite of a disadvantage that there are many side effects.

Symposium 16 Apheresis for various vasculitis

SY16-01 Therapeutic apheresis for cryoglobulinemic vasculitis in Japan

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2) Dialysis Division, University of Miyazaki Hospital, Miyazaki, Japan

Background: Cryoglobulins are immunoglobulins which have the unusual property of

precipitating in vitro at temperatures below 4°C and dissolving after rewarming to 37°C. Cryoglobulinemic vasculitis (CV), small-to-medium vessel vasculitis, refers to a systemic inflammatory disease that cryoglobulins make immunocomplexes with complements in vivo. The patient with CV usually presents with symptoms such as purpura, arthralgia, and peripheral neuropathy, and has nephropathy in about 30% of cases. Although there is an idiopathic CV without etiologic factor, most of CV are secondary with underlying diseases such as hepatitis C virus infection, autoimmune diseases and hematologic malignancies. Although steroids and immunosuppressants are often used for treatment of CV, we consider that plasma apheresis, in particular, cryofiltration (CF) is useful especially in serious conditions that may cause irreversible organ damage because of rapidly removing cryoglobulin from blood. Considering the use of immunosuppressant is associated with poor prognosis, the importance of CF is also increasing to avoid excessive immunosuppression.

Materials & Methods: We presented one case that CF was great effective for treatment of CV and examined the underlying disease, the treatment options, complications and prognosis in the other cases we experienced.

Results: Even in the cases which the underlying disease were treated, half died from infection. Even if the underlying diseases were not treated, renal death was avoided by CF or immunosuppressants. Renal death occurred in cases which neither treatment of the underlying disease nor treatment of immunosuppressants and/or CF were performed.

Conclusions: Consideration that about half of the patients die from infections and the use of immunosuppressants are a poor prognostic factor, CF is considered useful to reduce the use of immunosuppressants.

SY16-02 Extracorporeal Treatment Measures in Immune-Complex Small-Vessel Vasculitides

Andreas Kronbichler

Department of Internal Medicine IV (Nephrology and Hypertension,) Medical University Innsbruck, Austria

Both established extracorporeal therapeutic measures, plasma exchange (PLEX) and immunoabsorption (IAS), have been used as a mainstay in the management of anti-glomerular basement membrane (GBM) disease. Rapid reduction of GBM antibodies is necessary to control the disease and different therapeutic strategies will be discussed. Cryoglobulinemic vasculitis is a heterogeneous entity. Recent investigations provided evidence that apheresis is sufficient to improve the disease outcome in a significant proportion of affected cases. IgA vasculitis (former Henoch Schonlein purpura) is considered as a benign disease. In some cases, treatment refractoriness necessitates the use of PLEX to abrogate the inflammatory process. Strategies to perform apheresis without concomitantly administered immunosuppression have been successfully employed. The presentation will provide an overview of the presumed pathogenesis of the above mentioned diseases and treatment steps (in the case of cryoglobulinemic vasculitis and IgA vasculitis depending on the severity).



SY16-03 Plasma exchange therapy to reduce mortality in Japanese patients with microscopic polyangiitis, particularly diffuse alveolar hemorrhage

Yoshiyuki Abe

Department of Internal Medicine and Rheumatology, Juntendo University, Tokyo, Japan

Diffuse alveolar hemorrhage (DAH) is well known as a serious complication of microscopic polyangiitis (MPA) or anti neutrophil cytoplasmic antibody (ANCA) associated vasculitis (AAV), and it is associated with high mortality. Several clinical guidelines recommend plasma exchange therapy (PLEX) for DAH or rapidly progressive glomerulonephritis (RPGN) in patients with AAV. For RPGN, systematic review and meta analysis reported that plasma exchange therapy reduced renal death in patients with AAV. Several studies reported the effectiveness of plasma exchange in DAH patients with AAV. In Japan, the prevalence of microscopic polyangiitis (MPA) is much higher than that of granulomatosis with polyangiitis (GPA), and another AAV. In contrast, GPA is more frequent than MPA in Northern Europe. This difference affected that the treatment and prognosis in Japanese patients with AAV, because MPA is different clinical characteristics than GPA such as MPA patients are often elder than GPA patients. Because Japanese MPA patients included many elderly patients and elderly patients are compromised and high risk of immunosuppressive therapy, some physicians considered that their treatment may be able to fail to reflect directly the results of studies in European AAV patients. However, plasma exchange therapy may be higher tolerability in elderly patients than immunosuppressive therapy. The usability of plasma exchange therapy is high in actual clinical practice. We introduce the recent evidence and report on the effectiveness of PLEX therapy for MPA patients with DAH in our hospital.

SY16-04 Should we still plasma exchange in Vasculitis based on Pexivas results?

Wladimir Szpirt

Rigshospitale, Copenhagen, Denmark

Patients with ANCA vasculitis can suffer kidney failure or early death especially in those with reduced renal function or lung haemorrhage. Plasma exchange removes antibodies from the blood including the ANCA antibodies contributing to the damage caused by the disease and - beside removal of the autoantibodies - interference with complement, NETS, microparticles.

PEXIVAS RCT examined whether plasma exchange would improve ANCA vasculitis patients' health over the long term. Because steroids cause serious side effects and there is no current agreement on what dose of steroids is best, PEXIVAS also compared two steroid doses.

Using networks of vasculitis specialists in Europe, North America, Australia/New Zealand and Japan more than 100 centres participated in the study where patients were allocated randomly to either +/- plasma exchange, then to a 'reduced' or 'standard' steroid dose. All patients received an immunosuppression with cyclophosphamide or rituximab. The study aimed to see whether plasma exchange would delay the onset of kidney failure or death, and whether a reduced steroid dose had the same benefit in controlling the disease as a standard dose but was safer. 704 patients were recruited, between 2010 and 2016, and followed until the end of the trial in September 2017. 99 patients died and 137 developed kidney failure. Plasma exchange did not reduce the chances of death or kidney failure. There was no difference between the steroid

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dose groups in the number of deaths or patients developing kidney failure but there were fewer serious infections in the reduced steroid dose group.

The results of PEXIVAS do not support the routine use of plasma exchange for all patients with severe vasculitis, but have shown that the reduced steroid dose is just as effective as and safer than a 'standard' dose steroid regimen. These results have the potential to save money and make the treatment of vasculitis patients safer in the future.

Symposium 17 Lipoprotein Apheresis in Kidney Disease

SY17-02 Lipoprotein apheresis for kidney disease in adult

Norihiko Sakai¹⁾, Takashi Wada²⁾

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2) *Department of Nephrology and Laboratory Medicine, Kanazawa University, Kanazawa, Japan*

The number of patients taking dialysis therapy has been increasing throughout the world. One of the reasons to explain it is that there has been few specific medications to treat kidney diseases. Some drugs such as glucocorticoid and immunosuppressant sometimes show beneficial effects for immunological disorder-related kidney diseases including nephrotic syndrome, however, there are still some patients showing steroid-resistant nephrotic syndrome. In addition, side effects limit their therapeutic efficacy. Another reason for the increasing number of dialysis patients is high proportion of patients with diabetic kidney disease. Currently, some of anti-hypertensive drugs and blood glucose-lowering drug have been shown to be effective for relatively early stage of diabetic kidney disease (DKD). However, there might still be huge population requiring new therapeutic option. To combat these situations, other therapeutic strategy from a different point of view would be required to treat kidney diseases. Lipoprotein apheresis is a blood purification therapy that removes lipoproteins from a circulation. In Japan, there are three methods available, which are plasma exchange, double filtration and adsorption. Of these, the adsorption system using a dextran sulfate-cellulose adsorption column has been widely used in Japan to remove apoprotein B-containing lipoproteins such as LDL and very low-density lipoprotein. It would be a nice method to dramatically reduce LDL levels in blood, thereby contributing to reduce the toxicity of LDL in patients with primary hypercholesterolemia as well as secondary one due to nephrotic syndrome or DKD. Lipoprotein apheresis has been used to treat patients with refractory focal segmental glomerulosclerosis with the national health insurance coverage in Japan. In addition, a multi-center study to examine the effect of Lipoprotein apheresis on DKD has been underway in Japan. In this session, we will present the data associated with the impact of LDL-A on kidney diseases including nephrotic syndrome and DKD.

SY17-03 Lipoprotein apheresis for kidney disease in children in US

Katherine Twombly

Pediatrics, Medical University of South Carolina, USA

Nephrotic syndrome (NS) in children can be very difficult to treat both pre and post kidney transplantation. Prior to transplant NS, especially focal segmental glomerulosclerosis (FSGS), progresses to end stage renal disease around 10% of the time. Post-transplant can be even worse with >50% reoccurring. Some children progress/reoccur rapidly, while others progress/reoccur more slowly. In both groups, the persistent hyperlipidemia can contribute to a



significant amount of comorbidities such as atherosclerosis in the vessels, recurrent pancreatitis and progressive glomerular and tubulointerstitial injury. Unfortunately, there are limited options for pharmacotherapy in children as most of the options do not come in liquids. Many of these children who progress/reoccur are treated aggressively with therapies such as glucocorticoids, rituximab, cyclophosphamide or plasma exchange, but all of these therapies can carry high rates of side effects. Despite these treatments, many children do not respond and remain nephrotic. Lipoprotein Apheresis (LDL-A) is now an accepted therapy for children who present with NS. This session will discuss difficult cases where LDL-A treatment was successful when all other therapies failed. All patients in this session were treated with twice weekly LDL-A for three weeks and then weekly for the next 9 weeks. We will review all prior treatments, clinical courses and outcomes.

SY17-04 Lipoprotein apheresis for kidney disease in children in Japan

Naoto Kaneko, Kenichiro Miura, Motoshi Hattori

Department of Pediatric Nephrology, Tokyo Women's Medical University, Tokyo, Japan

Management of focal segmental glomerulosclerosis (FSGS) is challenging as many patients progress to end-stage renal disease if remission is not achieved by immunosuppressive treatment. Prolonged steroid therapy and immunosuppressants are used alone and/or in a variety of combinations, which can cause adverse effects such as infection, hypertension, hypercoagulable state, and dyslipidemia. In this context, low-density lipoprotein (LDL) apheresis is a potent therapy for children with FSGS, because it can reduce toxicity of steroids and immunosuppressive agents. As LDL apheresis removes both LDL and very low-density lipoprotein selectively, several proposed effects have been reported as follows; 1) reduction of direct lipotoxicity, 2) improvement of response to steroid and immunosuppressants, and 3) removal of fibrinogen and coagulator factors. In 1992, the National Health Insurance program in Japan approved LDL apheresis therapy for FSGS patients with total cholesterol levels greater than 250 mg/dl who are resistant to conventional therapy. We reported 11 children with steroid-resistant FSGS who were treated with combined LDL apheresis and prednisolone therapy. Seven patients successfully achieved complete or partial remission after 12 sessions of LDL apheresis (Am J Kidney Dis 2003). A multicenter prospective study (POLARIS study) indicated that LDL apheresis has long-term efficacy for drug-resistant nephrotic syndrome in adults (Nephron Extra 2015). Based on these results, the Clinical Practice Guideline for Pediatric Idiopathic Nephrotic Syndrome developed by the Japanese Society for Pediatric Nephrology in 2013 suggests that LDL apheresis may be a treatment option for patients with refractory steroid-resistant nephrotic syndrome (Grade C1). In this session, we will update on the current understandings of LDL apheresis for children with FSGS and discuss our recent experience of LDL apheresis in children with refractory FSGS.

Symposium 18 Applications and Effectiveness of Apheresis Therapy for Severe Conditions in Children

SY18-01 Hemolytic uremic syndrome in pediatric patients

Akira Ashida

Department of Pediatrics, Osaka Medical College, Japan

Hemolytic uremic syndrome (HUS) is characterized by microangiopathic hemolytic anemia,

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acute kidney injury, and thrombocytopenia. HUS is a rare disease occurring mainly in young children, and is a major cause of intrarenal acute kidney injury in childhood. An etiology-based classification of HUS has been adopted in Japan, and this includes Shiga toxin-producing *Escherichia coli* infection-associated HUS (STEC-HUS), complement-mediated HUS, and secondary-type HUS (due to, for example, cobalamin C deficiency, drugs, autoimmune disease, or pregnancy). Plasma therapy, including plasma exchange, has been indicated for complement-mediated HUS and as salvage therapy for STEC-HUS with neurological manifestations. Until recently, regular therapeutic plasma exchange was recommended for complement-mediated HUS for replacement of complement regulator protein and removal of autoantibodies against it. Responses to plasma exchange are variable and depend on the underlying complement abnormality. Eculizumab is a humanized monoclonal antibody against complement C5 and prevents the formation of C5b-9, the membrane attack complex of the terminal complement pathway. The efficacy and safety of eculizumab therapy have been demonstrated by observational studies and prospective multicenter trials. Therefore, in order to avoid the risk of complications associated with plasma exchange and central venous catheterization - including plasma hypersensitivity, hemorrhage, thrombosis, and infections - eculizumab has become a first-line therapy for pediatric patients with atypical HUS that is suspected to be complement-mediated. Here we discuss in detail the indications, clinical practice, efficacy, and complications of plasma exchange therapy for pediatric patients with HUS.

SY18-02 Plasma exchange therapy for cases refractory to IVIG treatment in Kawasaki disease in Japan

Masaaki Mori

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Background: The goal of treatment in Kawasaki disease (KD) is to suppress the strong inflammatory reaction of the acute phase as early as possible, and as a result, to minimize the onset frequency of the coronary artery lesions as severe complication. Therefore, it is important that treatment is effective before the 10th day of illness when a coronary lesion can occur. Plasma exchange (PE) therapy performed to approximately 150 intravenous immunoglobulin treatment (IVIG)-refractory cases for the purpose of the removal of inflammatory cytokine until now in our hospitals. In addition, PE gets consensus as the refractory treatment in the treatment guidelines for the Kawasaki disease.

Purpose: In this study, we examined the safety and efficacy of PE therapy for cases refractory to IVIG treatment in the multi-institutions in Japan.

Result: This therapy performed to approximately 260 cases in the 11 institutions, and we finally got good results.

Conclusions: The effectiveness in PE is known in some serious cases refractory to other treatments. And, by recent innovative technical progress, even a baby weighing 5 kg in weight came to be able to perform PE treatment. This report will show the future direction of PE therapy for cases refractory to IVIG treatment in KD.



SY18-03 Plasma exchange and chelator therapy rescues acute liver failure in Wilson disease without liver transplantation: Form our experiences

Jun Kido

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Wilson disease (WD) is an autosomal recessive disorder of copper metabolism associated with a defect in the ATP7B gene. WD patients develop a variety of symptoms including hepatic disorders, neuropsychiatric abnormalities, Kayser-Fleischer rings, and hemolysis in association with acute liver failure (ALF), because of the accumulation of copper in various organs. WD is a progressive disease that leads to liver cirrhosis. WD in patients developing ALF with a New Wilson Index (NWI) score 11 or more is fatal, and it was considered that WD patients who develop ALF and have an NWIS more than 11 cannot survive without LT. However, we had experienced WD patients with an NWIS more than 11 who recovered from ALF with plasma exchange (PE), zinc (Zn) therapy, and chelator therapy. Here, I describe the rescued patients developing with ALF in WD and discuss the available treatment options. Even in cases of severe ALF with grade I or II encephalopathy, patients with WD can be rescued in the combination treatment of Zn, chelator, PE and CHDF without LT. Therefore, it is important to evaluate the effect for combination treatment of Zn, chelator, PE and CHDF while preparing for LT, as the condition may not improve without LT. Pediatricians or physicians should ask transplant surgeons to perform LT urgently if required.

SY18-04 Therapeutic Plasma Exchange Treatment for Wilson's Disease in the USA

Chisa Yamada

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Background: Wilson's disease is an autosomal recessive genetic disorder with a higher prevalence seen in some countries due to high rates of consanguinity. The mutation in the ATP7B gene causes impaired biliary copper excretion resulting in copper accumulation in multiple organs, and hemolysis due to increased oxidative stress on the erythrocytes from the accumulation of copper in the cells. The asymptomatic patients are usually managed with diet and medications. However, many of the patients in the US are found to have Wilson's disease with sudden liver failure and receive therapeutic plasma exchange (TPE) in addition to pharmacological treatments until the patients receive liver transplantations (LTs).

Methods: TPE treatment for Wilson's disease in the US will be discussed with reference to the American Society for Apheresis (ASFA) guidelines and the publication of ASFA apheresis registry study on Wilson's disease.

Results: TPE treatment for fulminant Wilson's disease is a category I, Grade 1C recommendation in ASFA guidelines, which means TPE is strongly recommended but the quality of evidence is low. All reports were case reports due to rarity of the disease in the US, therefore, we created a Wilson's disease registry through ASFA research committee and collected data of 10 patients from multiple institutions. Among those patients, only one patient was previously diagnosed as Wilson's disease. All patients received 1 to 9 procedures daily or 3 times a week with plasma as sole or part of the replacement fluid. Nine patients received LT and all patients survived in study period, at least 6 months.

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Conclusions: The patients with fulminant Wilson's disease often receive frequent TPE treatments with plasma as the replacement fluid until they receive LT with good survival rate. Although definitive efficacy of TPE treatment cannot be assessed because it was retrospective study without control group, TPE treatment is strongly recommended.

Symposium 20 Therapeutic apheresis for rheumatic diseases

SY20-01 Plasma Exchange and Immunoabsorption in Connective Tissue Diseases

Andreas Kronbichler

Department of Internal Medicine IV (Nephrology and Hypertension,) Medical University Innsbruck, Austria

Plasma exchange (PLEX) and immunoabsorption (IAS) are reserved for specific indications in the management of specific connective tissue diseases. In the lecture, I will focus on rare indications for extracorporeal therapy measures. In cases with scleroderma renal crisis and concomitant microangiopathy or in patients with intolerance to angiotensin-converting enzyme inhibitors PLEX can be considered as a treatment option. Moreover, studies focused on progressive systemic sclerosis or cases with underlying Raynaud phenomenon. Introduction of biological agents reduced the importance of PLEX in the management of rheumatoid arthritis. A brief historical overview will be provided. Management of polymyositis and dermatomyositis may be challenging. A controlled trial assigned patients to undergo PLEX, leukapheresis or sham apheresis found no difference in the number of subjects with improvement of strength and functional capacity. PLEX was used in the management of cases with anti-synthetase or anti-MDA-5 dermatomyositis-pulmonary syndrome and outcome related to mortality does not support its use. PLEX has not proven to be effective in psoriatic arthritis. Finally, aspects of systemic lupus erythematosus (SLE) and extracorporeal measures will be discussed and results of an international survey among experts in the field of SLE and a proposed randomized controlled trial (IMMUNO-LUPUS) will be presented.

SY20-02 Extracorporeal Treatment in Systemic Lupus Erythematosus

Katharina Artinger

Division of Nephrology, Department of Internal Medicine Graz, Austria

Background: Systemic lupus erythematosus is a chronic autoimmune disease with systemic involvement and a wide range of clinical presentation. Autoantibodies, immune complexes and deposition of complement cause tissue injury which leads to organ damage. Current therapy options include cyclophosphamide, azathioprine, prednisone, methotrexate, mycophenolate mofetil, cyclosporine and strategies targeting immune cells like for example rituximab. Although immunosuppressive regimens improve the prognosis of many patients, patients with refractory disease do not show good response to conventional therapy. Since extracorporeal treatment is effective in different other antibody-mediated diseases, plasma exchange and immunoabsorption have been discussed as alternatives in the treatment of systemic lupus erythematosus for many years now.

Methods: Literature search was performed using PubMed and the following key words: plasma exchange, immunoabsorption, systemic lupus erythematosus, lupus nephritis.



Results: Both, plasma exchange and immunoadsorption remove antibodies in patients suffering from systemic lupus erythematosus. In systemic lupus erythematosus associated with critical illness (for example with CNS involvement or in association with diffuse alveolar hemorrhage), a beneficial effect of plasma exchange is well documented. In lupus nephritis, best evidence for a beneficial effect of plasma exchange and immunoadsorption was found in patients with severe, refractory disease since patients with new onset of disease are likely to respond well to conventional therapy initially. Further, improvement is expected in pregnant patients and patients with antiphospholipid syndrome considering current research.

Conclusion: Extracorporeal treatment with plasma exchange or immunoadsorption is beneficial in patients suffering from systemic lupus erythematosus with severe disease activity refractory to conventional therapy.

SY20-03 The improvement of severe systemic lupus erythematosus with the combined Plasmapheresis and immunosuppressive treatment: a cohort review

Yan Qin, Cai Yue, Ying Wang, Ke Zheng, Jie Ma, Liting Chen, Jinghua Xia, Limeng Chen, Xuewang Li, Xuemei Li

The Kidney Division of Peking Union Medical College Hospital, Beijing, China

Objective: To investigate the therapeutic effect of plasmapheresis on severe systemic lupus erythematosus(SLE), a retrospective review was carried out for all patients with severe SLE in our center between 2011 and 2019.

Methods: A total of 82 SLE patients diagnosed of lupus cerebritis, DAH, thrombotic microangiopathy(TMA), RPGN or antiphospholipid antibody syndrome (APS) were treated by double-membrane plasmapheresis combined with immunosuppressive treatment in Peking union medical college hospital from 2011 to 2018. Their clinical data were collected to compare the improvement of clinical and laboratory indicators before and after treatment and observe the side effects of plasmapheresis.

Results: 30 of the 82 SLE patients associated with TMA and 2 patients associated with APS. There were 96.8% patients with AKI, 38.7% with pulmonary involvement, 29% with central nervous system involvement, and 16.1% with cardiac involvement. Eighty-two patients underwent 3-15 times plasmapheresis, with a volume of 1-1.5 plasma equivalent. SLEDAI score (17.5 vs 11.5, $p<0.001$), serum creatinine level (283.3 ± 166.0 vs 229.6 ± 156.5 , $p=0.018$), ANA titer ($\log\text{ANA}2.51\pm 0.49$ vs 2.09 ± 0.45 , $p=0.001$), anti-double-stranded DNA antibody titer ($\log\text{ds-dna}1.19\pm 0.66$ vs 0.87 ± 0.40), ESR(37 vs 4) were decreased in all patients after plasma exchange. Complement C4(0.09 ± 0.05 VS 0.14 ± 0.07) was higher than before replacement. As for side effects, hypotension during plasma exchange was observed in 4 patients, pulmonary infection secondary to treatment in 6 patients, and bleeding in 3 patients.

Conclusion: Plasmapheresis combined with immunosuppressive agents can improve the SLEDAI score and renal function of patients with severe lupus. Plasmapheresis is an important adjuvant therapy for severe systemic lupus erythematosus.

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SY20-04 Therapeutic apheresis for anti-melanoma differentiation-associated gene 5 antibody-positive inflammatory myositis associated rapidly progressive interstitial lung disease

Makio Kusaoi, Go Murayama, Masahiro Kogami, Yoshiyuki Abe,
Takuya Nemoto, Naoto Tamura, Ken Yamaji

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Anti-melanoma differentiation-associated protein 5 (MDA5) antibody-positive inflammatory myositis present no or few muscular manifestations but typical cutaneous symptoms, termed Clinically amyopathic dermatomyositis (CADM). Rapidly progressive interstitial lung disease (RP-ILD) occur in about 71% of MDA5-positive CADM, is often refractory and has a fatal course. Multi-immunosuppressant combination therapy including methylprednisolone, calcineurin inhibitor, and cyclophosphamide is reported to improve the 2-year survival rate from approximately 30% to about 75%, although still about 25% of cases die of respiratory failure within 6 months of onset. In an analysis of the 1 year survival outcomes of 11 cases (7 cases received therapeutic plasma exchange (TPE), 4 cases are historical controls who did not received TPE) who did not respond to immunosuppressant combination therapy in our facility, Of the 4 patients who did not received the therapeutic plasma exchange, 3 died of respiratory failure associated with RP-ILD deterioration. In contrast, only one of the 7 patients treated with TPE died of aggravation of lung cancer. In this symposium, we will review the strategies for anti-MDA5 antibody related RP-ILD and summarize the usefulness of therapeutic apheresis including polymyxin B hemoperfusion and plasma exchange.

SY20-05 Efficacy of Plasma Exchange and Prognostic Factors in Anti-MDA5 Antibody-positive Dermatomyositis with Interstitial Lung Disease

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Background: Anti-MDA5 antibody-positive dermatomyositis (DM) is often associated with life threatening rapidly progressive interstitial lung disease (RP-ILD). Combined immunosuppressive therapy using high-dose glucocorticoids, calcineurin inhibitors and intravenous cyclophosphamide has been suggested to be effective in the disease, but some patients are still resistant to the therapy. We examined the utility of plasma exchange (PE) for such intractable cases and intended to investigate the prognostic factors of this disease and the good indication of PE.

Methods: A retrospective study included 38 anti-MDA5-positive DM-ILD patients who received the combined immunosuppressive therapy. Their clinical information was collected from medical records. Serum cytokines were evaluated by multiplex assay before treatment.



The patients were divided into two groups; those who achieved remission without exacerbation of respiratory dysfunction (n=25, group A) and those who progressed hypoxemia during the treatment (n=13, group B).

Results: PE was performed in 8 of group B, but none in group A. Among group B, five of the 8 treated with PE survived, while all of the 5 without PE deceased (P=0.04). Higher neutrophil/lymphocyte ratio, higher serum ferritin, hypoxemia before treatment and the increase of KL-6 in the first 4 weeks of the treatment were the prognostic factors for disease progression. Many kinds of serum cytokines such as sIL-1, IL-6, IL-8, IL-10, IL-12p70, IL-18, and sCD163 levels were higher in group B than group A.

Conclusion: PE seems to be one of the effective adjuvant treatments in anti-MDA5-positive DM with RP-ILD, probably preventing exacerbation of tissue damage by removing inflammatory cytokine storm derived from monocyte/macrophage as well as pathogenic autoantibody. Predicting disease course by combination of prognostic factors may help us to decide the indication of apheresis and patients to achieve favorable outcome.

Symposium 21 Role of apheresis therapy in liver failure 1

SY21-01 Advancement in Liver Failure and Artificial Liver

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Liver failure is a syndrome with rapid progress, poor prognosis and a high mortality estimated 60-80%. From middle 1980s to late 1990s, we began to use plasma exchange to treat liver failure and gradually developed a new artificial liver system called Li's artificial liver system (Li-ALS), provide detoxification metabolism, synthetic balance and other functions, to improve the survive rate of patients with hepatic failure. We lead to formulate 'the guidelines for the treatment of liver failure with non-biological artificial liver(Li-NABL)', normalized and standardized the treatment of artificial liver, simplified the clinical treatment process, reduced the dosage of plasma, improved the clinical treatment effect, and significantly improved the survival rate of patients with liver failure. The model experiment of treatment of acute liver failure in large animals with Li-ALS suggested that the survival time was significantly prolonged. We created a new method for the therapy of end-stage liver disease by combination of Li-ALS and liver transplantation to win the waiting time for liver transplantation and improve the survival rate of severe liver disease significantly. We have innovatively applied Li-ALS to the therapy of severe H7N9 patients, effectively blocking the H7N9 cytokine storm, improving multi-organ failure, and significantly reducing the case fatality rate. We developed a novel diversion-type microcapsule-suspension fluidized bed bioreactor, to better maintain the growth, activity and cell function in the reactor. Meanwhile some research has been done on improving cell source. In our research, large animal(pig) model of fulminant hepatic failure were rescued by intrahepatic transplantation of human bone marrow mesenchymal stem cell (hBMSC). Based on the latest research results domestic and overseas, we managed to formulate the latest version of the "guidelines for the diagnosis and treatment of liver failure" to further guide and standardize the diagnosis and treatment of liver failure in China.

