3. Clinical Results

3.1 Renal diseases

Renal diseases with either immunologic or non-immunologic origins have a poor prognosis without treatment, and the treatment is complicated for these diseases. The introduction of therapeutic apheresis (TA) over the past 45 years, combined with immunosuppressive therapies and/or human monoclonal antibodies (HMA), has led to a steady increase in survival rates over the last few years. Therapeutic apheresis is accepted in all severe renal diseases such as acute kidney injury (AKI), nephrogenic systemic fibrosis, rapid progressive glomerulonephritis (RPGN), hemolytic uremic syndrome (HUS), and renal transplant rejection. With hollow fiber modules, a complete separation of blood cells from plasma is achieved, an advantage over centrifugation, and due to increased blood flow, a higher efficacy is realized (1). Cell damage, such as that caused by thrombocytes, occurs less frequently using membranes than centrifugation for TA.

A shorter time using centrifuge TA has no advantage over membrane TA (2). More important is to maintain blood levels of antibodies and/or other toxic substances at a very low level over a long period during TA treatment, as this allows for the elimination of more toxic substances during that time. High numbers of technological, economic, and social factors have an impact on the practice of TA (3). The adsorption technologies with specially developed columns allow a better and selective elimination of the antibodies and other toxic substances from blood without the use of any substitution solutions.

Hollow fiber modules and adsorption technologies with special columns are used in nephrology because these TA methods can be integrated in available dialysis equipment (4). Indications in nephrology for TA expand the clinical practice of nephrologists (5). Renal diseases with an immunologic origin and available antibodies in the blood as well as non-immunological renal diseases, could be indicated for TA (6, 7). However, there are only a few prospective controlled, multicenter studies available to reach definitive conclusions regarding the therapeutic value of TA, because many diseases are rare and under investigation, and the details of treatment protocols vary widely between centers, making it difficult to compare studies (7).

Therapeutic apheresis is primarily used in renal diseases as an adjunct to conventional therapy. Renal disorders with immunologic origin require TA, immunosuppression (IS), steroids, cytotoxic agents, and HMA. The total therapy is individually tailored to the needs of the patient (8, 9). Therapeutic plasma exchange (TPE), double filtration plasmapheresis (DFPP), high volume plasma exchange (HVP), immunoadsorption (IA), adsorptive cytapheresis, and extracorporeal photopheresis (ECP) are used in renal diseases (1, 10). For all renal diseases in which TA is used, the Apheresis Application Committee (AAC) of the American Society for Apheresis (ASFA) is cited as a reference (10, 11).

The etiology of most renal diseases with immunological origin is unknown. Viral infections and other infections and influences can lead to altered native antigen with a loss suppression

(8). Against most nuclear structures antinuclear antibodies are to be found. In all these diseases, vasculitis is found and most easily demonstrated histologically in the precapillary arterioles and post-capillary venules (12). The release of different soluble substances as antibodies (abs) that diffuse away from the side of their production is accompanied by a complex set of events, called inflammation. Autoantibodies are not necessarily auto aggressive or destructive, they only lead to inflammatory tissue reaction when, through their binding to cells and through complement activation, the reaction chain of the serum complement system is triggered. Immune complex (IC) is a physiological process and serves to eliminate foreign material, such as bacteria, the components and viruses. The formed ICs are removed from blood in the liver and spleen by adhesion of the Fc-fragments of the abs to the corresponding phagocyte receptors. Immune complexes are deposited preferentially in the kidney, joints, lung and skin. They accumulate in the kidneys because the blood pressure in the glomerular capillaries is four times higher than in other capillaries and because the glomerulus retains ICs by a simple filtering effect (12). Circulating ICs (CICs) are involved in the regulation of various immune phenomena, and with TA it is possible to interrupt pathological processes by elimination of CICs. Therapeutic apheresis as initial, complementary treatment gives a positive response in terms of kidney and patient survival in patients with favorable initial renal functions (13).

Acute Kidney Injury (AKI)

Acute kidney injury is a multifactorial syndrome with high risk of short- and long-term complications as well as increased health care costs, and a life-threatening and organ-threatening therapeutic challenge that requires prompt, accurate diagnosis and treatment, and remains a reversible damage with oliguria or anuria (14, 15). Acute kidney injury is defined as acute, developing over hours or days, and resulting in renal insufficiency, which is measured by the glomerular filtration rate. In some cases, it can exhibit a polyuria course. The discovery of new functional and damage/stress biomarkers has enabled a more precise delineation of the etiology, pathophysiology, site, mechanisms, and severity of injury (15). Besides various other biomarkers, the three core apoptosis-related genes were identified as AKI biomarkers (16, 17). These biomarkers for AKI explored the roles in the progression of AKI and provided new ideas for clinical diagnosis and treatment of AKI.

The classification of the factors in pre-renal, renal, and post-renal disorders offers new possibilities due to the discovery of biomarkers (6, 17). The pre-renal disorders are circulatory-ischemic disorders, such as reduced blood pressure or volume. This can be directly influenced therapeutically. The vascular disorders, as the second group, are very difficult to remedy therapeutically, if at all.

The renal disorders include endogenous and exogenous substances, which circulate in the blood and can damage the kidney tissue. Besides endogenous and endogenous toxins, this group includes metabolic and decomposition products, as well immunologically active substances that circulate in the blood and damage the kidney (18): Exogenous factors such as Gram-negative cocci in sepsis can easily lead to severe renal injury. The application of antibiotics with intravenous immunoglobulins (IVIG), and in severe courses, TA and hemodialysis (HD) begin as early as possible to interrupt pathogenic chain reactions and could lead to improvement and recovery of the kidney function (19). Other exogenous toxins are mercurous chloride, carbon tetrachloride, glycol, oxalic, heavy metals and foreign substances with high molecular weight, possibly leading to destruction of kidney tissue (6). In COVID-19 with available abs and AKI, TA and HD is indicated in a very early stage (20).

