PROYECTO PROMETEO2

RECIDIVA DE LA ENFERMEDAD RENAL PRIMARIA

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Dosier Bibliográfico

Grupo II | **Diagnóstico y tratamiento de la recidiva de la glomeruloesclerosis focal y segmentaria, síndrome hemolítico-urémico, amiloidosis, glomerulopatías por depósito fibrilar no amiloide e hiperoxaluria**

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NOVARTIS

1. RECIDIVA DEL aHUS EN EL TRASPLANTE RENAL

A. CATEGORIZACIÓN DEL RIESGO DE RECIDIVA POR TRASTORNO GENÉTICO IDENTIFICADO

1. Eculizumab for the treatment of two recurrences of atypical hemolytic uremic syndrome in a kidney allograft
Alachkar N, Bagnasco SM, Montgomery RA.
Transpl Int. 2012 Aug;25(8):e93-5.

Letter to the editors

2. Combined Complement Gene Mutations in Atypical Hemolytic Uremic Syndrome Influence Clinical Phenotype
Bresin E, Rurali E, Caprioli J et al.
J Am Soc Nephrol 24: 475–486, 2013.

ABSTRACT
Several abnormalities in complement genes reportedly contribute to atypical hemolytic uremic syndrome (aHUS), but incomplete penetrance suggests that additional factors are necessary for the disease to manifest. Here, we sought to describe genotype–phenotype correlations among patients with combined mutations, defined as mutations in more than one complement gene. We screened 795 patients with aHUS and identified single mutations in 41% and combined mutations in 3%. Only 8%–10% of patients with mutations in CFH, C3, or CFB had combined mutations, whereas approximately 25% of patients with mutations in MCP or CFI had combined mutations. The concomitant presence of CFH and MCP risk haplotypes significantly increased disease penetrance in combined mutated carriers, with 73% penetrance among carriers with two risk haplotypes compared with 36% penetrance among carriers with zero or one risk haplotype. Among patients with CFH or CFI mutations, the presence of mutations in other genes did not modify prognosis; in contrast, 50%of patients with combined MCP mutation developed end stage renal failure within 3 years from onset compared with 19% of patients with an isolated MCP mutation. Patients with combined mutations achieved remission with plasma treatment similar to patients with single mutations. Kidney transplant outcomes were worse, however, for patients with combined MCP mutation compared with an isolated MCP mutation. In summary, these data suggest that genotyping for the risk haplotypes in CFH and MCP may help predict the risk of developing aHUS in unaffected carriers of mutations. Furthermore, screening patients with aHUS for all known disease-associated genes may inform decisions about kidney transplantation.

3. Genetica della Sindrome Emolitico Uremica atipica e recidiva nel trapianto
Bresin E.
G Ital Nefrol. 2015;32 Suppl 64:gin/32.S64.3.
Article in Italian

Genetics of aHUS and transplant recurrence

ABSTRACT
Hemolytic uremic syndrome (HUS) is a rare disease with a triad of microangiopathic hemolytic anemia, thrombocytopenia, and acute renal failure.
Several genetic and acquired abnormalities leading to abnormal activation of the alternative pathway of complement have been identified in patients with atypical HUS (aHUS).
Studies over the past decade have shown that the risk of post-transplant recurrence of aHUS depends on the underlying genetic abnormality. The risk is high in patients with mutations in genes (CFH, CFI, C3, CFB) encoding circulating complement proteins and regulators, while patients with mutations in membrane cofactor protein (MCP) and diacylglycerol kinase ε (DGKE) generally show good transplant outcome.
Recent data provided evidence about the efficacy of the anti-C5 monoclonal antibody Eculizumab in the prevention and treatment of post-transplant aHUS recurrences.

4. Actualización en síndrome hemolítico urémico atípico: diagnóstico y tratamiento. Documento de consenso

Campistol JM, Arias M, Ariceta G et al.
Nefrologia2015. Volume 35, Issue 5, September–October 2015, Pages 421-447
http://dx.doi.org/10.1016/j.nefro.2015.07.005

ABSTRACT
El síndrome hemolítico urémico (SHU) es una entidad clínica definida por la tríada anemia hemolítica no inmune, trombocitopenia e insuficiencia renal aguda, en la que las lesiones subyacentes están mediadas por un proceso de microangiopatía trombótica (MAT) sistémico. Distintas causas pueden desencadenar el proceso de MAT que caracteriza el SHU. En este documento consideramos SHU atípico (SHUa) como el subtipo de SHU en el que los fenómenos de MAT son fundamentalmente consecuencia del daño producido en el endotelio de la microvasculatura renal y de otros órganos por desregulación de la actividad del sistema del complemento. En los últimos años se han identificado diversas mutaciones en genes del sistema del complemento asociados a SHUa, que explicarían aproximadamente el 60% de los casos de SHUa, y se han caracterizado funcionalmente numerosas mutaciones y polimorfismos asociados a SHUa que han permitido determinar que la patología se produce como consecuencia de la deficiente regulación de la activación del complemento sobre las superficies celulares y que lleva al daño endotelial mediado por la activación del C5 y de la vía terminal del complemento. Eculizumab es un anticuerpo monoclonal humanizado que inhibe la activación del C5, bloqueando la generación de la molécula proinflamatoria C5a y la formación del complejo de ataque de membrana. En estudios prospectivos en pacientes con SHUa su administración ha demostrado la interrupción rápida y sostenida del proceso de MAT, con una mejora significativa de la función renal a largo plazo y una reducción importante de la necesidad de diálisis y el cese de la terapia plasmática. En función de las evidencias científicas publicadas y la experiencia clínica acumulada, el Grupo Español de SHUa publicamos un documento de consenso con recomendaciones para el tratamiento de la enfermedad (Nefrología 2013;33(1):27-45). En la presente versión online del documento se actualizan los contenidos sobre la clasificación etiológica de las MAT, la fisiopatología del SHUa, su diagnóstico diferencial y su manejo terapéutico.

5. Genetics of HUS: the impact of MCP, CFH, and IF mutations on clinical presentation, response to treatment, and outcome.

Caprioli J, Noris M, Brioschi S et al.

Blood. 2006 Aug 15;108(4):1267-79.

ABSTRACT

Hemolytic uremic syndrome (HUS) is a thrombotic microangiopathy with manifestations of hemolytic anemia, thrombocytopenia, and renal impairment. Genetic studies have shown that mutations in complement regulatory proteins predispose to non-Shiga toxin-associated HUS (non-Stx-HUS). We undertook genetic analysis on membrane cofactor protein (MCP), complement factor H (CFH), and factor I (IF) in 156 patients with non-Stx-HUS. Fourteen, 11, and 5 new mutational events were found in MCP, CFH, and IF, respectively. Mutation frequencies were 12.8%, 30.1%, and 4.5% for MCP, CFH, and IF, respectively. MCP mutations resulted in either reduced protein expression or impaired C3b binding capability. MCP-mutated patients had a better prognosis than CFH-mutated and nonmutated patients. In MCP-mutated patients, plasma treatment did not impact the outcome significantly: remission was achieved in around 90% of both plasma-treated and plasma-untreated acute episodes. Kidney transplantation outcome was favorable in patients with MCP mutations, whereas the outcome was poor in patients with CFH and IF mutations due to disease recurrence. This study documents that the presentation, the response to therapy, and the outcome of the disease are influenced by the genotype. Hopefully this will translate into improved management and therapy of patients and will provide the way to design tailored treatments.

6. Genetics and Outcome of Atypical Hemolytic Uremic Syndrome: A Nationwide French Series Comparing Children and Adults.

Fremeaux-Bacchi V, Fakhouri F, Garnier A et al.

Clin J Am Soc Nephrol 8: 554–562, 2013.

ABSTRACT

Background and objectives: Atypical hemolytic uremic syndrome (aHUS) is a rare complement-mediated kidney disease that was first recognized in children but also affects adults. This study assessed the disease presentation and outcome in a nationwide cohort of patients with aHUS according to the age at onset and the underlying complement abnormalities.

Design, setting, participants, &measurements: A total of 214 patients with aHUS were enrolled between 2000 and 2008 and screened for mutations in the six susceptibility factors for aHUS and for anti–factor H antibodies.

Results: Onset of aHUS occurred as frequently during adulthood (58.4%) as during childhood (41.6%). The percentages of patients who developed the disease were 23%, 40%, 70%, and 98% by age 2, 18, 40, and 60 years, respectively. Mortality was higher in children than in adults (6.7% versus 0.8% at 1 year) (P=0.02), but progression to ESRD after the first aHUS episode was more frequent in adults (46% versus 16%; P,0.001).

Sixty-one percent of patients had mutations in their complement genes. The renal outcome was not significantly different in adults regardless of genetic background. Only membrane cofactor protein (MCP) and undetermined aHUS were less severe in children than adults. The frequency of relapse after 1 year was 92% in children with MCP-associated HUS and approximately 30% in all other subgroups.

Conclusion: Mortality ratewas higher in children than adults with aHUS, but renal prognosis wasworse in adults than children. In children, the prognosis strongly depends on the genetic background.

7. Outcomes of Kidney Transplant Patients with Atypical Hemolytic Uremic Syndrome Treated with Eculizumab: A Systematic Review and Meta-Analysis

González Suárez ML, Thongprayoon Ch, Mao MA et al.
J. Clin. Med. 2019, 8, 919; doi:10.3390/jcm8070919

ABSTRACT

Background: Kidney transplantation in patients with atypical hemolytic uremic syndrome (aHUS) is frequently complicated by recurrence, resulting in thrombotic microangiopathy in the renal allograft and graft loss. We aimed to assess the use of eculizumab in the prevention and treatment of aHUS recurrence after kidney transplantation.

Methods: Databases (MEDLINE, EMBASE and Cochrane Database) were searched through February 2019. Studies that reported outcomes of adult kidney transplant recipients with aHUS treated with eculizumab were included. Estimated incidence rates from the individual studies were extracted and combined using random-effects, generic inverse variance method of DerSimonian and Laird. Protocol for this systematic review has been registered with PROSPERO (International Prospective Register of Systematic Reviews; no. CRD42018089438).

Results: Eighteen studies (13 cohort studies and five case series) consisting of 380 adult kidney transplant patients with aHUS who received eculizumab for prevention and treatment of post-transplant aHUS recurrence were included in the analysis. Among patients who received prophylactic eculizumab, the pooled estimated incidence rates of recurrent thrombotic microangiopathy (TMA) after transplantation and allograft loss due to TMA were 6.3% (95%CI: 2.8–13.4%, I^2 = 0%) and 5.5% (95%CI: 2.9–10.0%, I^2 = 0%), respectively. Among those who received eculizumab for treatment of post-transplant aHUS recurrence, the pooled estimated rates of allograft loss due to TMA was 22.5% (95%CI: 13.6–34.8%, I^2 = 6%). When the meta-analysis was restricted to only cohort studies with data on genetic mutations associated with aHUS, the pooled estimated incidence of allograft loss due to TMA was 22.6% (95%CI: 13.2–36.0%, I^2 = 10%). We found no significant publication bias assessed by the funnel plots and Egger's regression asymmetry test ($p > 0.05$ for all analyses).

Conclusions: This study summarizes the outcomes observed with use of eculizumab for prevention and treatment of aHUS recurrence in kidney transplantation. Our results suggest a possible role for anti-C5 antibody therapy in the prevention and management of recurrent aHUS.

8. Atypical Hemolytic Uremic Syndrome and C3 Glomerulopathy: Conclusions From a "Kidney Disease: Improving Global Outcomes" (KDIGO) Controversies Conference

Goodship THJ, Terence Cook H, Fakhouri F et al.
Kidney Int. 2017 Mar;91(3):539-551.

ABSTRACT

In both atypical hemolytic uremic syndrome (aHUS) and C3 glomerulopathy (C3G) complement plays a primary role in disease pathogenesis. Herein we report the outcome of a 2015 Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference where key issues in the management of these 2 diseases were considered by a global panel of experts. Areas addressed included renal pathology, clinical phenotype and assessment, genetic drivers of disease, acquired drivers of disease, and treatment strategies. In order to help guide clinicians who are caring for such patients, recommendations for best treatment strategies were discussed at length, providing the evidence base underpinning current treatment options. Knowledge gaps were identified and a prioritized research agenda was proposed to resolve outstanding controversial issues.

9. Absence of Thrombocytopaenia and/or Microangiopathic Haemolytic Anaemia Does Not Reliably Exclude Recurrence of Atypical Haemolytic Uraemic Syndrome After Kidney Transplantation.

Krishnan AR, Siva B, Chakera A et al.

Nephrology (Carlton). 2017 Feb;22 Suppl 1:28-31.

ABSTRACT

A 54-year-old man was diagnosed with atypical haemolytic uraemic syndrome (aHUS) with confirmed complement H mutation in 2012, requiring ongoing dialysis. He was commenced on eculizumab in 2014 once the pharmaceutical board approved this drug. After 4 months, he received a live unrelated donor renal transplant from his wife and continued eculizumab post-transplant. Three months later, there was a rise in his creatinine with no laboratory features of haemolysis and a kidney biopsy confirmed rejection, which was treated with increased immunosuppression. After completing 12 months of treatment with eculizumab, he opted for close monitoring rather than continuation with therapy. Five months post-cessation of the drug, there was a rise in creatinine, and once again, haematological parameters remained within reference range; however, his kidney biopsy showed features consistent with recurrence of aHUS; hence, eculizumab was recommenced with good effect. While there was no evidence of haemolysis, there was a gradual rise in LDH level and a drop in platelet count, although the parameters remained within the normal range. This suggests that aHUS can recur in the allograft in the absence of haematological abnormalities. Clinicians should have a low threshold for allograft biopsy if haematological parameters are not just outside the reference range, but possibly also if there are changes of at least >25% from baseline in platelet count and LDH levels, particularly in those patients who are no longer eligible for eculizumab.

10. Outcomes of Patients With Atypical Haemolytic Uraemic Syndrome With Native and Transplanted Kidneys Treated With Eculizumab: A Pooled Post Hoc Analysis

Legendre CM, Campistol JM, Feldkamp T et al.

Transpl Int. 2017 Dec;30(12):1275-1283.

ABSTRACT

Atypical haemolytic uraemic syndrome (aHUS) often leads to end-stage renal disease (ESRD) and kidney transplantation; graft loss rates are high due to disease recurrence. A post hoc analysis of four prospective clinical trials in aHUS was performed to evaluate eculizumab, a terminal complement inhibitor, in patients with native or transplanted kidneys. The trials included 26-week treatment and extension periods. Dialysis, transplant and graft loss were evaluated. Study endpoints included complete thrombotic microangiopathy (TMA) response, TMA event-free status, haematologic and renal parameters and adverse events. Of 100 patients, 74 had native kidneys and 26 in the transplant subgroup had a collective history of 38 grafts. No patients lost grafts and only one with pre-existing ESRD received a transplant on treatment. Efficacy endpoints were achieved similarly in both subgroups. After 26 weeks, mean absolute estimated glomerular filtration rate increased from baseline to 61 and 37 ml/min/1.73 m^2 in native ($n = 71$; $P < 0.0001$) and transplanted kidney ($n = 25$; $P = 0.0092$) subgroups. Two patients (one/subgroup) developed meningococcal infections; both recovered, one continued therapy. Eculizumab was well tolerated. Eculizumab improved haematologic and renal outcomes in both subgroups. In patients with histories of multiple graft losses, eculizumab protected kidney function.

11. Complement Genes Strongly Predict Recurrence and Graft Outcome in Adult Renal Transplant Recipients With Atypical Hemolytic and Uremic Syndrome.
Le Quintrec M, Zuber J, Moulin B et al.
Am J Transplant. 2013 Mar;13(3):663-75.