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SY21-02 Extracorporeal Liver Support (ELS) in acute and acute on chronic Liver Failure

Jan Stange

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Since 1990, ELS has shifted from investigator driven initiatives to commercially available options which enabled the conduct of larger trials and provided datasets to support the concept of ELS, specifically the concept of removing albumin bound toxins, such as bile acids. In addition it contributed to the formation of multiple consortia (such as APASL, CLIF and NACSELD) aiming to stratify patients in order to improve the probability of successfully extending survival for the patients by ELS. This research also identified the need for better biomarkers than just bilirubin. One new concept utilizes the patient's albumin binding function as a negative imprint to assess the extent of overload with liver failure related albumin bound toxins. The latter identified the need to further improve efficacy of current ELS systems, which have seen almost 20 years of a life cycle, to reconstitute the severely compromised binding functionality of patient's albumin in a safe manner. In terms of mechanism of actions, one has to differentiate between albumin dialysis such as MARS, ADVOS or OPAL, plasma filtration and/or adsorption such as PROMETHEUS or DIALIVE, hemo-adsorption such as CYTOSORB and more recent forms of extracorporeal cellular therapies such as ELAD. These therapies have strengths and weaknesses and in certain cases they may be used synergistically in the very near future. The largest datasets currently available exist for extracorporeal albumin dialysis (ECAD) which has made first META-Analysis possible. In general, authors agree that at least survival time can be extended, which is critical for patients on the transplant waiting list.

In conclusion, when the introductions of renal dialysis or ECMO are used as analogues, there are clear predictors that the use of these technologies will increase with improved devices and better understanding of patient stratification.

SY21-03 High-volume filtrate hemodiafiltration improves recovery rate from hepatic encephalopathy in acute liver failure patients

Ryuzo Abe

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Background: Although only liver transplantation (LT) is proven to be effective on mortality of acute liver failure (ALF), artificial liver support (ALS) systems are needed to maintain patients' condition until LT or recovery of the native liver. However, no specific method has been established yet.

Materials & Methods: Recovery rate from hepatic encephalopathy (HE) was analyzed in one hundred and twenty-one consecutive adult patients with ALF who underwent ALS between 1988 and 2018. During the study period, we utilized five types of ALS in combination of plasma exchange (PE) and hemodiafiltration (HDF). ALS was performed as follows: group-1) PE, group-2) PE+ continuous HDF (CHDF), group-3) high-flow dialysate CHDF (HFCHDF), (flow rate of dialysate: 300mL/min), group-4) HFCHDF (flow rate of dialysate: 500mL/min), group-5) high-volume filtration CHDF using on-line water delivery system (OLHDF) (flow rate of dialysate: 300mL/min, filtration rate: 200mL/min).



Results: Enhanced amount of blood purification results improved recovery rate from HE: group-1) 33.3% (n=3/9), group-2) 47.1% (n=16/34), group-3) 57.7% (n=15/26), group-4) 88.6% (n=31/35), group-5) 88.2% (n=15/17). Groups 4 and 5 demonstrated statistically significant difference between other three groups. In group 5, all patients recovered consciousness after OLHDF treatment, except for two patients who could not be fully treated because of circulatory failure, including those whose liver function were completely abolished. Comparison between group 3 and 4 revealed that flow rate of dialysate could directly affect arousal rate from HE. To avoid the bias of improvement of other treatments during study period, recovery rates of consciousness were examined after exclusion of patients who recovered without LT: significant differences were also observed between groups 4/5 and other three groups.

Conclusions: ALS systems whose intensity is enhanced can improve consciousness and general condition of ALF patients. It also makes possible gaining time for LT or liver regeneration.

SY21-04 Continuous Plasma Exchange with Dialysis for Patient with Acute Liver Failure

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Selective plasma exchange with dialysis (PED) is a type of apheresis in which simple plasma exchange is performed using a selective membrane plasma separator (Evacure EC-2A) while the dialysate flows out of hollow fibers. We developed continuous PED (cPED), which is performed in a single 48-hour session. To evaluate the effect of cPED, biochemical testing was performed in patients with acute liver failure (ALF). We examined 10 patients with ALF who received therapy (28 times in total). Creatinine levels and the international normalized ratio decreased significantly, while total protein and fibrinogen levels increased significantly after treatment. Continuous PED may be useful as blood purification therapy for removal of toxic substances and preservation of coagulation factors in patients with ALF.

Symposium 22 Role of apheresis therapy in liver failure 2

SY22-01 A referral system and an artificial liver support system as intensive care for patients with acute liver failure

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In Japan, acute liver failure (ALF) is defined as an acute liver injury with prolonged prothrombin time and is further classified into two groups, one with and the other without hepatic encephalopathy (HE). The survival rate in ALF with HE is extremely poor compared with that in ALF without HE. Thus, preventing and predicting HE development are important in the treatment strategy for ALF. To achieve this aim, identification of patients with high risk associated with HE development is crucial. For this purpose, we established a referral system of patients with ALF in a regional hospital at the north area of Tohoku (Takikawa Y, et al. J Hepatology, 2009). As a result of using this system, early intervention decreased the rate of HE development in patients with ALF (Kakisaka K, et al, Cytokine, 2016). However, some patients progressed to ALF with hepatic encephalopathy even though early intervention had been appropriately performed. In ALF patients with HE, the use of an artificial liver support

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(ALS) system plays an important role in maintaining the patients' good condition until recovery from ALF or during preparation for liver transplantation. Recently, on-line continuous hemodiafiltration (CHDF) has shown a high rate of recovery of conscious level in patients with ALF. Although on-line CHDF is the standard treatment method for ALS, it was not performed in general hospitals because it requires specific arrangements. We developed a new high-volume plasma purification system using an on-line CHDF system based on the existing off-line CHDF apparatus for renal replacement therapy. Moreover, the existing equipment to generate dialysate, which is required in the previous on-line CHDF, is not required. Therefore, the new on-line CHDF can be used at bedside for patients with ALF. This system showed extremely high efficacy for regaining consciousness and excellent safety as therapy for patients with ALF.

SY22-03 Overview of artificial liver support in Japan

Kazuaki Inoue

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The contribution of liver transplantation has improved the survival rate of acute liver failure (ALF), however, no liver support device has improved survival rate for this syndrome. The primary purpose of artificial liver support (ALS) is to sustain patients with ALF for long enough for the patient's liver to regenerate and regain its function. In cases where the liver cannot regenerate or is progressively deteriorating, ALS should support liver function until transplantation is successfully performed. If these liver support systems had the capability to sustain patients with ALF in a favorable condition, survival rates would be improved and the criteria for liver transplantation would be simpler and more accurate. The liver plays a central role in metabolism. Therefore, complicated metabolic abnormalities occur in ALF; bleeding as a result of depletion of clotting factors and coma due to the accumulation of neurotoxic metabolites are the two major life-threatening symptoms of ALF. In ALS systems, plasma exchange (PE) aims to replace coagulation factors while on-line hemodiafiltration (HDF) with huge volume of buffer aims to provide detoxification. It is generally accepted that promising observational data of medical interventions should be verified by RCTs. However, observational studies are rarely free from bias or confounding factors, and the outcome of patients with ALF is easily affected by etiology, complications and spontaneous recovery. Therefore, an RCT with a small number of patients is not also free from bias and confounding factors. PE and on-line HDF using huge volume of buffer is widely accepted as an effective standard treatment in Japan. In clinical practice, the pragmatic approach for decision-making should take into account the risks and benefits of the local situation, not those of the ideal situation. To sustain a patient that falls into an hepatic state in an alert condition is the ultimate endpoint of ALS.



Symposium 23 Recent advance in TPE for neurological disorders 1

SY23-01 Japan-Plasmapheresis Outcome and Practice Patterns Study (J-POPPS) for Neurological diseases: A multi-center real world survey

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- 6) General Hanamaki Hospital, Japan
- 7) Hokkaido Medical Center, Japan
- 8) Juntendo University Hospital, Japan
- 9) Okinawa National Hospital, Japan
- 10) Kagoshima City Hospital, Japan
- 11) Chiba University Hospital, Japan
- 12) Hyogo College of Medicine Hospital, Japan
- 13) Toyama University Hospital, Japan
- 14) Asahi-Kasei Medical Co., Japan
- 15) Nagasaki National Hospital, Japan

Background/Aim of Study: Disease-modifying drugs have widened therapeutic options in some neuroimmunological diseases. Plasmapheresis has been an approved therapy for acute relapse or progression of selected neuroimmunological diseases since the 1980s and is listed in the therapeutic guidelines. However, real-world studies regarding whom to administer plasmapheresis and how to manage the patients are lacking. We searched recent real-world data of plasmapheresis for neurological diseases for efficacy and safety, to obtain useful information to optimize management.

Materials & Methods: We recruited 210 patients among individuals subjected to plasmapheresis from June 2017 to March 2019 from 13 representative hospitals. We analyzed disease type and procedure approaches such as immunoadsorption plasmapheresis (IAPP), double filtration plasmapheresis (DFPP), and plasma exchange (PE), and evaluated their efficacy and safety. We adopted the modified Rankin Scale (mRS) and Barthel Index (BI) as a universal scale alongside each disease-specific scale.

Results: Eight-six cases of myasthenia gravis (MG), 30 cases of multiple sclerosis (MS), 25 cases of neuromyelitis optica (NMOs), four cases of Guillain-Barre syndrome (GBS), 10 cases of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) and 55 cases of other diseases including 33 cases of autoimmune encephalitis and six cases of Hashimoto thyroiditis were enrolled. IAPP, DFPP, and PE were performed 613, 53, and 200 times, respectively, while vascular access was achieved either by single puncture (n=606 times) or catheterization (n=288 times). Adverse effects were reported in 13 cases, comprising mostly nausea in six cases. Only two cases presenting catheter infection were discontinued. Comparison of efficacy before, during, and after the procedure showed, there was some tendency to relieve the symptoms after the procedure for MG, NMOs and other diseases, whereas efficacy was already better during

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the procedure in MS patients.

Conclusions: Plasmapheresis may be an efficient and safe therapy in additional neurological diseases besides the four currently approved diseases.

SY23-02 Therapeutic Plasma Exchange in Neurological Disorders

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Therapeutic apheresis has been an effective treatment modality in several disorders, including several neuromuscular disorders as well as central nervous system diseases. The American Society for Apheresis (ASFA) Journal of Clinical Apheresis (JCA) contributes evidence-based guidelines on the use of therapeutic apheresis for clinical practices, based upon extensive literature reviews and continuously revised incorporating new information. Indications for treatment are stratified into 4 categories. Diseases which therapeutic apheresis are accepted as first and second line therapies are listed in Category I and II, respectively. Therapeutic plasma exchange (TPE) has long been used. More recently, with increase in information on immunoadsorption (IA) method, recommendations have been revised and the JCA Eighth Edition was published in June 2019(1). In this new version, the list of neurological disease/condition in Category I which include Guillain Barre syndrome (GBS), chronic inflammatory demyelinating polyneuropathy (CIDP), moderate to severe myasthenia gravis (MG), paraproteinemic demyelinating neuropathy associated with IgG/IgA/IgM monoclonal gammopathy and N-methyl D-aspartate (NMDA) receptor antibody encephalitis) is similar to the Seventh Edition 2016(2) except that progressive multifocal leukoencephalopathy (PML) associated with natalizumab has been moved to Category III, and IA has become an alternative technique in GBS, CIDP, MG and NMDA receptor antibody encephalitis. Diseases in Category II are acute disseminated encephalomyelitis (ADEM) unresponsive to steroids, Lambert-Eaton myasthenic syndrome, pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS), acute relapses in multiple sclerosis (MS) and neuromyelitis optica spectrum disorders (NMOSD), diseases associated with voltage-gated potassium channel (VGKC) antibodies and steroid-responsive encephalopathy associated with autoimmune thyroiditis (SREAT) or Hashimoto's encephalopathy. Efficacy of immunoadsorption (IA) method has been added in MS, NMOSD and VGKC. With more newly recognized immune-mediated neurological disorders, studies on the efficacy of TPE, IA compared to other immunomodulatory treatment such as high dose steroids or intravenous immunoglobulins (IVIG) would continuously warrant revision of the indications for a better treatment outcome.

Reference:

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SY23-03 Plasmapheresis in Autoimmune Encephalitis

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Background/Aim of study: In the patients with autoimmune encephalitis (AIE), limbic encephalitis is a common clinical features presented with seizures, short term memory loss, or behavioral/psychiatric symptoms. The first line immunotherapies consist of high-dose corticosteroids pulse therapy, plasmapheresis, and intravenous immunoglobulins (IVIGs). The second line treatments consist of rituximab and cyclophosphamide. In this study, we will analyze the clinical presentation, brain MRIs and treatments among patients with different anti-neuronal autoantibodies.

Materials & Methods: Patients with encephalopathy/encephalitis with undetermined causes from August 2013 to September 2018 were recruited. We evaluate the demographic data, seizure classification, location of MRI lesions, EEG findings, and managements between subjects with different neuronal autoantibodies.

Results: Total 439 subjects (F:M=61:39) were recruited over a 5 - year period. 50 (11.4%) patients with anti-neuronal autoantibodies, including 34 cases with anti-NMDA antibodies, eight with GABAB, six with LGI-1, and two with AMPA 2, were collected for further analyses. Patients with anti-NMDA encephalitis tended to be younger female and have more frequent respiratory failure or arrhythmia compared to the other three groups. Seizures (84%) were common among the 50 AIE patients, while generalized seizures were predominantly seen in patients with anti-NMDA encephalitis and partial seizures were more often found in LGI-1 encephalitis. Brain MRIs were unremarkable in 20 cases (40%), and the most common abnormal lesions were located in temporal lobes (16 cases, 32%). 39 patients (78%) received first line immunotherapies, four patients in anti-NMDA encephalitis had additional second line therapies, and four cases (two anti-NMDA and two GABAB) had further chemotherapy. The mortality rate was 6%, and all the three patients had anti-NMDA encephalitis.

Conclusion: Autoimmune encephalitis is a rare but treatable disease. Early confirm diagnosis and prompt immunotherapies are very important.

Symposium 24 Recent advance in TPE for neurological disorders 2

SY24-01 Apheresis treatment to autoimmune disorders in central nervous system: Therapeutic strategy in relapsing NMOSD and MOG-IgG+disease

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Plasmapheresis (PP) has been widely used for the treatment of acute phase in autoimmune neurologic disorders, such as neuromyelitis optica spectrum disorders (NMOSD), anti-myelin oligodendrocyte glycoprotein (MOG) antibody-related neurologic disease (MOG-Ig-G+disease), multiple sclerosis, N-methyl-D-aspartic acid (NMDA) receptor encephalitis, Guillain-Barre syndrome, chronic inflammatory demyelinating polyneuropathy, myasthenia gravis. In this presentation, we discuss the therapeutic strategy for relapsing phase of autoimmune neurologic disorders in central nervous system, focused on NMOSD and MOG-IgG+disease. In relapsing phase, the first-line treatment is intravenous methylprednisolon (IVMP). The IVMP is effective in about 60% of cases, and PP is performed as a rescue therapy in such IVMP refractory cases. However, the effectiveness

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of PP depends on the timing of start, and early institution of PP is associated with the effectiveness. Therefore, predicting for efficacy of IVMP contributes to the early institution of PP. We have shown that IVMP effectiveness is associated with the degree of blood-cerebrospinal fluid (CSF) barrier disruption, indicated by quotient of CSF / serum albumin and IgG. The early rescue therapy such as PP should be considered in cases with severe blood-CSF barrier disruption. In this symposium, we introduce a therapeutic strategy for relapsing NMOSD and MOG-IgG+disease by prediction of IVMP failure.

SY24-02 Plasmapheresis in patients with dual diagnosis of myasthenia gravis and neuromyelitis optica spectrum disorder

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Coexistence of myasthenia gravis (MG) and neuromyelitis optica spectrum disorder (NMOSD) has rarely been documented. We report four patients with dual diagnosis of MG and NMOSD (MG-NMOSD) in our MG database registered for past 26 years and compare the clinical course to that of cases reported in the literature. In our series, 3 out of 4 patients (75%) presented with generalized MG first and achieved minimal manifestation status at the onset of NMOSD, which is consistent with previous observation. Regarding the myelitis part, over 60% MG-NMOSD patients had major motor disability in the literature, all our 3 patients with myelitis recovered well with minimal sequelae of numbness and neuropathic pain including one paraplegic attack rescued by IVMP pulse therapy and plasmapheresis (IVMP-PP). In contrast, the visual outcome of our 2 patients with optic neuritis (ON) were poor even partial recovery of one eye vision after IVMP-PP therapy. In summary, our Taiwanese MG-NMOSD patients followed the similar benign course of MG as reported, but had worse outcome of ON with better prognosis of myelitis as compared to the literature. IVMP-PP therapy might provide some rescue to prevent major disability due to severe attacks of NMOSD.

SY24-03 Apheresis for immune neuropathy: Proper use with IVIG

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High-dose intravenous immunoglobulin (IVIG) and plasma pheresis (PP) are equally effective in the treatment of immune neuropathies such as Guillain-Barre' syndrome and chronic inflammatory demyelinating polyneuropathy. In recent years, there are many facilities which use IVIG as the first choice because of simplicity and wideness of adaptation. However, IVIG cannot be used for patients with IgA deficiency, renal dysfunction, cardiac dysfunction, cerebrovascular disease or their history, and high risk of thrombosis or embolism. PP includes simple plasma exchange (PE), double filtration plasmapheresis (DFPP), and plasma adsorption (PA). Although the efficacy of these treatments is thought to be equally, it should be noted that only PE has been validated in large controlled trials. In Japan, DFPP and PA have been also approved by national insurance. DFPP or PA is often selected for patients who are at risk for PE treatment, such as the elderly and patients with marked changes in blood pressure, and patients who want to avoid the use of albumin, a blood product.



Guideline Session 1

GS1-01 The JSFA clinical practice guideline for Therapeutic Apheresis

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Therapeutic apheresis can be characterized by the application to seriously ill patients with an intractable disease and its involvement with a wide range of medical departments. Meanwhile, this treatment poses several problems. One of those problems is that due to the intractableness and seriousness of target diseases the background of patients and their course of treatment vary by individual cases and there is a limited number of such cases. Therefore, it is difficult to conduct major-scale randomized-control trials for securing high-quality evidences.

Guidelines have been prepared in various medical fields including the apheresis. Specifically, American Society for Apheresis (ASFA) issued its guideline in 2007, which has been repeatedly revised thereafter until its latest 2019 edition. However, since the centrifugal separation method is mainly employed for therapeutic apheresis in the U. S. and its target diseases as well as backgrounds are different from those of Japan, introducing ASFA guideline to Japan as it will create a lot of issues.

The Japanese therapeutic apheresis has several features and is a world-class treatment. In Japan, therapeutic apheresis has been developed which uses hollow-fiber blood purification equipment such as membrane plasma separators and adsorption blood purification equipment such as endotoxin adsorption columns. There is a clinical engineer technologist system to be proud of in the world. The clinical engineering technologist is the only one national certificate in the world that allows its holder to be in charge of clinical use and safety control of the equipment as a member of medical team. The clinical engineer technologist system plays the central role in medical-engineering collaboration.

The Japanese unique medical framework under which clinical engineering technologist as well as medical doctors are cooperatively responsible for therapeutic apheresis.

The purpose of this JASF guideline is to further advance therapeutic apheresis in Japan, and the Japanese original therapeutic apheresis technic delivering to the world.

GS1-02 The Chapter for the Kidney Diseases, the Japanese Society for Apheresis Guideline

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A wide range of kidney diseases is targets of therapeutic apheresis. The current version of the American Society for Apheresis (ASFA) guideline also includes kidney diseases. The working group set the scope of the chapter of kidney disease in this guideline as to the condition which fulfills the following criteria; condition reimbursed by Japanese health insurance system, included by the ASFA guideline, or anticipated to be included in the reimbursement system shortly. Thus, we selected eight conditions; desensitization before kidney transplantation, recurrence of FSGS in the transplanted kidney, anti-GBM antibody-associated RPGN, ANCA-associated RPGN, dialysis-related amyloidosis, diabetic nephropathy, cholesterol crystal

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embolism, and refractory nephrotic syndrome.

We performed a systematic review on the database of Pubmed and Ichushi by Japan Medical Abstract Society. The formal process of the systematic review revealed that the volume in the evidence obtained through the process was varied, especially for some modalities of therapeutic apheresis. Therefore, we did not perform a meta-analysis of the obtained evidence. We determined the category and recommendation grade for each condition; some of them are determined by the modalities of apheresis. This process was performed through the discussion and Delphi. In this lecture, we would like to present the process of a systematic review and the resultant category and grade of each condition in the field of kidney diseases.

GS1-03 Clinical practice guidelines for therapeutic apheresis in emergency and critical care

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The Japanese Society for Apheresis has published guidelines on the use of therapeutic apheresis in patients receiving emergency and critical care. The features of the guidelines are that case reports in Japanese were also surveyed because instructive case reports were occasionally written in Japanese. Second, we referred to plasma filtration with dialysis (PDF), which was developed in Japan. PDF is an apheresis by which simple plasma exchange is performed by using a selective membrane plasma separator while the dialysate flows out of the hollow fibers. In this session, we will present a brief discussion of these two guidelines.

GS1-04 The apheresis guidelines for digestive diseases

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The apheresis guidelines for digestive diseases are divided into the following four fields: acute



liver failure (ALF); ascites; acute pancreatitis (AP); inflammatory bowel disease (IBD).

ALF: The liver transplantation has improved the survival rate of ALF patients whereas liver support devices have not. The primary purpose of artificial liver support (ALS) is to sustain ALF patients long enough for the liver to regenerate and regain its function. In cases where the liver cannot regenerate or progressively deteriorates, ALS should support liver function until transplantation is successfully performed, which would increase the survival rate.

Ascites: Refractory ascites is common in cirrhotic and cancer patients. Cell-free and Concentrated Ascites Reinfusion Therapy (CART) is an excellent treatment causing no protein loss. CART consists of paracentesis, filtration and concentration, all of which have some problems in standardization, which were considered in the guideline.

AP: Severe AP (SAP) is characterized by persistent organ failure and/or hypoenhanced lesion in enhanced CT scans and is most commonly caused by gallstones, alcohol, and hypertriglyceridemia (HTG). Because of its high mortality, intensive care including apheresis has been applied. Continuous hemodiafiltration can be useful in managing water balance and modulating excessive inflammatory reactions. The risk of HTG-induced pancreatitis increases markedly when triglyceride level exceeds 1000 mg/dL. Plasma exchange is the modality of choice in such patients.

IBD: Ulcerative colitis (UC) and Crohn's disease (CD) are the major forms of IBD. Although their etiology is still not fully understood, activated leukocytes are significant factors in their exacerbations. In Japan, granulocyte and monocyte apheresis (GMA) and leukocytapheresis (LCAP) are approved for IBD treatment. They are recommended for remission induction in UC patients with mild-to-moderate activity, whether steroid-resistant or -dependent. Although GMA is recommended for remission induction in colonic type CD refractory to conventional therapy, its efficacy is lower than in UC patients.

GS1-05 Guideline of Apheresis in Cardiovascular Disease

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Apheresis treatment has been performed to prevent or treat cardiovascular diseases such as familial hypercholesterolemia (FH), arteriosclerosis obliterans (ASO), Burger's disease and dilated cardiomyopathy. FH is a genetic disease that has high LDL-C levels, cutaneous and tendon xanthomas and coronary artery disease due to premature atherosclerosis. Lipoprotein apheresis was developed to decrease low density lipoprotein (LDL) cholesterol in patients with homozygous or heterozygous FH whose LDL-C cannot be controlled by oral agents such as statins, ezetimibe etc. Recently, inhibitors of PCSK9 and MPT have been on the market and the number of patients having lipoprotein apheresis was decreased. On the other hand, apheresis has still significant roles in preventing atherosclerosis. ASO is an atherosclerotic disease that has ischemic condition due to stenosis or obstruction in a main artery. Burger's disease is caused by vascular proliferation and inflammation. In ASO and Burger's disease, lipoprotein apheresis is indicated in patients with diffuse lesion that operation cannot be performed. The

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mechanism of action is not through removal of LDL but through many kinds of mechanism such as improvement of blood viscosity, improvement of endothelial function, enhancement of production of NO and prostaglandin I₂, anti-inflammatory function including production inhibition of adhesion molecules in white blood cells, enhancement of production of vascular growth factors including HGF and VEGF and reduction of oxidative stress, etc. Dilated cardiomyopathy is a disease that shows a progressive ventricular dilation with contraction disorder. It is characterized by low cardiac output, pulmonary congestion and arrhythmia. Dilated cardiomyopathy may be caused by autoimmune disorder followed by viral infection. Removal of autoantibodies against myocardium by immunosorbent is considered to be useful in dilated cardiomyopathy.

GS1-06 Guidelines on the use of therapeutic apheresis in pulmonary diseases: the potential treatment with direct hemoperfusion with polymyxin B-immobilized fiber column (PMX-DHP) for diffuse alveolar damage (DAD)

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There has been no report of control trial for the therapeutic apheresis in pulmonary diseases in Japan. The international evidence-based guidelines do not recommend apheresis in pulmonary areas. Recent clinical studies in Japan have suggested the beneficial effects of direct hemoperfusion with polymyxin B-immobilized fiber column (PMX-DHP) on oxygenation and prognosis in acute exacerbation of idiopathic pulmonary fibrosis (AE-IPF). The pathogenesis of AE-IPF has been reported to be diffuse alveolar damage (DAD), which has also found in severe respiratory diseases, including ARDS (acute respiratory distress syndrome), collagen-vascular disease related interstitial pneumonia, drug-induced lung injury, and so forth. The prognosis of DAD is reported to be extremely poor and no effective treatment has been established so far. PMX is an endotoxin removal cartridge and has originally developed for sepsis treatment in Japan. Apheresis with PMX has reported to improve oxygenation and prognosis in not only AE-IPF, but also in ARDS and other DADs. PMX-DHP has been approved for the advanced medical treatment of AE-IPF in Japan. Exploratory research on the safety and efficacy of PMX-DHP for the treatment of AE-IPF has been conducted and the results have showed better survival. Mechanism of PMX in DAD is still unclear and supposed to affect activated neutrophils and consequential inflammatory cytokines. From these results, PMX-DHP should be considered as a therapeutic option for DAD. Further control studies will be needed to establish the efficacy of therapeutic apheresis on severe respiratory diseases.