The endogenous toxins, such as free hemoglobin and myoglobin, can be transfusion reactions, which result in hemolysis after HD, severe operations, disseminated intravascular coagulation (DIC), burns, tissue destruction, hemolytic uremic syndrome (HUS), and biomarkers, which can be quickly eliminated by TA. A part of the endogenous toxic renal damage is the cast nephropathy of plasmacytoma (6). The most common renal manifestations associated with cancer include AKI in the setting of myeloma, tumor lysis syndrome, post-hematopoietic stem cell therapy, and AKI associated with chemotherapy (21). In these diseases, TA and HD are also indicated in a very early phase to improve the outcome.

Liver diseases, such as hepatorenal syndrome, can lead to acute kidney injury due to the release of decomposition products, toxins, and phenols resulting from the destruction of liver cells in the setting of liver insufficiency. A reduced effective blood volume and the increased presence of vasoactive, humoral, or neuro-humoral substances, occurring as a result of liver damage, leading to vasoconstriction of the kidney and thus insufficient blood flow, are involved in the pathogenesis of hepato-renal syndrome (6). Acute pancreatitis can be caused by DIC aggravated by dehydration and often associated with AKI (22). Important for renal damage are toxic digestive enzymes released into the systemic circulation by a diseased pancreas. Active enzymes are amylase, esterase, nucleases, and inactive proenzymes, such as proteinase, peptidases, and phospholipase A, which are activated by trypsin, releasing highly toxic lysolecithin from lecithin, which can damage the organs, in particular the kidney, leading to AKI. Therapeutic apheresis could eliminate all the toxic substances and reduce damage before surgical intervention. The most fatal outcome of acute hemorrhage necrotizing pancreatitis can be improved in some severe cases through the early introduction of TA.

Only some controlled studies of TA in the treatment of AKI are available. It is difficult to start larger controlled studies due to the different etiology of the AKI; therefore, the physicians who treat patients with AKI must decide for themselves, taking into account the etiology of the AKI, whether TA or adsorber exchange are indicated or not (23). Acute kidney injury is a life-threatening disease. Therefore, it is necessary to discuss the risk factors of AKI and the therapeutic possibilities with all persons involved in the therapy, and multicenter, controlled studies are necessary.

Nephrogenic Systemic Fibrosis (NSF)

Nephrogenic systemic fibrosis is a rare but severe systemic disease in patients with acute or chronic kidney disease (CHD) and is often associated with the administration of gadolinium (Gd) (24). It occurs in 3-7 % of patients with renal insufficiency receiving Gd, however, in patients with a GFR < 30 ml/min/1.73 cm^2, in current thrombotic or inflammation, and in higher dose of Gd, in patients with hepato-renal syndrome and in the perioperative period following liver transplantation (25). Further causal factors include surgery, systemic infections, metabolic acidosis, high erythropoietin blood levels, and elevations of calcium, iron, copper, and phosphate.

Two to four weeks after Gd administration, NSF onset is observed. The range can be from 2 days to 8 years, then the skin shows a symmetrical erythematosus rash, non-pitting edema, paresthesia, and pruritus in the extremities (10). Other symptoms can be hair loss, gastroenteritis, conjunctivitis, bilateral pulmonary infiltrates, and fever. These symptoms result in joint contractures leading to wheelchair dependence and may include deeper tissue, including skeletal, heart, pericardium, pleura, lungs, diaphragm, esophagus, kidneys, and testis. Overall mortality amounts to up to 30 %. The disease progresses to death in weeks to months, and in a small group of patients with recovered renal function, the disease can enter remission (11). The etiology is mostly unknown; however, Gd may also directly induce fibrosis, and the administration of GD must be avoided in patients with GFR < 30 ml/min/1.73 m^2.

With one to three HD, 97 to 99 % of the dose of GD can be removed. Further therapies include IVIG, alefacept, pentoxifylline, imatinib, messy late chelation therapy with sodium thiosulfate, decorin, TPE, or ECP, or renal transplantation (26-30). With TPE or ECP, improvement of the skin, increased range of motion, improved ambulation and wheelchair-bound walking, decreased swelling, pain, and paresthesia are achieved (31). Therapeutic plasma exchange with a 1.5 total plasma volume (TPV) is introduced daily, with in total 10-14 treatments (10). The ECP of 1.5 L of whole blood volume varies to 2 total blood volume (TBV). The frequency is from 2 consecutive days every 2-4 weeks up to 5 sessions every other day, and the duration of ECP could be 4-16 months (28). The AAC of the ASFA has given the NSF the category II and the recommendation grade (RG) 2C (Table 1) (10, 11).

Rapid Progressive Glomerulonephritis (RPGN)

Rapid progressive glomerulonephritis is a diffuse glomerulonephritis (GN), and it frequently starts acutely. As a histologic diagnosis, RPGN can occur from many etiologies, including a rare anti-basement membrane antibody GN (ABM-ab-GN), antineutrophil cytoplasmic antibodies (ANCA), and IgA nephritis (32). Necrosis with emboli in the capillary walls and semi-lunar formation, and deposition of IgG and C3 along the glomerular basement membrane are usually the histological characteristics. An AKI is simultaneously accompanied in most patients with RPGN, and more than 90 % of these patients have anti-glomerular basement membrane antibodies (anti-GBM abs) in their circulation.