ABSTRACT
Atypical hemolytic and uremic syndrome (aHUS) is a severe disease strongly associated with genetic abnormalities in the complement alternative pathway. In renal posttransplantation, few data are available on recurrence risk and graft outcome according to genetic background in aHUS patients. The aim of this study was to identify risk factors for recurrence and transplant outcome and, in particular, the role of complement gene abnormalities. We retrospectively studied 57 aHUS patients who had received 71 renal transplants. A mutation in complement gene was identified in 39 (68%), in factor H (CFH), factor I (CFI), membrane cofactor-protein (MCP), C3 and factor B (CFB). At 5 years, death-censored graft survival was 51%. Disease recurrence was associated with graft loss ($p = 0.001$). Mutations in complement genes were associated with higher risk of recurrence ($p = 0.009$). Patients with CFH or gain of function (C3, CFB) mutations had a highest risk of recurrence. M-TOR inhibitor was associated with significant risk of recurrence ($p = 0.043$) but not calcineurin inhibitor immunosuppressive treatment ($p = 0.29$). Preemptive plasmatherapy was associated with a trend to decrease recurrence ($p = 0.07$). Our study highlights that characterization of complement genetic abnormalities predicts the risk of recurrence-related graft loss and paves the way for future genetically based individualized prophylactic therapeutic strategies.

12. Eculizumab use in kidney transplantation
Johnson CK, Leca N.
Curr Opin Organ Transplant. 2015 Dec;20(6):643-51.

ABSTRACT

Purpose of review: Eculizumab suppresses the effector functions of the complement system and represents a therapeutic breakthrough for patients with paroxysmal nocturnal hemoglobinuria or atypical hemolytic uremic syndrome (aHUS). Safety monitoring is ongoing; so far, most notable is the expected increase in infection risk with encapsulated organisms. Despite potential applicability in multiple complement-mediated disorders, the off-label use of eculizumab has been limited, mainly by its prohibitive cost. The purpose of this review is to summarize the current data relevant to the use of eculizumab in kidney transplantation.
Recent findings: In aHUS, prone to high rates of recurrence and allograft loss, eculizumab has made the most notable therapeutic impact. Further clarification of complement defects may help predict therapeutic responses and hopefully guide treatment duration. In C3 glomerulopathies, the clinical response to eculizumab appears more heterogeneous and less effective in processes mediated by upstream to C5 complement deregulation. A large clinical trial of eculizumab for prevention of delayed graft function is ongoing. In antibody-mediated rejection, the role of eculizumab is unclear as its use has been limited to very complex, mostly presensitized, patients in mixed combinations of therapeutic modalities.
Summary: Overall, eculizumab has raised awareness of complement-mediated disorders as an exciting, new therapeutic option with multiple potential applications in kidney transplantation. Further research is needed to develop a better understanding of eculizumab applicability, efficacy, and treatment monitoring and beyond, to future therapeutic tools targeting the complement.

13. Hemolytic Uremic Syndrome and Kidney Transplantation: A Case Series and Review of the Literature.

Manani SM, Virzì GM, Giuliani A et al.

Nephron. 2017;136(3):245-253.

ABSTRACT
Background: Hemolytic uremic syndrome (HUS) can be triggered by Shiga toxin producing Escherichia coli (STEC) infection or it can be defined as atypical HUS (aHUS) if it is related to uncontrolled complement activation. aHUS is characterized by a high incidence of recurrence after kidney transplantation, and it can also occur de novo in transplant recipients. Eculizumab is used both to prevent and to treat aHUS following kidney transplantation. In this paper, we report our centre experience and we present 4 cases of HUS in patients who underwent kidney transplantation.
Methods: This is a single-center experience about HUS development in transplanted patients.
Results: Patient 1 with end-stage renal disease (ESRD) due to STEC-HUS undergoing kidney transplantation without prophylactic therapy with eculizumab. Patient 2 with HUS secondary to an episode of diarrhea at 8 years old. After a slow progression to ESRD, she underwent kidney transplantation and she received prophylactic therapy with eculizumab due to the presence of anti-complement factor H antibodies. Patient 3 underwent pre-emptive living donor ABO-incompatible kidney transplantation and developed HUS secondary to antibody-mediated rejection. Patient 4 developed de novo HUS 16 years after kidney transplantation without a known cause.
Conclusion: The correct diagnosis of HUS and the identification of the complement component alterations in case of aHUS are important parameters required to predict the risk of post-transplant recurrence of the disease. In the cases we reported, eculizumab has been found to be effective both to prevent and to treat aHUS following kidney transplantation.

14. Managing and Preventing Atypical Hemolytic Uremic Syndrome Recurrence After Kidney Transplantation.

Noris M, Remuzzi G.

Curr Opin Nephrol Hypertens. 2013 Nov;22(6):704-12.

ABSTRACT

Purpose of review: Several genetic and acquired abnormalities leading to abnormal activation of the alternative pathway of complement have been identified in patients with atypical hemolytic uremic syndrome (aHUS). The purpose of this review is to shed light on how advances in the understanding of aHUS pathogenesis have impacted on prevention and cure of aHUS recurrence after kidney transplantation.

Recent findings: Studies over the past decade have shown that the risk of posttransplant recurrence of aHUS depends on the underlying genetic abnormality. The risk is high in patients with mutations in genes encoding circulating complement proteins and regulators, whereas patients with mutations in membrane cofactor protein generally show good transplant outcome. Given the poor outcome associated with recurrence, isolated renal transplantation had been contraindicated in aHUS patients. Combined kidney-liver transplantation and prophylactic plasma exchange have been used to prevent posttransplant recurrences. More recent data have provided evidence about the efficacy of the anti-C5 monoclonal antibody eculizumab in the prevention and treatment of posttransplant aHUS recurrences.

Summary: This review summarizes recent advances on preventing and managing aHUS recurrence after kidney transplantation and discusses the issues that still need clarification.

15. Differential Impact of Complement Mutations on Clinical Characteristics in Atypical Hemolytic Uremic Syndrome.

Sellier-Leclerc A-L, Fremeaux-Bacchi V, Dragon-Durey M-A et al.

J Am Soc Nephrol. 2007 Aug;18(8):2392-400.

ABSTRACT

Mutations in factor H (CFH), factor I (IF), and membrane cofactor protein (MCP) genes have been described as risk factors for atypical hemolytic uremic syndrome (aHUS). This study analyzed the impact of complement mutations on the outcome of 46 children with aHUS. A total of 52% of patients had mutations in one or two of known susceptibility factors (22, 13, and 15% of patients with CFH, IF, or MCP mutations, respectively; 2% with CFH+IF mutations). Age <3 mo at onset seems to be characteristic of CFH and IF mutation-associated aHUS. The most severe prognosis was in the CFH mutation group, 60% of whom reached ESRD or died within <1 yr. Only 30% of CFH mutations were localized in SCR20. MCP mutation-associated HUS has a relapsing course, but none of the children reached ESRD at 1 yr. Half of patients with IF mutation had a rapid evolution to ESRD, and half recovered. Plasmatherapy seemed to have a beneficial effect in one third of patients from all groups except for the MCP mutation group. Only eight (33%) of 24 kidney transplantations that were performed in 15 patients were successful. Graft failures were due to early graft thrombosis (50%) or HUS recurrence. In conclusion, outcome of HUS in patients with CFH mutation is catastrophic, and posttransplantation outcome is poor in all groups except for the MCP mutation group. New therapies are urgently needed, and further research should elucidate the unexplained HUS group.

16. Eculizumab Use for Kidney Transplantation in Patients With a Diagnosis of Atypical Hemolytic Uremic Syndrome.

Siedlecki AM, Isbel N, Walle JV et al.

Kidney Int Rep. 2018 Dec 3;4(3):434-446.

ABSTRACT

Introduction: Recurrence of atypical hemolytic uremic syndrome (aHUS) in renal allografts is common, leading to dialysis and graft failure. Pretransplant versus posttransplant initiation of eculizumab treatment in patients with aHUS has not been rigorously investigated. We hypothesized eculizumab pretransplant would reduce dialysis incidence posttransplant.

Methods: Of patients enrolled in the Global aHUS Registry (n = 1549), 344 had ≥1 kidney transplant. Of these, 188 had received eculizumab. Eighty-eight patients (47%) were diagnosed with aHUS and received eculizumab before, and during, their most recent transplant (group 1). A total of 100 patients (53%; group 2) initiated eculizumab posttransplantation. This second group was subdivided into those diagnosed with aHUS before (n = 52; group 2a) or after (n = 48; group 2b) their most recent transplant.

Results: Within 5 years of transplantation, 47 patients required dialysis; the risk of dialysis after transplantation was significantly increased in group 2b (hazard ratio [HR] 4.6; confidence interval [CI] 1.7-12.4) but not 2a (HR 2.3; CI 0.9-6.2). Graft function within 6 months of transplantation was significantly better in group 1 (median estimated glomerular filtration rate of 60.6 ml/min per 1.73 m^2) compared with 31.5 and 9.6 ml/min per 1.73 m^2 in groups 2a (P = 0.004) and 2b (P = 0.0001), respectively. One meningococcal infection (resolved with treatment) and 3 deaths (deemed unrelated to eculizumab) were reported.

Conclusions: Outcomes for transplant patients with aHUS treated with eculizumab were improved compared with previous reports of patients with aHUS not treated with eculizumab. Our findings suggest delayed aHUS diagnosis and therefore treatment is associated with an increased risk of dialysis posttransplantation and reduced allograft function.

17. Use of Eculizumab for Atypical Haemolytic Uraemic Syndrome and C3 Glomerulopathies.

Zuber J, Fakhouri F, Roumenina LT et al.

Nat Rev Nephrol. 2012 Nov;8(11):643-57.

ABSTRACT

In the past decade, a large body of evidence has accumulated in support of the critical role of dysregulation of the alternative complement pathway in atypical haemolytic uraemic syndrome (aHUS) and C3 glomerulopathies. These findings have paved the way for innovative therapeutic strategies based on complement blockade, and eculizumab, a monoclonal antibody targeting the human complement component 5, is now widely used to treat aHUS. In this article, we review 28 case reports and preliminary data from 37 patients enrolled in prospective trials of eculizumab treatment for episodes of aHUS involving either native or transplanted kidneys. Eculizumab may be considered as an optimal first-line therapy when the diagnosis of aHUS is unequivocal and this treatment has the potential to rescue renal function when administered early after onset of the disease. However, a number of important issues require further study, including the appropriate duration of treatment according to an individual's genetic background and medical history, the

optimal strategy to prevent post-transplantation recurrence of aHUS and a cost-efficacy analysis. Data regarding the efficacy of eculizumab in the control of C3 glomerulopathies are more limited and less clear, but several observations suggest that eculizumab may act on the most inflammatory forms of this disorder.

18. Eculizumab for Atypical Hemolytic Uremic Syndrome Recurrence in Renal Transplantation.
Zuber J, Le Quintrec M, Kird S et al.
Am J Transplant. 2012 Dec;12(12):3337-54.

ABSTRACT
Eculizumab (anti-C5) has been sporadically reported as an efficient therapy for atypical hemolytic uremic syndrome (aHUS). However, the lack of series precludes any firm conclusion about the optimal use of anti-C5 for preventing or treating aHUS posttransplant aHUS recurrence. We thoroughly studied 22 renal transplant recipients with aHUS who received off-label therapy with anti-C5, including 12 cases, which have not been reported yet. Nine patients, all carrying a complement genetic abnormality associated with a high risk of aHUS recurrence, received prophylactic anti-C5 therapy to prevent posttransplant recurrence. Eight of them had a successful recurrence-free posttransplant course and achieved a satisfactory graft function, while the remaining patient experienced early arterial thrombosis of the graft. Thirteen renal transplant recipients were given anti-C5 for posttransplant aHUS recurrence. A complete reversal of aHUS activity was obtained in all of them. Importantly, the delay of anti-C5 initiation after the onset of the aHUS episode inversely correlated with the degree of renal function improvement. Three patients in whom anti-C5 was subsequently stopped experienced a relapse. Altogether these data suggest that long-term eculizumab is highly effective for preventing and treating posttransplant aHUS recurrence. Our study also indicates that anti-C5 should be promptly started if a recurrence occurs.

19. New Insights Into Postrenal Transplant Hemolytic Uremic Syndrome.
Zuber J, Le Quintrec M, Sberro-Soussan R et al.
Nat Rev Nephrol. 2011 Jan;7(1):23-35

ABSTRACT
After renal transplantation, hemolytic uremic syndrome (HUS) may occur either as a recurrent or de novo form. Over the past decade, much effort has been devoted to elucidating the pathogenesis of atypical HUS (aHUS). Approximately 60-70% patients with aHUS have mutations in regulatory factors of the complement system or antibodies against complement factor H. The risk of post-transplant recurrence of aHUS depends on the genetic abnormality involved, and ranges from 15% to 20% in patients with mutations in the gene that encodes membrane cofactor protein and from 50% to 100% in patients with mutations in the genes that encode circulating regulators of complement. Given the poor outcomes associated with recurrence, isolated renal transplantation had been contraindicated in patients at high risk of aHUS recurrence. However, emerging therapies, including pre-emptive plasma therapy and anti-C5 component monoclonal antibody (eculizumab) treatment have provided promising results and should further limit indications for the risky

procedure of combined liver-kidney transplantation. Studies from the past 2 years have demonstrated genetic abnormalities in complement regulators in 30% of renal transplant recipients who experienced de novo HUS after renal transplantation. This finding suggests that the burden of endothelial injury in a post-transplantation setting may trigger de novo HUS in the presence of mild genetic susceptibility to HUS.

20. Targeted Strategies in the Prevention and Management of Atypical HUS Recurrence After Kidney Transplantation.

Zuber J, Le Quintrec M, Morris H et al.

Transplant Rev (Orlando). 2013 Oct;27(4):117-25.

ABSTRACT

Atypical hemolytic and uremic syndrome (aHUS) is associated with a high rate of recurrence and poor outcomes after kidney transplantation. Fortunately, recent advances in the understanding of the pathogenesis of aHUS have permitted an individualized risk assessment of post-transplant recurrence. Acquired or inherited dysregulation of the alternative complement pathway, thought to be the driving force of the disease, is identified in most aHUS patients. Notably, depending on the mutations involved, the risk of recurrence greatly varies, highlighting the importance of undertaking etiological investigations prior to kidney transplantation. In those with moderate to high risk of recurrence, the use of a prophylactic therapy, consisting in either plasmapheresis or eculizumab therapies, represents a major stride forward in the prevention of aHUS recurrence after kidney transplantation. In those who experience aHUS recurrence, a growing number of observations suggest that eculizumab therapy outperforms curative plasma therapy. The optimal duration of both prophylactic and curative therapies remains an important, yet unaddressed, issue. In this respect, the kidney transplant recipients, continuously exposed to endothelial-insulting factors, referred here as to triggers, might have a sustained high risk of recurrence. A global therapeutic approach should thus attempt to reduce exposure to these triggers.

21. Atypical Hemolytic Uremic Syndrome Recurrence After Kidney Transplantation

Matar D, Naqvi F, Racusen LC et al.

Transplantation. 2014 Dec 15;98(11):1205-12.

ABSTRACT

Background: Atypical hemolytic uremic syndrome (aHUS) is a rare disease with a high recurrence rate after kidney transplantation. In most cases, aHUS are caused by genetic mutations of components of the complement alternative pathway. In this single-center series, we present our data of 12 consecutive patients with aHUS and the outcome after kidney transplantation.

Methods: In this 10-year retrospective study, we identified 12 patients with aHUS who were managed in our center since 2003. We reviewed clinical data, including genetic testing, posttransplant course and response to therapy including the prophylactic use of eculizumab.

Results: Overall, eight patients are women. Six of our patients have at least one genetic mutation causing aHUS, including 4 with complement factor H mutations. Nine patients had at least one previous kidney transplant that failed secondary to recurrent aHUS (75% of our patients). Three

patients were treated with eculizumab and plasmapheresis for recurrent aHUS after kidney transplantation; two of them responded to the therapy. Four patients received prophylactic eculizumab; three of them received 6 months and one has been on life long therapy. No signs of recurrence have been observed in these 4 patients so far.
Conclusion: Genetic mutations of the complement alternative pathway were confirmed in half of our patients, most of those mutations are in CHF. We demonstrate that treatment or prophylaxis with eculizumab was effective in reversing or preventing aHUS whether or not genetic complement mutations were identified.