Guideline Session 2

GS2-01 Standardization of apheresis technologies

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Technical committee of the Japanese Society for apheresis (JSFA) has published the Apheresis Technical Manual every 5 years in Japan. The aim of publications is to provide the accurate knowledges for apheresis technologies to the medical staffs, nurses and clinical engineering technicians, in the blood purification unit of the medical institution and to practice safe and secure treatments. There are many types of devices in therapeutic apheresis, (1) hemofilters and hemodiafilters for continuous blood purification therapy (CBP), (2) plasma separators for therapeutic plasma exchange (PE), selective plasma exchange (SePE) and selective plasma filtration with dialysis (PDF), (3) plasma separators and plasma fractionators for double filtration plasmapheresis (DFPP) and cryofiltration, (4) hemoadsorbers or plasma adsorbers, (5) leukocyte removal filters for leukocytaphereis (LCAP) and granulocyte-monocyte adsorptive apheresis (GMA), (6) ascitic filtration filters and ascitic concentration filters for cell-free and concentrated ascites reinfusion therapies (CART), (7) centrifugation devices for therapeutic apheresis treatments, and etc. Proper selection of devices and machines, setting of adequate operating condition, safe and accurate operation should be established for each treatment by medical staffs. For the sake of putting this into practice, proper education and training are required for each medical staff. However, it depends on the situations in the institution. In the Apheresis Technical Manual, typical operating condition and optimal manipulations are standardized and described in briefly for each modality. It is useful for education and training for medical staffs.

GS2-02 Apheresis guideline in Japan for management and treatment of pemphigus, bullous pemphigoid and toxic epidermal necrolysis

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Pemphigus is an autoimmune bullous disease caused by autoantibodies to desmoglein 1 and 3. Pemphigus is classified into 2 types, pemphigus vulgaris and pemphigus foliaceus. Bullous pemphigoid is also an autoimmune bullous disease caused by autoantibodies to bullous pemphigoid antigens. The patients with these diseases are usually treated with systemic glucocorticosteroids. However, when they do not have enough effects, the treatments with plasmapheresis, intravenous high dose immunoglobulin, or immunosuppressants are added. Plasmapheresis is effective for the removal of autoantibodies and cytokines from the patients' sera. Double filtration plasmapheresis (DFPP) is covered by medical insurance once or twice a week up to for 3 months. Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are the severe types of drug eruption, characterized by fever, erythema, blisters, and erosions on the whole body skin surface and mucosal membranes. Use of the causative drugs is discontinued, and systemic glucocorticosteroids in high doses, including steroid pulse therapy, are widely known to be useful in the early stage. In addition, plasmapheresis is conducted, and

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intravenous high dose immunoglobulin is also applied. Plasma exchange (PE), selective PE or DFPP is used 2 or 3 times a week, totally up to 8 times to remove the cytokines, apoptosis-associated molecules, the causative agents, and the metabolites of the causative agents. Plasmapheresis is reported to be more useful when it starts at the early stage of these diseases. As the patients with these skin diseases, pemphigus, BP or SJS/TEN show a lot of erosions on the skin surface, it is most important to avoid skin infection, especially via blood vessel access. In addition, serum concentrations of immunoglobulin and albumin should be monitored. If they are reduced, these components should be supplied.

GS2-03 Japanese apheresis guidelines for the management and treatment of generalized pustular psoriasis, pustulosis palmoplantaris and psoriasis arthropathica

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Generalized pustular psoriasis (GPP) is a rare disease characterized by recurrent fever and systemic flushing accompanied by extensive sterile pustules. Treatments of GPP are usually topical corticosteroids, activated vitamin D3 ointment, ultraviolet light (UV) therapy, and oral administration of etretinate, cyclosporine, or methotrexate. Recently, biologics such as TNF- α inhibitors, anti-IL-17- and anti-IL-23 antibodies are used. Pustulosis palmoplantaris (PPP) is a chronic recurrent disorder of the palms and soles characterized by sterile intradermal pustules. PPP often accompanies joint symptoms. In some instances, PPP is associated with a focus of infection somewhere in the body; elimination of the infection sometimes improve symptom. Some treatments of GPP are used for PPP. Psoriatic arthritis (PsA) is a disease characterized by skin and nail psoriasis together with widespread musculoskeletal inflammation such as peripheral joint disease, axial joint disease, enthesitis, and dactylitis. Treatment of PsA is oral administration of NSAID's, cyclosporine, methotrexate and phosphodiesterase 4 inhibitors for mild to moderate cases. Biologics; TNF- α inhibitors, anti-IL-17- and anti-IL-23 antibodies; have been approved for severe or advanced cases. Granulocyte/monocyte adsorption apheresis (GMA) is an extracorporeal therapy designed to remove and suppress the functions of neutrophils, macrophages and monocytes that accumulate in the inflamed tissue and are involved in the pathogenesis. GMA may be considered as a safe treatment modality with few side-effects for GPP, PPP and PsA. The effect and safety of GMA have been reported mostly in case reports. Although the effect and safety of GMA were demonstrated in a multicenter study. GMA's utility is expected based on the mechanism of action.

GS2-04 JSFA guidelines for hematological disorders

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Plasmapheresis is applied for the treatment of many hematological disorders. Removal of toxic substances is the mainstay of the purpose for plasmapheresis. Infusion of large volume of beneficial substances into the space obtained by plasma removal is also important. Leukapheresis is performed to avoid leukostasis, tumor lysis syndrome and disseminated intravascular coagulation in the the case of hyperleukocytosis. Erythrocytapheresis is performed



to avoid hemostatic and thrombotic complications in the case of polycythemia. Plasma exchange applying fresh frozen plasma (FFP) is essential treatment to remove anti ADAMTS13 (a disintegrin like and metalloprotease with thrombospondin type 1 motif 13) antibodies and to infuse ADAMTS13 contained in FFP in the case of acquired thrombotic thrombocytopenic purpura (TTP). Plasmapheresis is sometimes performed to remove alloimmunized anti red cell antibodies in the case of red cell alloimmunization in blood type incompatible pregnancy when fetal anemia is severe and it is difficult to perform intrauterine transfusion. Plasmapheresis is sometimes performed to remove alloantibodies (hemophilia) or autoantibodies (acquired hemophilia) of coagulation factors if other treatments are unresponsive. Plasmapheresis is effective for the treatment of atypical hemolytic uremic syndrome (aHUS) with anti complement factor H antibodies to remove autoantibodies. Plasma exchange with FFP is often effective for aHUS patients with congenital complement regulation disorders to downregulate excessive complement activities. Plasmapheresis is performed to treat hyperviscosity syndrome associated with monoclonal hyperimmunoglobulinemia to remove monoclonal immunoglobulins to improve complications associated with hyperviscosity. Severe cases of Shigatoxin producing Escherichia Coli (Stec)HUS are sometimes treated with plasma exchange with FFP especially in the case with neurological complications.

GS2-05 JSFA Guidelines 2020 for Neurological Diseases

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Apheresis is a very effective treatment for neuroimmunological diseases. Apheresis is mainly given during the active phase of the disease for the purpose of calming and ameliorating the disease state. Furthermore, high therapeutic effects are expected by combining other treatments. In the Japanese insurance system, indications for apheresis for neurological diseases are limited to 4 diseases, myasthenia gravis, Guillain-Barre syndrome, chronic inflammatory demyelinating polyradiculoneuropathy, and multiple sclerosis/ neuromyelitis optica. However, apheresis has also been reported to be effective in other neurological diseases. In making the JSFA Guideline 2020, the new guidelines will examine the efficacy of apheresis therapy for the 40 diseases with reference to the 24 diseases of the neurological disorders in ASFA Guideline 2016. These neurological diseases are examined by category based on the evidence of apheresis treatment effect.

GS2-06 Description of new guidelines for therapeutic apheresis in the field of rheumatic disease

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The adaptive diseases of therapeutic apheresis in the field of rheumatology are rheumatoid arthritis(RA), systemic lupus erythematosus(SLE) with treatment-resistant rapidly progressive glomerulonephritis and/or neuropsychiatric symptoms, and ANCA-related vasculitis with refractory progressive glomerulonephritis. Furthermore, the efficacy of therapeutic apheresis for refractory anti-MDA5 antibody associated rapidly progressive interstitial lung disease(RPILD) whose fatal condition has become a major problem in Asia particularly in Japan has been reported in recent years. Although early Random Controlled Trial(RCT)s have not reported a clear advantage for plasma exchange in refractory lupus nephritis that does not respond to

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standard therapy, several observational studies have reported favorable outcomes with double filtration plasmapheresis and immunoabsorption plasmapheresis particularly in the early stage of lupus nephritis. For this reason, we rated the therapeutic apheresis recommendation for lupus nephritis as Grade 2B (Weak recommendation, moderate-quality evidence). Other SLE refractory conditions are classified as Grade 2C (Weak recommendation, low-quality or very low-quality evidence). In the cases of drug-resistant rheumatoid arthritis, there is a RCT which showed the significant efficacy of the Leukocytapheresis. The recommendation for apheresis for rheumatoid arthritis is determined to Grade 2B. For rapidly progressive interstitial lung disease associated with anti-MDA5 antibody-positive dermatomyositis refractory to multiple immunosuppressants, the evidence for the effectiveness of therapeutic apheresis is limited to a number of case reports. The recommendation is Grade 2C. Here we provide the new guidelines to present the latest findings on the timing, modality selection and number of treatments to incorporate the therapeutic apheresis into the treatment strategies for intractable rheumatic disease. Now, we would like to describe the guidelines we have prepared for SLE, RA, and anti-MDA5 antibody associated RPILD.

GS2-07 American Society for Apheresis (ASFA) Guidelines for Apheresis

Bruce Sachais

New York Blood Center, USA

The American Society for Apheresis (ASFA) has created evidence-based guidelines for apheresis indications and keeps these guidelines current by updating them regularly (approximately every 3 years). These guidelines are created by a special committee using systematic review and evidence-based approaches in the grading and categorization of apheresis indications. A fact sheet is generated for each indication which not only provides the ASFA categorization and GRADE designation, but describes the disease, overall treatment approach, and how apheresis may be incorporated into the treatment plan for the medical condition being reviewed. This talk will describe the process for guideline creation, the format and content of the fact sheets and highlight the evidence-based use of therapeutic apheresis in several diseases

Apheresis Manual Lecture

AM-01 Acute blood purification therapy in critical care

Takahisa Tabata

Acute blood purification therapy is often performed at the organ failure, such as liver failure and acute kidney failure. In recent years, CHDF (Continuous hemodiafiltration), which adsorbs mediators such as cytokines, is widely used in sepsis, multiple organ failure. PMX-DHP (Polymyxin B-immobilized fiber column-direct hemoperfusion), which adsorbs endotoxin, has also been used. The combination of selective plasma exchange and HDF (hemodiafiltration), PDF (plasma filtration with dialysis) has been generally available since 2015, and the choice of acute blood purification therapy has expanded. We comment on the treatment used in acute blood purification and introduce the combination of treatments in sepsis.



Technical Talk

TT1-01 Therapeutic plasma exchange

Therapeutic plasma exchange (TPE) is the most basic therapy of apheresis and can be performed on a membrane-based or centrifugation-based system. In Japan, almost all TPE is performed by membrane filtration and centrifugal TPE is performed in a few institutions. The appropriate TPE should be selected on the basis of the characteristics of the pathogenic substances, modalities, and replacement fluids, not to mention the patient's condition. In this technical seminar, how to perform TPE will be reviewed.

TT2-03 The safety and efficacy of selective plasma exchange

Selective plasma exchange (SePE) is a type of PE which uses a membrane plasma separator with a smaller pore size compared to conventional membrane plasma separators. A major feature of SePE is that small and medium molecular weight substances are removed, while larger molecular weight substances are not. Recently, SePE has become increasingly noted, because of its fewer side effects compared to PE, and its economic merits, as well as because there is fewer loss of coagulation factors compared to DFPP. In this presentation, I would like to discuss about the safety and efficacy of SePE.

TT2-04 Immunoabsorption in Japan

Immunoabsorption (IA) is an ideal modality for plasmapheresis because it does not need blood-derived products and eliminates pathogenic antibodies through plasma-adsorptive columns. In Japan, IA is usually performed for the treatment of autoimmune diseases using a membrane plasma separator with Immusorba TR-350 (IM-TR), Immusorba PH-350, or Selesorb column. However, these columns semiselectively adsorb due to electrostatic and hydrophobic interactions. For example, IM-TR has a high affinity for IgG3 and fibrinogen, moderate affinity for IgG1, and weak affinity for IgG2 and IgG4. The appropriate IA should be selected based on the characteristics of the pathogenic substances, membrane separators, and plasma-adsorptive columns.

TT3-05 Therapeutic Leukocytapheresis

Therapeutic leukocytapheresis is currently done by adsorptive granulomonocytapheresis (GMA) or by a leucocyte trapping filter called LCAP. As for the operation in real world, for GMA, treatment is done at a blood flow rate of 30mL/minute for 60 minutes, can be increased if desirable, while with the LCAP, the processed blood volume may be 30 mL/kg bodyweight with the flow rate at 30 to 50mL/minute depending on the patient's weight and the desired processed blood volume. In this presentation, we endeavour to share with the participants our long-term experience in therapeutic leukocytapheresis on apheresis settings and adverse event control.

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TT3-06 CART (cell-free and concentrated ascites reinfusion therapy)

CART(cell-free and concentrated ascites reinfusion therapy) is a treatment for refractory pleural effusion and ascites. It was covered by insurance in 1981. CART is now more commonly used for cancerous ascites than for hepatic ascites. CART in cancer patients is expected to reduce the frequency of ascites puncture, improve quality of life, and prolong OS. This workshop will explain the history and literature of CART, with insights from the implementation of CART in Our Hospital over 130 cases per year.

Workshop Workshop E-ISFA in Kyoto Japan

WS-01 Update on vasculitis treatment including plasma exchange

Wladimir Szpirt

Rigshospitale, Copenhagen, Denmark

During the last 15-20 years there have been better patient outcomes in ANCA vasculitides (AAV). This is due in part to several randomized control trials that were launched to evaluate and reduce the toxicity of drugs used in the immunosuppressive treatment of this chronic and relapsing disease entity. The randomized controlled trials (RCT) performed by European Vasculitis Study Group (EUVAS) has raised the awareness of adverse events due to drug toxicity. New less toxic treatment and reduction of total immunosuppressant exposure during the induction of remission has improved patient outcome especially in patients with renal failure. The use of cotrimoxazole as a Pneumocystis Jiroveci pneumonia (PCP) prophylaxis during cyclophosphamide (CYC) and Rituximab (RTX) treatment has lowered the incidence of PCP infection related treatment failure. RTX is more frequently used in younger patients because of the effect of CYC on male fertility. The long term outcome of AAV is influenced by diabetes, malignances, osteoporosis and cardiovascular adverse events, mostly related to corticosteroids (GCS). New less toxic drug regimens have already been proposed combining plasma exchange (PLEX) and low dose CYC (Szpirt) or low dose CYC and RTX (McAdoo). Another RCT Clear showed the positive effect of using CYC/RTX together with C5aR inhibitor (avacopan) for induction as a possible agent which can be used with reduced/or instead of GCS. Regular follow up schedules similar to those used in kidney transplant patients are recommended for monitoring bone marrow suppression during induction, and possible relapses during maintenance therapy - especially in patients with Granulomatosis with polyangiitis. Tailoring each treatment individually, based on phenotype, age, and renal deterioration would be the ideal solution to improve outcome prognosis. EULAR/ERA-EDTA guidelines can be effective tools in treatment planning and execution.

WS-03 Why should immunoadsorption be a therapy of continuing interest?

Bernd Hohenstein

Nephrological Center Villingen-Schwenningen, Germany

The existing evidence for the application of therapeutic apheresis generally depends on the



type of disease and acuteness. Immunoadsorption is a (important) part of these extracorporeal techniques offering a number of advantages over other procedures in terms of effectiveness, efficacy, selectivity and future perspectives. Today, there are only a few clear indications for the use of immunoadsorption as primary apheresis technique, while a pathophysiologic rationale is given in a wider range of diseases. For instance, in nephrology the use of immunoadsorption is commonly used to desensitize ABO incompatible kidney transplant recipients. However, for most indications the current evidence is far from ideal.

In contrast, other medical disciplines started to gain interest in the technical and nephrological know-how regarding these specialized procedures. Mainly driven by the detection of new and disease specific autoantibodies in recent years, they request the realization of this therapy in their sometimes severely ill patients. This is the reason why the development of new selective techniques and adsorber systems should be closely followed and chaperoned by apheresis specialists, mostly located in nephrologic units. This will help to gain expertise with established and upcoming procedures and in parallel avoid the realization of these therapies by other medical disciplines lacking the specific education and expertise in the field of therapeutic apheresis.

Apheresis -State of the Art 1 Critical Care Medicine/others

SA1-01 Current status of plasma exchange in critical ill patients in Vietnam

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Dai_Quang Huynh²⁾, Xuan_Thi Phan¹⁾, Thao_Thi Ngoc Pham¹⁾,
Linh_Thanh Tran¹⁾

1) Cho Ray Hospital, Ho Chi Minh, Vietnam

2) University of Medicine and Pharmacy, Hochiminh city, Vietnam

Background: After ASFA guidelines 2016, the clinical application of plasma exchange has expanded, significantly in high volume plasma exchange for acute hepatic failure. However, the clinical practice and efficacy of plasma exchange in critical ill patients has not been assessed. Therefore, a retrograde registry from January 2017 to June 2019 was established to evaluate the clinical indication, modes, adverse effects, efficacy of plasma exchange in intensive care unit.

Methods: An observational study of all patients, were treated with plasma exchange from January 2017 to June 2019 in ICU of Cho Ray Hospital, Viet Nam.

Results: In 18 months, there were 127 patients with 213 episodes, included 39 patients on high volume TPE. All TPE patients using membrane with exchange fluid is plasma or albumin. The most indications were acute hepatic failure 51.9% and hypertriglyceridemia 34.6%. The popular adverse effect is hypocalcemia (9.4%) and allergy reaction (5.6%).

Conclusion: Plasma exchange has expanded indication in ICU. HV-TPE was used more frequently in acute liver failure, but need to do more research to evaluate the efficacy of this therapeutic. TPE was consider using as a novel treatment in acute pancreatitis patient with severe hypertriglyceridemia.

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SA1-03 Results from the CAMI1 Study: Selective CRP apheresis as a new treatment option in acute myocardial infarction

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- 5) *Herz- und Gefaesszentrum Oberallgaeu-Kempten, Germany*
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- 9) *Herzzentrum Brandenburg, Immanuel Klinikum Bernau, Bernau, Germany*

Background: Inflammation is an important pathogenic feature in cardiovascular disease. In patients with ST-segment Elevation Myocardial Infarction (STEMI), C-reactive protein (CRP), is a marker of poor prognosis and independently predicts 30-day mortality. In STEMI, CRP is involved in myocardial damage. In animal experiments, CRP removal after STEMI reduces infarct size and results in a significantly better left ventricular ejection fraction (LVEF). A newly developed CRP-adsorber efficiently and selectively lowers CRP levels in humans. Here, we present the data of the human multi-center study on CRP-apheresis in Acute Myocardial Infarction (CAMI1).

Methods: 66 STEMI patients were enrolled in the study. 32 patients received CRP-apheresis, whereas 34 patients treated by standard protocols served as controls. CRP-apheresis started 24+-12h and 48+-12h after onset of symptoms and optionally after 72h. In each apheresis session, 6000 ml of plasma was treated via peripheral venous access. Primary study endpoint was myocardial infarction size as determined by Cardiac Magnetic Resonance on days 2-9 after STEMI.

Results: Apheresis sessions were well tolerated with no relevant side effects. The peak CRP level after AMI can be calculated precisely with 2-3 CRP quantifications during the first 24 h after the onset of symptoms. The regression coefficient for this analysis is 0.91. This mathematical step allows for the comparison of the CRP-apheresis group and the controls on the basis of their individual CRP peak levels. The statistical evaluation shows that the apheresis patients perform significantly better at all endpoints (infarct size, LVEF, circumferential strain). The CRP-apheresis has reduced the development of damage.

Conclusions: CRP-apheresis following STEMI is feasible and safe. A significant beneficial effect of CRP-apheresis on myocardial infarction size and wall motion was observed. For the first time an unequivocal association between infarct size and CRP is demonstrated. Selective CRP-apheresis emerges as a new approach in the treatment of AMI.



SA1-04 The improving effects of lipoprotein apheresis on cardiac vascular ultrasonic parameters

Dongliang Zhang

The Blood Purification Center of Nephrology Department, Peking University International Hospital, China

Objective: To study the effects of dual filtration lipid apheresis (DFLA) on cardiovascular parameters of ultrasound detection.

Methods: Blood tests were conducted before and after the first treatment of DFLA, which including blood regular test, plasma albumin, lipids, and so on. Cardiac and vascular Doppler ultrasound detections were proceeded before and after the treatment within 24 hours, respectively. The blood tests results and ankle brachial index (ABI), ejection fraction (EF), left ventricular diastolic end diameter (LVDED) were compared between two time points.

Results: There were 24 patients finished 36 DFLA sessions totally. Compared to the results before one therapy, several blood parameters decreased significantly after treatment, such as platelet (195.758 ± 69.190 vs. 214.001 ± 78.898 , $\sim 10^9/L$, $t = 2.227$, $P = 0.041$), albumin (33.709 ± 7.622 vs. 37.882 ± 8.069 , g/L , $t = 2.941$, $P = 0.010$), cholestole (2.745 ± 2.500 vs. 5.066 ± 4.117 , $mmol/L$, $t = 5.407$, $P = 0.000$), and triglyceride (2.152 ± 4.521 vs. 5.462 ± 10.300 , unit: $mmol/L$, $t = 2.336$, $P = 0.033$).

Conclusion: The treatment of DFLA can decline the levels of lipids effectively. The cardiovascular ultrasonic parameters can be improved after once DFLA session.

SA1-05 After EUPHRATIS Is LPS Apheresis for Sepsis obsolete? In-vitro investigation for a new concept of Endotoxin adsorption

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Background: Falkenhagen¹ showed that none of the commercially available devices for extracorporeal LPS-adsorption showed promising results for potential use in extracorporeal blood purification. Of the tested endotoxin removal materials, only DEAE-Sepharose and PMB-based adsorbers were able to reduce the LPS-activity. However, Falkenhagen was able to show that the reduction in LPS-activity in the PMB-based adsorber was caused by desorbed PMB, which inactivates endotoxins. This could be an explanation why in the EUPHRATIS study² Polymyxin-B haemoperfusion was not shown to be superior to placebo in the management of septic shock. The authors of the study itself claim, that one of the reasons could be the insufficient LPS binding capabilities of the Polymyxin-B-adsorber. Effective LPS binding in plasma is possible with DEAE-based material, but not commercially used because of its low biocompatibility and Heparin binding capability. For both problems a solution will be provided, which could make the material the best option for LPS-<A>adsorption in sepsis.

Materials & Methods: Adsorbers (DEAE-functionalized microporous hollow fibres) has been perfused with buffer and human plasma of two different pH-values, containing Endotoxins and Heparin. The adsorption of LPS, LTA, Heparin and coagulation factors are measured.

Results: The diethylaminoethyl groups deposited on the microporous fibers combine chemically with the endotoxin or heparin molecules, producing stable bonds on the surfaces

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of the microporous fibers at all pH values. Coagulation factors are adsorbed depending of and their isoelectric point and the pH value. At pH 5.1 no coagulation factors are removed from the plasma. Due to the large adsorbing capacity LPS/LTA adsorption is not limited in the presence of Heparin. It will be shown that a Heparin supplement procedure can replace the adsorbed Heparin in the extra-corporal circuit automatically.

Conclusions: DEAE based adsorbers are a promising opportunity for the treatment of septic shock.

Apheresis -State of the Art 2 Nephrology/others

SA2-01 Severe Nephrotic Syndrome with Hyperthyroidism and Acute Renal Failure Treatment with Plasmapheresis and Immunosuppressive drug: Tacrolimus

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Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand

Background: An old woman at age of 64 years suffered from progressive 24-kilogram weight gain within one month. She did not have diabetes nor history of thyroid diseases previously. On admission, physical exam showed marked edema and serum oozing from skin. Laboratory results were as follows: blood urea nitrogen 98 mg/dL, creatinine 3.23 mg/dL, total cholesterol 356 mg/dL, albumin 1.0 g/L, and massive proteinuria of 10 grams. Her fibrinogen level was 333 mg/dL. She was also diagnosed with new-onset hyperthyroidism.

Method: She was consecutively treated with plasmapheresis for five sessions within 10 days.

Results: After the 5th session of PE, renal function began to improve and she started diuresing. She was simultaneously given tacrolimus and intravenous cyclophosphamide for 2 sessions. She was also treated with thyroid hormone. Her weight progressively decreased. Serum cholesterol, blood urea nitrogen, serum creatinine, IgG, and fibrinogen all went down. She was maintained on tacrolimus, mycophenolate mofetil, thyroid hormone, and erythropoietin.

Conclusion: This report described the successfulness of apheresis as an induction therapy for severe nephrotic syndrome with severe hyperlipidemia. Apheresis is proposed to decrease lipotoxicity, blood viscosity, and enhancement to response to immunosuppressive drugs.

SA2-02 Effects of LDL-Apheresis in Adult Refractory Nephrotic Syndrome and Its Reproducibility

Hideki Takizawa, Takuto Maeda, Yoshinosuke Shimamura, Kouki Abe

The Department of Nephrology, Teine Keijinkai Hospital, Sapporo, Japan

Background: In 2018, Humanitarian device exemption allowed to utilize LDL-apheresis (LDL-A) for the treatment in adult patients with nephrotic-range focal segmental glomerulosclerosis (FSGS), but the efficacy is still uncertain. We performed case series of LDL-A in patients with refractory nephrotic syndrome, including FSGS, in a tertiary care center in Japan.

Methods: The efficacy of LDL-A was evaluated in 16 cases of refractory nephrotic syndrome (FSGS, n=5; minimal change disease (MCD), n=7; membranous nephropathy (MN), n=4)



enrolled from April 2008 to June 2019. Demographic and clinical parameters were compared before and after performing LDL-A. Additionally, the efficacy of the second trial of LDL-A was evaluated in relapsed cases after the first trial of LDL-A.

Results: In 16 patients, all patients, except one, received immunosuppressive agents (prednisolone, 15; cyclosporine, 6; cyclophosphamide, 2), and there was no statistically significant reduction in proteinuria before initiating LDL-A ($p=0.051$; t-test). However, there were statistically significant reduction in proteinuria after performing the first trial of LDL-A in all groups (FSGS, 7.5 ± 1.9 g/day to 2.2 ± 1.0 ; MCD, 5.4 ± 1.4 to 0.4 ± 0.1 ; MN, 6.4 ± 0.5 to 2.3 ± 0.5 ; $p<0.005$; MANOVA). Multivariate analysis revealed the rate of remission was higher in MCD compared to other groups ($R^2=0.49$, $p<0.005$). In relapsed cases after the first trial of LDL-A ($n=7$), the second trial of LDL-A was effective to reduce proteinuria, and there was no statistically difference in between the first trial and the second trial of LDL-A (First trial, 5.6 ± 1.1 to 0.7 ± 0.3 ; Second trial, 7.2 ± 1.5 to 0.8 ± 0.5 , $p=0.382$; MANOVA).

Conclusion: This study suggested that LDL-A was effective for reducing proteinuria in patients with refractory nephrotic syndrome, and its effectiveness was reproducible. This may contribute to planning treatment strategies in these patients.