In RPGN, a rapid loss of renal function with the histological findings of crescent formation in over 50 % of glomeruli is found (32). Histologically, a proliferation of cells within Bowman´s space of the glomeruli due to the extravasation of proteins into the space is observed. These cells consist of proliferating parietal epithelial cells as well as infiltrating macrophages and monocytes. The RPGN is a clinical syndrome with various etiologies. Immunoglobulin G, a linear disposition, due to autoantibodies (auto-abs) to type IV repressing anti-glomerular basement GN in 15 % (33).

The incidence is 0.85 per 100.000/year (34). The first-line therapy includes high-dose corticosteroids and cytotoxic immunosuppressive drugs such as cyclophosphamide or azathioprine (10). Other drugs are leflunomide, deoxyspergualin, tumor factor blockers, calcineurin inhibitors, antibodies against T cells, or rituximab (33-35). An oral C5a receptor antagonist, avacopan, was approved as an adjunctive therapy in antineutrophil cytoplasmic antibody-associated vasculitis. Patients treated with avacopan had more rapid reduction in albuminuria and greater recovery in GFR (36).

RPGN with dialysis dependence and a creatine blood level ≥ 5.7 mg/dL, and RPGN with diffuse alveolar hemorrhage (DAH) have received the category I and RG 1A and 1C from the ACC of the ASFA, and the RPGN without dialysis dependence has the category III with the RG 2C (Table 1) (10,11). The role of TPE has been investigated in pauci-immune and immune complex nephritis (ICN). The results indicated that TPE may be beneficial for dialysis-dependent patients with severe renal dysfunction. However, there is no therapeutic benefit over immunosuppression in milder disease. In these trials, the predominance of pauci-immune GN cases may account for these results (10).

Immunoadsorption effectively removes pathogenic immune complexes (ICs) from the blood (37). The frequency of TA is every other day, and the treated volume is 1-1.5 times the patient's volume. The substitution solution in TPE could be 5% human albumin electrolyte solution, and/or plasma. The duration of TA is usually 1-2 weeks by tapering with fewer treatments depending on the course

Table 1: Therapeutic Apheresis in Nephrology (10, 11)

Disease	Category	RG	TA-modality	Exchange Volume (TPV)	Replacement Fluid
Nephrogenic systemic fibrosis (NSF)	**II**	2C	TPE/ ECP**	1.5 TPV/ 1.5 L of blood	5 % HA, plasma
Rapid progressive GN (RPGN)					
-Dialysis dependence*	**I**	1A	TPE		
-Diffuse alveolar hemorrhage (DAH)	**I**	1C			
-Immune complex nephritis, dialysis dependent	**III**	1B			
Anti-glomerular basement disease (Goodpasture syndrome), DAH	**I**	1C			
-Dialysis-independence	**I**	1B,1C			
-Dialysisdependence*	**II**	2B			
Focal sclerosing glomerulonephritis					
-recurrent in kidney transplant	**I**	1B	TPE		
-recurrent in kidney transplant/ steroid resistant in native kidney	**II**	2C			
-steroid resistant in native kidney	**III**	2C			
Hemolytic uremic syndrome (HUS)					
-complement gene mutation	**II**	2C			
-fa**ctor H antibodies**	**I**	2C			
-MCP mutations	**IV**	IC			
Renal transplant rejection					
-ABO incompatible, ab-mediated rejection	**I**	1B	TPE, IA** Peptide-GAM**, Tryptophan**		
-Desensitization of living donor	**I**	1B			
-Desensitization	**III**	2C			
-ABO incompatible, desensitization, live donor	**I**	1B			
-Humoral rejection, group A2/A2B into B	**II**	1B			
Deceased donor	**IV**	1B			

(Category I: is accepted for TA as first-line therapy; Category II: accepted for TA as second-line therapy; Category III: not accepted for TA, decision should be individualized; Category IV: not accepted for TA, IMB approval is desirable if TA is undertaken.)

* Creatine ≥ 5.7 mg/dL, TA: therapeutic apheresis, RG: recommendation grade, TPV: total plasma volume, TPE: therapeutic plasma exchange, ECP: extracorporeal photopheresis, LA: lipid apheresis, ** ECP, IA, LA, Peptide-GAM, Tryptophan, no substitution solution is necessary.

of the disease. In PEXIVAS, the international controlled study, TPE was compared versus no TPE and standard versus reduced dose steroid regimen on the primary composite outcome of end-stage renal disease (ESRD) or death in patients with ANCA-associated vasculitis (AAV), the largest study on the role of TPE in AAV (38). Therefore, TPE was not significantly associated with their risk of primary outcomes, mortality, and other side effects. It was suggested that TPE might be effective in suppressing ESRD in the early stage of treatment (39). The PEXIVAS study did not show that the addition of TPE to standard therapy conferred benefits in patients with severe AAV; however, it did show that a reduced-dose regimen of oral glucocorticoids was non-inferior to a standard-dose regimen (40,41). However, the combination of TA and especially immunosuppressive therapies is a successful strategy for intensively treating severe renal diseases with antibodies (42). Therapeutic apheresis is a valuable and safe adjunct to immunosuppression in severe renal diseases (43).

Immune Complex Nephritis (ICN)

Many types of glomerulonephritis can be caused by the deposition of immune complexes. Immune complexes induce tissue injury via either engagement of Fc-receptors on effector cells or via complement activation (44). The consequence of systemic autoimmune disease is triggered by the generation of antibodies and the subsequent tissue deposition of ICs. The pathogenesis is disrupted by a modulation of the antibody response and by preventing the formation of ICs. Uncoupling IC formation from subsequent inflammatory response seems unlikely because of the apparent complexity of the IC-triggered inflammatory cascade (45).