22. Prevention and Treatment of Atypical Haemolytic Uremic Syndrome After Kidney Transplantation.
Okumi M, Tanabe K.
Nephrology (Carlton). 2016 Jul;21 Suppl 1:9-13.

ABSTRACT
Atypical haemolytic uraemic syndrome is a rare disorder characterized by an over-activated, dysregulated alternative complement pathway due to genetic mutation and environmental triggers. Atypical haemolytic uraemic syndrome is a serious, life-threatening disease characterized by thrombotic microangiopathy, which causes haemolytic anaemia, thrombocytopaenia, and acute renal failure. Since recurrences of atypical haemolytic uraemic syndrome frequently lead to end-stage kidney disease even in renal allografts, kidney transplantation for patients with end-stage kidney disease secondary to atypical haemolytic uraemic syndrome has long been contraindicated. However, over the past several years, advancements in the management of atypical haemolytic uraemic syndrome have allowed successful kidney transplantation in these patients. The key factor of this success is eculizumab, a humanized anti-C5 monoclonal antibody, which inhibits terminal membrane-attack complex formation and thrombotic microangiopathy progression. In the setting of kidney transplantation, there are different possible triggers of post-transplant atypical haemolytic uraemic syndrome recurrence, such as brain-death related injury, ischaemia-reperfusion injury, infections, the use of immunosuppressive drugs, and rejection. Principal strategies are to prevent endothelial damage that could potentially activate alternative complement pathway activation and subsequently lead to atypical haemolytic uraemic syndrome recurrence in kidney allograft. Published data shows that prophylactic eculizumab therapy is highly effective for the prevention of post-transplant atypical haemolytic uraemic syndrome recurrence, and prompt treatment with eculizumab as soon as recurrence is diagnosed is important to maintain renal allograft function. Further study to determine the optimal dosing and duration of prophylactic therapy and treatment of post-transplant atypical haemolytic uraemic syndrome recurrence is needed.

23. Renal Transplant Immunosuppression in Patients With Hemolytic Uremic Syndrome: Four Case Reports.
Galindo P, Ramirez M, Pérez Marfil A et al.
Transplant Proc. 2018 Mar;50(2):572-574.

ABSTRACT

A high rate of recurrence has been described in atypical hemolytic uremic syndrome renal transplant recipients, favored by certain immunosuppressant drugs that can induce complement activation. We present four case series in which three patients were diagnosed pretransplantation and a fourth who had onset in the very early post-transplantation period. The patients received different immunosuppression schedules, and all had improvement after more than 2-years. We suggest the need to stratify the risk of atypical hemolytic uremic syndrome recurrence using genetic studies and the available drugs as the main factors that allow graft survival improvement today.

24. The Risk of Recurrence of Hemolytic Uremic Syndrome After Renal Transplantation in Children.
Loirat C, Niaudet P.
Pediatr Nephrol. 2003 Nov;18(11):1095-101.

ABSTRACT
We reviewed the literature to analyze the risk of recurrence of hemolytic uremic syndrome (HUS) after renal transplantation in children. Among 118 children transplanted after post-diarrheal (D+) HUS, 1 (0.8%) had recurrence with graft loss. Among 63 children transplanted after HUS not associated with a prodrome of diarrhea (D-) of unknown mechanism, 13 (21%) had recurrence with graft loss. Of 11 patients with HUS associated with factor H deficiency who were transplanted, 5 lost the graft because of recurrence. Of 7 patients with HUS associated with normal factor H concentration but mutations in factor H gene who were transplanted, probably 2 had recurrence. Three patients with HUS associated with low serum C3, but no factor H deficiency or mutation lost their graft because of recurrence. The risk of recurrence in the autosomal recessive forms of HUS of unknown mechanism is not documented in children, but is around 60% in adults. A similar risk has been reported in the autosomal dominant forms. The only transplant patient with a constitutional deficiency of von Willebrand factor-cleaving protease had recurrence. Further efforts to document the post-transplant course of patients with D- HUS and progress in the understanding of the mechanisms and genetics of the disease are needed to allow more accurate prediction of the recurrence risk and to define therapeutic approaches.

B. RECIDIVA DE HUS EN CASOS SIN IDENTIFICACIÓN CONOCIDA DE ALTERACIÓN EN LA REGULACIÓN DEL COMPLEMENTO

25. Complement Genes Strongly Predict Recurrence and Graft Outcome in Adult Renal Transplant Recipients With Atypical Hemolytic and Uremic Syndrome.
Le Quintrec M, Zuber J, Moulin B et al.
Am J Transplant. 2013 Mar;13(3):663-75.

ABSTRACT
Atypical hemolytic and uremic syndrome (aHUS) is a severe disease strongly associated with genetic abnormalities in the complement alternative pathway. In renal posttransplantation, few data are available on recurrence risk and graft outcome according to genetic background in aHUS patients.

The aim of this study was to identify risk factors for recurrence and transplant outcome and, in particular, the role of complement gene abnormalities. We retrospectively studied 57 aHUS patients who had received 71 renal transplants. A mutation in complement gene was identified in 39 (68%), in factor H (CFH), factor I (CFI), membrane cofactor-protein (MCP), C3 and factor B (CFB). At 5 years, death-censored graft survival was 51%. Disease recurrence was associated with graft loss (p = 0.001). Mutations in complement genes were associated with higher risk of recurrence (p = 0.009). Patients with CFH or gain of function (C3, CFB) mutations had a highest risk of recurrence. M-TOR inhibitor was associated with significant risk of recurrence (p = 0.043) but not calcineurin inhibitor immunosuppressive treatment (p = 0.29). Preemptive plasmatherapy was associated with a trend to decrease recurrence (p = 0.07). Our study highlights that characterization of complement genetic abnormalities predicts the risk of recurrence-related graft loss and paves the way for future genetically based individualized prophylactic therapeutic strategies.

26. Atypical Hemolytic Uremic Syndrome Recurrence After Kidney Transplantation.
Matar D, Naqvi F, Racusen LC et al.
Transplantation. 2014 Dec 15;98(11):1205-12.

ABSTRACT

Background: Atypical hemolytic uremic syndrome (aHUS) is a rare disease with a high recurrence rate after kidney transplantation. In most cases, aHUS are caused by genetic mutations of components of the complement alternative pathway. In this single-center series, we present our data of 12 consecutive patients with aHUS and the outcome after kidney transplantation.
Methods: In this 10-year retrospective study, we identified 12 patients with aHUS who were managed in our center since 2003. We reviewed clinical data, including genetic testing, posttransplant course and response to therapy including the prophylactic use of eculizumab.
Results: Overall, eight patients are women. Six of our patients have at least one genetic mutation causing aHUS, including 4 with complement factor H mutations. Nine patients had at least one previous kidney transplant that failed secondary to recurrent aHUS (75% of our patients). Three patients were treated with eculizumab and plasmapheresis for recurrent aHUS after kidney transplantation; two of them responded to the therapy. Four patients received prophylactic eculizumab; three of them received 6 months and one has been on life long therapy. No signs of recurrence have been observed in these 4 patients so far.
Conclusion: Genetic mutations of the complement alternative pathway were confirmed in half of our patients, most of those mutations are in CHF. We demonstrate that treatment or prophylaxis with eculizumab was effective in reversing or preventing aHUS whether or not genetic complement mutations were identified.

27. Outcomes of Kidney Transplant Patients With Atypical Hemolytic Uremic Syndrome Treated With Eculizumab: A Systematic Review and Meta-Analysis.
Gonzalez Suarez ML, Thongprayoon C, Mao MA et al.
J Clin Med. 2019 Jun 27;8(7):919.

ABSTRACT

Background: Kidney transplantation in patients with atypical hemolytic uremic syndrome (aHUS) is frequently complicated by recurrence, resulting in thrombotic microangiopathy in the renal allograft and graft loss. We aimed to assess the use of eculizumab in the prevention and treatment of aHUS recurrence after kidney transplantation.
Methods: Databases (MEDLINE, EMBASE and Cochrane Database) were searched through February 2019. Studies that reported outcomes of adult kidney transplant recipients with aHUS treated with eculizumab were included. Estimated incidence rates from the individual studies were extracted and combined using random-effects, generic inverse variance method of DerSimonian and Laird. Protocol for this systematic review has been registered with PROSPERO (International Prospective Register of Systematic Reviews; no. CRD42018089438).
Results: Eighteen studies (13 cohort studies and five case series) consisting of 380 adult kidney transplant patients with aHUS who received eculizumab for prevention and treatment of post-transplant aHUS recurrence were included in the analysis. Among patients who received prophylactic eculizumab, the pooled estimated incidence rates of recurrent thrombotic microangiopathy (TMA) after transplantation and allograft loss due to TMA were 6.3% (95%CI: 2.8-13.4%, I2 = 0%) and 5.5% (95%CI: 2.9-10.0%, I2 = 0%), respectively. Among those who received eculizumab for treatment of post-transplant aHUS recurrence, the pooled estimated rates of allograft loss due to TMA was 22.5% (95%CI: 13.6-34.8%, I2 = 6%). When the meta-analysis was restricted to only cohort studies with data on genetic mutations associated with aHUS, the pooled estimated incidence of allograft loss due to TMA was 22.6% (95%CI: 13.2-36.0%, I2 = 10%). We found no significant publication bias assessed by the funnel plots and Egger's regression asymmetry test ($p > 0.05$ for all analyses).
Conclusions: This study summarizes the outcomes observed with use of eculizumab for prevention and treatment of aHUS recurrence in kidney transplantation. Our results suggest a possible role for anti-C5 antibody therapy in the prevention and management of recurrent aHUS.

28. Ten-year Outcome of Eculizumab in Kidney Transplant Recipients With Atypical Hemolytic Uremic Syndrome- A Single Center Experience.

Kant S, Bhalla A, Alasfar S et al.

BMC Nephrol. 2020 May 20;21(1):189.

ABSTRACT

Background: Atypical hemolytic uremic syndrome (aHUS) can result in severe kidney dysfunction, secondary to thrombotic microangiopathy. Eculizumab has been used to treat this disorder, and has resulted in favourable outcomes in both, native and transplanted kidneys. There is limited long term follow up data in kidney transplant recipients (KTRs) who received prevention and treatment with Eculizumab. We report our long term follow up data from our center to address safety and efficacy of this therapy in KTRs.
Methods: We performed a retrospective analysis of KTRs between January 2009 and December 2018. Clinical diagnosis of aHUS established with presence of thrombotic microangiopathy, acute kidney injury, absence of alternate identifiable etiology. We reviewed clinical data, including genetic testing for complement factor mutations, post-transplant course, and response to therapy including therapeutic and prophylactic use of eculizumab.

Results: Nineteen patients with aHUS received a total of 36 kidney transplants; 10 of them had 2 or more prior kidney transplants. Median age at time of last transplant was 37 years (range 27-59), 72% were female (n = 14), 78% Caucasian (n = 15), with 61% had live donor transplant (n = 12) as the last transplant. Eculizumab prophylaxis was given to 10/19 (56%) at the time of transplantation, with no aHUS recurrence during the follow up. Median duration of follow up was 46 (range 6-237) months. Mean estimated glomerular filtration rate (eGFR) at the time of last follow up was 59.5 ml/min/m^2. No infections secondary to encapsulated organisms or other major infectious complications occurred during the follow up.
Conclusions: Eculizumab prophylaxis is safe and effective in KTRs with aHUS. Long term follow up demonstrates that it may be possible to discontinue prophylaxis carefully in selected patients with no evidence of complement mutations.

C. ¿EN LA APARICIÓN DE NOVO EN UN TRASPLANTE RENAL DE UN SÍNDROME HEMOLÍTICO URÉMICO EN UN TRASPLANTE RENAL HACE NECESARIO ESTUDIO DE FACTORES REGULADORES DEL COMPLEMENTO?

29. De Novo Thrombotic Microangiopathy After Kidney Transplantation
Garg N, Rennke HG, Pavlakis M et al.
Transplant Rev (Orlando). 2018 Jan;32(1):58-68.

ABSTRACT
Thrombotic microangiopathy (TMA) is a serious complication of transplantation that adversely affects kidney transplant recipient and allograft survival. Post-transplant TMA is usually classified into two categories: 1) recurrent TMA and 2) de novo TMA. Atypical hemolytic uremic syndrome (aHUS) resulting from dysregulation and over-activation of the alternate complement pathway is a rare disease but the most common diagnosis associated with recurrence in the allografts. De novo TMA, on the other hand, represents an overwhelming majority of the cases of post-transplant TMA and is a substantially more heterogeneous entity than recurrent aHUS. Here, we review the etio-pathogenesis, diagnosis and treatment options for de novo post-transplant TMA. It is usually in the setting of calcineurin inhibitor use, mammalian target of rapamycin inhibitor use, or antibody mediated rejection; recently genetic mutations in complement regulatory genes for Factor H and Factor I similar to those described in aHUS have been reported in up to a third of these patients. Systemic signs of TMA are frequently absent, and a renal allograft biopsy is often needed to establish the diagnosis. Although withdrawal of the offending agents is usually the first line of treatment and resolution of laboratory abnormalities has been documented with this approach in several case reports and case series, available retrospective data demonstrate lack of benefit in long-term graft outcomes. Co-stimulation blockage with belatacept provides an effective alternate immunosuppressive strategy for these patients. Anti-complement therapy with eculizumab is effective in some cases; further work is required to define which patients with TMA (with and without concomitant antibody-mediated rejection) would benefit from receiving this treatment, and what biomarkers can be used to identify them.

30. Malignant Hypertension: Diagnosis, Treatment and Prognosis With Experience From the Bordeaux Cohort

Rubin S, Cremer A, Boulestreau R et al.

J Hypertens. 2019 Feb;37(2):316-324.

ABSTRACT

Background: Malignant hypertension, the most severe form of hypertension, is defined by high blood pressure and acute ischemic organ damage. It has a worse prognosis than other forms of hypertension, especially in black patients. New tools to assess organ damage, especially that of the heart and brain, are now available and may contribute to a better evaluation of these patients. This report improves knowledge of the characteristics of involved organs to facilitate diagnosis and to evaluate the effectiveness of our treatment protocol.

Method: The Bordeaux registry, started in 1995, recruited 168 patients. In addition to evaluations of their eyes and kidneys, these patients had a systematic evaluation of their hearts with ECG and echocardiography and, since 2007, a systematic brain MRI. Blood pressure was lowered with a protocol based on blockers of the renin-angiotensin system started at a very low-dose with forced titration over 48 h. Only an oral route was used for antihypertensive medication.

Results: Systematic MRIs found significant brain damage in 93% of patients. Heart involvement was highly prevalent: 82% had left ventricular mass more than 60 g/m, and 56% had systolic dysfunction (estimated by global longitudinal strain). Renal involvement and thrombotic microangiopathy were respectively present in 55 and 15% of patients. Median follow-up was 48 months. Renal survival at 5 years was 90.8%, similar to other studies.

Conclusion: Malignant hypertension is a systemic disease causing severe damage to the brain, heart, kidneys and eyes, even in absence of symptoms. Renin-angiotensin system blockers seem to be the cornerstone of treatment.

31. Severe Hypertension With Renal Thrombotic Microangiopathy: What Happened to the Usual Suspect?

Van Laecke S, Van Biesen W.

Kidney Int. 2017 Jun;91(6):1271-1274.

ABSTRACT

Patients with atypical hemolytic uremic syndrome (aHUS) and malignant hypertension can both present with concomitant hypertension and thrombotic microangiopathy (TMA), rendering policy decisions complex. Timmermans et al. report that patients with severe hypertension and renal TMA might have unrecognized aHUS with underlying complement abnormalities. Based on this, they assert that all patients presenting with severe hypertension and renal TMA should be evaluated for aHUS. It remains uncertain whether this holds equally true for patients with malignant hypertension and renal TMA.