SA2-03 Plasmapheresis Reduces Mycophenolic Acid Concentration: A Study of Full AUC0-12

Sudarat Piyasiridej, Suwasin Udomkarnjananun, Somratai Vadcharavivad, Salin Wattanatorn, Krit Pongpirul, Yingyos Avihingsanon, Kriang Tungsanga, Kearkiat Pradipornsilpa, Somchai Eiam-ong, Natavudh Townamchai

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Background: Mycophenolic acid (MPA) and plasmapheresis are simultaneously used for the management of various immune-related diseases. While plasmapheresis has been proven for removing many substances from the blood, its evidence on MPA levels remains unestablished.

Objectives: To evaluate the full pharmacokinetics by measuring the area under the time-concentration curve (AUC0-12) of MPA after each plasmapheresis session, and to compare between the AUC0-12 on the day with and without plasmapheresis.

Methods: A cross-sectional study was conducted in kidney transplantation recipients who were taking a twice-daily oral dose of mycophenolate mofetil (MMF, Cellcept) and undergoing plasmapheresis at King Chulalongkorn Memorial Hospital, Bangkok, Thailand, during 2018 and 2019. The MPA levels were measured by enzymatic method (Roche diagnostic) at 0, 1/2, 1, 2, 3, 4, 6, 8 and, 12 hours for AUC0-12 calculation on the day with and without plasmapheresis sessions. Plasmapheresis was started within 4 hours after the oral morning dose of MMF. Our primary outcome was the difference of AUC0-12 between the day with and without plasmapheresis.

Results: Forty complete AUC measurements included 20 measurements on the plasmapheresis day of six kidney transplant patients. The mean age of patients was 56.2 ± 20.7 years. All patients had received MMF 1,000 mg/day for at least 72 hours before undergoing 3.5 ± 1.2 plasmapheresis sessions. Mean AUC on the day with plasmapheresis was lower than the day without plasmapheresis sessions (28.22 ± 8.21 vs 36.79 ± 10.29 mg x hour/L, $p=0.001$) and the percentage of AUC reduction was 19.49 ± 24.83 %. This was mainly the result of a decrease in AUC0-4 of MPA (23.96 ± 28.12 % reduction).

Conclusions: Plasmapheresis significantly reduces the level of full AUC0-12 of MPA. The

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present study is the first to measure the full AUC0-12 in MPA-treated patients undergoing plasmapheresis. Our study suggests that a supplementary dose of MPA in patients undergoing plasmapheresis is necessary.

SA2-04 **Immunoadsorption treatment of recurrent primary focal segmental glomerulosclerosis: A single center experience**

Hamza Naciri Bennani, Thomas Jouve, Johan Noble, Juste Bonzi, F Terrec, S Boudemaa, Diane Giovannini, Benedicte Janbon, L Motte, Paolo Malvezzi, Lionel Rostaing

Department of Nephrology, Hemodialysis, Apheresis and Renal Transplantation, CHU Grenoble-Alpes, Grenoble, France

Background: Primary focal and segmental glomerulosclerosis (FSGS) frequently reoccurs on kidney transplants and may lead to premature allograft loss. FSGS pathophysiology is controversial and circulating factors, such as suPAR, SCD40L, can cause injury. There are no guidelines for FSGS recurrence on an allograft; treatment is based on apheresis (plasma exchange [PE], semi-specific immunoadsorption [IA] with reusable columns) in association with rituximab therapy. However, these therapies have not demonstrated efficacy in preventing recurrent FSGS.

Aim of study: We report on seven patients with FSGS that recurred on the allograft (proteinuria >2g/L or >3g/day since transplantation); they were treated with IA. Our primary objective was to reduce proteinuria by >50%.

Material and Methods: Patients' mean age was 45+/-10 years. Post-operative immunosuppression relied on steroids, mycophenolate mofetil, tacrolimus, with an induction therapy of basiliximab or antithymocyte globulins. Prophylaxis for FSGS recurrence was either rituximab alone (n=2) or rituximab plus either PE or IA or nothing (n=1). There was a mean of 12+/-2 sessions per IA column. Mean follow-up was 14+/-8 months.

Results: At 1 month after starting IA, all patients had partial remission; at 12 months, allograft survival was 100%. One patient had complete long-term remission after 14 IA sessions. The mean reduction in proteinuria within an IA session was 45+/-15%. The most frequent adverse event was cytomegalovirus reactivation (n= 13), which subsided after valganciclovir therapy.

Conclusion: We have demonstrated that recurrence of FSGS can be controlled long-term with IA plus rituximab. However, patients remained dependent on IA.

SA2-05 **Apheresis therapy for steroid-resistant idiopathic nephrotic syndrome: Report on three cases**

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Department of Nephrology, Hemodialysis, Apheresis and Renal Transplantation, CHU Grenoble-Alpes, Grenoble, France

Background: Idiopathic nephrotic syndrome (INS) is the result of either minimal-change disease (MCD) or focal-segmental glomerulosclerosis (FSGS). In adult patients, first-line treatment relies on steroids. In cases of steroid-dependence or steroid-resistant INS, second-line therapy relies on calcineurin-inhibitors, cyclophosphamide, mycophenolate-mofetil, or rituximab.



Aim of study: We report on three immunosuppressive-resistant INS cases that were submitted to apheresis sessions.

Material and methods: Apheresis relied on either semispecific immunoabsorption (IA) and/or double filtration plasmapheresis (DFPP) sessions. In addition, the patients received immunosuppressive therapy. The duration of treatment was adapted according to the decrease in proteinuria and/or INS resmission.

Results: This resulted in i) full remission in one case (with steroid withdrawal), ii) partial remission in one case with apheresis dependency (one session/week); and iii) partial remission with IA dependency in the third case, but the patient refused long-term therapy.

Conclusion: We conclude that apheresis therapy (IA and/or DFPP) is an option for immunosuppressive-resistant INS.

SA2-06 Rationale and Study Design of LDL apheresis-mediated Endothelial activation Therapy to Severe-Peripheral Artery Disease study (LETS-PAD study)

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Background/Aim of Study: Despite current progress in revascularization therapies for peripheral arterial disease (PAD), there still remain many revascularization-resistant PAD cases. Low-density lipoprotein apheresis (LDLA) has been applied to severe hypercholesterolemia. We previously reported that LDLA exerts a variety of anti-arteriosclerotic effects in addition to lipoprotein removal, which include suppression of oxidative stress and amelioration of endothelial dysfunction (Tsurumi-Ikeya Y, et al. *Arterioscler Thromb Vasc Biol*, 30:1058-65, 2010; Tamura K, et al. *Ther Apher Dial*, 17: 185-92, 2013). Therefore, LDLA may be effective for conventional therapy-resistant PAD patients without hypercholesterolemia. The aim of this study is to assess the efficacy and safety of LDLA in severe PAD patients with normal or controlled cholesterol levels.

Materials & Methods:

[Study Design] This is a single-center, interventional, and single-arm study.

[Patients] The subject is conventional therapy-resistant PAD with normal or controlled cholesterol levels. Required sample size is 35. The inclusion criteria are as follows: aged between 20-79, Fontaine classification>=IIb, ABI<0.7, serum total cholesterol=<220mg/dL and LDL-cholesterol=<140mg/dL, and refractory to conventional revascularization therapies and correction of atherosclerotic risk factors.

[Intervention] Each patient undergoes 10 sessions of LDLA (1-2 sessions per week), where dextran sulfate cellulose columns are used as absorber.

[Outcomes] The primary outcomes are change in ABI and VasuQOL, a PAD-specific quality-of-life questionnaire, before and after 10 consecutive LDLA sessions. Secondary outcomes include evaluations of intermittent claudication, rest pain, and ulcers, skin perfusion pressure, and image evaluation with contrast-enhanced CT. For safety analysis, adverse events are recorded during and soon after the treatment period. In addition, endothelial function (RH-PAT, FMD) and oxidative stress (MDA-LDL, pentosidine, dROMs, BAP) are measured in order to explore the underlying mechanisms.

Conclusions: This ongoing study is designed to clarify the effectiveness and safety of LDLA for PAD without uncontrolled hypercholesterolemia.

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Apheresis -State of the Art 3 LDL

SA3-02 Establishing Low-Density Lipoprotein Apheresis Tolerability in Patients with Prior Anaphylactoid Reactions to Lipid Apheresis using Magnesium Sulfate

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Background/Aim of Study: Lipoprotein apheresis (LA) tolerability is a key factor for the utilization of this therapy. The most common reactions to LA are hypotension, nausea, and vomiting. More serious reactions include severe hypotension and allergic/anaphylactoid reactions, which occur more rarely (0.13%-1.3% and 0.2%-0.4%, respectively). These reactions are driven by the dextran sulfate-adsorption system (DSA) contact activation of the plasma kallikrein system and ultimately the bradykinin response and can be worsened with the use of angiotensin-converting-enzyme inhibitors. Efforts to mitigate these reactions are necessary for patient tolerability of LA with a dextran sulfate-adsorption system.

Materials & Methods: In an effort to increase apheresis tolerability, patients at two different centers (University of Kansas, Department of Clinical Pharmacology; Amitabha Medical Center, Santa Rosa, California), including 7 University of Kansas patients who had prior anaphylactoid reactions to the DSA despite pharmaceutical intervention, were treated with a pre-apheresis magnesium infusion protocol developed by co-author Eliaz. This protocol consists of 1.5 g of magnesium sulfate (147.9 mg of elemental magnesium, 12.18 mEq of magnesium) administered intravenously over a 45-minute period.

Results: Total of 35 patients, including the 7 patients with previous anaphylactoid reaction to the Liposorber, were treated with intravenous magnesium sulfate immediately prior to LA. No serious allergic reaction to DSA LA has been reported in these patients. Over 200 apheresis sessions have been performed using this protocol, and treatment tolerability has remained.

Discussion and conclusions: Magnesium infusion prior to DSA LA has been demonstrated to establish tolerability in all patients. Proposed mechanisms of action include reduction of nitric oxide and reduction of sympathetic response.

SA3-03 Impact of PCSK9 inhibitors on LDL apheresis

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Background: LDLc target is often not achieved in most severe forms of familial hypercholesterolemia despite maximum lipid lowering treatment. LDL apheresis (LA) represents a rescue treatment. The revolutionary introduction of PCSK9 inhibitors (PCSK9i) that determine a significant LDLc reduction represents indeed an alternative to LA. The aim of this study was to analyze the impact of PCSK9i introduction on LA.

Methods: 82 FH patients (50 heterozygous, 32 homozygous) are currently treated with LA at the apheresis unit, Pitie Salpetriere Hospital. The techniques utilized are dextran sulphate cellulose adsorption (57 patients), double filtration plasmapheresis (14 patients), and direct



adsorption of lipoproteins (10 patients). 56 patients were given PCSK9i according to the following protocol: Step 1 (week0 to week 6): introduction of PCSK9i in association with LA; Step 2 (week 6 to week14) : evaluation of treatment efficacy and choice about the LA treatment. Patient would quit LA if an LDLC <140 mg/dl was obtained, corresponding to an average reduction of 30percent.

Results: 36 patients (65.5 percent) had a good response to PCSK9i; 28 patients quit LA. 8 patients had an insufficient response and LA frequency was reduced at one per month. Four patients had an allergic reaction to PCSK9i. 16 patients (30 percent) PCSK9i had no effect. Interestingly, 18 patients (22 percent) refused the new treatment. 37 patients (39 percent) are still treated with LA once every two weeks.

Conclusions: 51 percent of LA treated FH patients quit the LA definitively once PCSK9i were introduced and 14.5 percent LA treated patients reduced LA frequency. LA is an important treatment for severe FH also because and LDLC <140 but higher than 70 to 100 mg/dl makes them still at residual cardiovascular risk.

SA3-04 Beyond cholesterol, pleotropic effects of lipoprotein apheresis

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Lipoprotein apheresis (LA) is a well-established extracorporeal treatment in modality of severe hyperlipoproteinemia. Besides effective reduction of LDL cholesterol (LDL-C) and Lipoprotein (a) (Lp(a)) and modifications to physiology of lipoprotein and lipid metabolism, LA may have crucial and a concert of multiple, beneficial effects at the same time on many other atherogenic factors as vascular inflammation, rheology and gene expressions in involved cell types. Atherosclerosis is an inflammatory disease and LA had shown that it could temper these inflammatory settings. In a recent NMR-based lipoprotein analysis for patients with severe hypercholesterolemia undergoing LA or PCSK9-inhibitor (PCSK9i) therapy (NAPALI-Study), LA reduced the lipoprotein particle amount very effectively in one treatment, when compared to PCSK9i therapy. This result is a further landmark for LA, because of no other lipid-lowering regimen therapy (e.g. statins, PCSK9i, or anti-sense oligonucleotide (ASO)) than LA could reduce the therapeutic target LDL-C, Lp(a) or inflammatory parameters in such a short time. These observations could be of fundamental importance in the clinical use of LA in the future, perhaps not only in chronic but also in acute settings like myocardial infarctions.

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SA3-05 Apheresis in preeclampsia - Lipids, angiogenetic factors or else? (The APPROVE project, a controlled multi-center apheresis trial)

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Introduction:

Preeclampsia is a life-threatening complication of pregnancy. The only cure today is the preterm delivery of the fetus by cesarean section. Since each gained day of pregnancy reduces the mortality risk of the pre-term fetus (<28th gestational week (GW.)) by 2-3 %, a prolongation of pregnancy is eagerly needed.

Methods and Results:

In a recent pilot study by our group 6 early-onset preeclamptic patients were treated with H.E.L.P.-apheresis. Time of admission to delivery was 15.0 days in patients receiving H.E.L.P.-apheresis compared to 6.3 days in historical controls without LA ($p = 0.027$), however, sFlt-1 was not reduced. Other groups used dextran sulfate apheresis (DSA) and achieved a similar prolongation of pregnancy. DSA eliminated a modest amount of sFLT-1, and thus the contribution of sFLT-1 elimination to the success of apheresis is currently debated. To further elucidate the role of lipoproteins, angiogenetic and other factors, a larger, randomized multicenter-study is organized. Since safety and prolongation of pregnancy was already shown by different lipid apheresis (LA) techniques, we suggest that any LA may be applied. To validate the magnitude of the prolongation effect a randomized comparison to conventional therapy is planned. It is intended to include 30 preeclamptic patients before the 28th GW that are randomized to either LA or conventional therapy. For an expected study duration of 2-3 years a number of at least 8 study centres appears to be necessary.

Discussion:

Reducing lipoproteins and pleiotropic pro-inflammatory factors appears to me more relevant for the treatment effect of LA in preeclampsia than sFlt-1, as sFlt-1 is not reduced by H.E.L.P.-apheresis. However, sound data are still lacking. Further, it is yet not proven, whether LA indeed prolongs preeclamptic pregnancies, because a randomized control group was lacking in previous trials. This is intended to be addressed in the planned study.



Apheresis -State of the Art 4 Hepatology

SA4-01 Artificial liver treatment improves survival in patients with acute-on-chronic liver failure: A prope

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Background/Aim of Study: The artificial liver support system (ALSS) is recognized as a bridge to liver transplantation in hepatitis B virus-related acute-on-chronic liver failure (HBV-ACLF) patients; however, its impact on patient survival remains unknown. This study aimed to assess the effects of ALSS on survival with personalized models in patients with HBV-ACLF.

Methods: The clinical data of HBV-ACLF patients receiving ALSS plus standard medical treatment (SMT) (ALSS group, n=507) or only SMT (SMT group, n=417) were collected for survival assessment from a large, prospective, multicentre open cohort (COSSH study). The main endpoints were cumulative survival rates at days 7/14/21/28/90. A propensity score-matched analysis was used to reduce bias between the treatment groups.

Results: In the unmatched cohort, the cumulative survival rates at days 7/14/21/28/90 were significantly higher in patients who underwent ALSS treatment, especially in patients with ACLF-2, than in those who underwent only SMT ($P < 0.01$, respectively). After propensity score matching, the median survival time was significantly longer in the ALSS group than in the SMT group (54 days vs 25 days, $P < 0.05$). A significantly higher survival rate was also observed in the ALSS group, regardless of ACLF-1, -2, or -3, than in the SMT group on days 7/14/21/28/90 (87.4% vs 78.2%, 79.4% vs 66.5%, 75.2% vs 58.8%, 70.8% vs 56.9%, 58.4% vs 49.0%, $P < 0.01$, respectively). In the multivariate analysis, ALSS treatment was independently associated with a reduced 7/14/21/28/90-day transplant-free mortality risk. However, the effect was not significant for ACLF-3 ($P = 0.134$). A significant improvement in biochemical functions was observed post-ALSS treatment.

Conclusions: ALSS improved short-term survival in patients with HBV-ACLF, especially ACLF-1 and ACLF-2, in both the unmatched and propensity score-matched cohorts. The effects of ALSS treatment in ACLF-3 patients needs a larger sample size to clarify.

SA4-02 1,5-Anhydroglucitol predicts proliferation of liver parenchymal cells during liver regeneration

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Aim: To elucidate the dynamic alterations of metabolites in plasma of rats during liver

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regeneration and search for potential biomarkers of liver regeneration.

Methods: Sixty-five Male Sprague-Dawley rats were divided into three groups: 70% partial hepatectomy group (PHx, n=30), sham-operated group (Sham, n=30) or Pre-PHx group (Pre-PHx, n=5). Liver regeneration and liver injury were evaluated after 30min, 6h, 24h, 48h, 72h and 168h of surgery. Gas chromatography-mass spectrometry (GC-MS)-based metabolomic approach was used to identify the dynamic metabolites.

Results: Liver regeneration in the rats was evidenced by an increase in liver/body weight ratio, expression of Proliferating Cell Nuclear Antigen (PCNA) and Yes-associated protein (YAP). The metabolites in the Sham group and the PHx group showed good separation based on the multivariate analysis results. Thirty-four metabolites were differentially expressed, which included Lactamide, Catechin, 3-(4-Hydroxyphenyl) Propionic Acid, Erythronic Acid Lactone, Alanine-Alanine, and 2-Deoxytetronic Acid. Moreover, we conducted multivariate analysis for the PHx group by dividing the rats into 3 phases according to the timepoints: the initiation phase (30m, 6h), the inductive phase (24h, 48h), the angiogenic phase (72h, 168h). We found that 1,5-Anhydroglucitol performed well at discriminating the inductive phase from the initiation and angiogenic phases, with areas under curve (AUCs) higher than 0.8. Thus, 1,5-Anhydroglucitol was identified as a novel hallmark of liver regeneration, especially indicated proliferation of liver parenchymal cells.

Conclusion: With the progression of liver regeneration, a series of metabolic changes occurred and 34 differentially expressed metabolites were identified compared with the Sham group. 1,5-Anhydroglucitol was a novel hallmark of proliferation of liver parenchymal cells during liver regeneration.

SA4-03 **Transcriptomics identifies immune-metabolism disorder in development and progression of hepatitis B virus-related acute-on-chronic liver failure**

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Background: The pathophysiology of hepatitis B virus-related acute-on-chronic liver failure (HBV-ACLF) remains unclear. This study aims to characterize the molecular basis of HBV-ACLF using transcriptomics.

Method: 360 subjects with HBV-ACLF (n=120), acute-on-chronic hepatic dysfunction (ACHD, n=60), liver cirrhosis (LC, n=60), chronic hepatitis B (CHB, n=60), and normal controls (NC, n=60) from a prospective multi-center cohort were studied among which 65 subjects were sequenced. Multi-omics cross-validation network analysis of function synergy (MOCNAS) was used to identify gene and biological process variations in pathophysiology of HBV-ACLF.

Results: Principal component analysis (PCA) shows that the mRNA profiling of ACLF patients were significantly different with that of ACHD, LC and CHB patients. MOCNAS analysis focusing on eight categories of bioprocesses and top 500 differentially expressed genes (DEGs) showed that virus-processes were associated to all disease stages from CHB to ACLF. Excessive innate immune activation (e.g. positive regulations of mast cell and NK cell chemotaxis,



microphage differentiation) as the most prominent change and disorder triggered by HBV exacerbation drove CHB or LC to ACHD and ACLF. Mild inflammation dysregulation (e.g. IL-6/4/1/2/9) were observed in ACHD and mostly restored in ACLF (only IL-8 and antigenic stimulus could be observed). The metabolic dysregulation (e.g. glycogen, phospholipid, hyaluronan) were significantly observed in ACHD and intensively dysregulated in ACLF. The processes of coagulation, wounding and renal failure reflected the consequences of end-stage liver failure were also identified in ACHD and ACLF. External validation of 12 DEGs underlying above molecular basis confirmed their specifics and indicated their biomarker potentials in diagnosis and prognosis of HBV-ACLF.

Conclusions: This study highlights immune-metabolism disorder triggered by HBV exacerbation as an important axis that aggravates HBV-ACLF, which may direct a novel diagnosis and treatment target to reduce its high mortality.

SA4-04 Aristolochic Acid I induced FLAP/CysLTs/CYLD signaling axis in premalignant liver tissue

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Aim of Study: Short-term aristolochic acid I (AAI) exposure displays potential hepatocarcinogenesis. However, the initiation mechanism is controversial. 5-lipoxygenase (5-LO) appears in some cancer types, but it has only been seldom investigated in hepatocellular carcinoma (HCC) pathogenesis. Reduced tumor suppressor gene cylindromatosis (CYLD) expression contributes to HCC development.

Objectives: This study aimed to evaluate 5-LO pathway associated CYLD downregulation and their prognostic significance in hepatic premalignancy.

Materials & Methods: Canine livers receiving AAI were explored for the relevance of functional components in 5-LO pathway and Cyld transcription. Liver tissues from HCC patients or donors, and HCC patient-based large data were evaluated for 5-LO cysteinyl leukotrienes (CysLTs) signaling and CYLD expression. Human HCC cell lines were used to reveal the possible mechanism in vitro.

Results: In the livers of canine receiving AAI, 5-LO-activating protein (FLAP) overexpressed in prenuclear membrane of hepatocytes. Enhanced CysLTs biosynthesis, overexpressed CysLT receptor 2 (CysLTR2), and decreased Cyld transcription appeared in parallel, accompanied by miR-362 overexpression. Liver tissues from HCC patients exhibited FLAP and CysLTR2 overexpression in HCC cells, but membrane-embedded microsomal glutathione-S-transferase 2 mainly appeared in paracancerous tissue. HCC tissues from patients displayed little CYLD. High FLAP transcription significantly shortened the time of 50% survival rate of HCC patients. FLAP knockdown led to CYLD overexpression through a miR-362-5p or p-JNK signaling-independent mechanism in AAI-treated-human HCC cells.

Conclusions: Our findings highlight a novel mechanism in the initiation process of hepatocarcinogenesis, and FLAP-CysLTs signaling determines CYLD expression may be potential biomarkers for early HCC detection and be explored for anti-HCC therapy.

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SA5-01 Neuro-Apheresis: From stroke to Alzheimer's Disease

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Background: We are the largest academic lipoprotein-apheresis (LA) Center in Europe, having treated overall 200 patients over 30 years. LA has been shown to have beneficial effects with respect to the reduction of cardiovascular events as reported by the Pro(a) Life study group and documented in the German LA registry. Data on cerebrovascular event reduction is scarce compared to coronary event reductions through LA. LA does not only decrease atherogenic lipoproteins but has also shown pleiotropic effects. Therefore we aimed to elucidate the effect of regular LA on cerebrovascular events (ischemic stroke, carotid thrombendarterectomy, carotid stent implantations) as well as its potential role in neurodegenerative disease and further analyse pleiotropic effects.

Material and Methods: We analysed data of LA patients with a history of cerebrovascular events in Germany in respect to event reductions under LA. Furthermore we treated patients with Alzheimer's disease with LA measuring lipid parameters as well as inflammatory parameters and stress hormone levels.

Results: Data of our patients on regular LA in Germany with a history of cerebrovascular events will be presented. Our recent pilot evidence would also suggest that patients with neurodegenerative disease might benefit from LA. The role of metabolic factors as a potential cause for Alzheimer's disease became more evident: Novel results discussing the potential of LA for Alzheimer's Disease including targeting lipids, inflammatory parameters and stress hormones will be presented. We documented reductions of the chemokine RANTES, of fibrinogen, of CRP, of alpha-2-macroglobulin, of ECP and of TNF-alpha all of which may be involved in the pathophysiology underlying Alzheimer's disease.

Conclusions: We believe that extracorporeal therapy may have a perspective in this field taking into account the lack of available alternative effective therapeutic approaches with drugs.

SA5-02 Long-term lipoprotein apheresis: effects on natriuretic peptides, PCSK9, and immunological parameters

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Background: Lipoprotein apheresis (LA) has been proven as a highly effective therapy significantly reducing cardiovascular events. Major anti-atherosclerotic effects were attributed to the reduction of plasma cholesterol and lipoprotein(a). Pleiotropic effects, specifically



associated with different LA technologies, seem to contribute to long-term clinical outcome. The aim of our study was to characterize acute and long-term effects of LA on the immune system, natriuretic peptides (NPs), and PCSK9 during different LA procedures.

Materials & Methods: In total, 62 patients, treated with one of six LA techniques were studied: lipid filtration, whole-blood dextran sulfate adsorption, MONET, DALI, HELP, and immunoabsorption. Cellular and humoral parameters were analyzed before and after five LA sessions over two years.

Results: Acute effects of LA were characterized by reductions of ANP, BNP, and PCSK9, but not by CNP. Analysis of long-term fluctuations of NPs and PCSK9 did not reveal any significant changes in pre- or post-apheresis values for any of the LA procedures. Additional application of PCSK9-inhibitors resulted in drastic increases in plasma PCSK9 levels. Lymphocytes and monocytes isolated from blood before and after apheresis displayed clear shifts in cytokine secretion and proportional subset composition. Changes in blood microparticles originating from neutrophils after apheresis were inconsistent, but revealed a tendency to increase after LA. Microfluidic assessments of leukocyte-endothelial interactions revealed a consistently reduced leukocyte adhesion after LA.

Conclusions: Our data suggest that although different LA techniques considerably differ in their acute effects on NPs during LA, they did not alter long-term levels. Regarding shifts in monocyte and lymphocyte population pattern and cytokine secretion it could not be excluded that LA exert in part an unfavorable effect on immune system. LA effects on neutrophil microparticles suggest that pre-activation of neutrophils during LA may reduce their functional capability for further interaction with endothelial cells and reducing their atherogenic capability.

SA5-03 A Nationwide Population Based Study of Therapeutic Plasma Exchange for 10 years in Korea

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Background/Aim of Study: The indications for therapeutic plasma exchange (TPE) have expanded over the years and the number of procedures are increasing in Korea. But there are not many comprehensive researches on the current status of TPE in Korea based on the nationwide population.

Materials & Methods: TPE cases were retrospectively identified during January 2008 to December 2017 from the Korean Health Insurance Review and Assessment Service (HIRA) database. Patients' characteristics, primary diagnosis, clinical department, treatment and procedures were analyzed.