In idiopathic RPGN, the therapeutic strategies are not as clear as in anti-glomerular basement membrane antibody nephritis. With pulse therapy of corticosteroids or TPE, an improvement in renal function in more than 60 % of the patients is possible. Therefore, TPE in combination with immunosuppression should be carried out as quickly as possible, given the devastating pathophysiologic consequences of the interaction between CIC and the basement membrane (7). Therapeutic apheresis is a valuable adjunctive therapy in severe ANCA-associated renal diseases.

For remission induction of ANCA-associated vasculitis, a therapy is indicated with a combination of corticosteroids, cyclophosphamide or rituximab or eculizumab, and/or mycophenolate mofetil (MMF), and tacrolimus (TAC) (46,47). This multitarget therapy of corticosteroids, HMA, MMF, and TAC has shown a remission induction of intractable ANCA-associated GN which developed independently of systemic lupus erythematosus (SLE).

Anti-basement Antibody Glomerulonephritis (Goodpasture Syndrome, ABM-ab-GN)

The ABM-ab-GN is a rare life-threatening small-vessel vasculitis affecting pulmonary and/or glomerular capillaries, which is caused by the deposition in alveolar and/or glomerular basement membrane of circulating autoantibodies (44). The incidence is 0.5-1 per million population (45). The patients commonly represent an RPGN, accompanied by alveolar capillaries and pulmonary hemorrhage. In ABM-ab-GN, antibodies are directed against a peptide component of one of the two non-collagen parts of type IV collagen. Type IV collagen is found not only in the kidney but also in the vessels of the lungs (48). The autoantibodies in the glomerular basement membrane in the kidney and alveolar capillary walls in the lung lead to severe organ injury with a high risk of morbidity and mortality (49). The mechanism of the production of autoantibodies against antigens is unknown.

A large number of diseases have been associated with Goodpasture syndrome in various cases, with the most reported associations being with membranous nephropathy and antineutrophil cytoplasmic-associated vasculitis. Only a small part of ANCA GN has anti-GBM antibodies; mostly, it seems to be an environmental or infectious exposure that triggers these diseases. It has been speculated that both membranous and ANCA-positive vasculitis damage to the kidney elicits an immune response against the GBM, leading to the production of autoantibodies (50). The production of anti-basement abs is frequently limited in duration, and the auto-abs cause severe disturbances in the permeability in the lung with severe disturbances in the permeability in the lung with severe deterioration in diffusion capacity and hemoptysis. The deposition of these auto-antibodies in the kidney leads to rapid deterioration in renal function. A necrotizing GN in part is seen histologically, and the linear deposits of IgG can be immunohistologically observed at the basement membranes of the lung and the kidney (39, 40). The antigen with a probable size of 26,000 – 28,000 Daltons is considered responsible for these deposits; its immunogenic epitopes being located on the stable glomerular domain NC1 of collagen IV (44). The antigen is presented as a hexamer and forms monomers and dimers (40,44). The antigen determinants are exposed after dissociation and can thus bind specific antibodies. These molecules seem to be present in all basal membranes, in particular in those of the glomeruli, renal tubuli, the Bowman capsule, the lung, and the plexus chorioideus, in the placenta, and also in those of the aorta and small intestine.

Acute and chronic tubulointerstitial lesions predict the GFR at 12 months; it was the use of TPE and the number of normal glomeruli on biopsy that remained positive predictors of dialysis independence in the same time interval (51). Unaffected glomeruli determine long-term renal outcome at one year (52). The TPE for renal vasculitis study (MEPEX) showed in 69 dialysis-dependent patients that TPE was superior to pulse corticoid therapy to the change in the need for dialysis (50).

Some patients with an ABM-ab.GN become dialysis dependent; therefore, an aggressive therapy with daily TPE, pulse therapy of corticoids, and/or cytotoxic drugs was necessary (53). There are successful reports with MMF, cyclosporine, and in severe cases, rituximab, an HMA, and imlifldase were successful as "add-on" to standard therapy (44). Rituximab showed a rapid reduction of anti-GBM antibodies but without benefits on renal outcome. With the use of TPE, the pulmonary bleeding can be stopped and improved in cases with the same immunological process, even when renal function is already irreversibly impaired (54). A final long-term prognosis for patients whose condition improved after TPE cannot be made. Recovery, or at least partial recovery, is possible. Even in patients with ABM-ab-GN after COVID-19 vaccination, the treatment with pulse methylprednisolone, cyclophosphamide and TA was successful (55).

The AAC of the ASFA has given the ABM-ab-GN with dialysis independence and/or DAH, the category I and the RG 1C and 1B, respectively, and with dialysis dependence and no DAH, the category III and the RG 2B (Table 1) (10,11). The frequency of TA is every other day until anti-glomerular basement membrane antibodies are detectable. The treatment is for 1-2 weeks, followed by tapering with less frequent treatment. The duration of the therapy with TA is not well defined in the literature, and TA should be carried out until abs are no longer detectable (12).

Rapid Progressive Glomerulonephritis with or without Glomerular Deposition (ANCA-ab), Pauci-Immune RPGN

About 60 % of patients with RPGN present with crescentic glomerulonephritis characterized by few or absent immune deposits, the so-called pauci-immune RPGN. In these patients, a Wegener´s granulomatosis, an ANCA-associated vasculitis, polyarthritis nodosa, or "renal-limited" pau-

ci-immune GN is diagnosed (56). A single disease may represent a spectrum of manifestations, because there is marked overlap and histopathologic features, and many patients have ANCA in their blood, which is more common than anti-GBM. In some patients, the ANCA abs correlate with the disease activity, and the ANCA may contribute to the pathophysiology of pauci-immune RPGN through reactivity with neutrophils or endothelial cells, and/or other inflammatory mechanisms (57).