32. Eculizumab in Secondary Atypical Haemolytic Uraemic Syndrome

Cavero T, Rabasco C, López A et al.

Nephrol Dial Transplant. 2017 Mar 1;32(3):466-474.

ABSTRACT

Background: Complement dysregulation occurs in thrombotic microangiopathies (TMAs) other than primary atypical haemolytic uraemic syndrome (aHUS). A few of these patients have been reported previously to be successfully treated with eculizumab.

Methods: We identified 29 patients with so-called secondary aHUS who had received eculizumab at 11 Spanish nephrology centres. Primary outcome was TMA resolution, defined by a normalization of platelet count (>150 × 10 9 /L) and haemoglobin, disappearance of all the markers of microangiopathic haemolytic anaemia (MAHA), and improvement of renal function, with a ≥25% reduction of serum creatinine from the onset of eculizumab administration.

Results: Twenty-nine patients with secondary aHUS (15 drug-induced, 8 associated with systemic diseases, 2 with postpartum, 2 with cancer-related, 1 associated with acute humoral rejection and 1 with intestinal lymphangiectasia) were included in this study. The reason to initiate eculizumab treatment was worsening of renal function and persistence of TMA despite treatment of the TMA cause and plasmapheresis. All patients showed severe MAHA and renal function impairment (14 requiring dialysis) prior to eculizumab treatment and 11 presented severe extrarenal manifestations. A rapid resolution of the TMA was observed in 20 patients (68%), 15 of them showing a ≥50% serum creatinine reduction at the last follow-up. Comprehensive genetic and molecular studies in 22 patients identified complement pathogenic variants in only 2 patients. With these two exceptions, eculizumab was discontinued, after a median of 8 weeks of treatment, without the occurrence of aHUS relapses.

Conclusion: Short treatment with eculizumab can result in a rapid improvement of patients with secondary aHUS in whom TMA has persisted and renal function worsened despite treatment of the TMA-inducing condition.

33. Thrombotic Microangiopathy in Malignant Hypertension and Hemolytic Uremic Syndrome (HUS)/ Thrombotic Thrombocytopenic Purpura (TTP): Can We Differentiate One From the Other?

Shibagaki Y, Fujita T.

Hypertens Res. 2005 Jan;28(1):89-95.

ABSTRACT

Patients with malignant hypertension sometimes exhibit microangiopathic hemolytic anemia/thrombocytopenia known as thrombotic microangiopathy (TMA). On the other hand, severe hypertension is sometimes associated with hemolytic uremic syndrome (HUS)/thrombotic thrombocytopenic purpura (TTP). Because the clinical features of the two entities overlap significantly, it is sometimes difficult to distinguish one from the other. However, such differentiation is indispensable, since early performance of plasmapheresis is critical in HUS/TTP. It has been suggested that severe thrombocytopenia is one of the most useful differential points in diagnosing HUS/TTP from malignant hypertension caused by other etiologies. Early performance of plasmapheresis can be justified in the presence of both TMA and thrombocytopenia. However, thrombocytopenia can be seen in the cases with malignant hypertension from etiologies other than HUS/TTP, and in these particular cases, plasmapheresis is useless and can be harmful. Recently, the plasma level of ADAMTS13 (a disintegrin and metalloprotease domain, with thrombospondin type 1 motif 13), which is a von Willebrand Factor cleaving protease, has been shown to be very low in familial or some of the sporadic cases of TTP, and a low level of ADAMTS13 is very specific to TTP.

Some reports have shown that patients with a very low plasma level of ADAMTS13 respond very well to plasmapheresis. We recently experienced two cases with TMA. Although both of our patients had severe hypertension with TMA, different therapeutic strategies ameliorated their illness: symptomatic treatment was effective in case 1, which showed normal ADAMTS13 activity, whereas plasma infusion was necessary to save case 2, which showed low ADAMTS13 activity. Thus, patients with a low level of ADAMTS13 activity might respond well to plasmapheresis or plasma infusion. When presented with patients with severe hypertension and thrombotic microangiopathy, ADAMTS13 activity may prove to be a promising adjunctive tool in differentiating TTP from TMA due to other etiologies, but in the meantime, we should make the choice of whether or not to perform plasmapheresis based on the degree of thrombocytopenia.

34. Patients With Hypertension-Associated Thrombotic Microangiopathy May Present With Complement Abnormalities

Timmermans SAMEG, Abdul-Hamid MA, Vanderlocht J et al.

Kidney Int. 2017 Jun;91(6):1420-1425..

ABSTRACT

Thrombotic microangiopathy (TMA) is a pattern of endothelial damage that can be found in association with diverse clinical conditions such as malignant hypertension. Although the pathophysiological mechanisms differ, accumulating evidence links complement dysregulation to various TMA syndromes and in particular the atypical hemolytic uremic syndrome. Here, we evaluated the role of complement in nine consecutive patients with biopsy-proven renal TMA attributed to severe hypertension. Profound hematologic symptoms of TMA were uncommon. In six out of nine patients, we found mutations C3 in three, CFI in one, CD46 in one, and/or CFH in two patients either with or without the risk CFH-H3 haplotype in four patients. Elevated levels of the soluble C5b-9 and renal deposits of C3c and C5b-9 along the vasculature and/or glomerular capillary wall, confirmed complement activation in vivo. In contrast to patients without genetic defects, patients with complement defects invariably progressed to end-stage renal disease, and disease recurrence after kidney transplantation seems common. Thus, a subset of patients with hypertension-associated TMA falls within the spectrum of complement-mediated TMA, the prognosis of which is poor. Hence, testing for genetic complement abnormalities is warranted in patients with severe hypertension and TMA on renal biopsy to adopt suitable treatment options and prophylactic measures.

35. Hemolytic Uremic Syndrome in Pregnancy and Postpartum

Bruel A, Kavanagh D, Noris M et al.

Clin J Am Soc Nephrol. 2017 Aug 7;12(8):1237-1247.

ABSTRACT

Background: Pregnancy is associated with various forms of thrombotic microangiopathy, including hemolytic uremic syndrome. A previous small French study suggested that pregnancy-associated hemolytic uremic syndrome was to be included in the spectrum of atypical hemolytic uremic syndrome linked to complement alternative pathway dysregulation.

Design, setting, participants, & measurements: We sought to retrospectively analyze the presentation, outcome, and frequency of complement alternative pathway gene variants in a larger international (France, United Kingdom, Italy) cohort of patients with pregnancy-associated hemolytic uremic syndrome.
Results: Eighty-seven patients with pregnancy-associated hemolytic uremic syndrome were included. Hemolytic uremic syndrome occurred mainly during the first pregnancy (58%) and in the postpartum period (76%). At diagnosis, 56 (71%) patients required dialysis. Fifty-six (78%) patients underwent plasma exchanges, 21 (41%) received plasma infusions, and four (5%) received eculizumab. During follow-up (mean duration of 7.2 years), 41 (53%) patients reached ESRD, 15 (19%) had CKD, and 18 (28%) patients experienced hemolytic uremic syndrome relapse. Twenty-four patients (27%) received a kidney transplant and a recurrence of hemolytic uremic syndrome occurred in 13 (54%) patients. Variants in complement genes were detected in 49 (56%) patients, mainly in the CFH (30%) and CFI genes (9%).
Conclusions: Pregnancy-associated hemolytic uremic syndrome and atypical hemolytic uremic syndrome nonrelated to pregnancy have the same severity at onset and during follow-up and the same frequency of complement gene variants.

36. A Retrospective Study of Pregnancy-Associated Atypical Hemolytic Uremic Syndrome
Huerta A, Arjona E, Portoles J et al.
Kidney Int. 2018 Feb;93(2):450-459.

ABSTRACT
Pregnancy-associated atypical hemolytic uremic syndrome (aHUS) refers to the thrombotic microangiopathy resulting from uncontrolled complement activation during pregnancy or the postpartum period. Pregnancy-associated aHUS is a devastating disease for which there is a limited clinical understanding and treatment experience. Here we report a retrospective study to analyze the clinical and prognostic data of 22 cases of pregnancy-associated aHUS from the Spanish aHUS Registry under different treatments. Sixteen patients presented during the first pregnancy and as many as nine patients required hemodialysis at diagnosis. Identification of inherited complement abnormalities explained nine of the 22 cases, with CFH mutations and CFH to CFHR1 gene conversion events being the most prevalent genetic alterations associated with this disorder (66%). In thirteen of the cases, pregnancy complications were sufficient to trigger a thrombotic microangiopathy in the absence of genetic or acquired complement alterations. The postpartum period was the time with highest risk to develop the disease and the group shows an association of cesarean section with pregnancy-associated aHUS. Seventeen patients underwent plasma treatments with a positive renal response in only three cases. In contrast, ten patients received eculizumab with an excellent renal response in all, independent of carrying or not inherited complement abnormalities. Although the cohort is relatively small, the data suggest that pregnancy-associated aHUS is not different from other types of aHUS and suggest the efficacy of eculizumab treatment over plasma therapies. This study may be useful to improve prognosis in this group of aHUS patients.

37. Pregnancy-associated Hemolytic Uremic Syndrome Revisited in the Era of Complement Gene Mutations

Fakhouri F, Roumenina L, Provot F et al.
J Am Soc Nephrol. 2010 May;21(5):859-67.

ABSTRACT
In contrast to pregnancy-associated thrombotic thrombocytopenic purpura, the pathogenesis and presentation of pregnancy-associated atypical hemolytic uremic syndrome (P-aHUS) remain ill-defined. We conducted a retrospective study to assess the presentation and outcomes of patients presenting with P-aHUS and the prevalence of alternative C3 convertase dysregulation. P-aHUS occurred in 21 of the 100 adult female patients with atypical HUS, with 79% presenting postpartum. We detected complement abnormalities in 18 of the 21 patients. The outcomes were poor: 62% reached ESRD by 1 month and 76% by last follow-up. The risk for P-aHUS was highest during a second pregnancy. Thirty-five women, 26 (74%) of whom had complement abnormalities, had at least one pregnancy before the onset of a non-pregnancy-related aHUS. Outcomes did not differ between patients with pregnancy-related and non-pregnancy-related aHUS. Mutations in the SCR19-20 domains of factor H were less frequent in P-aHUS patients compared with non-pregnancy-related aHUS. Pregnancies in female patients with complement abnormalities (n = 44) were complicated by fetal loss and preeclampsia in 4.8% and 7.7%, respectively. Better understanding of complement dysregulation in pregnancy complications is essential, especially to guide development of pharmacologic agents to modulate this system.

38. Obstetric Nephrology: AKI and Thrombotic Microangiopathies in Pregnancy
Fakhouri F, Vercel C, Frémeaux-Bacchi V.
Clin J Am Soc Nephrol. 2012 Dec;7(12):2100-6.

ABSTRACT
AKI in pregnancy remains a cause of significant fetomaternal mortality and morbidity, particularly in developing countries. Hypertensive complications of pregnancy (preeclampsia/eclampsia or hemolysis, elevated liver enzymes, and low platelets count syndrome) are the leading cause of AKI in pregnancy worldwide. Thrombotic microangiopathy is another peculiar and devastating cause of AKI in pregnancy. During the last decade, our understanding, and in some cases, our management, of these causes of AKI in pregnancy has dramatically improved. For instance, convincing data have linked pre-eclampsia/eclampsia to an increase in circulating antiangiogenic factors soluble Flt 1 and endoglin, which induce endothelial cell dysfunction, hypertension, and proteinuria. Several distinct pathogenic mechanisms underlying thrombotic microangiopathy, including thrombotic microangiopathy occurring during pregnancy, have been established. Thrombotic microangiopathy, which can present as hemolytic uremic syndrome or thrombotic thrombocytopenic purpura, can be reclassified in four potentially overlapping subtypes: disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 deficiency-related thrombotic microangiopathy, complement alternative pathway dysregulation-related thrombotic microangiopathy, secondary thrombotic microangiopathy (verotoxin and antiangiogenic drugs), and thrombotic microangiopathy of undetermined mechanism. In most cases, pregnancy is only a precipitating factor for thrombotic microangiopathy. Treatment of thrombotic microangiopathy occurring during pregnancy should be tailored to the underlying pathogenic mechanism: (1) restoration of a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 serum activity

in the setting of thrombotic thrombocytopenic purpura through plasma exchanges and in some cases, B cell-depleting therapy and (2) inhibition of complement alternative pathway activation in atypical hemolytic uremic syndrome using antiC5 blocking antibody (eculizumab).

39. Pregnancy-related Thrombotic Microangiopathies: Clues From Complement Biology
Fakhouri F.
Transfus Apher Sci. 2016 Apr;54(2):199-202.

ABSTRACT
Pregnancy is a high-risk period for various types of thrombotic microangiopathies (TMA). The improvement of our understanding of the pathophysiology of TMAs has translated into better management of pregnancy-related TMAs. The two main types of TMA, TTP (thrombotic thrombocytopenic purpura) and hemolytic uremic syndrome (HUS), can both occur during pregnancy and postpartum. TTP is related in most cases to acquired or congenital deficiency of ADAMTS13; it tends to develop mainly during the second and third trimesters of pregnancy. The treatment of pregnancy-TTP aims to restore a detectable ADAMTS13 activity through plasma therapy, and if needed, to induce or sustain remission, immunosuppressive agents. In contrast, HUS develops mainly in the postpartum period. Accumulating data indicate that pregnancy-HUS is an atypical, i.e., complement-mediated HUS, triggered by pregnancy. Its treatment therefore should include the use of the anti-C5 humanized monoclonal antibody eculizumab. In other TMA-like disorders associated with pregnancy, including HELLP (hemolysis, elevated liver enzymes, low platelets) and pre-eclampsia/eclampsia, complement involvement, and the need for specific anti-complement therapies, is an active area of investigation.

40. Atypical Hemolytic Uremic Syndrome and C3 Glomerulopathy: Conclusions From a "Kidney Disease: Improving Global Outcomes" (KDIGO) Controversies Conference
Goodship TH, Cook HT, Fakhouri F et al.
Kidney Int. 2017 Mar;91(3):539-551.

ABSTRACT
In both atypical hemolytic uremic syndrome (aHUS) and C3 glomerulopathy (C3G) complement plays a primary role in disease pathogenesis. Herein we report the outcome of a 2015 Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference where key issues in the management of these 2 diseases were considered by a global panel of experts. Areas addressed included renal pathology, clinical phenotype and assessment, genetic drivers of disease, acquired drivers of disease, and treatment strategies. In order to help guide clinicians who are caring for such patients, recommendations for best treatment strategies were discussed at length, providing the evidence base underpinning current treatment options. Knowledge gaps were identified and a prioritized research agenda was proposed to resolve outstanding controversial issues.

41. How We Manage Thrombotic Microangiopathies in Pregnancy
Thomas MR, Robinson S, Scully MA.

Br J Haematol. 2016 Jun;173(6):821-30.

ABSTRACT
Differentiation between the thrombotic microangiopathies (TMAs) that present in pregnancy may be clinically challenging, but is critical to ensure correct management because of the impact on fetal and maternal outcomes. Thrombotic thrombocytopenic purpura (TTP) and atypical haemolytic uraemic syndrome (aHUS) are medical/obstetric emergencies that require specialist input, both at the time of acute diagnosis and follow-up in subsequent pregnancies. Features of preeclampsia and HELLP syndrome (haemolysis, elevated liver enzymes, low platelets) may precede or be present in evolving TTP or aHUS. Clinicians need to be mindful of how a presumed diagnosis of a specific TMA in pregnancy may evolve and be prepared to frequently reassess signs and symptoms and revise the diagnosis and management plan accordingly.

42. From Gestational Hypertension and Preeclampsia to Atypical Hemolytic Uremic Syndrome
Tsai HM, Kuo E.
Obstet Gynecol. 2016 May;127(5):907-10.