Results: A total of 9,944 patients underwent 62,606 TPE procedures. The median number of TPE procedures per patient was 5 (interquartile range, 3-7). The majority of TPE procedures were performed at tertiary referral hospitals (86.4%) and secondary hospitals (13.6%). The number of procedures increased from 2,499 in 2008 to 9,232 in 2017. Internal medicine (45.9%) was the most frequently requesting department followed by general surgery (36.1%), neurology (10.6%), pediatrics (4.8%), cardiothoracic surgery (1.0%) and emergency department (0.7%). According to the primary diagnostic codes, the most common indication category was renal diseases (38.5%) followed by hepato-biliary diseases (17.5%), connective tissue diseases (12.5%), neurologic diseases (10.7%), hematologic diseases (6.2%) and others (13.6%). Of these, renal diseases increased from 529 (21.2%) cases in 2008 to 4,107 (44.5%) cases in 2017,

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Conclusions: The number of TPE procedures performed annually increased approximately 3.7 times from 2008 to 2017. The proportion of renal and hepato-biliary related procedures increased significantly which reflects the increase of transplantation in Korea.

SA5-04 The Challenges of Placebo Controlled Clinical Trials in Therapeutic Apheresis

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Background: The gold standard of clinical trials is the placebo controlled trial. In the field of therapeutic apheresis (TA), such trials are uncommon because the diseases treated with TA are uncommon, the number of patients is small and such trials present significant challenges.

Materials and Methods: We participated in two trials: one evaluating of an immunoadsorption column and another the efficacy of conventional plasma exchange for Alzheimer's disease.

Results: Both studies were successfully completed. The following challenges were encountered. 1. In the column study, the challenge was to shield the blood pathway from view. The view of the column was obstructed by a curtain. 2. Another challenge was the question of whether this design was a true placebo. 3. In the Alzheimer's study, a challenge was to mimic the flow of blood through the device without actually passing the patient's blood through the machine. The challenges of this approach were safety, availability and cost. 4. Peripheral vascular access was a challenge in both studies. 5. Patients experienced significant stress. 6. Significant financial commitment.

Conclusion: There have been only two studies involving TA in the US that were placebo controlled. The rarity of the diseases treated by TA and the above challenges may justify exploring other ways of evaluating the efficacy of therapeutic apheresis.

Apheresis -State of the Art 6 Neurology/Dermatology/Critical Care Medicine

SA6-01 Our Achievement In Establishment Of In-house Neurology Driven Therapeutic Plasma Exchange (TPE) Infrastructure In A Resource-Limited Public Hospital In Malaysia

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Background/Aim of study: The use of therapeutic plasma exchange (TPE) in treatment of immune-mediated neurological disorders is expanding with our increasing knowledge of various disease pathophysiology and clinical evidence of its efficacy. However, the accessibility and availability of TPE in Malaysia are restricted due to its cost and inadequate health resources. Hence, we aimed to establish a cost effective and sustainable in-house neurology driven TPE infrastructure and to provide a framework for other interested parties who wish to establish their own TPE services.

Materials and Methods: We reviewed the spectrum of immune-related neurological disorders



seen in Kuala Lumpur Hospital from 1990- 2015 to justify the need of our own neurology driven TPE infrastructure. A central TPE development group and technical and specification committee were formed to identify the necessary measures and requirements needed to set up the TPE service.

Results: Funding was approved for acquisition of a centrifugal TPE machine, related consumable items and annual maintenance. A single-bedded room in neurology ward was converted into a TPE suite for cost-saving purpose. A local TPE protocol and check list were constructed to ensure safe and uniform delivery of TPE service. We conducted regular training and privileging for TPE nursing staffs to ensure competency in the handling of TPE. Furthermore, the local TPE registry was set up to collect information on indications, procedure parameters, complications and outcome efficacy to facilitate regular auditing to improve services. A total of 38 patients from May 2015 to end of 2017 underwent TPE via centrifugal system at our TPE suite with good tolerability.

Conclusion: It is possible to establish a safe, successful and sustainable TPE service with concerted efforts despite limited resources.

SA6-02 Establishment of South East Asia Regional Neurological Disorders Therapeutic Plasma Exchange Consortium

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Objectives: The use of Therapeutic Plasma Exchange (TPE) for neurological disorders in Southeast Asia (SEA) is different in many ways. We aspire to establish a SEA TPE consortium to improve delivery of TPE service for neurological disorders as well as to create regional collaboration program and establish a regional database.

Materials and Methods: A pre-meeting survey to regional key opinion leaders (KOLs) was organised to garner perception on disease spectrum, practice challenges and the necessity for a regional TPE consensus. Feasibility of forming a regional consortium was included.

Results: A total of 14 neurologists from Indonesia, Laos, Malaysia, Myanmar, Singapore, Thailand and Vietnam responded. Challenges recognized include limited funding in supporting

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diagnostic workup, TPE therapy, as well as development of infrastructure. Lack of neurologists and staff with TPE expertise was another challenges identified. There was interest in developing a working plan contextualized to this region, including cooperation towards formation of regional SEA TPE consortium. Strategies to overcome challenges were discussed. This include the need for a comprehensive referral system and network of regional TPE centers suited to local requirement, supported by innovative TPE delivery programs. Other important objectives identified were setting up of regional biomarker testing facilities; identify funding methods for diagnostic antibody testing, enhancing engagement between patients and doctors to improve understanding on the use of TPE and creation of educational materials.

Conclusion: Concerted efforts from members of SEA countries are paramount towards the development of a regional TPE consortium for neurological disorders.

SA6-03 **MicroRNA and granulocyte and monocyte adsorption apheresis on neutrophilic skin diseases**

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Neutrophilic skin diseases are a group of disorders characterized by intense dermal infiltration of neutrophils without infection. They include a variety of diseases, such as pyoderma gangrenosum, pustular psoriasis, and palmoplantar pustulosis. We demonstrated that granulocyte and monocyte adsorption apheresis (GMA) is a useful treatment modality for such refractory skin diseases. Microarray analysis of microRNAs (miRNAs) was performed using sera of patients with neutrophilic skin diseases before and after GMA. Several miRNAs significantly increased in patients compared to control subjects. The expression of three miRNAs decreased after apheresis, suggesting that these miRNAs might be involved in the pathogenesis of neutrophilic skin diseases. To prove the function of these miRNAs, HL-60, a human acute promyelocytic leukemia cell line, was differentiated by the treatment of all-trans retinoic acid (ATRA). When HL-60 was differentiated to neutrophilic cells, the HE-staining shows an increased cytoplasm to nucleus ratio, condensed chromatin, and nuclear segmentation. The expression of three miRNAs increased during the neutrophilic differentiation. Stimulation of ATRA-treated HL-60 by some cytokines altered miRNA expressions. Moreover, manipulation of these miRNAs changed proliferation of cultured keratinocytes. These data suggest that miRNAs play an important role in regulating neutrophilic differentiation and proliferation of keratinocytes in case of neutrophilic disorders such as psoriasis. These miRNAs could be markers of disease severity and response of GMA.

SA6-04 **The use of therapeutic plasma exchange in clinical settings: an economic evaluation in a single institution in China**

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Objectives: Therapeutic plasma exchange (TPE) is a procedure that removes pathogenic



substances of high molecular weight such as antibodies, endotoxins, circulating immune complexes and cholesterol-containing lipoproteins from plasma. During TPE procedure, patient blood is drawn into the medical device that separate and remove plasma from cellular component. The removed plasma goes into the waste bag and replaced with plasma substitute fluid, which are then returned to the patient. According to 2016 guidelines of the American Society of Apheresis (ASFA), TPE was recommended first line treatment in various disease category; neurology, transplantation, intensive care settings, renal and hematology. Plasma exchange can be perform using centrifugal or membrane filtration method. This study assessed the cost associated with these techniques from payer perspective.

Methods: TPE procedures and cost data were collected from hematology and intensive care unit department in Longyan First Municipal Hospital, China. A cost minimization analysis model was created on Excel spreadsheet using micro-costing approach with the following cost components; device acquisition, maintenance, consumables, venous access, replacement fluids, labor. Data on procedure efficiency and clotting frequency were sought from published literatures. The model assumed similar clinical outcome in these techniques.

Results: A total of 325 TPE procedures were performed annually in Longyan First Municipal Hospital with majority of the patients were prescribed centrifugation method. The estimated cost per procedure for centrifugal and membrane TPE were USD 228 (CNY 1,563), rounded to nearest integer, and USD 2036 (CNY 13,978), respectively. Payer can expect to save USD 1,808 (CNY 12,415) for every TPE performed using centrifugal compare to membrane method.

Conclusion: The economic evaluation between these two plasma exchange methods showed centrifugal TPE had a better cost benefit than membrane TPE.

SA6-05 Cost savings with centrifugal therapeutic plasma exchange in intensive care unit Vietnam

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2) *Friendship Hospital Hanoi, Vietnam*

3) *Terumo BCT Asia, Singapore*

Background: Therapeutic plasma exchange (TPE) is a procedure that removes pathogenic substance that cause the underlying disease such as harmful antibodies immune complexes, cytokines or endotoxins from patient's plasma. In a typical TPE procedure, 1 to 1.5 plasma volumes were removed and replaced with another fluid (human albumin or fresh frozen plasma). In the American Society for Apheresis guidelines, TPE was recommended first line therapy in management of various renal, hematological and neurological diseases. TPE can be performed using two categories of devices; membrane or centrifugal. This study assessed the cost associated with these techniques from public payer perspective.

Methods: TPE procedures and cost data were collected from two intensive care unit; Ho Chi Minh City Hospital and Friendship Hospital, Vietnam. A cost minimization analysis model was created on Excel spreadsheet using micro costing approach with the following cost component; device acquisition, maintenance, consumables, venous access, replacement fluids, labor. Data on procedure efficiency and clotting frequency were sought from published literatures. Clotting defined as filter replacement to continue procedure. The model assumed similar clinical outcome in these techniques.

Results: On average, 120 TPE procedures prescribed annually at Ho Chi Minh City Hospital while Friendship Hospital recorded 100 TPE procedures. The estimated cost per procedure for

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centrifugal and membrane TPE were USD 351 (VND 8,170,606), rounded to nearest integer, and USD 1,465 (VND 34,108,346), respectively. For each TPE procedure performed on centrifugal technique, payer can expect to save USD 1,114 (VND 25,938,948).

Conclusions: The economic evaluation between these two plasma exchange techniques showed centrifugal TPE had a better cost benefit than membrane TPE. For a hospital with similar characteristics, we expect positive economic impact with application of centrifugal TPE.

SA6-06 The 5-year Experiences and Outcomes in Plasmapheresis of non-Transplantation Patients in Limited-Resource Center of Thailand

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Background: Plasmapheresis (PP) is a useful technique for removed pathogenic molecules from plasma. There are several indications of PP for non-transplantation patients. However, the total cost is still expensive and strictly reimbursed by Thailand's government. The data of practice patterns and outcomes in this setting are scarce.

Objective: To review and analyze PP of non-transplantation indications in terms of characteristics, indications, PP prescriptions and outcomes in limited-resource setting.

Material and methods: We retrospectively reviewed PP-registry of single center. We extracted data from non-transplantation patients whom were did PP in past 5 years. The clinical responsiveness and in-hospital mortality were analyzed as outcomes.

Results: Between January 1st, 2014 and December 31st, 2018, there were 130 PP-sessions [n = 24 patients]. The first-three leading indications were thrombotic thrombocytopenic purpura/hemolytic uremic syndrome [n = 5, 20.8%], neuromyelitis optica [n = 5, 20.8%] and diffuse alveolar hemorrhage from autoimmune disease [n = 5, 20.8%]. Of 24 patients, the nine [37.5%] critically ill patients were initiated PP at intensive care unit (ICU) and the remaining were initiated at dialysis unit. The median dose of PP was 1.5 times [inter-quartile range: 1.3 - 1.5] of plasma volume. All cases were done by hemodialysis machine incorporated with plasma separator. For the response to PP, there were 9 [37.5%], 9 [37.5%] and 6 [25%] patients for complete response, partial response and non-response, respectively. The hospital mortality was 7 [29.2%] patients and sepsis [n = 6; 85.7%] were leading cause of death. All of the hospital mortality was significantly in critically ill patients whom initiated PP at ICU [Odds ratio 28.0, 95% confident interval: 2.4 - 326.7, p-value = 0.003].

Conclusions: Even PP has been still performed by the cost-saving way, the outcomes were quite good. The infection is still a big problem after PP in developing country.



English Oral Session 1 Critical Care Medicine

EO1-01 Nafamostat mesylate inhibition of LZD metabolism via its antioxidant effects

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Introduction: Linezolid (LZD) has potent antibacterial activity against Gram-positive cocci. LZD is metabolized via the oxidation of the morpholine ring, and is dependent upon microsomal proteins and NADPH. Reactive oxygen species are important in this pathway. Nafamostat mesylate (NM) is a serine protease inhibitor and has antioxidant and anti-inflammatory effects. NM is frequently used as an anticoagulant during renal replacement therapy (RRT). The molecular weight of LZD is 337 and the plasma protein-binding level is 31%; therefore, LZD is removed by RRT. However, the plasma concentration of LZD has been reported to be high in RRT patients. The antioxidant effects of NM could, therefore, influence the plasma LZD concentration. However, limited information is available on this relationship. The aim of this study was to evaluate whether LZD plasma concentration was affected when co-administered with NM.

Method: Mice were allocated into two groups: “LZD and NM” and “LZD and saline”. The mice were treated with 1 mL of an LZD suspension (100 mg/kg) and 0.2 mL of either an NM suspension (30 mg/kg, intraperitoneal injection) or 0.2 mL of saline. Intraperitoneal injections, of either NM or saline, were performed at each hour after administration of LZD. Mice were euthanized 5 h after administration of LZD and plasma were collected for biochemical analyses.

Results: Plasma LZD concentration After LZD was administered for 5 h, the plasma concentration of LZD was significantly higher ($20.6 \pm 9.8 \mu\text{g/ml}$) in the LZD and NM group than in the LZD and saline group ($3.6 \pm 1.2 \mu\text{g/ml}$) ($p < 0.001$). These results showed that NM induced an increase in the plasma concentration of LZD. The antioxidant effects of NM may inhibit LZD metabolism. Coadministration of NM and LZD in RRT could also increase the plasma concentration of LZD and adversely affect LZD.

EO1-02 The mechanism of the decrease in cardiac output measurement by transpulmonary thermodilution has been elucidated

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Introduction: The cardiac output (CO) measured by transpulmonary thermodilution (TPTD) during blood purification is known to be underestimated. However, the mechanism has not been clarified. We have previously reported that it is the blood purification itself that effects CO measurement.

Hypothesis: We hypothesized that the difference between returning blood temperature and core body temperature may correlate with the CO measurement error.

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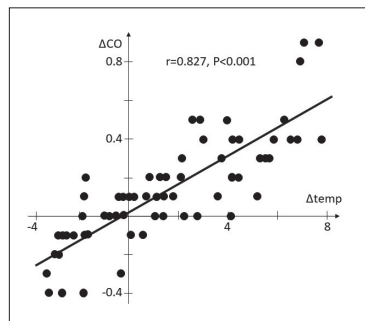
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Methods: Four female pigs (35-40 kg) were studied. EV1000 monitor™ (Edwards Lifesciences) and a catheter with a temperature sensor placed in the left femoral artery were used to measure the core body temperature and CO. A catheter for blood purification was placed in the right jugular vein, and a thermometer was installed in the blood returning side of the circuit. A catheter for cold saline injection was placed in the superior vena cava. The blood circuit was submerged in a thermostat bath set at 35, 40, 45 and 50°C upon measuring CO. The differences between returning blood temperature and core body temperature, and the differences between CO measurement with or without blood purification were recorded. The correlation between these differences were studied. Ejection fraction (EF) was evaluated by echocardiography in one pig.

Results: With the thermostat bath set at 35, 40, 45 and 50°C, the differences between returning blood temperature and core body temperature were -2.4 (-2.8 - -1.8) (median, (IQR)), 0.05 (-0.3 - 0.6), 2.4 (1.7 - 3.2), 5.8 (5.0 - 6.8)°C, respectively. The differences between the CO with or without blood purification were -0.10 (-0.23 - -0.10), 0.05 (-0.03 - 0.10), 0.25 (0.08 - 0.40), 0.35 (0.20 - 0.43) L/min, respectively. A strong correlation was observed between the two differences (Pearson's correlation coefficient 0.827, $P < 0.001$) (figure). EF was not affected with blood purification.

Conclusion: The difference between returning blood temperature and core body temperature correlates with the CO measurement error.



EO1-03 Treatment of chronic Heavy Metal Intoxication by Plasmapheresis, Promise or Illusion?

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Background: Long term intake of environmental pollutants like heavy metals (HM) leads to chronic intoxication and long term health impairment even when pollutant intake is diminished. While high environmental standards are protecting people in high income countries, chronic intoxication affects many people in emerging economies with high industrial production like China or India. Especially children and pregnant women are at high risk. Furthermore, gadolinium as essential contrast agent has been recently restricted in several countries because of described cases of toxicities. Since apheresis is able to eliminate toxins from human plasma, plasmapheresis has been suggested to treat chronic HM intoxication.

Materials & Methods: We used the International Commission on Radiological Protection model (Leggett RW, 1993) to simulate lead body distribution with long term low dose intake. We simulated the impact of single and repeated use of standard chelating agents (SCA), standard plasmapheresis with high protein elimination and a combination of long circulating scavengers that are eliminated by plasmapheresis after several days as a novel approach.

Results: At steady state, only minute amounts of total lead are found in plasma. Thus simple plasmapheresis treatments are useless in chronic HM intoxication, even if plasma concentrations of HM are significantly reduced. Repeated treatments with SCA have only modest impact on



long term brain and end organ concentration. In contrast, the combination of a long circulating scavenger for HM (and potentially other pollutants) followed by scheduled plasmapheresis allowed a reduction in brain, liver and kidney lead concentration. Even with this approach, several treatments are needed.

Conclusion: Simple plasmapheresis treatments are useless in chronic HM intoxication. Repeated treatments with SCA have only modest impact. The development of a suitable scavenger that can be eliminated by scheduled apheresis may hold high potential for the treatment of chronic HM intoxication.

EO1-04 A Case series -Use of Therapeutic Plasma Exchange (TPE) in the management of Patients with Snake bite

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Introduction: Snake bite patients(Pts) develop systemic effects including Acute Kidney Injury(AKI) and thrombotic-microangiopathy(TMA). Chronic kidney disease(CKD) occurs after Russell's Viper (RV) and hump-nosed-pit-viper (HNV) bites. Treatments include Anti-venom serum(AVS) for envenomation, Haemodialysis(HD) for AKI, Plasma(FFP) and Platelet-concentrate(PC) transfusions for venom-induced-consumptive-coagulopathy. Pts with TMA are referred for TPE.

Aims: To assess the starting time, number, duration & effect of TPE to renal recovery(RR) and TMA recovery (TMA-R); Haemoglobin(Hb) stabilization and Platelet(plt) rise.

Method: Pts' records were analysed retrospectively(July 2017-December 2018).

Details noted: Date of AKI, Hb drop(HbD), Plt drop(PD), lowest plt count(LP), PC & FFP transfusions(Tx), INR and TMA-R.

Results: Total 21 patients. Significant findings were, TPEs performed using FFP to 13 patients. RR was seen in 9(70%). Among them, 67% had AKI in day(D)2 & LP30-20x10⁹ inD4. 100% had INR<1.5, 67% had 3TPEs, 67% had 1stTPE onD4, 88% had Last onD8. 88% had TMA-R byD7. RR wasn't seen in 3(23%). Among them, 67% had AKI in D1. 100% had LP<20x10⁹ byD4 & INR>1.5. 66% had 4TPEs from D3toD8. 67% had TMA-R byD7. One(7%) died with no TMA-R after 3TPEs. TPEs weren't performed in 8 patients. RR was seen in 6(75%). Among them, AKI was seen in D2(50%),D3(50%). 67% had LP 50-75x10⁹ byD4. Daily FFP Tx given for 75% pts from D2toD5, who had INR>1.5(67%). TMA-R was 100% byD8. RR wasn't seen in 2(25%). Among them, AKI was seen in D2(50%),D3(50%). 100% LP 50-75x10⁹ byD3, <1.5. 100%TMA-R inD5.

Conclusions: 3TPEs during D3-D8 were needed for TMA-R(byD7) & for RR in severe TMA patients(LP30-20x10⁹), with AKI inD2.3- 4TPEs during D3-D8 were needed for TMA-R(byD7) without RR in more severe TMA patients(LP<20x10⁹), with AKI inD1. FFP transfusions during D2-D5 were needed for TMA-R(byD8) & for RR for less severe TMA patents(LP>50x10⁹) with AKI in D2 or D3.

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EO1-05 Biocompatibility and efficacy of self-anticoagulative chitosan- κ -carrageenan composite hydrogel for simultaneous endotoxin adsorption and bacteria capture in septic blood

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Backgrounds and aim: Sepsis is defined as life-threatening acute organ dysfunction secondary to infection and associated with high in-hospital mortality. Blood purification is an important supplementary therapy to manage severe sepsis and septic shock. However, the problem that clinically available techniques are not capable of simultaneous endotoxin removal and bacteria capture remains unsolved. Herein we aimed to develop a new chitosan- κ -carrageenan composite (C-K) sorbent and to evaluate its biocompatibility and septic blood cleansing efficacy.

Methods: The C-K sorbent was first fabricated via phase-phase inversion and genipin-crosslinked techniques. Its chemical composition was then well characterized. Biocompatibility evaluation assays including blood routine and hemolysis ratio test, clotting times, complement system activation levels were systemically performed to study the feasibility of this technique for septic blood cleansing. We studied the endotoxin removal behavior and *S. aureus* trapping efficacy of the novel sorbent via hemoperfusion-mimic adsorption models and bacteria culture and colony counting techniques.

Results: The C-K sorbent significantly inhibited blood-biomaterial interactions in contrast to native chitosan hydrogel. Severe adverse reactions including hemolysis, complement and contact system activation were not obvious. In fact, the C-K sorbent could prolong the APTT of incubated plasma to 110s and TT to 37s, making it possible to serve as a self-anticoagulative column. Besides, the sorbent significantly decreased the endotoxin level of septic blood from 30.0 to 11.2 Eu/mL (62.7%) with an ideal adsorption capacity of 95.0 Eu/g during a 3-h dynamic adsorption treatment. Bacteria capture experiments further showed that the C-K sorbent could reliably trap 74.0% of *S. aureus* from the simulative septic blood with an initial bacteria load of 10^5 CFU/mL.

Conclusions: Our findings suggested that the novel C-K sorbent markedly decreased both endotoxin and bacteria levels of septic blood without obvious adverse interactions with human blood and therefore could serve as a potential adsorption column.

EO1-06 Lactate predicts the 28-day survival rate in patients with septic shock treated with the combination of PMX-DHP and rTM

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We have previously reported that combination therapy with Polymyxin-B direct hemoperfusion



(PMX-DHP) and recombinant thrombomodulin (rTM) is effective to patients with septic shock accompanied by disseminated intravascular coagulation (DIC). There is a report that the early initiation of PMX-DHP for septic shock results in better outcome. But there is no study reported that focus on the combination. Here, we retrospectively examined the effect of how early PMX-DHP is performed for improving hemodynamic derangement in the above combination therapy on prognosis.

Forty-seven patients who underwent the combination therapy for septic shock with DIC from August 2011 to August 2016 in our hospital were enrolled. The patient characteristics were as follows; age 71.9 ± 10.1 years, 26 men (55%), APACHE II score 32.7 ± 7.7 , lactate 26 (18-41) mg/dL. The 28-day survival rate after PMX-DHP initiation was 76.6%. The patients were divided into two groups; early group (N=25) that received PMX-DHP within 12 hr after catecholamine administration and late group (N=22) that received PMX-DHP later than 12 hr. The 28-day survival rate was not significantly different in the two groups. However, in the early group, APACHE II score was significantly lower ($p=0.02$), but lactate was higher ($p=0.005$) compared to the late group. Multivariate logistic regression analysis showed that lactate was the only predictor of 28-day mortality (odds ratio per +1 mg/dL of lactate, 1.08; 95%CI, 1.03-1.19; $p=0.037$) after the adjustment by age, sex, APACHE II score, lactate and how early PMX-DHP is performed.

The addition of rTM to PMX-DHP may not only improve the therapeutic effect of PMX-DHP, but may also modify the effect of how early PMX-DHP is performed on the prognosis. Time after lactate elevation may be an appropriate indicator to discuss how early PMX-DHP is performed in the combination therapy rather than that after catecholamine administration.

English Oral Session 2 Nephrology/others

EO2-01 Comparing the Outcomes of Desensitization for ABO Incompatible and HLA Incompatible Kidney Transplantation

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Background: ABO incompatible (ABOi) transplantation is an alternative treatment to deceased donor kidney transplantation which require waiting time. We report the outcomes of ABOi by compare with HLA incompatible (HLAi) kidney transplantation which are considered as high immunologic risk kidney transplantation.

Method: We compared the outcomes of living donor ABOi, HLAi (negative CDC-AHG / positive Luminex; HLAi-LKT), combined ABOi with HLAi (ABOi + HLAi), and deceased donor HLAi (HLAi-DKT) from 2008, the first year of ABOi in Thailand. All of living donor transplantation recipients underwent desensitization which has been adjusted according to ABO

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antibody and HLA antibody levels. The desensitization protocol consists of apheresis, IVIg, rituximab. HLAi-DKT recipients have been transplanted without desensitization due to limited pre-transplant time. Preemptive strategy was used for CMV prevention in most of our cases.

Results: Of total 68 recipients, there were 18, 26, 7, and 17 recipients with ABOi, HLAi-LKT, ABOi + HLAi, and HLAi-DKT, respectively. Early active antibody mediated rejection (ABMR) was found in 5.6%, 15.4%, 28.6% and 52.9%, respectively. The ABOi group provided better death-censored rejection free survival compared to other high-risk groups ($p = 0.004$, figure 1). CMV viremia/disease was found in 11%, 35%, 43% and 71% of our patients respectively ($p < 0.05$). The rate of BK viremia, viremia and BKVAN were not difference between the four groups.

Conclusion: ABOi kidney transplantation provides better outcomes compare to other high immunologic risk groups. Desensitization for ABOi is a good option for patients without compatible donor.

EO2-02 Clinical outcome of the apheresis therapy for acute antibody-mediated rejection after kidney transplantation in our institute

Yasushi Mochizuki¹⁾, Tsuyoshi Matsuda²⁾, Yuta Mukae²⁾, Hiromi Nakanishi²⁾, Kojiro Oba²⁾, Mineaki Kitamura^{1,3)}, Satoko Kitamura^{1,3)}, Tadashi Uramatsu³⁾, Yasuyoshi Miyata²⁾, Masaharu Nishikido⁴⁾, Tomoya Nishikido⁴⁾, Hideki Sakai^{1,2)}

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3) *Department of Nephrology, Nagasaki University Hospital, Japan*

4) *Department of Urology, Nagasaki Medical Center, Japan*

Background: Acute antibody-mediated rejection (AAMR) at early stage after kidney transplantation (KT) is an important complication because it is a cause of allograft deterioration. We report 8 cases of AAMR after KT and review the literatures.