The pauci-immune RPGN has, in general, a poor prognosis. To get exact therapeutic recommendations from the literature is difficult because of the different types of RPGN in the investigated trials. Without therapy with pulse corticosteroids, high-dose immunosuppression or cytotoxic drugs, about 80 % of such patients progress to ESRD. Therapeutic apheresis as an adjunct to conventional therapy in patients with pauci-immune RPGN has been evaluated as beneficial in some studies (58,59). The results of randomized studies argue against the role of TA in milder forms of pauci-immune RPGN. However, TA suggests a potential benefit in patients with severe disease when TA is used as an adjunct to immune suppressive therapy from the start (31). This relative lack of efficacy reflects the efficiency of immunosuppressive agents in halting inflammation and preserving renal function in most patients. This is supported by the results of uncontrolled studies, suggesting a response rate of 70 % in patients with RPGN treated with TA, similar to that of patients treated with immunosuppressive therapy, with a response rate of 60 %. Therapeutic apheresis should be introduced as therapy in the early phase of the disease as early as possible.

In the MEPEX study, it was found that in patients with dialysis dependence, ANCA-associated vasculitis, the chances of recovery differ on the type of adjunctive treatment, the percentage of normal glomeruli and glomerulosclerosis, the extent of tubular atrophy, and the presence of arteriosclerosis. Even with an ominous biopsy at diagnosis in combination with dialysis dependence, the chance of renal recovery exceeds the chance of therapy-related death when TPE is used as adjunctive therapy (52). However, the PEXIVAS study did not show that the adjunctive TPE to conventional therapy conferred benefits in patients with severe ANCA-associated vasculitis, but it showed that a reduced-dose regimen of oral glucocorticoids was non-inferior to a standard-dose regimen (51). In patients with high titers of CICs or other antibodies, which could damage the kidney and other organs, IA with protein-A can be more effective than TPE.

Therapy of RPGN, Recommendations

The combination of TA and immunosuppression therapy seems to be advisable, particularly given the unfavorable prognosis of RPGN, with its complex causes. Only a few uncontrolled and controlled studies are available (60-63). Therapeutic apheresis in combination with glucocorticoids as pulse or oral therapy, cyclophosphamide as pulse or oral therapy, or azathioprine, and/or rituximab is indicated in the following cases:

- RPGN with serum creatinine (Cr) ≥ 5.7 mg/dL without oliguria in anti-GBM disease
- All severe forms of RPGN with or without ANCA ab, like the pauci-immune complexes (Cr ≥ 6 mg/dL or patient on dialysis).
- Goodpasture syndrome with life-threatening hemoptysis, or diffuse alveolar hemorrhage from ANCA or microscopic polyangiitis (MPA), independent of renal function status (33,64).

Therapeutic apheresis is used even in elderly patients with renal diseases and is relatively safe. Trends towards death in this group of patients may be multifactorial and not necessarily related to TA (63). With TA, a decrease in end-stage renal disease or death in patients with RPGN can be reached (65). A combination of TA with immunosuppressive therapies, including biologics, seems

to be more effective than TA alone (33,66-68). In cyclophosphamide-resistant ANCA-associated GN, others prefer a multi-target therapy with a combination of corticosteroids, MMF, TAC, or the C5a receptor antagonist avacopan (46, 69). Further investigations are necessary to determine what kind of therapy would be preferable.

Glomerulonephritis with Nephrotic Syndrome (NS)

The classification of NS is morphological. Differing etiologies can result in considerable variations in the clinical features, as well as course and prognosis. It is challenging to establish generally applicable therapeutic concepts and tailor treatment to individual patients (34). Conducting controlled therapy studies is almost impossible due to the diverse clinical courses of this heterogeneous disease group. Therapy successes are to be found, as are therapy-produced complications, e.g., infections, sterility, loss of hair, and others. The benefits of the immunosuppression therapy must be weighed against these complications. The aim of the GN must be to prevent renal insufficiency and NS.

The causes of NS are changes in the electrophysiological characteristics of the filtration barriers and the plasma proteins. The anionic charge on albumin is retained by the negative charge of the glomerular filter, including the basement membrane and the epithelium, which plays a decisive role (7). Hemodynamic changes, such as the increase in venous pressure, can favor the filtration process. Proteinuria can lead to the formation of cellular or fibrous crescents with reciprocal development of RPGN or focal glomerulosclerosis (70). Proteinuria can also lead to overload and dysfunction of tubular epithelial cells, resulting in tubular and interstitial fibrosis. Nephrotic syndrome following COVID-19 vaccination has been reported (71). The pathogenesis is the activation of angiotensin-converting enzyme-2 receptors, leading to podocyte effacement, and a renal biopsy is necessary for correct identification.

NS of different GN often reacts to corticosteroids in varying doses over 4-8 weeks. Patients with frequent relapses could also be treated with 2-3 mg/kg body weight (BW)/day cyclophosphamide (31). Cyclosporine A and/or high doses of immunoglobulins have also been successfully applied in NS (9). Further drugs are anticoagulants, thrombocyte inhibitors, angiotensin converting enzyme (ACE) inhibitors, immunosuppressive drugs, lipid reducers, HMAs, and diet (72,73). Rituximab is especially indicated in refractory NS in children and adults (74). Hypogammaglobulinemia is a frequent adverse event after rituximab treatment, also IgG levels slightly increase during B cell depletion, and low serum IgG levels under rituximab treatment in refractory NS are risk factors for the development of hypogammaglobulinemia (75).