ABSTRACT
Background: Preeclampsia is a leading cause of morbidity and mortality during pregnancy. The variability of clinical features suggests that preeclampsia is not a single disease. Atypical hemolytic uremic syndrome, resulting from defective regulation of the alternative complement pathway, is less well known and may be mistaken for preeclampsia.
Case: We describe a woman with atypical hemolytic uremic syndrome who was given the diagnosis of gestational hypertension during her first pregnancy and preeclampsia and hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome followed by thrombotic thrombocytopenic purpura and hemolytic uremic syndrome during her second pregnancy, before the correct diagnosis of atypical hemolytic uremic syndrome was recognized in the postpartum period of her third pregnancy. The patient was treated with anticomplement therapy and had a rapid improvement.
Conclusion: This case illustrates the importance of distinguishing atypical hemolytic uremic syndrome from preeclampsia.

43. Thrombotic microangiopathy/haemolytic Uraemic Syndrome. Histopathology Update
Vázquez Martul E.
Rev Esp Patol. Jul-Sep 2018;51(3):170-177.

ABSTRACT
Thrombotic microangiopathy (TMA) encompasses different entities known as haemolytic uraemic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP). The histopathological characteristics have remained constant since the initial description and consist in glomerular-type affectation with the presence of double contours, mesangiolysis and microthrombi. It is generally accepted that the vascular damage is related to the prognosis. Ultrastructure, together with conventional histology, shows notable changes in both capillaries and endothelial cells. A comprehensive histopathological study of the renal biopsy, using electronmicroscopy, is useful in

the confirmation of a clinical suspicion and demonstrates the pathogenetic mechanisms in the microcirculatory damage. The close resemblance between the ultrastructural appearance and that seen with the light microscope of TMA and transplant glomerulopathy (TG) is precisely what suggests that both entities are subject to the same etiopathogenetic mechanism in which the endothelial cell is targeted. Recent advances in the pathology of atypical HUS, its relation with complement system and the discovery of specific therapeutic targets, has rekindled an interest in the study of TMA and the importance of renal biopsy.

44. The Pathology of Renal Transplants
Vázquez Martul E.
Rev Esp Patol. Apr-Jun 2018;51(2):110-123.

ABSTRACT
In order to make an objective assessment of the histopathology of a renal biopsy during a kidney transplant, all the various elements involved in the process must be understood. It is important to know the characteristics of the donor organ, especially if the donor is older than 65. The histopathological features of the donor biopsy, especially its vascular status, are often related to an initial poor function of the transplanted kidney. The T lymphocyte inflammatory response is characteristic in acute cellular rejection; the degree of tubulitis, together with the amount of affected parenchyme, are important factors. The proportion of cellular sub-populations, such as plasma cells and macrophages, is also important, as they can be related to antibody-mediated humoral rejection. Immunofluorescent or immunohistochemical studies are necessary to rule out C4d deposits or immunogloblulins. The presence of abundant deposits of C4d in tubular basement membranes supports a diagnosis of humoral rejection, as does the presence of capillaritis, glomerulitis which, together with vasculitis, are typical diagnostic findings in C4d negative cases. Interstitial fibrosis, tubular atrophy and glomerular sclerosis, although non-specific, imply a chronic phase. Transplant glomerulopathy and multilamination in more than 6 layers of the tubular and glomerular basement membranes are quasi-specific characteristics of chronic humoral rejection. Electron microscopy is essential to identify of these pathologies as well as to demonstrate the presence of other glomerular renal diseases.

45. Practice Guidelines for the Emergency Treatment of Thrombotic Microangiopathy
Romero S, Sempere A, Gómez-Seguí I et al.
Med Clin (Barc). 2018 Aug 10;151(3):123.

ABSTRACT
Background and aim: The term thrombotic microangiopathy (TMA) involves a heterogeneous group of diseases that can be overwhelming or invalidating, with an acute development, characterised by microangiopathic haemolytic anaemia and thrombocytopaenia. Its management during its initial hours is essential to improving the prognostic of these patients. The aim of this review is to give recommendations about the optimisation of TMA initial treatment and to accelerate the aetiological diagnosis.

Patients and methods: We provide a practice guideline based on four steps for the initial management of TMA: diagnosis of suspicion, syndromic confirmation, emergent treatment and complementary tests.
Results: The detection of microangiopathic haemolytic anaemia (characterised by elevated reticulocytes, LDH and indirect bilirubin, negative direct Coombs test and schistocytes in peripheral blood), and thrombocytopaenia not explained by other secondary aetiologies confirm the syndromic diagnosis of microangiopathic haemolytic anaemia and thrombocytopaenia (MAHAT). These patients require admission to an Intensive Care Unit to initiate plasma exchange therapy as soon as possible, ideally within the first 4-8hours. Prior to this, samples for ADAMTS13 and complement study should be obtained. Finally, it is important to request the complementary tests necessary to have a correct aetiological diagnosis.
Conclusions: Adherence to the agreed recommendations in this guideline will improve therapeutic results by facilitating cooperation between different specialists involved in TMA management.

46. Secondary Thrombotic Microangiopathy and Eculizumab: A Reasonable Therapeutic Option
Román E, Mendizábal S, Jarque I et al.
Nefrología. Sep-Oct 2017;37(5):478-491.

ABSTRACT
Understanding the role of the complement system in the pathogenesis of atypical haemolytic uraemic syndrome and other thrombotic microangiopathies (TMA) has led to the use of anti-complement therapy with eculizumab in these diseases, in addition to its original use in patients with paroxysmal nocturnal haemoglobinuria andatypical haemolytic uraemic syndrome. Scientific evidence shows that both primary and secondary TMAs with underlying complement activation are closely related. For this reasons, control over the complement system is a therapeutic target. There are 2scenarios in which eculizumab is used in patients with TMA: primary or secondary TMA that is difficult to differentiate (including incomplete clinical presentations) and complement-mediated damage in various processes in which eculizumab proves to be efficacious. This review summarises the evidence on the role of the complement activation in the pathophysiology of secondary TMAs and the efficacy of anti-complement therapy in TMAs secondary to pregnancy, drugs, transplant, humoral rejection, systemic diseases and glomerulonephritis. Although experience is scarce, a good response to eculizumab has been reported in patients with severe secondary TMAs refractory to conventional treatment. Thus, the role of the anti-complement therapy as a new treatment option in these patients should be investigated.

47. Atipical Uremic Hemolityc Syndrome in Pregnancy
Pérez-Calatayud ÁA, Briones-Garduño JC, Álvarez-Goris M del P et al.
Cir Cir. Jul-Aug 2016;84(4):344-9.

ABSTRACT
Atypical haemolytic uraemic syndrome is one of the main variants of thrombotic microangiopathy, and is characterized by excessive complement activation in the microvasculature. It is also characterised by the clinical triad; non-immune haemolytic anaemia, thrombocytopenia, and acute

renal failure. In addition, 60% of patients have mutations in the genes encoding complement regulators (factor H, factor I, membrane cofactor proteins, and thrombomodulin), activators (factor B and C3), as well as autoantibodies against factor H. Multiple factors are required for the disease to manifest itself, including a trigger and gene mutations with adequate penetration. Being one of the differential diagnoses of preeclampsia- eclampsia and HELLP syndrome means that the clinician must be familiar with the disease due to its high mortality, which can be modified with early diagnosis and comprehensive treatment.

48. Interferon ß, Nephrotic Syndrome and Thrombotic Microangiopathy
Quintana LF, Campistol JM.
Med Clin (Barc). 2015 Jan 20;144(2):65-6.

No abstract available

49. Diagnostic and Therapeutic Guidelines of Thrombotic Microangiopathies of the Spanish Apheresis Group
Contreras E, de la Rubia J, Del Río-Garma J et al.
Med Clin (Barc). 2015 Apr 8;144(7):331.e1-331.e13.

ABSTRACT
Thrombotic microangiopathies (TMA) are disorders defined by the presence of a microangiopathic hemolytic anemia (with the characteristic hallmark of schistocytes in the peripheral blood smear), thrombocytopenia and organ malfunction of variable intensity. Thrombotic thrombocytopenic purpura and hemolytic uremic syndrome are the most important forms of TMA and, without the adequate treatment, they are associated with high morbimortality. In recent years, significant advances in the knowledge of the pathophysiology of TMA have occurred. Those advances have allowed us to move from a syndromic diagnosis with a similar treatment to all entities to the search of etiologic diagnosis which would lead to a specific treatment, finally leading to a better outcome of the patient. This document pretends to summarize the current status of knowledge of the pathophysiology of TMA and the therapeutic options available, and to offer a diagnostic and therapeutic practical tool to the professionals caring for the patients.

50. Case Report of Thrombotic Microangiopathy Associated With Subcutaneous Interferon beta-1a: An Emerging Complication?
Azkune Calle I, Sánchez Menoyo JL, Ruiz Ojeda J et al.
Neurología. Septiembre de 2016; 31 (7): 508-9.

No abstract available

51. Thrombotic Microangiopathy Associated With Tacrolimus in Lung Transplantation
Reig Mezquida JP, Jover AS, Ansótegui Barrera E et al.
Arch Bronconeumol. Mayo de 2015; 51 (5): e23-4.

ABSTRACT
Thrombotic microangiopathy (TMA) is a rare complication associated with the use of calcineurin inhibitors in lung transplantation, irrespective of the underlying disease of the graft recipient. It usually occurs in incomplete forms, complicating and delaying diagnosis until damage is already irreversible. It is unrelated to time from transplantation and often presents with concomitant infection, which tends to confound diagnosis. The cases discussed here have a common causative agent and all present with concomitant infection. Treatment recommendations have changed in recent years with the introduction of plasmapheresis or, more recently, the availability of the antibody eculizumab. Notwithstanding, the most cost-effective measure is withdrawal or switching of the calcineurin inhibitor. TMA is an underdiagnosed clinical entity that should be considered in the management of transplantation patients.

52. Primary Antiphospholipid Syndrome Presented as Thrombotic Microangiopathy in Renal Transplantation
Bada-Bosch T, Redondo B, Sevillano AM et al.
Nefrología. 2020 enero-febrero; 40 (1): 108-110.

No abstract available

53. Acute Renal Failure Due to Thrombotic Microangiopathy Associated With Castleman's Disease
López Montes A, Andrés Mompeán E, Martínez Villaescusa M et al.
An Med Interna. 2007 Dec;24(12):591-4.

ABSTRACT
We report a case of a 30-year-old man presenting with abdominal pain, fever, homodynamic instability, hepatosplenomegaly, acute renal failure, cervical lymph nodes, anaemia and thrombocytopenia. The patient was treated with empiric antibiotics, high dose corticosteroids, gammaglobulins, noradrenalin and diary intermittent haemodialysis, with an excellent response. The renal biopsy showed a thrombotic microangiopathy, the lymph node biopsy showed a Castleman s disease. Castleman s disease (also known as giant lymph node hyperplasia or angiofollicular lymph node hyperplasia) is a clinicopathological entity of unknown aetiology. A number of renal alterations have been described in association with the Castleman s disease.

54. Thrombotic microangiopathy associated with parvovirus B 19 infection after renal transplantation.
Murer L, Zacchello G, Bianchi D et al.
J Am Soc Nephrol. 2000;11(6):1132.

ABSTRACT
Human parvovirus B19 is considered an etiologic agent of aplastic anemia in immunosuppressed patients. Microscopic vasculitis, with or without renal involvement, has recently been attributed to this viral infection in immunocompetent patients. This study describes four cases of thrombotic renal graft microangiopathy presumably secondary to B19 infection. Twelve to 50 days after transplantation, four patients presented a renal graft dysfunction with creatinine rising to 360 to 1088 micromol/L and requiring hemodialysis in three cases. Renal involvement appeared after a systemic illness characterized by fever, fatigue and arthralgia, aplastic anemia (hemoglobin ranged from 5.3 to 7.8 g/dl), and thrombocytopenia. A thrombotic microangiopathy was observed in the renal biopsies, and the parvovirus B19 genome was isolated by PCR from the specimens. All four patients also became IgM-positive for parvovirus. Three of the four renal biopsies taken at the time of transplantation (T0) from the same patients were found positive for the B19 genome. Graft function recovered, with resolution of the aplastic anemia, within 22 to 110 d. Twenty biopsies performed as routine controls or for suspected acute rejection and nine T0 biopsies of patients with no signs of B19 infection were used. The B19 genome was found in two of 20 posttransplant biopsies and in one of nine T0 biopsies. The temporal association between aplastic anemia and the onset of thrombotic graft microangiopathy, isolation of the viral genome in renal specimens, seroconversion, and endothelial tropism of the virus suggests that B19 could be the etiologic agent of thrombotic microangiopathy in these cases. The development of the disease after infection could depend on other detrimental cofactors, which make the patient more susceptible to microthrombi formation in the renal microvasculature. The renal graft could represent the route of B19 transmission.

55. De novo hemolytic uremic syndrome postrenal transplant after cytomegalovirus infection.
Waiser J, Budde K, Rudolph B et al.
Am J Kidney Dis. 1999;34(3):556.
ABSTRACT
After renal transplantation, hemolytic uremic syndrome (HUS) may occur as recurrent disease or de novo. Here, we describe the de novo occurrence of HUS immediately after the onset of primary cytomegalovirus (CMV) disease in two renal allograft recipients. Patient no. 1 had primary CMV disease with biopsy-proven CMV esophagitis 2 months after transplantation. Patient no. 2 experienced primary CMV disease with fever and leukopenia 8 years after transplantation. Both patients were treated with intravenous ganciclovir. Both patients developed HUS with biopsy-proven thrombotic microangiopathy in the renal allograft only a few days (3 to 5 days) after the onset of CMV disease. The short interval between the onset of CMV disease and HUS, as well as the parallel course of CMV viremia and HUS in both patients, indicate there may be a pathophysiological link between both diseases. However, because antiviral therapy with ganciclovir was started before the onset of HUS in both patients, we cannot definitely rule out that HUS was triggered by ganciclovir.

56. Posttransplantation cytomegalovirus-induced recurrence of atypical hemolytic uremic syndrome associated with a factor H mutation: successful treatment with intensive plasma exchanges and ganciclovir.
Olie KH, Goodship TH, Verlaak R et al.

Am J Kidney Dis. 2005;45(1):e12.

ABSTRACT

Atypical hemolytic uremic syndrome (HUS) can recur after renal transplantation and often leads to graft loss. In some series of familial HUS, the risk of early graft loss due to recurrence of HUS approaches 100% despite any therapy. This led some authors to claim that kidney transplantation is contraindicated in those patients. The authors describe an 8-year-old girl with end-stage renal failure owing to familial atypical HUS with a factor H mutation who underwent successful transplantation using continuous prophylactic plasma exchange (PE). Twenty-four months after transplantation, plasma creatinine level is 1.2 mg/dL (106 micromol/L) despite 2 recurrences of HUS contemporaneous to 2 cytomegalovirus infections, which resolved with PE intensification and ganciclovir. This strongly suggests that cytomegalovirus infection may trigger posttransplant recurrent HUS. The feasibility of kidney transplantation in case of atypical HUS related to factor H mutation using continuous prophylactic PE intensified during relapses should be confirmed in prospective studies.

57. Postrenal transplant hemophagocytic lymphohistiocytosis and thrombotic microangiopathy associated with parvovirus b19 infection.

Ardalan MR, Shoja MM, Tubbs RS et al.

Am J Transplant. 2008 Jun;8(6):1340-4.

ABSTRACT

Persistent anemia is a known consequence of Parvovirus B19 (B19) infection following renal transplantation. However, to date, no description of B19-related hemophagocytic lymphohistiocytosis (HLH) exists in renal transplant recipients. We report a 24-year-old male kidney recipient, who presented with fever, severe anemia and allograft dysfunction two years following transplantation. Hyperferritinemia, hypertriglyceridemia, elevated serum lactate dehydrogenase, pancytopenia and fragmented red blood cells on the peripheral blood were also noted. Bone marrow examination revealed giant pronormoblasts and frequent histiocytes with intracellular hematopoietic elements, consistent with HLH. Renal allograft biopsy revealed closure of the lumen of glomerular capillaries and thickening of the capillary walls compatible with thrombotic microangiopathy. The presence of anti-B19 IgM antibody and viral DNA in the patient's serum (detected by real-time PCR) confirmed an acute B19 infection. Following high-dose intravenous immunoglobulin therapy, the anemia gradually resolved and renal function improved. As far as we know, this is the first report of B19-associated HLH and thrombotic microangiopathy in a renal transplant recipient.