Material and Methods: Among 253 patients who underwent KT at our hospital, eight cases (2 males and 6 females) were clinically and pathologically diagnosed with AAMR and received with various treatments options. All cases are living-donor KT, and their mean \pm SD age at KT was 47 \pm 13 years. Four cases were ABO-compatible KT and other four were ABO-incompatible one. Before KT, three cases were judged as positive of donor specific anti-HLA antibody.

Results: Six of eight patients were treated with desensitization therapy including apheresis treatment before KT. Median onset period of AAMR was 5.5 days after KT (1-18 days). For all patients, combined treatment including apheresis, high-dose steroid therapy, intra-venous immunoglobulin, and rituximab administration was immediately performed. In the observation period (5.7 \pm 3.8 years), there was no graft loss due to the occurrence of AAMR. On the other hand, one patient died by sudden onset of cardiac disease with good engraftment and other seven patients survived with stable functioning graft. However, two cases are pathologically diagnosed with chronic active antibody-mediated rejection by periodic allograft biopsy and need observation with strict immunosuppressive therapy.

Conclusions: Although the treatment methods of AAMR after KT have not established, various treatment strategies, including apheresis, are reported to be useful for short-term favorable outcomes. However, the onset of AAMR may affect the kidney function for a long period after KT. We summarize the clinical course and treatment options of experienced cases and review the literatures associated with apheresis therapy for AAMR.



EO2-03 Cost analysis of therapeutic plasma exchange procedure at Middlemore Hospital, New Zealand

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2) *Nephrology Department, Middlemore Hospital, Auckland, New Zealand*

Background: Therapeutic plasma exchange (TPE) is a procedure that removes pathogenic substances of high molecular weight such as antibodies, endotoxins, circulating immune complexes and cholesterol-containing lipoproteins from plasma. TPE can be performed using centrifugal or membrane filtration method. At present, Middlemore Hospital exchange plasma via membrane filtration method. This study aims to assess the economic burden of adopting a new TPE technology from public payer perspective.

Methods: A cost minimization analysis model was created on Excel spreadsheet using micro-costing approach with the following cost component; device acquisition, maintenance, consumables, venous access, replacement fluids, labor. TPE utilization and cost data were collected from nephrology department, Middlemore Hospital. Centrifugal TPE data on adverse events, procedure efficiency and clotting frequency were sought from published literatures. The model assumed similar clinical outcome in these techniques.

Results: A total of 55 TPE procedures were performed annually. On average, each patient required 10 TPE procedures. Membrane TPE reported 50% clotting event for every 55 procedures and it takes 57% longer time (2.5 hrs) to complete TPE procedure. Total procedure time includes device setup time. The results from cost minimization analysis showed cTPE is less costly than mTPE. Cost of cTPE and mTPE procedure were NZ\$ 654 and NZ\$ 923, respectively. These estimates take into account centrifugal capital device investment and zero investment cost for membrane device. The main cost drivers for mTPE procedure were clotting, central access catheter, staff time and disposables. Middlemore Hospital expected to save NZ\$ 14,791 annually on 5 patients requiring TPE treatment. In 5 years, the projected total savings was NZ\$ 73,955.

Conclusions: Adoption of centrifugal technique for TPE procedure increase clinical operation efficiency while delivering quality patient care and reduce hospital operation cost. TPE procedure on centrifugal device free up Middlemore hospital operation cost that can be reinvested in patient care.

English Oral Session 3 Collagen Disease/Rheumatology/other

EO3-01 Prognosis of anti-MDA5 antibody positive clinically amyopathic dermatomyositis treated with plasma exchange; a case series of single center experience

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[Background] Anti-melanoma differentiation-associated gene 5 (MDA5) antibody is a specific antibody for dermatomyositis which is commercially available in recent years. Anti-MDA5

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antibody positive dermatomyositis likely to present amyopathic symptoms, especially, rapid progressive interstitial lung disease (RP-ILD) which is a life-threatening complication. Plasma exchange (PE) is one of the options for induction therapy for RP-ILD complicated cases, however, the criterion for initiation nor the duration period is not well established.

[Materials & Methods] We experienced five cases of anti-MDA5 antibody amyopathic dermatomyositis which underwent PE in our hospital from June 2017 to June 2019. We focused on the clinical features of each case, especially on the laboratory findings at the time of referral and the content of induction therapy.

[Results] We experienced one male patient and four female patients. The mean age was 66.0 years old, mean CRP, KL-6, and ferritin at the time of referral were 3 mg/dL, 786 U/mL, 3090 ng/mL, respectively. The titer of the anti-MDA5 antibody was exceeded the upper limit of analysis in three patients. The male patient survived for 6 months, but all female cases died. The survived case was treated with intravenous methylprednisolone followed by oral steroids, intravenous cyclophosphamide, rituximab, tofacitinib, tacrolimus, and four consecutive PEs. Of the death cases, three cases were died of progression of RP-ILD within two months from the appearance of the first symptom, though the cases had received the first PE on the next day of referral.

[Conclusion] Though the heterogeneity of the disease, the RP-ILD is critical for the disease prognosis. Our cases showed that though the early PE did not respond to severe cases, within the use of a high dose of immunosuppressants and immunomodulators. Further investigation is necessary to establish a therapeutic strategy for inducing favorable outcomes, though, PE might be necessary for treatment among severe cases.

EO3-02 Case series: Successful treatment of Adult Onset Still's Disease (AOSD) using Plasma Exchange

Fumika Homma¹⁾, Osamu Yamazaki¹⁾, Sachiko Kitagawa¹⁾, Kurumi Asako²⁾, Hajime Kono²⁾, Yoshikazu Nemoto¹⁾, Shinichiro Asakawa¹⁾, Michito Nagura¹⁾, Shigeyuki Arai¹⁾, Yoshifuru Tamura¹⁾, Shigeru Shibata¹⁾, Yoshihide Fujigaki¹⁾

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Background: Adult onset Still's disease (AOSD) is a rare clinical entity with unknown etiology, characterized by arthritis, fever, evanescent rash and other systemic presentations. Here we experienced AOSD patients who received Plasma Exchange therapy. Both patients improved clinical symptom after Plasma Exchange.

Case Presentation:

[Case 1] Female, 43-years-old. The moment of the first appointment, confusion of consciousness, arthritis of multiple joints, skin scratches, elevation of inflammatory markers and transaminases are noted. We diagnosed AOSD and started steroid therapy. Thrombotic microangiopathy (TMA) occurred on day 36 following steroid therapy. We initiated Plasma Exchange therapy and clinical symptom was improved. We add oral Methotrexate (MTX) and she discharged on day 96.

[Case 2] Female, 31-years-old. She diagnosed AOSD at 17-years-old and treated with oral corticosteroid, tacrolimus, and tocilizumab. Her leg arthritis are worsen and AST, ALT, ferritin are elevated. She has allergy for multiple drugs, therefore, we decided to choose Plasma Exchange. After six times of therapeutic sessions, her clinical symptom and laboratory data were getting improved.



Conclusion: Efficacy of Plasma Exchange therapy is that it removes not only small molecules but also wide-range of molecules including cytokines, inflammatory factors. Plasma Exchange is a potential therapeutic option against AOSD.

EO3-04 The economic impact of centrifugal technique for therapeutic plasma exchange; public hospital perspective

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- 2) Terumo BCT Asia, Singapore

Background: Therapeutic plasma exchange (TPE) is a procedure in which blood of the patient is passed through a medical device which separate plasma from other components of blood and the plasma is removed (ASFA 2016). It is a common treatment modality in management of various renal, hematological and neurological diseases. Through TPE, pathologic substances that cause the underlying disease such as inflammatory mediators; autoantibodies, complement components and cytokines are eliminated and substantially improve patient quality of life. TPE can be performed using two categories of devices; membrane or centrifugal. This study assessed the cost associated with these techniques from public payer perspective.

Methods: TPE procedures and cost data were obtained from hematology department, National Cheng Kung University Hospital in Taiwan. A cost minimization analysis model was created on Excel spreadsheet using micro-costing approach with the following cost components; device acquisition, maintenance, consumables, venous access, replacement fluids, labor. Data on procedure efficiency and clotting frequency were sought from published literatures. Clotting defined as filter replacement to continue procedure. The model assumed similar clinical outcome in these techniques.

Results: A total of 500 TPE procedures were performed annually with almost equal proportion used of both TPE methods (52% mTPE; 48% cTPE). The estimated centrifugal and membrane TPE cost per procedure was USD 318 (NT\$ 10,368), rounded to nearest integer, and USD 495 (NT\$ 15,321), respectively. The projected annual cost savings from using centrifugal technique for plasma exchange was USD 52,346 (NT\$ 1,621,319).

Conclusions: The cost comparison between these two plasma exchange techniques showed centrifugal TPE had a better cost benefit than membrane TPE.

EO3-05 Effectiveness of Therapeutic Plasma Exchange in the Treatment of Catastrophic Antiphospholipid Syndrome: A 15-year Retrospective Review

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Background: Catastrophic Antiphospholipid Syndrome (CAPS) is rare, life-threatening variant of APS, involving multiple venous and/or arterial thromboses in ≥ 3 organ systems and presence of antiphospholipid antibodies (abs). Treatment includes: managing precipitating factors, systemic anticoagulation (AC), high-dose corticosteroids (CS), plasma exchange (TPE), and IVIG.

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Methods: We reviewed the records of 47 CAPS patients (pts) from 1/2004 through 1/2019. Median age 49 years (26-73 years); 29 pts (62%) were female. 39 (83%) pts had lupus anticoagulant and/or IgG anticardiolipin abs. 45 (96%) pts had radiographic and/or clinical evidence of thrombosis in small vessels of ≥ 3 organ systems (kidneys, lungs, heart, brain, gastrointestinal tract, or lower extremities). 41 (87%) pts had precipitating factors (infection [27%], neoplasm [16%], surgery [15%], warfarin withdrawal [13%], SLE [9%], other [7%]).

Results: In addition to treating precipitating factors, and starting therapeutic AC (IV heparin in 46 [98%] pts), pts received: high-dose IV methylprednisolone X 3 days followed by prednisone taper (47 [100%] pts), daily TPE X 3-5 days using FFP (or 5% albumin/FFP) (42 [89%] pts), and IVIG X 5 days (33 [70%] pts). 9 (19%) pts had thrombotic microangiopathy and received weekly rituximab; 4 (9%) pts had SLE exacerbation and received cyclophosphamide. Of 47 CAPS pts, 5 (11%) pts recovered fully with treatment of precipitating factors, systemic AC, and CS alone. Of remaining 42/47 (89%) pts with refractory CAPS, 42 (100%) pts received TPE treatment; 33/42 (79%) pts received IVIG. Highest initial recovery rate (35/42 [83%] pts) in refractory CAPS achieved with systemic AC, CS, and TPE with/without IVIG treatment. Over 30-day period, 9/47 (19%) CAPS pts died (due to complications of sepsis, CVA, or MI).

Conclusions: High-dose CS, TPE, and IVIG are useful adjunctive therapies for refractory CAPS (in addition to managing precipitating factors and systemic AC), and appear to provide the highest rate of recovery.

EO3-06 The efficacy of plasmapheresis for multiple sclerosis and neuromyelitis optica unresponsive to steroid-pulse therapy and its immunological prognostic markers

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Background/Aim of study: The recent advance of disease-modifying therapies and immunosuppressive agents help reduce relapse rates in many patients with multiple sclerosis (MS) and neuromyelitis optica (NMOsd). However, some patients do not fully recover from the symptoms of the acute relapse and progression, even after repeated trials of steroid-pulse therapy. We evaluated the efficacy of plasmapheresis in patients with MS and NMOsd with residual symptoms after steroid-pulse therapy, and searched for an immunological marker in responders.

Materials & Methods: Since 2005, we have proactively performed plasmapheresis for symptom management in patients with neuroimmunological diseases. We analyzed patients with relapsing-remitting MS (RRMS, n=45), secondary-progressive MS (SPMS, n=32) and NMOsd (n=20) treated from 2005-2011 (early era), and RRMS (n=41), SPMS (n=32) and NMOsd (n=44) treated from 2016-2017 (late era). Patients were started on immunoadsorption plasmapheresis (IAPP) and changed to double filtration plasmapheresis (DFPP) or plasma exchange (PE) according to their responsiveness. Treatment efficacy was objectively evaluated using the extended disease status scale (EDSS) and functional scale (FS). We checked plasmablasts and IFN γ +Th1 and IL-17+Th17 cells.



Results: In the early era, 37.0% (RRMS), 27.3% (SPMS) and 47.8% (NMOsd) responded to IAPP, and 25.0% (RRMS), 35.3% (SPMS) and 45.5% (NMOsd) responded to DFPP/PE. In the late era, 65.9% (RRMS), 39.4% (SPMS) and 26.3% (NMOsd) responded to IAPP, and 50.0% (RRMS), 50.0% (SPMS) and 57.7% (NMOsd) responded to DFPP/PE. Plasmablast counts were lower in IAPP responders and higher in DFPP/PE responders. Th1 was significantly higher in IAPP responders.

Conclusion: Plasmapheresis is effective in some patients with steroid-unresponsive MS and NMOsd. Most patients with RRMS tended to respond to IAPP, whereas some with SPMS and NMOsd responded better to DFPP/PE. The efficacy of IAPP and DFPP/PE varies according to the number of plasmablast, and Th1 cells were especially useful for predicting IAPP responders.

English Oral Session 4 IBD/Ascites/CART/Technology

EO4-01 Treatment result of the curative effect of GCAP for the intractable UC in our Hospital (examination about the blood throughput)

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Abstract/Background: As for the polymorph adsorption therapy developed in Japan (GCAP), there is insurance coverage for seriously ill cases, intractable cases, and, for steroid (ST)-resistant dependent UC, the enforcement in moderate degree cases is more than it is recommended in the guidelines. For the GCAP cases that we treated in enforced in our blood purification therapy. We judged the curative effect and, a earlier sector as, recognized the improvement of clinical manifestations in all cases for ST-resistant dependent UC from April 2011 to December 2017. We considered whether we influence it though GCAP this time. We report ed it.

EO4-02 Modification of the Dialysate Port of Plasma Separator; A measure against mix-up of plasma separator with hemofilter (final report)

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As a measure to prevent the fatal mix-up of plasma separator with hemofilter in 2011, the modification of the plasma separator dialysate port was proposed by a volunteer meeting composed of both blood purification specialists and members of manufacturers of blood purification equipment. This proposal was also supported by the Japan Association for Blood Purification for Critical Care, the Japanese Society for Technology of Blood purification, the Japan Association for Clinical Engineers, the Japanese Association for Artificial Organs, the Japan Academy of Nephrology Nursing, the Japanese Association of Dialysis Physicians, the

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Japanese Society for Dialysis Therapy, and the Japanese Society for Apheresis. Although the policy was confirmed by the Ministry of Health, Labor and Welfare of Japan in May 2015, we had to wait the announcement of a new standard by the International Organization for Standardization (ISO). In September 2016, a new standard was developed by the ISO and was immediately agreed by the government. Therefore, the blood purification subcommittee of Medical Technology Association of Japan was decided to change the slip-in type (ISO 8637) to a Luer lock shape (ISO 80369-7) to make the plasma separator incapable to connect to a hemofilter circuit. This modification will be also applied to a plasma separator for selective plasma exchange, but not to plasma fractionator for double filtration plasmapheresis. This modification was approved by the government in November 2018, together with a temporal use of intermediate connectors to connect an old separator to a new circuit. A blood circuit packing with the intermediate connector has already begun shipping, and the insurance coverage of the new plasma separator is scheduled for September 2019. Although the use of the intermediate connector may pose a new risk, a plasma separator with a modified dialysate port to prevent misconnection has finally come to the market.

EO4-03 Cell-Free and Concentrated Ascites Reinfusion Therapy against refractory ascites on various disease

Masahiro Hattori, Shuhei Kii, Masanori Sato, Nobuyuki Taniyama, Junichi Goto, Hiroaki Takahashi, Takashi Horie, Kazuhiko Onodera, Kazutaka Kukita, Junichi Meguro, Motoki Yonekawa

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Background: Refractory ascites cause many physical and psychological sufferings to the patients with decompensated cirrhosis, carcinomatous peritonitis or other various diseases. Cell-free and Concentrated Ascites Reinfusion Therapy (CART) has been performed generally, but the efficacy of CART is controversial.

Method: We conducted 178 times of CART in total to 41 patient in five years of 2014/1/1-2018/12/31. Ascites were collected under ultrasound guided puncture, then many cells including bacteria or malignant cells are removed through the filtration, and concentrated ascites in 10 times is reinfused to the patient. The patients were divided to 4 groups, HA group: the patients with decompensated cirrhosis, CA group: with the peritoneal carcinomatosis, Mixed group: considered of both hepatic and malignant reason, and Other group: nephrosis, post chemotherapy, poor nutrition, GVHD, and so on.

Results: In 41 cases, HA group has 16 cases, CA 15 cases, Mixed 4 cases, and Other 6 cases. The amount of collected and concentrated ascites is 3194-3530ml and 324-354ml respectively. The average number of times of CART was 6.6 times in HA, 2.9 in CA, 4.3 in Mixed, and 2.2 in Other. The days from the CART started to the final outcome are 217, 38, 68, and 287 days on average respectively.

Discussion: In HA, more frequent CART contributed to improve nutritional status and abdominal distention for longer duration than CA and Mixed. In CA, operation of CART as a palliative therapy showed improvement of QOL, but fewer implementation of CART complicates to show improvement of the prognosis.

Conclusion: While CART enables to reinfuse self-proteins instead of human blood products, and improve the abdominal distention in various diseases, meanwhile the advantage of CART compared with simple abdominal puncture requires some clear evidences in the future. The standardization of medical indication and assessment of therapeutic effect are expected.



EO4-04 Assessing cost of membrane and centrifugal techniques for therapeutic plasma exchange in Thailand

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Background: Therapeutic plasma exchange (TPE) is one of the therapeutic apheresis procedures where it removes pathogenic substances that cause the underlying disease such as autoantibodies and circulating immune complexes from the plasma. TPE continued to play a key role in management of various diseases and remained as the treatment choice as per 2016 guidelines of the American Society of Apheresis for Guillain-Barre syndrome, ANCA associated rapidly progressive glomerulonephritis, thrombotic thrombocytopenic purpura and renal transplantation, to name a few. TPE can be performed using two techniques; membrane or centrifugal. This study examined the cost associated with these techniques from payer perspective.

Methods: TPE procedures and cost data were collected from nephrology department in Chulalongkorn University Hospital, Bangkok. A cost minimization analysis model was developed using micro-costing approach with the following cost components; device acquisition, maintenance, consumables, venous access, replacement fluids, labor. Data on procedure efficiency and clotting frequency were sought from published literatures. The model assumed similar clinical outcome in these techniques.

Results: A total of 200 TPE procedures were performed in Chulalongkorn University Hospital. Out of these, 75% TPE procedures used membrane plasma filter for plasma exchange. The estimated cost per procedure for centrifugal and membrane TPE was USD 369 (THB 11,304), rounded to nearest integer, and USD 708 (THB 21,671), respectively. Public payer can expect to save USD 339 (THB 10,384) for each TPE procedure performed using centrifugal method.

Conclusion: The economic evaluation between these two plasma exchange techniques showed centrifugal TPE had a better cost benefit than membrane TPE. For a hospital with similar characteristics, we expect positive economic impact with application of centrifugal TPE.

English Oral Session 5 Dermatology/Neurology

EO5-01 A case of pustular psoriasis deteriorated during the second pregnancy was successfully treated with intensive GMA and certolizumab pegol

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A 31-year-old woman with the IL36RN gene mutation developed psoriasis at 3 years old. As she had pustular psoriasis at 16 years old, she was treated with cyclosporine (Cys), resulting in remission at 20 years old. Afterwards, she had been maintained by topical treatment for long years. During the first pregnancy at the age of 29, she developed pustular psoriasis at 29 weeks of gestation. She received one course of granulocyte / monocyte adsorption apheresis (GMA)

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with Cys and prednisolone (PSL), and gave birth to a girl at 33 weeks of gestation. The baby was a low birth weight child, but is healthy and has no problems in growth and development until now. However, the patient did not sufficiently improve symptoms after delivery. We thus started the treatment with infliximab (IFX) BS at 2 months postpartum. During the second pregnancy at the age of 30, we continued the IFX-BS administration. She had erythema and pustules rapidly enlarged from 23 weeks of pregnancy. Oral administration of PSL and GMA were started. However, we switched the therapy to intensive GMA (twice in a week), because the effect was insufficient. Initially, administration of IFX-BS was scheduled to end at 30 weeks of gestation, but due to unstable symptoms, we considered it was necessary to use another biologics even after 30 weeks of gestation. We switched to non-placental certolizumab pegol (CTZ) from 26 weeks of gestation and continued the administration until delivery, and she gave birth to a girl at 35 weeks of gestation. Although the baby was a low birth weight child, there was no physical abnormality and the baby was discharged after gaining weight. After delivery, administration of CTZ was discontinued and the PSL dose was gradually reduced. However, reintroduction of biologics is under consideration, because erythema and pustules still remain.

EO5-02 Plasma Exchange in Neuromyelitis Optic Spectrum Disorders

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Background: Neuromyelitis Optica Spectrum Disorders (NMOSD) is a rare disease, with poor evidence-based treatment. The aim of our study is to describe *shortterm* outcomes of plasma exchange (PLEX) in flares, after initial corticosteroids therapy.

Methods: We retrospectively analyzed 122 adults treated with 673 PLEX sessions by filtration and albumin substitution for NMOSD acute attacks in two high quality centers at Bogota, Colombia, from January 2011 to May 2019. We used Wingerchuk NMOSD diagnosis criteria. The primary outcome was Visual Outcome Scale (VOS) and Expanded Disability Status Scale (EDSS) score improvement during hospitalization. We describe clinical characteristics, PLEX prescription, and complications. Then we estimate factors associated with improvement.

Results: Mean age was 42 (SD=13.7), 73% female, 52% first flare, 60% with unilateral optic nerve (ON) followed by 14.7% with both, ON and spinal cord compromise. *Pre-PLEX* EDSS was 3 (IQR=3-5) and VOS 5 (IQR=4-7), 56% had *aquaporin-4* antibodies with 62% positive report. We start PLEX at 7 (IQR=5-11) days after flare diagnosis. More than 90% were treated with at least 5 PLEX sessions; median dose 1.17 (SD=0.33) plasmatic volumes and 56.6% of sessions were performed daily. 28.7% didn't have improvement in EDSS, and 23.6% with ON lesion didn't improve VOS. Median improvement in EDSS and VOS was 1 point. 45% had EDSS<2 and 46% VOS<3 after last PLEX. As adverse events 24.5% of PLEX sessions presented low fibrinogen and 21% hypocalcaemia. Catheter dysfunction in 4%, 2.46% presented any infection, 1.78% hypotension and 1 patient had controlled *major-hemorrhage*. Median hospital stay was 12 (IQR=10-17) days. Adjusted factors associated with VOS improvement (>2

points or VOS=0) were lower age, higher initial VOS and lower initial EDSS and for EDSS improvement (at least 1 point) was lower age ($p<0.05$).

Conclusions: PLEX improves NMOSD significantly, it's safe and age, initial EDSS and VOS were associated with PLEX response.

EO5-03 Efficacy of intravenous methylprednisolone and plasmapheresis in relapsing MOG-IgG+disease: early institution of plasmapheresis

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Objective: To clarify the efficacy of intravenous methylprednisolone (IVMP) and plasmapheresis (PP) in patients with anti-myelin oligodendrocyte glycoprotein (MOG) antibody-related neurologic disease (MOG-IgG+disease).

Patients and Methods: A total of twenty-four attack in twenty patients with MOG-IgG+disease was investigated, retrospectively. The efficacy was evaluated as three groups such as complete (CR), partial (PR) and poor/no response (NR). We analyzed the frequency of patients who show the CR, PR and NR after IVMP or PP. The initial treatment was performed with IVMP in most cases, and PP was used in cases with PR or NR to IVMP. A course of IVMP consisted of methylprednisolone 1g/day, 5 consecutive days; and PP comprised 3 sessions of immunoadsorption with tryptophan, or plasma exchange.

Results: Among 24 cases, the efficacy of the first course of IVMP was shown as CR 50% (12/24), PR 42% (10/24) and NR 8% (2/24). The efficacy of the second course of IVMP in 10 patients who showed PR, NR to the first course of IVMP was as follow: CR 20% (2/10), PR 60% (6/10) and NR 20% (2/10). Among 10 patients who were treated with PP after refractory to IVMP, 2 cases (20%) showed CR, 8 cases (80%) PR to PP. PP was started after the first IVMP in 4 cases and after the second IVMP in 6 cases. Effectiveness of PP in each timing of start was as follow: CR 50% (2/4), PR 50% (2/4) after the first IVMP, and CR 0% (0/6), PR 100% (6/6) after the second IVMP. The efficacy of PP after the first IVMP was higher than those after the second IVMP. This suggests that PP effectiveness is dependent on the timing of start. In conclusion, early institution of PP should be considered in MOG-IgG+disease with refractory to the first course of IVMP.

English Oral Session 6 Neoplasm / Cardiology / Nephrology

EO6-01 The application of the adsorbent for LAP positive T cells to cancer therapy

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We have developed the synthetic adsorbent for immunoregulatory cells expressing LAP-TGF-beta complex. When cancer rats were treated with the hemoperfusion column, LAP positive cells and IL-10 producing cells were decreased and the tumor growth was suppressed and their survival times were prolonged.

EO6-02 Immunotherapy employing dendritic cell vaccination for patients with advanced or relapsed esophageal cancer

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Background: The prognosis of patients with advanced esophageal cancer is poor with a 5-year overall survival rate of 20-30%. In the present pilot study, we have evaluated the clinical and immunological responses in patients with advanced or relapsed esophageal cancer who received dendritic cell (DC) vaccination in combination with a toll like receptor (TLR) 4 agonist, OK-432.

Methods: Fifteen patients (7 males, 8 females; aged 50-76 years) were enrolled. Autologous DCs were generated by culturing adherent mononuclear cells with interleukin-4 and granulocyte-macrophage colony stimulating factor. DCs were then loaded with synthetic peptides derived from Wilms' tumor 1 (WT1) and/or MUC1 mucin. DCs and OK-432 were administered intradermally every 2 weeks for 5-7 times. Induction of vaccine-induced T cell responses was evaluated using a HLA-tetramer assay and an ELISPOT assay.

Results: The treatment was well tolerated and none of the patients experienced more than grade 2 adverse events. Two had partial response (PR), 3 had stable disease (SD) and 10 had disease progression (PD) after one course of vaccination. Median overall survival was 7.0 months from the initiation of a vaccination. Survival of patients achieving PR or SD (responder) was longer than those who did not respond to the treatment (non-responder) (median overall survival; 18.3 vs 5.8 months). Significant increase in the positivity of WT1-specific CD8 positive T cells following vaccination was observed in responders in comparison with non-responders; 33.7 and 0.45 fold in responders and non-responders, respectively. Similar result was observed in ELISPOT assays.

Conclusions: DC vaccine-based immunotherapy combined with a TLR agonist was demonstrated to be safe and elicit immune responses against tumor antigen which were correlated with clinical outcome. These results suggest that DC vaccination might be a promising novel strategy for the treatment of patients with advanced or relapsed esophageal cancer.