Focal sclerosing glomerulonephritis (FSGN) has a poorer prognosis and is usually accompanied by NS, and patients with FSGN and NS have a survival of 70 % after 6 years, whereas without NS, this rate reaches 85 %. Patients with steroid-resistant FSGN could be treated with cyclophosphamide, chlorambucil, cyclosporine A, or other immunosuppressive drugs (34). The FSGN is caused by different factors, and the type after transplantation is associated with circulating factors and could be treated with TA. After transplantation, more than 40 % of patients with NS have recurrences (10). For FSGN post-transplant, a combination of cyclophosphamide, biologics, and TPE is mostly used, or high-dose cyclosporine, ACE, indomethacin, and/or tacrolimus could be applied. To prevent recurrent FSGN, several sessions of preemptive TPE immediately before and following the transplant is recommended (7). Rituximab and MMF have also been used in conjunction with diagnosis to halt the process and maintain renal function (10).

The AAC of the ASFA has given the FSGN recurrent in kidney transplantation the category I with the RG 1B, and the FSGN recurrent in kidney transplantation/steroid-resistant in native kidney the category II with the RG 2C, and steroid-resistant in native kidney the category III with the RG 2C (Table 1) (10,11). The first-line therapy for native kidneys with FSGN is corticosteroids, and the second-line therapies are immunosuppression, such as cyclophosphamide, and/or TPE, LA. and IA, because of different circulating factors that alter the glomerular barrier to protein filtration (31).

The immediate onset of proteinuria following transplant is mediated by a glycoprotein of molecular weight (MW) of 30-50 kDa, and prophylactic TPE may be instituted in high-risk patients (10). Immunoadsorption with Staphylococcal Protein A columns is also recommended. The treatment starts with three daily sessions, followed by at least six more TPE over several weeks or months (9). Besides TPE and IA, corticosteroids, immunosuppression, calcineurin inhibitors, and MMF, or rituximab are recommended (76, 77).

A common complication of glomerular disease in children and adults is the NS, consisting of massive proteinuria, hypoalbuminemia, edema, and hyperlipidemia. The annual incidence of NS ranges from 2-7 per 100,000 children, and prevalence from 12-16 per 100,000 (31). The most common cause of NS is idiopathic. It seems to be related to the immune system in pediatric minimal change glomerulonephritis (MCGN). Relapses are commonly triggered by minor infections and occasionally by reactions to certain foods or poisoning. An indirect indication of an immune etiology is provided by the induction of remissions with corticosteroids, alkylating agents, or cyclosporine therapy (10).

Patients with MCGN and massive proteinuria do not have a generalized glomerular leak of macromolecules. The clearance of neutral macromolecules in MCGN is less than normal over a range of molecular radii, and the clearance of anionic macromolecules is significantly increased. Proteinuria, therefore, results from a loss of fixed negative charges of anionic glycosaminoglycans in the glomerular capillary wall (10). A massive albuminuria in NS causes a decrease in intravascular oncotic pressure, which allows extravasation of fluid and hypovolemia, increased aldosterone and antidiuretic hormone secretion, and renal salt and water retention. With the therapy with prednisolone and cyclophosphamide over 8-12 weeks and with LA, a significantly rapid relief can be observed (78). With LA, a rapid improvement of hypercholesterolemia in steroid-resistant NS can provide more rapid relief from NS than from steroid therapy alone. In steroid-resistant NS in children, intravenous high-dose steroids with alkylating agents, cyclophosphamide, and MMF are recommended, too (79). Rituximab can reduce the risk of recurrence and help to decline or discontinue the use of glucocorticoids in the treatment of adult glucocorticoid-dependent/relapsing FSGN (80).

Membranoproliferative glomerulonephritis (MPGN) is usually combined with NS and hypertension, and has a poorer prognosis (34). Whether corticosteroids or pulse therapy, cyclophosphamide, anticoagulants, and IVIG are effective is not clarified. The treatment with protein-A-IA in patients with relapsing seems to be successful.

Nephrotic syndrome is the main symptom in peri-membranous GN and has a poorer prognosis. High doses of prednisolone as a pulse therapy over 3-5 days or with 2 mg/kg BW in decreasing dosage for 3 to 5 months are recommended in acute NS. A combination with TPE should be considered, especially with a more selective procedure such as DFPP, IA, or LA (31). The symptoms in mesangioproliferative glomerulonephritis are not usually homogeneous, and in severe, corticosteroid-resistant cases, a combination therapy of TA and immunosuppression is indicated, regardless of the degree of renal insufficiency.

Larger doses of albumin administration can improve dysproteinemia and edema. Therapeutic apheresis is theoretically a way of achieving mainly an improved effect on the basal membrane.

The atherogenic risk for patients with NS is reduced by the elimination of cholesterol, LDL, and triglycerides, thereby preventing progression. Therapeutic apheresis should be a useful therapeutic tool (34). The more selective procedures, such as DFPP, IA, and LA, are very useful in the treatment of NS and show promise for treating severe cases of NS if conservative treatment fails. In steroid-resistant NS, a therapy with a combination of TA and rituximab or obinutuzumab, and MMF is recommended (81, 82). In severe cases and, if conservative therapy fails, other renal diseases, such as light chain nephropathy, dense deposit disease, and others, can be treated with TA (31).

Hemolytic Uremic Syndrome (HUS)

Hemolytic uremic syndrome is characterized by microangiopathic hemolytic anemia, thrombocytopenia, and AKI, and is a severe disease that can lead to AKI and often to other serious sequelae, including death. The disease is associated with dysregulation of the immune complement system, especially of the alternative pathway (83). The etiology and pathogenesis of HUS are not yet completely understood, and therefore, the therapy is complex. The introduction of TPE as a supportive therapy in HUS was highly successful in 87% of treated patients, and especially in severe courses, TPE is indicated and superior to other available therapies (84). Other studies reported improvements in renal and hematological parameters with the treatment with HMAs, such as eculizumab or ravulizumab (85, 86).