58. Cyclosporine-associated thrombotic microangiopathy in renal allografts

Zarifian A, Meleg-Smith S, O'donovan R et al.

Kidney Int. 1999;55(6):2457.

ABSTRACT

Background: The association between cyclosporine (CsA) and thrombotic microangiopathy (TMA) in renal allografts is well documented. However, predisposing factors and therapy guidelines are not adequately characterized.
Methods: We reviewed 188 patients with kidney or kidney-pancreas transplants who were treated between January 1994 and December 1996 with prednisone, CsA, or tacrolimus, and azathioprine or mycophenolate. We analyzed 50 patients who had graft biopsies: 26 with TMA and 24 with no TMA, as well as 19 patients with well-functioning grafts who never required biopsy.
Results: TMA was observed in 26 of 188 renal graft recipients (14%). TMA was confined to the allograft kidney without any systemic evidence in 24 of the 26 patients. At the time of the diagnosis of TMA, 24 of the patients were on CsA, with 19 on the microemulsion form. Conversely, 5 of 18 control patients with no graft dysfunction were on the microemulsion form of CsA (P = 0.0026). Graft loss was seen in 8 of 26 patients with TMA. Conversion from CsA to tacrolimus resulted in a one-year salvage of graft function in 13 of 16 (81%) patients.
Conclusions: TMA was the cause of renal graft dysfunction in 14% of renal graft recipients and was associated with the use of the microemulsion form of CsA. Systemic signs of TMA were rare, underscoring the importance of the graft biopsy in making the diagnosis. The most successful strategy was switching from CsA to tacrolimus, with good graft function in 81% of the recipients one year after the TMA episode.

59. Preservation of peritubular capillary endothelial integrity and increasing pericytes may be critical to recovery from postischemic acute kidney injury.

Kwon O, Hong SM, Sutton TA et al.

Am J Physiol Renal Physiol. 2008 Aug;295(2):F351-9.

ABSTRACT

Decreased renal blood flow following an ischemic insult contributes to a reduction in glomerular filtration. However, little is known about the underlying cellular or subcellular mechanisms mediating reduced renal blood flow in human ischemic acute kidney injury (AKI) or acute renal failure (ARF). To examine renal vascular injury following ischemia, intraoperative graft biopsies were performed after reperfusion in 21 cadaveric renal allografts. Confocal fluorescence microscopy was utilized to examine vascular smooth muscle and endothelial cell integrity as well as peritubular interstitial pericytes in the biopsies. The reperfused, transplanted kidneys exhibited postischemic injury to the renal vasculature, as demonstrated by disorganization/disarray of the actin cytoskeleton in vascular smooth muscle cells and disappearance of von Willebrand factor from vascular endothelial cells. Damage to peritubular capillary endothelial cells was more severe in subjects destined to have sustained ARF than in those with rapid recovery of their graft function. In addition, peritubular pericytes/myofibroblasts were more pronounced in recipients destined to recover than those with sustained ARF. Taken together, these data suggest damage to the renal vasculature occurs after ischemia-reperfusion in human kidneys. Preservation of peritubular capillary endothelial integrity and increasing pericytes may be critical to recovery from postischemic AKI.

60. Drug-induced thrombotic microangiopathy: a systematic review of published reports.
Al-Nouri ZL, Reese JA, Terrell DR et al.
Blood. 2015 Jan;125(4):616-8.

ABSTRACT
Many patients with syndromes of thrombotic microangiopathy (TMA), including thrombotic thrombocytopenic purpura and hemolytic-uremic syndrome, have been reported to have a drug-induced etiology, and many different drugs have been suspected as a cause of TMA. We established criteria to assess the strength of evidence for a causal association of a drug with TMA and systematically searched for all published reports of drug-induced TMA. We identified 1569 articles: 604 were retrieved for review, 344 reported evaluable data for 586 individual patients, 43 reported evaluable data on 46 patient groups. Seventy-eight drugs were described; 22 had evidence supporting a definite causal association with TMA. Three drugs accounted for 61 of the 104 patient reports with definite evidence (quinine, 34; cyclosporine, 15; tacrolimus, 12). Twenty additional drugs had evidence supporting a probable association with TMA. These criteria and data can provide support for clinicians evaluating patients with suspected TMA.

61. Drug-induced thrombotic microangiopathy: Experience of the Oklahoma Registry and the BloodCenter of Wisconsin.
Reese JA, Bougie DW, Curtis BR et al.
Am J Hematol. 2015;90(5):406.

ABSTRACT
Many drugs have been reported to cause thrombotic microangiopathy (TMA), often described as thrombotic thrombocytopenic purpura (TTP) or hemolytic-uremic syndrome (HUS). We recently established criteria to evaluate the evidence for a causal association of a drug with TMA and then we systematically reviewed all published reports of drug-induced TMA (DITMA) to determine the level of evidence supporting a causal association of the suspected drug with TMA. On the basis of this experience, we used these evaluation criteria to assess the Oklahoma TTP-HUS Registry patients who had been previously categorized as drug-induced, 1989-2014. We also reviewed the experience of the BloodCenter of Wisconsin with testing for drug-dependent antibodies reactive with platelets and neutrophils in patients with suspected immune-mediated DITMA, 1988-2014. Among 58 patients in the Oklahoma Registry previously categorized as drug-induced (15 suspected drugs), 21 patients (three drugs: gemcitabine, pentostatin, quinine) had evidence supporting a definite association with TMA; 19 (90%) of the 21 patients had quinine-induced TMA. The BloodCenter of Wisconsin tested 40 patients with suspected DITMA (eight drugs); drug-dependent antibodies, supporting a definite association with TMA, were identified in 30 patients (three drugs: oxaliplatin, quinine, vancomycin); 28 (93%) of the 30 patients had quinine-induced TMA. Combining the data from these two sources, 51 patients (five drugs) have been identified with evidence supporting a definite association with TMA. DITMA was attributed to quinine in 47 (92%) of these 51 patients.

62. Thrombotic microangiopathy associated with intravenous injection of extended-release oxycodone.

Robson KJ, Clucas D, Filshie R et al.
BMJ Case Rep. 2017;2017.

ABSTRACT
We describe the case of a 35-year-old man presenting with thrombotic microangiopathy (TMA) and renal impairment following, as he later disclosed, intravenous injection of oral formulation tamper-resistant extended-release oxycodone hydrochloride (Oxycontin). Recurrent misuse of this agent was associated with relapsing TMA despite treatment with terminal complement inhibitor eculizumab. Cases of TMA have been reported in the USA in association with intravenous misuse of extended-release oxymorphone (Opana ER) after the introduction of a new non-crushable formulation in 2012. There are two reported accounts of TMA associated with tamper-resistant Oxycontin, which became available in Australia in 2014. This is the first documented case in which eculizumab was used. This case illustrates the practical diagnostic challenges in identifying TMA disorders, and the importance of a detailed drug history. It also highlights the need to clarify what role, if any, eculizumab therapy has in cases of drug-associated TMA.

63. VEGF inhibition and renal thrombotic microangiopathy.
Eremina V, Jefferson JA, Kowalewska J et al.
Engl J Med. 2008;358(11):1129.

ABSTRACT
The glomerular microvasculature is particularly susceptible to injury in thrombotic microangiopathy, but the mechanisms by which this occurs are unclear. We report the cases of six patients who were treated with bevacizumab, a humanized monoclonal antibody against vascular endothelial growth factor (VEGF), in whom glomerular disease characteristic of thrombotic microangiopathy developed. To show that local reduction of VEGF within the kidney is sufficient to trigger the pathogenesis of thrombotic microangiopathy, we used conditional gene targeting to delete VEGF from renal podocytes in adult mice; this resulted in a profound thrombotic glomerular injury. These observations provide evidence that glomerular injury in patients who are treated with bevacizumab is probably due to direct targeting of VEGF by antiangiogenic therapy.

64. Type I interferon causes thrombotic microangiopathy by a dose-dependent toxic effect on the microvasculature.
Kavanagh D, McGlasson S, Jury A et al.
Blood. 2016;128(24):2824.

ABSTRACT
Many drugs have been reported to cause thrombotic microangiopathy (TMA), yet evidence supporting a direct association is often weak. In particular, TMA has been reported in association with recombinant type I interferon (IFN) therapies, with recent concern regarding the use of IFN in multiple sclerosis patients. However, a causal association has yet to be demonstrated. Here, we adopt a combined clinical and experimental approach to provide evidence of such an association between type I IFN and TMA. We show that the clinical phenotype of cases referred to a national

center is uniformly consistent with a direct dose-dependent drug-induced TMA. We then show that dose-dependent microvascular disease is seen in a transgenic mouse model of IFN toxicity. This includes specific microvascular pathological changes seen in patient biopsies and is dependent on transcriptional activation of the IFN response through the type I interferonα/βreceptor (IFNAR). Together our clinical and experimental findings provide evidence of a causal link between type I IFN and TMA. As such, recombinant type I IFN therapies should be stopped at the earliest stage in patients who develop this complication, with implications for risk mitigation.

65. Relapsing thrombotic microangiopathy and intravenous sustained-release oxycodone.
Nataatmadja M, Divi D.
Clin Kidney J. 2016;9(4):580.

ABSTRACT
Thrombotic microangiopathy (TMA) associated with injecting sustained-release oxymorphone, an opioid intended for oral use, has previously been reported. We report a case of TMA secondary to intravenous use of sustained-release oxycodone, and the first case to demonstrate relapsing disease due to persistent intravenous opioid use. In cases such as these, TMA is suspected to be due to a polyethylene oxide (PEO) coating found on these drugs, and the disease is likely due to a directly toxic effect of PEO to endothelial cells. We hypothesize that there are unidentified genetic predispositions causing some persons to be susceptible to developing this disease.

66. Drug-induced thrombotic microangiopathy: An updated systematic review, 2014-2018.
Saleem R, Reese JA, George JN.
Am J Hematol. 2018;93(9):E241.

No abstract available

67. Quinine-Induced Thrombotic Microangiopathy: A Report of 19 Patients.
Page EE, Little DJ, Vesely SK et al.
Am J Kidney Dis. 2017;70(5):686.

ABSTRACT
Background: Quinine can cause diverse and severe immune-mediated adverse reactions, including thrombotic microangiopathy (TMA). Our objective was to describe the presenting features and long-term outcomes of patients with quinine-induced TMA.
Study design: A case series of 19 patients with quinine-induced TMA treated with plasma exchange.
Setting&Participants: Patients with quinine-induced TMA initially suspected of having thrombotic thrombocytopenic purpura (TTP) were identified among patients enrolled in the Oklahoma TTP-Hemolytic Uremic Syndrome Registry.
Outcomes: The clinical course of the initial episode and morbidity and mortality following recovery.
Measurements: The diagnosis of quinine-induced TMA was confirmed by documentation of quinine-dependent antibodies reactive with platelets or neutrophils and/or by previous quinine-

associated systemic symptoms. Clinical data from the initial episode and long-term follow-up were described, focusing on kidney function.
Results: 19 of the 509 patients enrolled in the registry in 1989 to 2015 had quinine-induced TMA. 18 patients had quinine-dependent antibodies reactive with platelets and/or neutrophils (1 patient died before testing); 8 patients had a history of quinine-associated systemic symptoms. All patients were white; 18 were women. Quinine exposure was in pill form for 18 patients and as tonic water for 1. All patients had microangiopathic hemolytic anemia, thrombocytopenia, and acute kidney injury. All were initially misdiagnosed as having TTP or hemolytic uremic syndrome, and adverse reactions to quinine were not initially suspected. 1 patient died before treatment began; 17 of the 18 surviving patients required dialysis. 14 patients developed chronic kidney disease, 3 of whom developed end-stage renal disease. 8 patients died.
Limitations: Patients for whom plasma exchange was not requested were not identified.
Conclusions: Quinine-induced TMA causes severe acute kidney injury that commonly results in chronic kidney disease.

68. Sunitinib associated thrombotic microangiopathy in a patient with renal cell carcinoma: A new cause of TTP-HUS?.
Hofmann Jan C, Kiprov Dobri D.
J Clin Apher. 2008;23:42.

No abstract available

69. Drug-induced thrombotic microangiopathy.
George J N, Cuker A.
Revisión de literatura actualizada hasta **mayo de 2020. |** Última actualización de este tema: **17 de octubre de 2019.**

No abstract available

70. Kidney transplantation in adults: Thrombotic microangiopathy after kidney transplantation.
Klein CL, Java A, Brennan DC.
Revisión de literatura actualizada hasta **mayo de 2020. |** Última actualización de este tema: **13 de marzo de 2019.**

No abstract available

71. Development of transplant renal artery thrombosis and signs of haemolytic-uraemic syndrome following the change from cyclosporin to tacrolimus in a renal transplant patient.
Kiykim AA, Ozer C, Yildiz A et al.
Nephrol Dial Transplant. 2004;19(10):2653.

No abstract available

72. Sirolimus-induced thrombotic microangiopathy is associated with decreased expression of vascular endothelial growth factor in kidneys.
Sartelet H, Toupance O, Lorenzato M et al.
Am J Transplant. 2005;5(10):2441.

ABSTRACT
The aim of this study was to examine the clinical characteristics, the histological features and the renal expression of vascular endothelial growth factor (VEGF) of five patients with sirolimus-associated thrombotic microangiopathy (TMA). Sirolimus-induced TMA occurs preferentially in kidneys with concomitant endothelial injury: it was observed in three patients with acute cellular rejection on calcineurin inhibitor-free regimen, in one patient with chronic graft rejection on a calcineurin inhibitor-free protocol and in one patient with chronic calcineurin inhibitor nephrotoxicity. We found that renal VEGF expression during sirolimus-induced TMA was significantly lower than VEGF expression in normal transplanted kidneys ($p<0.01$). Decreased expression of VEGF seems to be a consequence of sirolimus treatment since (i) analysis of two biopsies performed after the switch of sirolimus to calcineurin inhibitor showed reappearance of VEGF expression, (ii) no decreased expression of VEGF was found in five kidneys with classical TMA and, (iii) an increased expression of VEGF was observed in seven kidneys with acute cellular rejection on a sirolimus-free immunosuppressive regimen ($p<0.01$). The potential role of sirolimus-induced downregulation of VEGF as a predisposing factor to the development of TMA is discussed.

73. Follow-up of kidney graft recipients with cyclosporine-associated hemolytic-uremic syndrome and thrombotic microangiopathy.
Bren A, Pajek J, Grego K et al.
Transplant Proc. 2005;37(4):1889.

ABSTRACT
The study was based on 462 patients who underwent kidney transplantation from 1986 through 2004. Cyclosporine (CsA)-related thrombotic microangiopathy (TMA) was observed in 15 (3.3%) patients. The donor ages ranged from 9 to 51 years and cold ischemia times from 12 to 31 hours. Hemolytic-uremic syndrome (HUS) developed 2 weeks after transplantation in 14 patients and later in 1 subject. Histopathologic examination demonstrated glomerular-type TMA in 3 patients, a mixed type (glomerular and vascular) in 11 patients, and a nonspecific mesangial widening with tubulointerstitial lesions in 1 patient. Follow-up biopsies revealed resolution of TMA in 4 patients and chronic vascular TMA in 1 patient. Six patients with mixed-type TMA needed transient hemodialysis. No patient with the glomerular-type TMA needed dialysis ($P = .103$), and 14 of 15 had good resolution of graft function after CsA dose reduction or temporary discontinuation or continuation of optimal dose. Only 1 graft with mixed-type TMA was lost due to irreversible HUS. The mean glomerular filtration rate (GFR), predicted by the Nankivell equation, was 76 +/- 13 mL/min and 80 +/- 27 mL/min at 1 month after discharge for glomerular- and mixed-type TMA, respectively ($P>.05$). GFRs 1 year after HUS were 82 +/- 12 and 87 +/- 21 mL/min for the glomerular

and the mixed types, respectively(P>.05). We concluded that the mixed-type TMA was associated with a more severe early clinical course than the glomerular-type TMA. The 1-year prognosis was good in the majority of patients, with no significant differences between those with the glomerular- and mixed-type TMA.