EO6-03 Apheresis treatment for refractory nephrotic syndrome by focal segmental glomerulosclerosis; A systematic review of published cases

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Background and aim; Currently, the Japanese Society for Apheresis is developing guidelines for the apheresis treatment for many diseases. Our team conducted literature search on the effectiveness and safety of apheresis therapy for refractory nephrotic syndrome (rNS) by focal segmental glomerulosclerosis (FSGS), most of which were case reports, and performed systematic review.

Methods; The effectiveness was determined as complete remission (urinary protein < 0.3 g / day; CR) or incomplete remission type I (urinary protein; 0.3-1.0 g / day; ICR-I) even after various treatments for more than 6 months. The safety was defined as the occurrence of adverse events. The outcome was determined as the remission rate (CR or ICR-I), renal prognosis, all-cause mortality and adverse events. Three hundred and eighty-six reports of plasma exchange (PE), 19 of double filtration plasmapheresis (DFPP), 32 of IAPP, 68 of LDL apheresis (LDL-A) and 4 of cytapheresis were identified. We screened papers and selected 6 papers for PE / DFPP (16 cases) and 22 papers for LDL-A (115 cases). Randomized controlled trials had not been conducted in this area. The IAPP and CAP were not employed at this time.

Results and discussion; Steroids with or without immunosuppressants therapy have been used before apheresis treatment in most cases, but the dose was not described in some papers. It was difficult to evaluate the effectiveness of PE or DFPP, however, we confirmed several effective cases by PE or DFPP. The remission rate by LDL-A was 51% (59/112), indicating the effectiveness of LDL-A for rNS by FSGS. There is no description on life prognosis and adverse events, and publication bias is frequently observed.

Conclusion; LDL-A seems to be effective to control rNS by FSGS. To clarify the degree of recommendation, it is necessary to collect case series that clearly describes the outcomes on a larger scale.

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Japanese Oral Session 1 Ascites/CART

JO1-01 Investigation of washing volume for Back-filtration cleaning in CART

It is difficult to concentrate massive cancerous ascites because of membrane obstruction in CART. We have previously reported the novel back-filtration cleaning method for a clogged membrane in an internal-pressure CART system. Here, we investigated the efficacy of washing volume for this method. We prospectively analyzed washing volume of saline. Washing volume in each session was divided into 250ml and 500ml alternately. We analyzed 10 and 11 cleaning sessions in 250ml and 500ml groups. There was no difference in ascites volume between cleaning sessions. Total protein and albumin in cleaning waste were lower in 250ml group.

JO1-02 Examination of the optimal ascites concentration rate when using blood purification equipment “Plasauto μ <CART mode>”

The blood purification equipment “Plasauto μ <CART mode>” is a machine that can perform CART safely and easily from the start of treatment to the end by an automatic control system. However, it is necessary to consider the setting of filtration rate, concentration rate, pressure, etc. for each type of ascites, and to set appropriately. In this study, we will report the result of the examination of the optimal ascites concentration rate when using Plasauto μ .

JO1-04 Evaluation of safety in CART using blood purification equipment Plasauto μ

The new blood purification device Plasauto μ (Plasauto) is expected to contribute the expansion of facilities to perform CART. This time, we compared the safety and operability between Plasauto and ACH- σ (ACH). The new clinical engineer performed CART using Plasauto and ACH. It was easy to operate Plasauto by connecting the circuit according to the guidance. On the other hand, it took a lot of time to handle ACH because the circuit configuration was complicated. There were no major adverse events attributable to the devices in both devices.

Japanese Oral Session 2 IBD

JO2-01 Effect of cellulose acetate beads on the release of interleukin-13 at different temperatures

We investigated the effect of cellulose acetate (CA) beads, carriers for granulocyte and monocyte adsorptive apheresis (GMA), on the release of interleukin (IL)-13, an inflammatory cytokine. We incubated peripheral blood with and without CA beads at 5°C, 25°C, 37°C, and 43°C and measured the IL-13 concentration. The IL-13 concentration in the samples incubated without CA beads increased as the temperature increased; however, the IL-13 concentration in the samples incubated with CA beads decreased as the temperature increased from 5°C to 37°C. These results suggest that the optimal temperature of GMA for anti-inflammatory effects may be at body temperature.



JO2-02 Examination of the therapeutic effect in our hospital GMA LCAP (CAP) therapy

We examined the improvement rate, remission induction rate, and treatment effect retrospectively in 35 patients with ulcerative colitis (UC) who received CAP therapy from 2014 to 2018. The therapeutic effect was showed with partial Mayo score used for evaluation of UC. The improvement rate was 91%, and the remission induction rate was 66%. The partial Mayo score was significantly reduced from 6 before treatment to 2 after treatment, and CRP value was also reduced from 0.39 mg / dl before treatment to 0.14 mg / dl after treatment.

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Japanese Oral Session 3 Collagen Disease/Rheumatology/other

JO3-01 Plasma exchange in 3 patients with antiphospholipid syndrome

We reviewed plasma exchange in three patients with antiphospholipid syndrome (APS). In the first case, there was a giant thrombus within the aorta, which was resistant to anticoagulation but improved with plasma exchange. In the second case, plasma exchange was performed for patients with recurrent APS after kidney transplantation, but kidney function did not recovery. Renal pathology showed numerous fibrin thrombi within the arterioles and glomerulus. The third case developed AKI during treatment with romiplostim for ITP. A kidney biopsy revealed fibrous intimal hyperplasia with occlusion of the arterioles and endothelial cell injury, diagnosed as thrombotic microangiopathy (TMA) and vasculopathy.

JO3-03 Six cases of anti MDA-5 antibody positive clinically amyopathic dermatomyositis with rapidly progressive interstitial lung disease treated with plasmapheresis

This is a retrospective review of 6 Japanese patients with clinically amyopathic dermatomyositis (CADM) with rapidly progressive interstitial lung disease (RP-ILD). Anti-MDA5 antibody was positive in all the patients. Their respiratory statuses deteriorated despite the administration of glucocorticoid, calcineurin inhibitors, and cyclophosphamide therapy. We subsequently combined with plasmapheresis to the patients. Two patients were died, while four patients were survived. Early and intensive treatment and careful monitoring are critical in the treatment of CADM with RP-ILD. More studies are needed to establish the protocol including plasmapheresis.

JO3-04 Apheresis for Immune-related adverse events of immune checkpoint inhibitors

Immune checkpoint inhibitors are the next treatment strategy for advanced cancer. Immune-related adverse events (irAEs) of immune checkpoint inhibitors have been reported. irAE often persists after discontinuation of medication. Apheresis is considered if corticosteroid immunosuppressants, and intravenous immunoglobulin are not effective. Apheresis was performed in 5 cases, we got good response.



JO3-05 In the case of thrombotic microangiopathy treated by simple plasma exchange with albumin as the replacement solution

[Case] The 60-years-old woman was diagnosed as renal crisis complicated with thrombotic microangiopathy (TMA). Initially, we treated with cyclophosphamide and PE with the replacement of FFP. Although antihistamine was used on the first time, anaphylactic reactions appeared after the operation. From the second PE, as the replacement solution, 5% albumin solution was used initially, then, used FFP. After that, there was no recurrence of anaphylaxis and the PE was able to finish in 8 times. It seemed to be indicated that the substitution liquid was not necessarily FFP in PE of the secondary TMA with the anaphylactosis case.

Japanese Oral Session 4 Technology 1

JO4-05 The effect of double-filtration plasmapheresis thermo-mode(DFT) on hemodialysis patients complicated with peripheral artery disease(PAD)

The technical and clinical effects of DFT(double-filtration plasmapheresis thermo-mode) for PAD (peripheral artery disease) were evaluated in this center. Hemodialysis with DFT was performed at the same time for 4 patients. The measurement of SPP(skin perfusion pressure) was evaluated before and after DFT comparing LDL apheresis alone in 2 patients DFT perfomed safely with stable condition in each session.After DFT, SPP significantly increased without any complication.

JO4-06 Survey of adverse events and measures for apheresis therapy

We examined the adverse events and measures of apheresis treatment. We targeted all 536 apheresis treatment that we performed in our hospital for approximately six years from April, 2013. Adverse events were reviewed retrospectively on PE, DFPP, PA, GMA, LCAP, PMX, and PBSCH. The incidence rate of adverse events was different depending on the treatment method, and various symptoms such as mood discomfort, blood pressure reduction, headache, and flare were recognized. Also, there were very few adverse events associated with treatment discontinuation. The coping method was implemented considering the treatment method and the patient background.

Japanese Oral Session 5 Technology 2

JO5-01 Relationship between replacement rate of albumin solution/fresh frozen plasma combination and changes of plasma fibrinogen levels in plasma exchange

Plasma exchange (PE) typically uses either fresh frozen plasma (FFP) or albumin solution (Alb). It is well-known that extensive use of FFP potentially causes hypocalcemia and transfusion reaction, while Alb causes low fibrinogen (Fib) and IgG levels. For the optimal



use of these replacement fluids, we investigated the relationship between replacement rate of Alb/FFP combination and changes of plasma Fib levels. Replacement rate of Alb/FFP was significantly correlated with changes of plasma Fib levels. However, its relationship changed according to plasma Fib levels at initiation of PE. We speculated that this result could be attributable to Fib concentration of FFP.

JO5-02 Clinical use of a solute kinetics simulation method for double filtration plasmapheresis

This study presents the results of the clinical use of a solute kinetic simulation method for DFPP. We verified whether changes in concentrations of IgG, IgM, Fbg, Alb and TP could be predicted using a newly developed mass balance formula. The post-treatment solute concentrations in 11 patients were predicted using a formula derived from pre-treatment solute concentrations and treatment conditions. The results showed significant correlation between predicted and clinical values for all solute concentrations. This prediction formula is useful for establishing appropriate treatment conditions for various diseases and patients.

JO5-03 Comparing centrifugal and membrane therapeutic plasma exchange procedures in Japan

In Japan, therapeutic plasma exchange (TPE) is usually performed on a membrane-based system (mTPE). On the other hand, TPE on a centrifugation-based system (cTPE) is the most commonly performed in the United States. Here, we investigated the time and removal rate for procedures of cTPE and mTPE. In our study, percent reductions of immunoglobulin G and fibrinogen were almost same in both TPE. The preparing time of mTPE was shorter than that of cTPE. However, the treatment and total time of cTPE were shorter than those of mTPE. cTPE is a useful option for plasmapheresis.

JO5-04 A case report of low-density lipoprotein apheresis using centrifugal separation and dextran sulphate adsorption

Low-density lipoprotein (LDL) apheresis is one of the useful treatments of refractory focal segmental glomerulosclerosis (FSGS). In Japan, a combination of membrane plasma separation and dextran sulphate adsorption of LDL (DSAL) is a well-established method of LDL apheresis. However, DSAL by membrane separation (mDSAL) needs much blood flow because filtration rate is limited. Here, we present a case report of successful treatment using DSAL by centrifugal plasma separation (cDSAL) for FSGS. cDSAL could perform efficient LDL removal in a much shorter time with peripheral veins than mDSAL. cDSAL can be a useful method of LDL apheresis.

Japanese Oral Session 6 Nephrology/Transplantation

JO6-03 Complete remission of steroid-resistant minimal-change nephrotic syndrome by the treatment with a combination of LDL-apheresis and cyclosporin

We report a 62-year-old man with steroid-resistant minimal change nephrotic syndrome

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(MCNS). On admission, his proteinuria level was 21.1g/gCr with a low serum albumin. He was treated with two courses of methyl-prednisolone pulse therapy, but his nephrosis continued. We tried low-density lipoprotein apheresis (LDL-A) treatment, but his proteinuria did not decrease (14.4g/gCr). After cyclosporine was administered, his proteinuria gradually reduced after the 12th LDL-A. His protein level decreased at the time of discharge (0.27g/gCr). We speculated LDL-A improved hyperlipidemia and strengthened the effect of cyclosporine. In steroid-resistant MCNS, it is considered worthwhile to consider cyclosporine initiation in combination with LDL-A.

JO6-04 Comparison study of AcuFil Multi 55X-II dedicated circuit SHG-1.0 (PS) and Prismaflex HFset (PAES)

There is no classification or evaluation criteria for hemofilter used in continuous renal replacement therapy. There is a dedicated circuit in each blood purification machine, but there is no circuit structure rule. Has been reported difference of circuit usable time due to dedicated circuit shape. It was suggested that the biocompatibility of HFset is excellent that we compared AcuFil Multi 55X-II dedicated circuit SHG-1.0 and Prismaflex HF set. It is considered that the adhesion of the thrombus was small due to the Dialysis chamber of Prismaflex dedicated circuit.

Japanese Oral Session 7 Hematology/ PAD

JO7-02 Successful plasmaexchange(PE) for ABO-incompatible liver transplantation in a 2-year-old child with peliosis hepatis and myotubular myopathy

A 2-year-old boy was admitted to our hospital due to intrahepatic bleeding as a complication of peliosis hepatis and myotubular myopathy. Before PE, IgG and IgM antibody titers were equally elevated (1:128). We used 1200ml fresh frozen plasma for each session, and set the upper limits of blood flow and the separation speed at 5mL/kg/min and 20%, respectively. Nafamostat mesylate as anticoagulant was used at the speed of 10ml/h. During each session, hemodynamics were stable and no apparent side effects were observed. After three sessions of PE, IgG and IgM antibody titers were decreased (1:4 and 1:16, respectively).

JO7-03 A case of Goodpasture syndrome successfully treated with continuous plasma exchange with dialysis

A 53-year-old woman with acute kidney injury and systemic edema was transferred to Akita University Hospital for further examination. The patient was diagnosed Goodpasture syndrome (GPS) and continuous plasma exchange with dialysis (cPED) was performed three times to remove anti GBM antibody and MPO-ANCA, and to improve renal function. Continuous PED may be effective for severe symptoms associated with GPS.



Japanese Oral Session 8 Critical Care Medicine/Pediatrics

JO8-02 Study of acute poisoning cases treated with direct hemoperfusion in ICU

We examined cases of acute poisoning in ICU who treated with direct hemoperfusion(DHP). There were very few cases ,who treated with DHP, with 0-2 cases in one year. The poisoning cases treated with DHP were Pilsicainide poisoning, carbamazepine poisoning, theophylline poisoning, caffeine poisoning, etc. The treatment median time per a DHP column was 7.8 hours. Most of the patients who received DHP were treated concurrently with continuous renal replacement therapy. The mortality was lower than predicted from severity score. Further research is needed.

JO8-03 Successful treatment with cyclosporine for infant with Kawasaki disease refractory to both Infliximab and plasma exchange: a case report

We report the case of a 4-month-old boy with refractory Kawasaki disease (KD). The patient received intravenous immunoglobulin twice, corticosteroid, infliximab and plasma exchange (PE), but did not achieve clinical relief. Subsequently, cyclosporine was administered, resulting in clinical remission. There are no definite treatment for refractory KD. Reports of the efficacy of infliximab and PE in refractory KD have increased. Cyclosporine has been reported in relatively few cases, probably because of its various side effects, but there have been some reports showing its efficacy. Cyclosporine may be an effective treatment option for KD refractory to infliximab or PE.

Japanese Oral Session 9 Technology

JO9-01 The oncotic pressure and electrolyte composition in the various albumin solutions as replacement fluids of plasma exchange

Therapeutic plasma exchange (TPE) requires replacement fluids, and albumin is the most commonly used replacement fluid. However, there are some different types of albumin (concentration of albumin and electrolyte composition) and diluting solutions, and the most useful method of preparing albumin solution as replacement fluids has not been decided. Here, we investigated the oncotic pressure and electrolyte composition in the various albumin solutions. In our study, albumin solutions prepared by diluting 25% albumin in lactated Ringer's solution and 10% sodium chloride to maintain the osmotic pressure can be the most useful replacement fluid of TPE.

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JO9-03 An example in which securing blood access by echo utilization was effective in CAP therapy

We examined the method of securing blood access in CAP therapy. In advance, echo is used to obtain information on veins and blood vessels to examine the puncture position. In addition, the probability of success for indwelling is high by puncture using echo. In this case, it was possible to reduce patient pain and maintain throughput of CAP therapy by using echo.



Poster Presentation 1 Hepatology

PP1-04 Fructus Psoraleae-induced severe liver injury and treatment with two artificial liver support systems: A case series study

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Aims: To describe the clinical features and outcomes of patients with suspected Fructus Psoraleae (FP)-induced severe liver injury who underwent treatment with two artificial liver support systems (ALSSs).

Methods: The cases of 12 patients with severe liver injury by FP were enrolled. We evaluated the tolerability of, and changes in biochemical parameters after treatment with plasma exchange combined with hemofiltration (PE+HF) and double plasma molecular absorption system (DPMAS), and 6-month follow-up information were collected.

Results: The median age of the 12 patients was 60 years (range: 54 -77 years) and nine (75%) patients were females. All patients had jaundice as the initial symptom. The types of liver injury were hepatocellular (seven cases), cholestatic (three cases), and mixed (two cases). Two ALSS types were used to treat the patients. The group that underwent PE+HF showed remarkable improvements in AST, TB, and GGT levels, and the levels of ALP, TB, and TBA decreased significantly in the DPMAS group after treatment. During 6 months of follow-up, two patients died, two became chronic, and eight recovered to normal.

Conclusions: FP can cause clinically severe liver injury, characterized by digestive symptoms and jaundice, which can lead to death or become chronic. ALSS was safe and well tolerated in DILI patients. After ALSS treatment, the levels of biochemical indicators of liver function improved significantly, indicating that ALSS might be beneficial for patients with severe DILI.

Poster Presentation 2 Ascites/CART/IBD

PP2-01 Biochemical Evaluation of Processed Ascites in Patients Undergoing Cell-Free and Concentrated Ascites Reinfusion Therapy

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The composition and concentration of processed ascites differ from institution to institution and have not been well investigated. This prospective study evaluated the characteristics of processed ascites in patients treated with cell-free and concentrated ascites reinfusion therapy (CART). We prospectively administered 24 sessions of CART to 12 consecutive patients with liver cirrhosis and malignancy. The common chemistry panel included total

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protein, immunoglobulins (Ig), electrolytes, and osmolarity in drained ascites and processed ascites. A common serum chemistry panel was also conducted before and after reinfusion of processed ascites. The characteristics of drained ascites vs. processed ascites were as follows (median, interquartile range): volume: 5700 (3350-8000) vs. 675 (305-800) mL, total protein: 88.0 (44.2-108.0) vs. 66.4 (30.4-83.6) g, total bilirubin: 0.50 (0.3-0.8) vs. 3.3 (1.4-5.3) mg/dL, lactate dehydrogenase (LDH): 59.5 (46.0-88.8) vs. 448.5 (376-503.5) IU/L, IgG; 20260 (7422-35786) vs. 15570 (6489-29454) mg, IgA: 5748 (3339-11614) vs. 4302 (2055-8212) mg, and IgM: 1417 (525.8-2780) vs. 550 (211-1550) mg. A comparison of common serum chemistry panels between pre- and post-reinfusion of processed ascites showed a significant decrease in blood urea nitrogen and creatinine levels. No significant change was observed in the remaining common serum chemistry panel. The processed ascites included 2.29% (15.5 g/675 mL) and 15.5 g of IgG, which corresponds to 3-6 times of 5% IgG products. Serum pH and electrolytes of processed ascites were within normal limits, and LDH was higher and HCO₃ lower compared with drained ascites. Osmolarity in both processed ascites and serum was within normal limits. Our data indicated no significant adverse effects related to common chemistry panels. When administering CART, these characteristics of processed ascites must be considered.

PP2-02 Suppression of inflammation during cell-free concentrated ascites reinfusion therapy (CART) using a blood purification device

Some patients experience fever during CART. We mixed 20 of raw ascites with hexadecyl-ligand adsorbent and centrifuged them to obtain adsorbed ascites. The IL-6 concentration of adsorbed ascites (2033 pg/mL) were significantly lower than that in raw ascites (4830 pg/mL). Furthermore, we added raw ascites or adsorbed ascites to human liver cancer cell line and compared the gene expression of serum amyloid A (SAA). The SAA expression by adsorbed ascites (6 times) were significantly lower than that in raw ascites (37 times). Our results suggest that incorporation of the hexadecyl-ligand adsorbent into CART will suppress the inflammatory response after reinfusion.

PP2-03 The washing using the normal saline to drain to the two directions for the clogged filtration filter is effective

We developed a novel CART equipment, which can wash the clogged filtration filter automatically using normal saline and drain to the two directions. In the washing experiment, recovery rates of surface color and the processed dose by one washing significantly improved in the drainage group to the two directions than drainage group to one direction. In the clinical evaluations, processing of the ascites of the total dose was possible in all cases. The aggregates of the inlet of the follow fiber could be removed.



PP2-04 Development and clinical evaluation of an ascites filtration and concentration equipment by interprofessional collaboration

We had built a consortium consisting of Tokushima University, Tokushima University Hospital, affiliated hospitals, and a medium-sized manufacturing company in 2013, and developed a novel compact and lightweight CART specialized equipment (M-CART) in 2019. M-CART can safely and easily process a large quantity of ascites without the constant attendance of an operator. The collaboration of medical staff (clinical engineers, nurses, and doctors), researchers, and developers of companies enables the development of safe and easy-to-use medical devices.

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PP2-05 Clinical factors associated with relapse of ulcerative colitis after granulocyte-monocyte adsorption

Clinical factors correlated with early relapse of ulcerative colitis (UC) after granulocyte-monocyte adsorption (GMA) were investigated. The data from 61 UC patients treated by a series of 10 sessions of GMA were collected retrospectively. UC was relapsed in 14 patients (23%) within 24 weeks after GMA. Compared with non-relapse group, relapse group had significantly higher value of Seo index (SI) evaluated before and after GMA treatment. Binomial logistic regression analysis showed that SI was significantly correlated with UC relapse. Relapse rate was significantly different between groups divided according to SI. Seo index may associated with early relapse of UC.

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PP2-06 Efficacy and safety of granulocyte and monocyte adsorptive apheresis in elderly vs. non-elderly patients with ulcerative colitis

We retrospectively investigated the efficacy and safety of Granulocyte and Monocyte Adsorptive Apheresis (GMA) therapy between 15 elderly patients vs. 19 non-elderly patients with ulcerative colitis. While the remission rates and response rates in non-elderly patients were 33.3% and 94.4%, these rates were 40.0% and 93.3% in elderly patients. There were no significant differences in the 1-year relapse-free rates between elderly and non-elderly patients (71.4% and 50.0%, respectively, $P=0.453$). These results suggest that GMA therapy is an efficient and safe treatment in elderly patients with ulcerative colitis.

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PP2-07 Development of a tube holder-type circuit set for cell free and concentrated ascites reinfusion therapy (CART)

We developed a tube holder-type circuit set for a novel CART equipment (M-CART). All tips of the connection tubes are clipped to two tube holders that are hanging on the hooks of two poles from the left side to the right side based on the order of connection. The place of the tips and the order of connection were easy to understand, and risk that a connection tip can become unclean decreased by the contact to the floors. Moreover, the tube holder-type circuit set was downsized compared with the panel type, and the amount of medical waste decreased.

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Poster Presentation 3 Technology

PP3-03 Utilization of the newly established dialysis training system using magnetic particles for apheresis training

We have been developed the dialysis training system to reproduce abnormalities during dialysis treatment. In this paper, we tried a utilization this system for apheresis training. This system circulates the magnetic particle suspension in the dialysis circuit, controls the internal pressure with external magnetic field strength, and reproduces the impossible blood coagulation. However, this system has the drawback of magnetic particle deposition at low flow rates, and this time we have examined the minimum flow rate. As a result, the minimum flow rate was 50 mL/min, which suggested that it could be applied to apheresis training.

PP3-05 Our experiences with plasm apheresis therapy from 2008 to 2018

St. Mary's Hospital is a tertiary-care hospital with 1097 beds and 41 departments. We proactively administer plasma apheresis to patients, and conducted an investigation of all apheresis cases at our hospital from 2008 to 2018. During that time we administered apheresis therapy a total of 4449 times to 958 patients with diseases such as infection, malignancy, and autoimmune disease, using various methods such as CART, CHDF, LCAP/GCAP, PE, and PBSCH. Through this investigation we revealed solid data and identified the wide range of departments and diseases for which we chose apheresis therapy at our hospital.

PP3-06 Long-term results of treatment for critical limb ischemia in maintenance dialysis patients

Critical limb ischemia (CLI) developing in maintenance dialysis patients is intractable. We have carried out the combined therapy used the dextran sulfate LDL adsorption apheresis (DSAL) and other treatments for CLI in 67 dialysis patients. Curative effects such as reduction of leg pain, improvement of ulcer and/or necrosis were recognized in 59 of 67 patients (88%). In 64 cases that were able to confirm clinical progress, a five-year overall and amputation-free survival rate were 56% and 53%, respectively. DSAL could play a significant role in the cases such as dialysis patients that had strong disturbance of microcirculation.

Poster Presentation 4 Neurology, Rare disease, Nursing

PP4-01 Red cell exchange verse blood transfusion therapy: improving patient outcomes

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Introduction: A local review of the Sickie Cell patient cohort at this institution has seen treatment modalities change intermittently from red cell exchange to blood transfusion and vice versa. This led



to the question of what treatment is most effective and what do we measure efficacy against?

Objectives/Aims: To compare hospital admission rates, pain crisis/events, haemoglobin S level, ferritin levels and patients' wellbeing when receiving red cell exchange verse blood transfusion to ensure we are providing the highest quality, safest, most efficacious and cost-effective treatment.

Description/Methodology: 5 patients with sickle cell disease or with the combined traits of sickle cell disease/beta thalassemia will be retrospectively reviewed, using electronic charts, adverse event rates, admission records, medication records, and pathology results to gather the quantitative data. A physical and psychosocial assessment of patients will be conducted through verbal communication at regular visits to gain qualitative data on patients' wellbeing whilst also using a distress screening tool as a reference.

Results/Outcomes: Preliminary data has indicated that hospital admissions for pain crisis has significantly reduced in at least 3/5 patients since the recommencement of red cell exchange post stand-alone blood transfusions with further investigations pending. It has also been identified that patient's psychosocial wellbeing is poorly documented in this patient group.

Conclusion: Although only a small amount of data has been collected, it has already shown that hospital admission rates have decreased in 3/5 patients reviewed. It has also identified an improvement opportunity in the assessment and care of these patients through recognising that psychosocial wellbeing and distress scores of these patients is poorly documented.

PP4-02 Successful Treatment with Early Plasmapheresis in Secondary Hemophagocytic Lymphohistiocytosis(HLH) with Cytomegalovirus Infection in Myasthenia Gravis

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Hemophagocytic lymphohistiocytosis(HLH) is a infrequent and life-threatening syndrome caused by over-activation of macrophages and cytotoxic T-cells (CTLs) and hypercytokinemia. It is usually relevant to other disease in Adults. We reported a 32-year-old woman who had history of myasthenia gravis under the treatment of azathioprine and prednisolone. She developed myasthenia gravis with acute exacerbation and fever of unknown which was diagnosis as HLH with CMV infection according to the criteria HLH-2004 . We conducted plasmapheresis and pulse therapy for five cycles. After two times plasmapheresis and pulse therapies, the leukopenia and the level of C-reactive protein dramatic improved and fever subsided. We gave ganciclovir for CMV infection and changed azathioprine to cyclosporin A for immunosuppressant. She discharged two weeks later.Elimination trigger factor and suppressing hyperinflammation are the crucial way for successful treatment of secondary HLH. According to the guideline of JCA, they suggest plasma exchange in refractory HLH and life-threatening condition. Few reports discuss plasmapheresis. The Plasmapheresis is less toxic approach which could effective eliminate the hypercytokinemia. We report a case with CMV associated HLH successful treated with early plasmapheresis and pulse therapy. Early plasmapheresis in rapid-deterioration HLH patient could control hyperinflammation and stabilize clinical condition until the elimination of triggers or immunosuppressant drugs becoming effective.