Infections with enterohemorrhagic E. coli (EHEC) are the most common cause of HUS. These bacteria can be transmitted through contaminated food, animals, and person-to-person contact. The HUS is described as “typical” and needs to be differentiated from genetic disorders, which are of importance. Other types of factors, including genetic disorders, are of importance. Three different types of subdivisions lead to HUS, which are caused by infection, idiopathic HUS (non-Shiga toxin-HUS), and HUS in systemic diseases and after toxin exposures (87).

Spontaneous recovery from HUS has been reported. Different etiologies and pathogenetic assumptions have produced various therapy concepts. With the introduction of dialysis, the total lethality in HUS was first reduced to 20 % (31). If dialysis is administered early enough, two-thirds of cases recover without any impairment, and in 10-20% of cases, lasting renal damage occurs. In severe coagulation problems, the substitution of plasma or coagulation factors is often necessary.

The introduction of TA in the treatment of HUS was very successful (88-91). Therapeutic apheresis might be more effective for plasma or coagulation factor infusions alone, as TA removes potentially toxic substances from blood, especially in situations that limit the amount of plasma that can be infused, such as renal or heart failure. TA should be considered the first-line therapy. Plasma infusion as treatment is contraindicated in S. pneumoniae-induced non-Stx HUS, because this treatment may exacerbate the disease, considering that adult plasma contains antibodies against the Thomas Friedrich antigen (92). The advantage of TA over other conservative therapies is that TA intervenes at an early stage in the pathogenic processes by rapidly removing immune complexes and other toxins. Other high molecular complexes, fibrinogen and fibrinogen degradation, which can both support and inhibit coagulation, were eliminated by TA. All other toxins produced by bacteria and viruses, such as Shiga toxin, the pathogenic pathway, which follows the activation of the complement system of the factor HF1 with partial HF1 deficiency, and all other toxic substances, can be rapidly removed by TA (10,11). Therapeutic apheresis seems a reasonable option for the poor prognosis of HUS in adults (84). The early application of HMAs, eculizumab, or ravulizumab leads to improvements in hematologic, kidney, and systemic manifestations in patients with atypical HUS, even with apparent dialysis dependency (93). Pre- and post-transplant use of eculizumab is effective in the prevention of atypical HUS recurrence.

In Germany, between May and July 2011, an outbreak of *Escherichia coli* (O104:H4) resulted in 3,167 cases without hemolytic uremic syndrome (HUS), including 16 deaths, and 908 cases with HUS, of which 34 patients died (94). 241 patients with HUS were treated with TPE, and 193 patients with a combination of TPE and eculizumab. The treatment strategy depended on the severity of the disease (95). Therapeutic apheresis in combination with eculizumab seems to be prudent and necessary before establishing new treatment guidelines. The HMAs, eculizumab or ravulizumab, were introduced successfully in the treatment of HUS (94, 96, 97). Especially in renal graft survival in atypical HUS, the prophylactic application of eculizumab was very successful (98, 99). The conversion from TA to eculizumab therapy should be considered in patients with HUS who show an incomplete response to TA. With the administration of eculizumab, careful attention should be paid to meningococcal infection, eculizumab-related infusion reactions, and allergic reactions (100). The combination of TA, HMAs, and immunosuppressive drugs provides benefits in HUS. Especially in pregnancy and HUS, the treatment with TA alone showed a rapid improvement (101). The combination of TA, immunosuppression, and/or HMAs showed promising results in the short and long term (102). Further multicenter, randomized trials are necessary.

The AAC of the ASFA has divided HUS into 3 groups for treatment with TA. Group 1, diarrhea-associated HUS is a HUS due to a complement factor gene mutation and is category II with RG 2C. Group 2 is a HUS due to an antibody to factor H, atypical HUS, which is category I with RG 2C. Group 3 is the typical HUS < 18 years, MCP mutations, and has the category IV with RG 1C (Table 1) (10,11). No exact guidelines are available for the therapy of HUS, due to the various and very different causes that can lead to HUS.

Kidney Transplant Rejection

Kidney transplantation is the decisive alternative to permanent dialysis in renal end-stage disease. Rejection of the transplanted kidney is a severe problem, and in the last decades, different therapeutic interventions are used to delay or prevent rejection, including steroids, IVIG, immunosuppressive drugs, HMAs, cyclosporine A, triple drug, OKT3, and other immunosuppressive therapies. The most common complications of transplantation are infections and rejection reactions (103, 104). Acute kidney transplant rejection is an indication for TA (103, 105).

Preformed donor-specific abs or a high degree of immunization can complicate the outcome of donor transplantation. In the management of rejection crisis due to specific abs or a high degree of immunization, TA is indicated (104). The outcome of donor transplantation is complicated by immunological problems, like high postoperative antibody-mediated rejection or drug-related side effects of the medication. Acute allograft rejection is one of the important complications after renal transplantation, and is a deleterious factor for long-term survival (34). Rejection is a complex pathophysiologic process, which has been explained by transcriptome and proteome in RNA transcripts and protein levels, respectively (106, 107). Therapy strategies include a primary avoidance of immunization, careful patient selection, a meticulous workup, a proper follow-up, and TA improved therapy (108, 109). For ABO incompatible kidney transplantation, the procedure has gained widespread acceptance and has been implemented in most transplant centers. A variety of therapy protocols have been developed (106, 107); these include immunosuppressive therapy with tacrolimus, MMF, and steroids with induction therapy of an IL-2 receptor blocking agent. The CD19/20-positive pre-B cells, with a single infusion of rituximab four weeks prior to transplantation, and in a second step, the already existing abs are depleted by using TA. Isoagglutinine antibodies against the donor can also be eliminated. Novel sensitization and production of abs is thereby efficiently prevented (108, 109). The disadvantage of TPE is the elimination of

physiological proteins, therefore, some groups used IA with unselective IgG columns. Patients with preformed HLA abs, i.e., a high percentage of panel reactive abs, accumulate on the waiting list for kidney transplantation and can experience a substantially longer waiting time (104). Center-specific desensitization protocols were developed.