74. Cytomegalovirus-induced thrombotic microangiopathy after renal transplant successfully treated with eculizumab: case report and review of the literature.
Java A, Edwards A, Rossi A et al.
Transpl Int. 2015;28(9):1121. Epub 2015 Apr 24.

ABSTRACT
De novo thrombotic microangiopathy (TMA) after renal transplant is rare. Cytomegalovirus (CMV)-related post-transplant TMA has only been reported in 6 cases. We report an unusual case of a 75-year-old woman who developed de novo TMA in association with CMV viremia. The recurrence of TMA with CMV viremia, the resolution with treatment for CMV, and the lack of correlation with a calcineurin inhibitor (CNI) in our case support CMV as the cause of the TMA. What is unique is that the use of eculizumab without plasmapheresis led to prompt improvement in renal function. After a failure to identify a genetic cause for TMA and the clear association with CMV, eculizumab was discontinued. This case provides insight into the pathogenesis and novel treatment of de novo TMA, highlights the beneficial effects of complement inhibitors in this disease, and shows that they can be safely discontinued once the inciting etiology is addressed.

75. Eculizumab in Secondary Atypical Haemolytic Uraemic Syndrome.
Cavero T, Rabasco C, López A et al.
Nephrol Dial Transplant. 2017 Mar 1;32(3):466-474.

ABSTRACT
Background: Complement dysregulation occurs in thrombotic microangiopathies (TMAs) other than primary atypical haemolytic uraemic syndrome (aHUS). A few of these patients have been reported previously to be successfully treated with eculizumab.
Methods: We identified 29 patients with so-called secondary aHUS who had received eculizumab at 11 Spanish nephrology centres. Primary outcome was TMA resolution, defined by a normalization of platelet count (>150 × 10 9 /L) and haemoglobin, disappearance of all the markers of microangiopathic haemolytic anaemia (MAHA), and improvement of renal function, with a ≥25% reduction of serum creatinine from the onset of eculizumab administration.
Results: Twenty-nine patients with secondary aHUS (15 drug-induced, 8 associated with systemic diseases, 2 with postpartum, 2 with cancer-related, 1 associated with acute humoral rejection and 1 with intestinal lymphangiectasia) were included in this study. The reason to initiate eculizumab treatment was worsening of renal function and persistence of TMA despite treatment of the TMA cause and plasmapheresis. All patients showed severe MAHA and renal function impairment (14 requiring dialysis) prior to eculizumab treatment and 11 presented severe extrarenal manifestations. A rapid resolution of the TMA was observed in 20 patients (68%), 15 of them showing a ≥50% serum creatinine reduction at the last follow-up. Comprehensive genetic and

molecular studies in 22 patients identified complement pathogenic variants in only 2 patients. With these two exceptions, eculizumab was discontinued, after a median of 8 weeks of treatment, without the occurrence of aHUS relapses.
Conclusion: Short treatment with eculizumab can result in a rapid improvement of patients with secondary aHUS in whom TMA has persisted and renal function worsened despite treatment of the TMA-inducing condition.

76. Primary Antiphospholipid Syndrome Presented as Thrombotic Microangiopathy in Renal Transplantation.
Bada-Bosch T, Redondo B, Sevillano AM et al.
Nefrologia2020;40(1):104–112.

No abstract available

77. Eculizumab as a Treatment for Atypical Hemolytic Syndrome Secondary to Carfilzomib.
Moliz C, Gutiérrez E, Cavero T et al.
Nefrologia2019;39(1):84–109 .

No abstract available

78. Thrombotic Microangiopathy After Kidney Transplantation.
Noris M, Remuzzi G.
American Journal of Transplantation 2010; 10: 1517–1523. https://doi.org/10.1111/j.1600-6143.2010.03156.x

ABSTRACT
Thrombotic microangiopathy (TMA) is a severe complication of kidney transplantation that often causes graft failure. TMA may occur de novo , often triggered by immunosuppressive drugs and acute antibody-mediated rejection, or recur in patients with previous history of hemolytic uremic syndrome (HUS). Recurrent TMA is very rare in patients who had developed end-stage renal failure following HUS caused by Shiga-toxin producing E. scherichia coli , whereas disease recurrence is common in patients with atypical HUS (aHUS). The underlying genetic defect greatly impacts the risk of posttransplant recurrence in aHUS. Indeed recurrence is almost the rule in patients with mutations in genes encoding factor H or factor I, whereas patients with a mutation in membrane-cofactor-protein gene have a good transplant outcome. Prophylactic and therapeutic options for posttransplant TMA, including plasma therapy, combined kidney and liver transplantation and targeted complement inhibitors are discussed in this review.

79. Thrombotic microangiopathy after renal transplantation: Current insights in de novo and recurrent disease.
Abbas F, El Kossi M, Kim JJ et al.

World J Transplant. 2018 Sep 10; 8(5): 122–141.

ABSTRACT

Thrombotic microangiopathy (TMA) is one of the most devastating sequalae of kidney transplantation. A number of published articles have covered either *de novo* or recurrent TMA in an isolated manner. We have, hereby, in this article endeavored to address both types of TMA in a comparative mode. We appreciate that *de novo* TMA is more common and its prognosis is poorer than recurrent TMA; the latter has a genetic background, with mutations that impact disease behavior and, consequently, allograft and patient survival. Post-transplant TMA can occur as a recurrence of the disease involving the native kidney or as *de novo* disease with no evidence of previous involvement before transplant. While atypical hemolytic uremic syndrome is a rare disease that results from complement dysregulation with alternative pathway overactivity, *de novo* TMA is a heterogenous set of various etiologies and constitutes the vast majority of post-transplant TMA cases. Management of both diseases varies from simple maneuvers, e.g., plasmapheresis, drug withdrawal or dose modification, to lifelong complement blockade, which is rather costly. Careful donor selection and proper recipient preparation, including complete genetic screening, would be a pragmatic approach. Novel therapies, e.g., purified products of the deficient genes, though promising in theory, are not yet of proven value.

80. De Novo Tacrolimus-Induced Thrombotic Microangiopathy in the Early Stage After Renal Transplantation Successfully Treated With Conversion to Everolimus.

Cortina G, Trojer R, Waldegger S et al.

Pediatr Nephrol. 2015 Apr;30(4):693-7.

ABSTRACT

Background: Calcineurin inhibitor (CNI)-induced thrombotic microangiopathy (TMA) is a rare complication after renal transplantation. It may be difficult to distinguish from CNI toxicity and acute antibody-mediated rejection (AMR). Its clinical presentation may vary from isolated localised forms up to catastrophic systemic presentations.

Case: We report a case of tacrolimus-induced TMA soon after renal transplantation in an 11-year-old boy who received his second renal transplantation. His first graft was lost because of AMR. On day 12 after his second renal transplantation, his renal function started worsening and a kidney biopsy was performed, which showed histopathological signs of TMA. The diagnosis of tacrolimus-induced TMA was established after excluding AMR and other causes of de novo TMA. Genetic complement investigation disclosed two complement factor H risk polymorphisms as possible modifiers of TMA emergence. Treatment was based on replacing tacrolimus with everolimus, with a subsequent normalisation of renal function.

Conclusion: A prompt diagnosis of de novo TMA by early allograft biopsy is essential for the allograft outcome and genetic investigations for possible complement abnormalities are reasonable, not only for patients with a systemic aspect of their post-transplant TMA. Replacing tacrolimus with everolimus effectively controlled the TMA and stabilised renal function in our patient.

81. Microangiopatía trombótica secundaria y eculizumab: una opción terapéutica razonable.

Román E, Mendizábal S, Jarque I et al.

Nefrologia. 2017;37:478-91. DOI: 10.1016/j.nefro.2017.01.006

ABSTRACT

El conocimiento del papel del complemento en la patogenia del síndrome hemolítico urémico atípico y otras microangiopatías trombóticas (MAT) ha fomentado el desarrollo de la terapia anticomplemento con eculizumab más allá de su indicación original en la hemoglobinuria paroxística nocturna y en el síndrome hemolítico urémico atípico. La evidencia científica demuestra un estrecho límite entre MAT primarias y secundarias con activación del complemento subyacente en ambas. Por ello, el control del complemento se convierte en una diana terapéutica. El uso de eculizumab en MAT secundarias contempla 2escenarios: diagnóstico diferencial difícil entre MAT primaria y secundaria (incluidos cuadros clínicos incompletos) o daño por complemento en procesos distintos, donde se demuestra la eficacia del tratamiento. Esta revisión es una síntesis de la evidencia científica sobre el papel de la activación del complemento en la fisiopatología de las MAT secundarias y la eficacia de la terapia anticomplemento en MAT asociadas a embarazo, fármacos, trasplante, rechazo humoral, enfermedades sistémicas y glomerulonefritis. La experiencia es aún limitada, pero la respuesta a eculizumab en pacientes con MAT secundarias graves y refractarias al tratamiento convencional abre una puerta a la investigación de la terapia anticomplemento como nueva opción terapéutica.

D. QUÉ SITUACIONES REQUIEREN PROFILAXIS DE LA RECAÍDA CON BLOQUEO DEL COMPLEJO DE ATAQUE A LA MEMBRANA? ¿CUÁNDO INICIAR LA PROFILAXIS?

82. Low efficacy of vaccination against serogroup B meningococci in patients with atypical hemolytic uremic síndrome.

Mülling N, Rohn H, Vogel U et al.

Biosci Rep. 2020 Mar 27;40(3):BSR20200177.

ABSTRACT

Background: The C5 complement inhibitor eculizumab is first-line treatment in atypical hemolytic uremic syndrome (aHUS) going along with a highly increased risk of meningococcal infections. Serogroup B meningococci (MenB) are the most frequently encountered cause for meningococcal infections in Europe. Efficacy of the protein-based MenB-vaccine Bexsero in aHUS has not been determined and testing is only possible in patients off-treatment with eculizumab as a human complement source is required.

Methods: Patients with aHUS were vaccinated with two doses of the protein-based MenB-vaccine Bexsero. Serum bactericidal antibody (SBA) titers against factor H binding protein (fHbp) of MenB were determined in 14 patients with aHUS off-treatment with eculizumab.

Results: Only 50% of patients showed protective human serum bactericidal antibody (hSBA) titers (≥1:4) against MenB following two vaccinations. Bactericidal antibody titers were relatively low (≤1:8) in three of seven patients with protective titers. While 71% of patients were on immunosuppressive treatment for either thrombotic microangiopathy or renal transplantation at either first or second vaccination, all four patients not receiving any immunosuppressive treatment showed protective bactericidal antibody response. Time between second vaccination and titer

measurement was not significantly different between patients with protective titers compared with those with non-protective titers, while time between first and second vaccination was significantly longer in patients with protective titers going along with a tendency for reduction in immunosuppressive treatment.
Conclusions: Efficacy of vaccination against MenB is insufficient in patients with aHUS. Response to vaccination seems to be hampered by immunosuppression. Therefore, implementation of adequate antibiotic prophylaxis seems pivotal.

83. Eculizumab for Atypical Hemolytic Uremic Syndrome Recurrence in Renal Transplantation.
Zuber J, Le Quintrec M, Kird S et al.
Am J Transplant. 2012 Dec;12(12):3337-54.

ABSTRACT
Eculizumab (anti-C5) has been sporadically reported as an efficient therapy for atypical hemolytic uremic syndrome (aHUS). However, the lack of series precludes any firm conclusion about the optimal use of anti-C5 for preventing or treating aHUS posttransplant aHUS recurrence. We thoroughly studied 22 renal transplant recipients with aHUS who received off-label therapy with anti-C5, including 12 cases, which have not been reported yet. Nine patients, all carrying a complement genetic abnormality associated with a high risk of aHUS recurrence, received prophylactic anti-C5 therapy to prevent posttransplant recurrence. Eight of them had a successful recurrence-free posttransplant course and achieved a satisfactory graft function, while the remaining patient experienced early arterial thrombosis of the graft. Thirteen renal transplant recipients were given anti-C5 for posttransplant aHUS recurrence. A complete reversal of aHUS activity was obtained in all of them. Importantly, the delay of anti-C5 initiation after the onset of the aHUS episode inversely correlated with the degree of renal function improvement. Three patients in whom anti-C5 was subsequently stopped experienced a relapse. Altogether these data suggest that long-term eculizumab is highly effective for preventing and treating posttransplant aHUS recurrence. Our study also indicates that anti-C5 should be promptly started if a recurrence occurs.

84. Eculizumab Use for Kidney Transplantation in Patients With a Diagnosis of Atypical Hemolytic Uremic Syndrome.
Siedlecki AM, Isbel N, Walle JV et al.
Kidney Int Rep. 2018 Dec 3;4(3):434-446.

ABSTRACT
Introduction: Recurrence of atypical hemolytic uremic syndrome (aHUS) in renal allografts is common, leading to dialysis and graft failure. Pretransplant versus posttransplant initiation of eculizumab treatment in patients with aHUS has not been rigorously investigated. We hypothesized eculizumab pretransplant would reduce dialysis incidence posttransplant.
Methods: Of patients enrolled in the Global aHUS Registry (n = 1549), 344 had ≥1 kidney transplant. Of these, 188 had received eculizumab. Eighty-eight patients (47%) were diagnosed with aHUS and received eculizumab before, and during, their most recent transplant (group 1). A total of 100

patients (53%; group 2) initiated eculizumab posttransplantation. This second group was subdivided into those diagnosed with aHUS before (n = 52; group 2a) or after (n = 48; group 2b) their most recent transplant.
Results: Within 5 years of transplantation, 47 patients required dialysis; the risk of dialysis after transplantation was significantly increased in group 2b (hazard ratio [HR] 4.6; confidence interval [CI] 1.7-12.4) but not 2a (HR 2.3; CI 0.9-6.2). Graft function within 6 months of transplantation was significantly better in group 1 (median estimated glomerular filtration rate of 60.6 ml/min per 1.73 m^2) compared with 31.5 and 9.6 ml/min per 1.73 m^2 in groups 2a (P = 0.004) and 2b (P = 0.0001), respectively. One meningococcal infection (resolved with treatment) and 3 deaths (deemed unrelated to eculizumab) were reported.
Conclusions: Outcomes for transplant patients with aHUS treated with eculizumab were improved compared with previous reports of patients with aHUS not treated with eculizumab. Our findings suggest delayed aHUS diagnosis and therefore treatment is associated with an increased risk of dialysis posttransplantation and reduced allograft function.

85. Targeted Strategies in the Prevention and Management of Atypical HUS Recurrence After Kidney Transplantation.
Zuber J, Le Quintrec M, Morris H et al.
Transplant Rev (Orlando). 2013 Oct;27(4):117-25.

ABSTRACT
Atypical hemolytic and uremic syndrome (aHUS) is associated with a high rate of recurrence and poor outcomes after kidney transplantation. Fortunately, recent advances in the understanding of the pathogenesis of aHUS have permitted an individualized risk assessment of post-transplant recurrence. Acquired or inherited dysregulation of the alternative complement pathway, thought to be the driving force of the disease, is identified in most aHUS patients. Notably, depending on the mutations involved, the risk of recurrence greatly varies, highlighting the importance of undertaking etiological investigations prior to kidney transplantation. In those with moderate to high risk of recurrence, the use of a prophylactic therapy, consisting in either plasmapheresis or eculizumab therapies, represents a major stride forward in the prevention of aHUS recurrence after kidney transplantation. In those who experience aHUS recurrence, a growing number of observations suggest that eculizumab therapy outperforms curative plasma therapy. The optimal duration of both prophylactic and curative therapies remains an important, yet unaddressed, issue. In this respect, the kidney transplant recipients, continuously exposed to endothelial-insulting factors, referred here as to triggers, might have a sustained high risk of recurrence. A global therapeutic approach should thus attempt to reduce exposure to these triggers.