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PP4-03 Treatment of Stiff-person syndrome using double filtration plasmapheresis and immunoadsorption

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Stiff-person syndrome (SPS) is a rare autoimmune disease caused by high level of autoantibodies to glutamic acid decarboxylase (anti-GAD) in the blood and cerebrospinal fluid and characterized by trunk and/or limb muscle spasticity.

Purpose: to evaluate of the effectiveness of double filtration plasmapheresis (DFPP) and immunoadsorption (IA) in the treatment of the SPS.

Objects and methods: Five patients aged 37, 50, 42, 51, 56 y.o. with an idiopathic form of SPS were examined and treated. All patients were dynamically examined for the level of anti-GAD. Medication included immunosuppressive therapy (glucocorticosteroids 1 g/kg, cyclophosphamide 1000 mg) and symptomatic agents. All patients were dynamically examined for the level of anti-GAD. In the first SPS case, two DFPP were used on the devices OctaNova with plasma component separators Cascadeflo EC-20W (ASAHI KASEI MEDICAL, Japan), with perfusion of 80% of circulating plasma volume (CPV); in other cases, three IA (90-100% of the CPV) were used Spectra Optia devices (TERUMO BCT, USA) and Immuno-Adsopak columns (POCARD, Russia). Clinical and immunological effects of therapeutic apheresis (TA) was assessed.

Results: In the first SPS case, immunosuppressive therapy reduced the multiplicity and severity of painful muscle spasms, while the level of anti-GAD decreased from 242 433 to 190 434 U/ml (-24%). Two subsequent DFPP significantly reduced the spasticity index from 5 to 3 and the sensitivity index from 4 to 1, while the anti-GAD level was 74 340 U/ml (-61%). In other cases, when using IA, a decrease in the level of anti-GAD by 65-72% was obtained, while normalization of muscle tone was gradually observed within 2 weeks against the background of continued immunosuppressive therapy. The spasticity index reduced from 5 to 1-2 and the sensitivity index from 5 to 1-2.

Conclusions: Methods of TA in patients with SPS are effective tool of pathogenetic therapy.

PP4-04 Plasma Exchange to Myopathy without Optic Neuritis or Quadriplegia in Neuromyelitis Optica Spectrum Disorders: A Case Report

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Neuromyelitis optica spectrum disorders (NMOSD) usually present as optic neuritis or quadriplegia due to myelitis, and it has been reported that early plasma exchange (PEX) could be useful. Some cases of NMOSD accompanied by myopathy were reported; however, myopathy has not been known as a main presentation without optic neuritis or quadriplegia of this disorder and the therapy is unknown. A 72-year-old woman presented with general fatigue and dizziness after mountain climbing. At that time no significant abnormality was detected in her physical examination including gait evaluation. Laboratory tests revealed high CPK, WBC,



and CRP. After hospitalization iliopsoas muscle weakness and parareflexia were revealed and she could not stand on her feet, but anterior tibial muscle, triceps surae muscle, and upper limb's muscle strength were intact. Examination revealed no eye or cranial nerves abnormalities. Magnetic resonance imaging of the spine showed longitudinally extensive transverse myelitis from C7 to Th7 level. She was treated with intravenous methylprednisolone, but the symptom did not improve. Then result for anti-AQP4 antibody proved to be positive, and finally she was diagnosed with NMOSD. Her muscle weakness did not respond to additional intravenous methylprednisolone, so she was treated with PEX on the twenty seventh hospital day. Her muscle weakness was improved and she was able to rise to her feet. We found out two important clinical issues. NMOSD can present as myopathy without optic neuritis or quadriplegia. PEX could be useful for the therapy of this condition even if taking several days to diagnose. Like this case there might be cases of NMOSD presenting mainly myopathy and difficult to be diagnosed. We report this case including information about NMOSD and AQP4 in muscle.

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PP4-05 Efficacy of plasmapheresis for patients with stiff person syndrome. Summary of casestudy reports

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Background: Because Stiff person syndrome (SPS) is a rare disease, there is no randomized controlled trial article which has examined the efficacy of plasmapheresis. Therefore, we decided to clarify the efficacy of plasmapheresis for SPS by aggregating the literatures from databases.

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Methods: PubMed and The Cochrane Library were used as target databases. We searched for articles about patients with SPS. We selected articles that described the treatment content and clinical course of each patient in detail. Hence, we focused on the case-study reports.

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Results: As a result of database search, 907 articles were selected. After abstract review, excluding duplicates and pediatric cases, 43 articles with treatment contents and clinical course were available. In these articles, 48 patients (16 men and 32 women) were included. The median age was 48 (40-58.25) years. There were 14 diabetic and 14 cancer-bearing patients. The anti-GAD antibody was positive at 77.8% (35/45) and the anti-amphiphysin antibody was positive at 25.0% (4/16). As first-line therapy, 83.3% patients were treated with benzodiazepine, 60.4% with antispasmodic agents and 20.8% with antiepileptic agents. Plasmapheresis was performed in 33.3% (16 patients), and it was basically performed as second-line therapy. The modalities of plasmapheresis were plasma exchange in 15 patients and immunoadsorption plasmapheresis in one patient. The number of sessions ranged from 3 to 20 in the short term. Two patients received chronic plasmapheresis. The therapeutic efficacy was observed at 75% (12/16). In the group receiving plasmapheresis, the number of therapeutic agents is significantly larger (7(5.75-9) vs 5(2-7), P=0.0184), and positivity for anti-GAD or anti-amphiphysin antibodies was significantly higher (100% vs 68.75%, P=0.0196).

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Conclusion: In patients with SPS receiving plasmapheresis as second-line therapy, 75% patients showed therapeutic efficacy. It is considered to be one of the effective options in patients who have not responded to first-line therapy.

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PP4-07 Efficacy of plasmapheresis for autoimmune limbic encephalitis

The efficacy of plasmapheresis was retrospectively investigated in 14 patients with autoimmune limbic encephalitis. Nine cases with encephalitis-related autoantibodies were found: 6 cases including anti-NMDA receptor antibody, 1 case anti-VGKC antibody, 1 case anti-GAD antibody, 3 cases anti-GluR ϵ 2 antibody, 1 case anti-Ma-2 antibody, including duplicates. In 13 of 14 patients, improvement in Glasgow Coma Scale (GCS) was observed within 2 weeks after plasmapheresis. The relationship between Q-Alb that an indicator of blood-brain barrier function, and the therapeutic effect of plasmapheresis therapy was discussed. Plasmapheresis has been shown to be an effective treatment for autoimmune limbic encephalitis.

Poster Presentation 5 Nephrology/Collagen Disease/Rheumatology

PP5-01 Long-term Ig apheresis in the treatment of lupus nephritis

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Treatment of lupus nephritis remains one of the unsolved problems of rheumatology.

In this study we evaluated the effectiveness of the long-term Ig apheresis in treating of the patient with lupus nephritis (nephrotic syndrome), who had insufficient efficiency and complications of drug therapy.

Materials and methods: Ig apheresis was performed using 2 Ig Adsopak columns, 400ml volume (POCARD Ltd.,Russia) and Spectra Optia (Terumo BCT,USA). 2 immunosorption procedures were performed within 3-4 days every 25-35 days. Column's regeneration was carried out of-line. The volume of plasma perfusion was 1.9 ± 0.3 calculated plasma volume (4500-5000ml). During each session 35-40g of IgG were removed. To date, treatment has been carried out for more than 3 years, 68 immunosorption procedures have been performed. Monitoring of clinical and laboratory parameters, disease activity (SLEDAI) and quality of life (QoLSF-36) is conducted.

Results: Against the background of long-term immunosorption, there was a decrease in the disease activity (SLEDAI) from 22 to 3-4, the cushingoid have disappeared, the menstrual cycle was restored, the GCS dose reduced to 15 mg/day, serum creatinine is 0,6-1,0 mg/dl, total protein 65-69g/l, creatinine clearance 105-140ml/min, proteinuria 130-200mg/day. The serum IgG is 2-15g/l, anti-dsDNA 40-550IU/ml and it decreases after the immunosorption cycle and increases by the beginning of the next treatment session. The QoL has improved: physical component score from 22 to 48, mental component score from 25 to 43. There were no side effects or complications during long-term Ig apheresis.

Conclusions: With a lack of efficacy and pronounced side effects of immunosuppressive therapy, long-term Ig apheresis is a promising and safe treatment for lupus nephritis. It allows to control the disease, maintain kidney function, and ensure the normal quality of life. Reusable immunosorption columns make it possible to remove any required quantity of target molecules. This reduces the cost of the extracorporeal procedure.



PP5-02 Pleiotropic effects of double filtration plasmapheresis in the prevention of in-stent restenosis in patients with stable coronary artery disease

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Despite success coronary stenting, the main factor limiting its long-term efficacy remains the restenosis. We investigated the DFPP possibility carried out in the early post-implantation period, to influence markers of endothelial dysfunction, the underlying mechanisms of the in-stent restenosis.

Materials and methods: 25 patients (men aged 58±5years) with a high risk of in-stent restenosis were treated DFPP - 1-2 times a month. We investigated the rejection coefficient of plasma fractionators (PF) Cascadeflo EC-40W(n=12) and EC-50W(n=13) of the following markers: selectins - sP-selectin, sE-selectin, sL-selectin; adhesion molecules - sICAM-1, sPECAM-1, sVCAM-1; tissue plasminogen activator (t-PA); plasminogen activator inhibitor-1 (PAI-1); von Willebrand factor (vWF). The blood samples for analysis were conducted during the DFPP, before and after PF when the pressure before PF was 100 mm Hg.

Results: For the first time carried out a comparison of the rejection coefficient of adhesion molecules by Cascadeflo EC40W and EC50W. The efficiency of removal of adhesion molecules was higher by Cascadeflo EC-40W for all the investigated markers: sP-selectin (74% and 25%), sE-selectin (55% and 20%), sL-selectin (11% and 2%); sICAM-1 (30% and 12%), sPECAM-1 (30% and 19%), sVCAM-1 (41% and 19%). It was found more pronounced removal of level PAI-1 by the Cascadeflo EC-40W compared with EC-50W (94% and 72% respectively). The rejection coefficient of vWF and t-PA were comparable for both PF (95% and 86%).

Conclusions: The results of the study showed a more pronounced removal of adhesion molecules, PAI-1 by Cascadeflo EC-40W. The rejection coefficient for t-PA and vWF were comparable for both EC-40W and EC-50W. In our view, application of therapeutic apheresis, in particular DFPP, goes beyond the correction of dyslipidemia in patients with coronary heart disease. A promising area of research is to explore the possibilities of methods of therapeutic apheresis to influence markers of endothelial function underlying the pathogenesis of atherosclerotic disease.

PP5-04 Low-density Lipoprotein Apheresis in Patients with Acute Kidney Injury due to Minimal Change Disease requiring Acute Renal Replacement Therapy

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Nephrotic syndrome (NS) such as minimal change disease (MCD) is often difficult to control fluid volume, may cause acute kidney injury (AKI) and require acute renal replacement therapy (ARRT). We report here two cases at Nippon Medical School Chiba Hokusoh hospital. A 49-year-old Japanese woman and a 71-year-old Japanese man with AKI due to MCD had to undergo hemodialysis (HD) to control fluid volume and treat their renal function. The patients also received the treatment with corticosteroids, however, their AKI and MCD did not improve sufficiently. Hyperlipidemia is a frequent finding with NS. We decided to initiate Low-density lipoprotein apheresis (LDL-A) for them as a treatment because their serum total cholesterol

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was high at the time of admission. The timing of LDL-A initiation was when they received the treatment with corticosteroid for 21 days and 24 days respectively. After the additional LDL-A treatment, their fluid volume control and renal function were improved, so they were able to discontinue ARRT. LDL-A has been generally used for the treatment for drug-resistant NS due to focal segmental glomerulosclerosis (FSGS) in Japan. The effectiveness of LDL-A is not only reducing serum Low-density lipoprotein, but LDL-A may also have various other benefits such as anti-inflammatory effects. There are few reports that LDL-A improved in AKI requiring ARRT due to MCD, however, it may be possible that LDL-A is effective for AKI on ARRT and drug-resistant NS due to such as MCD.

PP5-05 A case of atypical hemolytic uremic syndrome, which steroid pulse therapy and plasma exchange were effective but eculizumab was ineffective

A 50-year-old man with seizures was admitted to our hospital. He was diagnosed with acute necrotizing encephalopathy, due to MRI findings showed high-intensity on bilateral thalamus. He received steroid pulse therapy and plasma exchange. MRI findings and his conscious level were improved. On the other hand, laboratory test revealed schistocytes and elevation in the LDH, creatinine level. Then, we diagnosed atypical HUS. We initiated dialysis and started eculizumab. Just after, his condition and hematological data got worse. We immediately restarted plasmapheresis and steroid pulse. However, his condition was not recovered and died. Autopsy findings showed severe endothelial injury in kidney.

PP5-07 Successful treatment of LDL-A for skin ulcers in a patient with systemic sclerosis

A 77-year-old woman was diagnosed with systemic sclerosis based on her clinical symptoms. She noticed skin ulcers in the toes, she was treated with beraprost, however, skin ulcers were worsened. She was admitted in our hospital because of her skin ulcers. She was started on LDL apheresis (LDL-A). A series of LDL-A sessions was carries out. After LDL-A treatment, skin ulcers was improved. Skin ulcers in the toes due to systemic sclerosis are often refractory complication, and life-threatening disease. Although LDL-A apheresis therapy for skin ulcers with systemic sclerosis has not been established, it can be expected to be effective.

Poster Presentation 6 Critical Care Medicine

PP6-01 LPS adsorption with Toxipak columns in treatment of sepsis

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LPS adsorption is the effective sepsis treatment. The purpose of this study was to evaluate the



effectiveness of the Toxipak columns (POCARD Ltd. Russia) for the LPS adsorption.

Materials and methods: The study included 25 patients aged 34-75 years with abdominal(19), urological(4), pulmonological(1) and gynecological(1) sepsis. 9 patients were in septic shock. The SOFA score was 9.5 ± 0.9 (from 5 to 20). The perfusion rate was 60-100 ml/ min; the perfusion volume was 1.5-2 of the calculated blood volume. The blood was stabilized by heparin or heparin + sodium citrate. In 20 patients 1 session of LPS adsorption was performed, in 5 patients - 2 LPS adsorptions. We have investigated the SOFA score, body temperature, heart rate, PO₂/FiO₂ index, diuresis, cellular and biochemical blood composition, endotoxin concentration (Hycult biotech, Netherlands), CRP, PCT, IL6, IL8, IL1, TNF (ELISA, Vector Best, Russia).

Results: The next morning after LPS adsorption SOFA score significantly decreased from 9.5 ± 0.9 to 6.9 ± 1.0 , the body temperature - from 38.08 ± 0.20 to 37.11 ± 0.16 ; HR - from 106.4 ± 3.5 to 92.7 ± 2.5 , the PO₂/FiO₂ index increased from 228.7 ± 16.4 to 270.6 ± 17.4 ; diuresis - from 1593 ± 242 to 2357 ± 358 ml/day, the endotoxin level significantly decreased from 2.88 ± 0.43 to 1.20 ± 0.19 EU/ml, CRP - from 275.1 ± 45.5 to 223.9 ± 35.6 mg/l, PCT - from 66.1 ± 8.7 to 29.8 ± 7.8 ng/l, IL6 - from 234.0 ± 32.1 to 73.8 ± 21.3 pg/l. In patients with septic shock norepinephrine doses were reduced from 0.45 ± 0.11 to 0.19 ± 0.07 mcg/kg/min and then to zero. Concentration of pathogenetic molecules decreased direct after Toxipak column: endotoxin (60-38%), CRP (37-19%), IL1 (65-28%), IL8 (59-27%). No serious adverse reactions to the procedures were observed. The positive clinical effect was obtained in all 25 patients. But 3 people died in the ICU at 2-3 days after LPS adsorption. 22 patients were transferred from the intensive care unit.

Conclusions: Toxipak columns effectively remove endotoxin (LPS) from the blood and improve clinical and laboratory parameters of patients.

PP6-06 Clinical study of pressure difference between membranes and effective period of use of membranes with continuous hemodiafiltration therapy for sepsis

Purpose, Pressure loss and at CHDF enforcement, treatment period, outcome after withdrawal, was examined backward view in patients with sepsis. For five years from April 2010 to March 2016, 54 cases diagnosed as septic. Pressure loss and during treatment introduction using three types of hemodialysis filter, Life time, treatment period, was compared outcome after withdrawal. Results, It was suggested that the low L/D ratio may be effective in reducing the pressure loss applied to the membrane. There was no significant difference in effective period of use of membranes due to the difference in membranes from this study.

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LS2-01 Vascular punctures for GMA treatment

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Introduction

We can provide the GMA treatment by venepuncture without VAC detaining you like other blood purification therapy. The puncture by the peripheral vein puncture is easy, but, on the other hand, it often becomes difficult to secure blood flow necessary for extracorporeal circulation enough and is one of the trouble factors of the GMA treatment. We use an echo to evade a puncture trouble in our institution. We introduce the approach this time.

Approach method

The site of puncture uses brachial veins basically. There is little valve of vein as a reason and chooses the blood stream because securing of blood flow with a little meandering is relatively easy. However, the depth from skin may be deepened as compared with the erosion blood vessel such as radius cutaneous veins, and the like, too, and attention is necessary. We often perform GMA in outpatient department at this hospital, and order enters the new induction when a chief physician judged induction from an encounter. Therefore it is difficult to obtain the patients information beforehand and a blood vessel echo uses site of puncture after the patients admission and is determined and performs the puncture in echo guides, if necessary. Also, the judgments such as the dehydration, and the like are possible by using an echo, and there is the merit that they receive instructions such as the transfusion load, and the like in what we report to a chief physician, and can dissolve puncture difficulty.

Conclusion

One of the troubles of the GMA treatment has securing of access. If extracorporeal circulation is possible without poor blood removal, we can provide GMA treatment more effectively. We regard the echo inflection of that purpose as a required device on providing GMA treatment.

LS2-02 Tips for ensuring vascular access and maintaining extracorporeal circulation in pediatric blood purification therapy

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Ensuring reliable vascular access (VA) and maintaining stable extracorporeal circulation are the most basic aspects of blood purification therapy (BPT). In children and neonates, specific tips could be helpful for BPT.

VA guidelines were published in 2011 and management methods have been unified. To ensure VA, it is necessary to determine a suitable placement site and catheter size (diameter and length), adjust the catheter tip position, and manage the catheters appropriately. It is common to use dialysis catheters for BPT, placing them in the central and peripheral veins. In neonates,



the umbilical vein could also be one of the options, and central venous catheters and peripheral vein catheters could be used for BPT. In order to maintain stable extracorporeal circulation, it is necessary to maintain sufficient intravascular volume and blood pressure, set appropriate blood flow rates, and adjust the type and amount of anticoagulant. In children who cannot cooperate, sedation management and catheter fixation should be performed to stabilize extracorporeal circulation.

There are also tips specialized for each disease state. In neonates, there is a high risk of intracranial hemorrhage and nafamostat mesylate is often used as an anticoagulant. In addition, it is necessary to increase the dose of anticoagulant or administer it from two places in the circuits. In patients with severe inflammatory bowel diseases, intestinal bleeding continues despite increased clotting function and hypovolemia is common. Heparin and nafamostat mesylate are chosen as anticoagulants. During BPT, monitoring activated clotting time, administering minimal anticoagulants, and administering transfusion and fluid load are useful methods to maintain stable extracorporeal circulation.

BPT might be a powerful therapeutic tool for children as well as adults, ensuring reliable VA and maintaining stable extracorporeal circulation.

LS3-01 Adsorption mechanism of Immunopure

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Monocytes, activated granulocytes and platelets play a crucial role in the pathogenesis of ulcerative colitis (UC). Immunopure is a granulocyte monocyte adsorption apheresis device offering a strong platelet as well as granulocyte/monocyte adsorption capacity, making it attractive for UC patients with high platelet numbers and coagulation disorders.

To attempt to elucidate the adsorption mechanism of the Immunopure adsorber, we performed *in vitro* circulation experiments using minimodules and sham modules with blood from healthy volunteers. Further, *in vivo* animal experiments using healthy premature pigs and two uncontrolled studies including patients with active UC were carried out.

In vitro, the reduction of platelets in the outflow was up to 76%, of neutrophils 42%, and of monocytes 63%, while lymphocytes were only minor affected (3%). Platelet depletion was accompanied by a significant decrease of platelet aggregates with monocytes, T cells and CD11+ cells (PLAs) to 30-60% and proinflammatory CD14+CD16+ monocytes to 41% only in the filled minimodules. Plasma soluble CD40L concentrations were two to threefold higher in circulation experiments using the filled minimodules indicating an enhanced platelet activation. Complement activation was low (plasma C5a up to 2.40±1.51 ng/ml). Confocal laser microscopy pictures showed an adsorption of fibrinogen, CD42b+ platelets, CD11b+, CD14+, and CD3+ leukocytes to the bead surface. Results were confirmed *in vivo* with regard to cell and PLA adsorption as well as soluble CD40L induction. However, these effects were temporary as values had been reduced or increased to basic levels before the next apheresis session started. Immunopure treatments were well tolerated and improved disease activity with remission rates of 80% (first study) and 67% (second study). In conclusion, the suggested adsorption mode of the Immunopure adsorber includes both fibrin formation on the bead surface with platelet binding and formation of PLAs. Further impact on regulatory mechanisms needs to be elucidated.

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LS3-02 **Apheresis for treatment of active ulcerative colitis: evidence and developments**

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Inflammatory Bowel Disease (IBD) encompasses mainly two entities, Crohns's Disease (CD) and ulcerative colitis (UC). While CD is characterized by transmural inflammation throughout the bowel wall and localization all along the intestines, UC is more confined to the mucosa of the colon. It is well known that active IBD is exacerbated and perpetuated by the so-called pro-inflammatory cytokines including TNF- α , interleukin (IL)-1 β , IL-23 and many more. Cytokines are produced by patients' own cellular elements, notably by the myeloid lineage leucocytes which in patients with IBD are elevated with activation behavior and prolonged survival time. Therefore, elevated circulating myeloid lineage leucocytes appear logical targets of therapy.

Granulocyte and monocyte apheresis (GMA) are able to deplete inflammatory cytokine releasing leucocytes and to increase the function of the regulatory lymphocytes. While numerous studies describe therapeutic effects of GMA, inconsistent trial results and many as yet unanswered questions prevent GMA from being a generally recommended treatment in international guidelines.

Currently, the focus of GMA is rather UC than CD. Indication of this treatment is mainly induction of improvement or remission in active disease. In the beginning, GMA was often studied in patients' refractory to standard therapies or in severe cases. But meanwhile the discussion about irreversibly damaged intestinal tissue has led to a new approach with treatments in patients with early phases of the disease.

In addition, new absorber systems have been developed, which are able to eliminate not only circulating myeloid lineage leucocytes but also platelets. Platelets have been described to play a role in the pathogenesis of active IBD. Thus apheresis, which can eliminate both activated leucocytes and platelets may have an even increased therapeutic efficacy.

We conducted a pilot study with such a new absorber system (Immunopure TM, Nikkiso, Japan) in active UC, refractory to first line therapy with mesalazine but without progression to irreversible bowel damage. Moreover, the apheresis treatment was compared to standard prednisolone therapy. No statistical differences between the two treatment arms could be demonstrated. This opens an alternative management to the use of steroids in those patients. While apheresis shows a very good safety and tolerability profile, corticosteroids have many unfavorable adverse effects and many patients and attending physicians search urgently for better tolerable alternative treatments.

In summary, apheresis is a very promising treatment for patients with active UC, particularly for those who are refractory to mesalazine.

LS4-01 **Pathogenic Antibodies and Lipoproteins – Current Trends in Therapeutic Apheresis**

Reinhard Klingel

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Autoantibodies and lipoproteins are pathogenic factors of neurological and cardiovascular



diseases and represent major targets for Therapeutic Apheresis (TA) performed as plasma exchange, or selectively with immunoadsorption (IA) or double filtration plasmapheresis. The American Society for Apheresis guidelines represent a key resource on the utilization of TA and were published in its eighth edition in 2019*.

Autoantibodies have received increasing attention in autoimmune neurological diseases. TA can offer therapeutic options with rapid response for severe acute neurologic symptoms, and stable rehabilitation in long-term clinical outcome. TA in these situations is part of multimodal or escalating immune treatment strategies in combination or in competition with immunologically active medications. TA, in particular IA, may be the preferred treatment in situations of high urgency. With IA side effects seem to be less frequent, especially those related to allo-protein substitution.

LDL particles cause atherosclerotic cardiovascular disease (ASCVD). Additional indices of risk severity strengthen the need for targeted LDL-C lowering. Based on huge clinical experience lipoprotein apheresis (LA) is currently the best option to lower LDL-C levels in severely hypercholesterolemic patients, including patients with homozygous FH and those with heterozygous FH and very high levels of untreated LDL-C. PCSK9-inhibition with monoclonal antibodies has complemented the armamentarium of escalating lipid lowering treatment before the final step of LA. The combination of PCSK9-inhibition with LA at individually-optimized treatment frequencies appeared as promising approach. The termination of long-term LA, which has prevented the progression of ASCVD, requires careful individual risk assessment. In the context of targeted LDL-C lowering, lipoprotein(a) must be additionally considered as causal, independent risk factor for ASCVD, representing an indication for LA.

* Padmanabhan, Connelly-Smith, Aqui, Balogun, Klingel, Meyer, Pham, Schneiderman, Witt, Wu, Zantek, Dunbar, Schwartz. Guidelines on the Use of Therapeutic Apheresis in Clinical Practice: The Eighth Special Issue. *J Clin Apheresis* 2019;34:171-354.

ES1-01 Treatment of inflammatory bowel disease in Europe

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Inflammatory bowel diseases (IBD) are chronic disabling gastrointestinal disorders impacting every aspect of the affected individual's life and account for substantial costs to the health care system and society. New epidemiological data suggest that the incidence and prevalence of the diseases are increasing and medical therapy and disease management have changed significantly in the last decade. An estimated 2.5-3million people in Europe are affected by IBD, with a direct healthcare cost of 4.6-5.6bn Euros/year. Therefore, the aim of this presentation is to describe the burden of IBD in Europe by discussing the latest epidemiological data, the disease course and risk for surgery and hospitalization, mortality and cancer risks, as well as the economic aspects, patients' disability and work impairment.

Program
Friday, Oct.
18, 2019

Program
Saturday, Oct.
19, 2019

Program
Sunday, Oct.
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Therapeutic Apheresis and Dialysis

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