Different protocols were established for intensive procedures, consisting of the application of IVIG, intensified immunosuppression, and desensitization of the recipient if transplantation from a living donor is planned. These strategies require an intensive procedure, e.g. HMAs pre- and postoperative, and carry a higher risk for ab-mediated rejection (104, 109, 110). Immunoadsorption with a selectivity for immunoglobulins would be considered the best option.

Acute allograft rejection of organ allografts follows a severe dysfunction with a high risk for the allograft. In antibody-mediated rejection (AMR), HLA abs are involved (111). Therapeutic apheresis accompanied by T cell depletion (ATG, ALG, or OKT3) conversion to a tacrolimus-based immunosuppression and pulsed steroids, are used to limit the interstitial and vascular damage (112). The use of IA targeted against IgG has been successfully performed and was superior to TPE and DFPP (113).

In transplant patients, the use of calcineurin inhibitors or mechanistic target of rapamycin (mTOR) inhibitors has been associated with acute vascular rejection as well as the recurrence or de novo development of thrombotic microangiopathy (TMA). Infections such as HIV, CMV, Para virus B 19, an inhibited or decreased activity of the von Willebrand factor cleaving metalloprotease ADAMTS13 or mutations in complement receptors may also trigger microangiopathy with either limited or systemic manifestation (104).

If switching to a different immunosuppressive regimen or treatment of an underlying infection does not lead to an improvement of the TMA, TA can be attempted to ameliorate the course of the disease and subsequent graft damage (114). If daily TA is stopped, up to 50 % of patients demonstrate a prompt exacerbation. The recurrence rate can be reduced by continuation of TA on an alternative day strategy for at least two additional treatments. The TMA reduces graft survival in both recurring and de novo TMA, and treatment may not alter the progression of the disease (104).

Therapeutic apheresis has been shown to deplete the patient effectively of antibodies and halt disease progression (31). A rapid removal of the antibodies with a daily session is possible with TA. Therapeutic apheresis treatment is accompanied by an intensified immunosuppression to suppress further antibody formation (104). New complement blockers raise hope to reduce the ab-mediated rejection significantly, and nephropathy recurrence in outcomes after kidney transplantation (115). Only some information about FSGN is available in kidney transplantation in adults regarding long-term results. Therapeutic apheresis has been successfully applied in patients with recurrent FSGN. A dramatic effect in the reduction of proteinuria has been observed in patients treated with IA in combination with cyclophosphamide (104).

Therapeutic apheresis is accepted in AMR or blood group system (ABO) transplantation, and TA has allowed to develop strategies to provide the best organ replacement to patients with high degree of immunization thereby expanding the use of living donation; TPE is more and more replaced by the more selective methods of IA. The AAC of the ASFA described the ab-mediated rejection and HLA desensitization as follows and give the AMR renal transplant recipients and desensitization living donor, due to donor specific HLA ab, the category I with RG 1B. The desensitization high panel-reactive antibody (PRA) deceased donor has the category III with RG 2C (Tab. 1) (10,11). Antibody-mediated rejection affects less than 10 % of the renal allografts. Recipients at increased risk include those with previous transplant and high panel reactive abs (10).

New immunosuppressive drugs are continually being developed to prevent and treat acute allograft rejection, and all transplant recipients are placed on immunosuppressive therapy. An op-

timal regimen has not yet been defined, but includes, besides cyclosporine, tacrolimus, MMF, azathioprine, and antilymphocyte globulin (12, 33). Calcineurin inhibitors may contribute to improving long-term metabolic and allograft outcomes in kidney transplant rejections (116,117). Monoclonal human antibodies are successfully introduced such as rituximab, eculizumab, etc. (10). Clazakizumab, or nivolumab, are successfully introduced in the treatment of AMR in kidney transplantation (116-118).

Antibody-mediated rejection and DSA, which are generated after transplantation, can be removed by TPE, DFPP, IA, and lymphoplasmapheresis (10). In a preparatory regimen for ABO renal transplantation, TPE is included in combination with other immunosuppressive/ immunomodulatory drug therapies. In high loss rates with acute vascular rejection, the current regimen includes TA, which has a graft survival rate of 70-80 % (7). To remove HLA antibodies, TA can also be used before transplantation, and TA is always used in combination with immunosuppressive drugs where AMR occurs. Approximately five TA sessions preoperatively will allow the titer of ≤ 32 to become negative pre-transplant until cross-match is negative, and is continued usually postoperatively, and reinitiated in cases where AMR occurs. The risk of AMR is approximately 30 % with a small number of graft losses (33).

The therapy of patients should start with immunosuppression before initiating TA to limit antibody re-synthesis. A correlation must be between the number of TPE needed pre-operatively to obtain a negative crossmatch and the antibody titer in the desensitization protocols (10).

Therapeutic apheresis plays a significant role in various aspects of kidney transplantation; however, more investigations and controlled trials will be necessary will show the importance of TA in the therapy strategies (119). Financial aspects of TA are matters of negotiation and preference. The transplant centers should define their needs for a standard reimbursement and try to limit the variation of this very expensive therapy to simplify reimbursement (104). Besides TA, immunosuppression, new HMAs such as alemtuzumab or felzartamab, and other inhibitors should be individually introduced in patients with acute or chronic kidney rejection, and this must be clarified in further studies (120-123).

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