86. Ten-year Outcome of Eculizumab in Kidney Transplant Recipients With Atypical Hemolytic Uremic Syndrome- A Single Center Experience.
Kant S, Bhalla A, Alasfar S et al.
BMC Nephrol. 2020 May 20;21(1):189.

ABSTRACT

Background: Atypical hemolytic uremic syndrome (aHUS) can result in severe kidney dysfunction, secondary to thrombotic microangiopathy. Eculizumab has been used to treat this disorder, and has resulted in favourable outcomes in both, native and transplanted kidneys. There is limited long term follow up data in kidney transplant recipients (KTRs) who received prevention and treatment with Eculizumab. We report our long term follow up data from our center to address safety and efficacy of this therapy in KTRs.
Methods: We performed a retrospective analysis of KTRs between January 2009 and December 2018. Clinical diagnosis of aHUS established with presence of thrombotic microangiopathy, acute kidney injury, absence of alternate identifiable etiology. We reviewed clinical data, including genetic testing for complement factor mutations, post-transplant course, and response to therapy including therapeutic and prophylactic use of eculizumab.
Results: Nineteen patients with aHUS received a total of 36 kidney transplants; 10 of them had 2 or more prior kidney transplants. Median age at time of last transplant was 37 years (range 27-59), 72% were female (n = 14), 78% Caucasian (n = 15), with 61% had live donor transplant (n = 12) as the last transplant. Eculizumab prophylaxis was given to 10/19 (56%) at the time of transplantation, with no aHUS recurrence during the follow up. Median duration of follow up was 46 (range 6-237) months. Mean estimated glomerular filtration rate (eGFR) at the time of last follow up was 59.5 ml/min/m^2. No infections secondary to encapsulated organisms or other major infectious complications occurred during the follow up.
Conclusions: Eculizumab prophylaxis is safe and effective in KTRs with aHUS. Long term follow up demonstrates that it may be possible to discontinue prophylaxis carefully in selected patients with no evidence of complement mutations.

87. Long-term outcomes of the Atypical Hemolytic Uremic Syndrome after kidney transplantation treated with eculizumab as first choice.
Modelli de Andrade LG, Moraes Contti M, Nga HS, et al.
PLoS One. 2017 Nov 14;12(11):e0188155.

ABSTRACT
Introduction: The treatment of choice for Atypical Hemolytic Uremic Syndrome (aHUS) is the monoclonal antibody eculizumab. The objective of this study was to assess the efficacy and safety of eculizumab in a cohort of kidney transplant patients suffering from aHUS.
Methods: Description of the prospective cohort of all the patients primarily treated with eculizumab after transplantation and divided into the therapeutic (onset of aHUS after transplantation) and prophylactic use (patients with previous diagnosis of aHUS undergoing kidney transplantation).
Results: Seven cases were outlined: five of therapeutic use and two, prophylactic. From the five cases of therapeutic use, there was improvement of the thrombotic microangiopathy in the 48 hours following the start of the drug and no patient experienced relapse during an average follow-up of 21 months in the continuous use of eculizumab (minimum of 6 and maximum of 42 months). One patient died at 6 months, due to Aspergillus infection. From the two cases of prophylactic use, one patient experienced relapsed thrombotic microangiopathy after 4 months and another patient remained asymptomatic after 16 months of follow-up, both on chronic treatment.
Discussion: The therapeutic use of eculizumab showed to be effective, with improvement of the microangiopathy parameters and persisting up to the end of the follow-up, without relapses. The

additional risk of immunosuppression, leading to opportunistic infections, was well tolerated. The prophylactic use showed to be effective and safe; however, the doses and intervals should be individualized in order to avoid relapsed microangiopathy, especially in patients with factor H mutation.

88. Midterm Outcomes of 12 Renal Transplant Recipients Treated With Eculizumab to Prevent Atypical Hemolytic Syndrome Recurrence.
Levi C, Frémeaux-Bacchi V, Zuber J et al.
Transplantation. 2017 Dec;101(12):2924-2930.

ABSTRACT
Background: Atypical hemolytic uremic syndrome (aHUS) is an orphan disease with a high rate of recurrence after kidney transplantation. However, reports of successful prevention of posttransplant aHUS recurrence with eculizumab emerged a few years ago. To further delineate its optimal use, we describe the largest series of kidney transplant recipients treated with prophylactic eculizumab.
Methods: Twelve renal transplant recipients with aHUS-related end-stage renal disease received eculizumab: 10 from day 0 and 2 at the time of recurrence (days 6 and 25). Clinical and histological features, complement assessment, and free eculizumab measurements were analyzed. The median follow-up was 24.6 months.
Results: Five patients had failed at least 1 previous renal transplant from aHUS. A genetic mutation was identified in 9 patients, anti-H antibodies were found in 2. No patient demonstrated biological recurrence of thrombotic microangiopathy under treatment. Three antibody-mediated rejections (AMRs) occurred without detectable C5 residual activity. AMR was associated with subclinical thrombotic microangiopathy in 2 patients. One patient lost his graft after several complications, including AMR. One patient experienced posttransplant C3 glomerulonephritis. The last median serum creatinine was 128.2 ± 40.8 µmol/L.
Conclusions: These data confirm that eculizumab is highly effective in preventing posttransplantation aHUS recurrence, yet may not fully block AMR pathogenesis.

89. Outcomes of Kidney Transplant Patients with Atypical Hemolytic Uremic Syndrome Treated with Eculizumab: A Systematic Review and Meta-Analysis
González Suárez ML, Thongprayoon Ch, Mao MA et al.
J. Clin. Med. 2019, 8, 919; doi:10.3390/jcm8070919

ABSTRACT
Background: Kidney transplantation in patients with atypical hemolytic uremic syndrome (aHUS) is frequently complicated by recurrence, resulting in thrombotic microangiopathy in the renal allograft and graft loss. We aimed to assess the use of eculizumab in the prevention and treatment of aHUS recurrence after kidney transplantation.
Methods: Databases (MEDLINE, EMBASE and Cochrane Database) were searched through February 2019. Studies that reported outcomes of adult kidney transplant recipients with aHUS treated with eculizumab were included. Estimated incidence rates from the individual studies were extracted and

combined using random-effects, generic inverse variance method of DerSimonian and Laird. Protocol for this systematic review has been registered with PROSPERO (International Prospective Register of Systematic Reviews; no. CRD42018089438).
Results: Eighteen studies (13 cohort studies and five case series) consisting of 380 adult kidney transplant patients with aHUS who received eculizumab for prevention and treatment of post-transplant aHUS recurrence were included in the analysis. Among patients who received prophylactic eculizumab, the pooled estimated incidence rates of recurrent thrombotic microangiopathy (TMA) after transplantation and allograft loss due to TMA were 6.3% (95%CI: 2.8–13.4%, I^2 = 0%) and 5.5% (95%CI: 2.9–10.0%, I^2 = 0%), respectively. Among those who received eculizumab for treatment of post-transplant aHUS recurrence, the pooled estimated rates of allograft loss due to TMA was 22.5% (95%CI: 13.6–34.8%, I^2 = 6%). When the meta-analysis was restricted to only cohort studies with data on genetic mutations associated with aHUS, the pooled estimated incidence of allograft loss due to TMA was 22.6% (95%CI: 13.2–36.0%, I^2 = 10%). We found no significant publication bias assessed by the funnel plots and Egger's regression asymmetry test ($p > 0.05$ for all analyses).
Conclusions: This study summarizes the outcomes observed with use of eculizumab for prevention and treatment of aHUS recurrence in kidney transplantation. Our results suggest a possible role for anti-C5 antibody therapy in the prevention and management of recurrent aHUS.

90. Failure of First Meningococcal Vaccination in Patients With Atypical Haemolytic Uraemic Syndrome Treated With Eculizumab.
Gäckler A, Kaulfuß M, Rohn H et al.
Nephrol Dial Transplant. 2020 Feb 1;35(2):298-303.

ABSTRACT
Background: The C5 complement inhibitor eculizumab is a first-line treatment in atypical haemolytic uraemic syndrome (aHUS). Therapy with eculizumab is associated with a highly increased risk for meningococcal infection. Therefore, vaccination is highly recommended before beginning treatment. Efficacy of quadrivalent meningococcal vaccines (MenACWY) in patients treated with the C5 complement inhibitor eculizumab in aHUS has not yet been determined.
Methods: Patients with aHUS received one dose of a MenACWY conjugate vaccine before eculizumab treatment commenced. Bactericidal titres against meningococcal serogroups A, C, W and Y were determined using baby rabbit complement in 25 patients.
Results: Full immune response to meningococcal vaccination was detected in five patients (20%), while seven patients (28%) showed no immune response in any of the tested serogroups. The remaining 13 patients showed incomplete immune response with proof of protective antibody titres for one to three serogroups without perceptible preference for any serogroup. Bactericidal titres after re-vaccination were available for 17 patients. Nine patients with incomplete immune response after first vaccinations showed protective antibody titres for all serogroups after re-vaccination. Kidney function had improved in >50% of patients at the time of re-vaccination compared with the time of first vaccination and immunosuppressive therapy was only applied to re-vaccinated patients following kidney transplantation.

Conclusions: Immunogenicity of first quadrivalent meninongococcal vaccination is insufficient in patients with aHUS. Booster response is promising, but incomplete. Therefore, establishing antibiotic prophylaxes seems pivotal.

91. Use of Highly Individualized Complement Blockade Has Revolutionized Clinical Outcomes After Kidney Transplantation and Renal Epidemiology of Atypical Hemolytic Uremic Syndrome.
Zuber J, Frimat M, Caillar S et al.
J Am Soc Nephrol. 2019 Dec;30(12):2449-2463.

ABSTRACT
Background: Atypical hemolytic uremic syndrome (HUS) is associated with high recurrence rates after kidney transplant, with devastating outcomes. In late 2011, experts in France recommended the use of highly individualized complement blockade-based prophylaxis with eculizumab to prevent post-transplant atypical HUS recurrence throughout the country.
Methods: To evaluate this strategy's effect on kidney transplant prognosis, we conducted a retrospective multicenter study from a large French nationwide registry, enrolling all adult patients with atypical HUS who had undergone complement analysis and a kidney transplant since January 1, 2007. To assess how atypical HUS epidemiology in France in the eculizumab era evolved, we undertook a population-based cohort study that included all adult patients with atypical HUS (n=397) between 2007 and 2016.
Results: The first study included 126 kidney transplants performed in 116 patients, 58.7% and 34.1% of which were considered to be at a high and moderate risk of atypical HUS recurrence, respectively. Eculizumab prophylaxis was used in 52 kidney transplants, including 39 at high risk of recurrence. Atypical HUS recurred after 43 (34.1%) of the transplants; in four cases, patients had received eculizumab prophylaxis and in 39 cases they did not. Use of prophylactic eculizumab was independently associated with a significantly reduced risk of recurrence and with significantly longer graft survival. In the second, population-based cohort study, the proportion of transplant recipients among patients with ESKD and atypical HUS sharply increased between 2012 and 2016, from 46.2% to 72.3%, and showed a close correlation with increasing eculizumab use among the transplant recipients.
Conclusions: Results from this observational study are consistent with benefit from eculizumab prophylaxis based on pretransplant risk stratification and support the need for a rigorous randomized trial.

92. Prophylactic Eculizumab Use in Kidney Transplantation: A Review of the Literature and Report of a Case With Atypical Hemolytic Uremic Syndrome.
Kasapoğlu U, Ruhi Ç, Tuğcu M et al.
Ann Transplant. 2015 Dec 1;20:714-9.

ABSTRACT
Background: Atypical hemolytic uremic syndrome (aHUS) is a very rare disease, which presents with microangiopathic hemolytic anemia, thrombocytopenia, and acute kidney injury. Progression to end-stage renal disease (ESRD) from acute kidney injury is observed in 60% of aHUS cases. The

prognosis of aHUS patients who undergo kidney transplantation (Ktx) is generally poor, but these patients should be treated prophylactically with eculizumab to prevent recurrence after transplantation.
Case report: An 18-year-old man was referred to our center with a history of rapid progression to ESRD with unknown etiology. He had anemia, thrombocytopenia, high levels of LDH, and indirect bilirubin and creatinine on initial laboratory results. Our diagnosis was aHUS due to initial results, normal level of ADAMTS activity, and lack of predisposing factors seen in typical HUS. We planned to perform genetic analysis for the patient and the donor candidate (mother). The variations found on exon 7 of the CFH gene had not been reported previously. According to PolyPhen analysis, this mutation was reported as a potential cause for aHUS. We decided to perform Ktx under eculizumab prophylaxis. Weekly administration of prophylaxis was extended to 1 month. The graft functioned immediately after Ktx. The patient has completed his first year uneventfully in our follow-up, with a creatinine 0.79 mg/dl at his last control visit.
Conclusions: We found favorable results of an aHUS case successfully treated with kidney transplantation combined with short-term prophylactic eculizumab therapy.

E. OTRAS ALTERNATIVAS EN LA PROFILAXIS DE RECIDIVA DE aHUS

93. Liver Transplantation for aHUS: Still Needed in the Eculizumab Era?
Coppo R, Bonaudo R, Peruzziet RL et al.
Pediatr Nephrol. 2016 May;31(5):759-68.

ABSTRACT
Background: The risk of disease recurrence after a kidney transplant is high in patients with atypical hemolytic uremic syndrome (aHUS) and mutations in the complement factor H (FH) gene (CFH). Since FH is mostly produced by the liver, a kidney transplant does not correct the genetic defect. The anti-C5 antibody eculizumab prevents post-transplant aHUS recurrence, but it does not cure the disease. Combined liver-kidney transplantation has been performed in few patients with CFH mutations based on the rationale that liver replacement provides a source of normal FH.
Methods: We report the 9-year follow-up of a child with aHUS and a CFH mutation, including clinical data, extensive genetic characterization, and complement profile in the circulation and at endothelial level. The outcome of kidney and liver transplants performed separately 3 years apart are reported.
Results: The patient showed incomplete response to plasma, with relapsing episodes, progression to end-stage renal disease, and endothelial-restricted complement dysregulation. Eculizumab prophylaxis post-kidney transplant did not achieve sustained remission, leaving the child at risk of disease recurrence. A liver graft given 3 years after the kidney transplant completely abrogated endothelial complement activation and allowed eculizumab withdrawal.
Conclusions: Liver transplant may definitely cure aHUS and represents an option for patients with suboptimal response to eculizumab.

94. Liver-kidney Transplantation to Cure Atypical HUS: Still an Option Post-Eculizumab?
Saland J.
Pediatr Nephrol. 2014 Mar;29(3):329-32.

ABSTRACT
Patients with end-stage renal disease (ESRD) due to atypical HUS (aHUS) now have several potential options that can enable successful kidney transplantation. This editorial addresses these options by considering key factors that are important when making an individual treatment decision.

95. Use of Eculizumab and Plasma Exchange in Successful Combined Liver-Kidney Transplantation in a Case of Atypical HUS Associated With Complement Factor H Mutation
Tran H, Chaudhuri A, Concepcion W et al.
Pediatr Nephrol. 2014 Mar;29(3):477-80.

ABSTRACT
Background: Atypical hemolytic uremic syndrome (aHUS) evolves into end-stage renal failure in nearly half of affected patients and is associated with defective regulation of the alternative complement pathway. Patients with a complement factor H (CFH) mutation have a 30-100% risk of graft loss due to aHUS recurrence or graft thrombosis. Since CFH is produced predominantly by the liver, combined liver-kidney transplant is a curative treatment option. One major unexpected risk includes liver failure secondary to uncontrolled complement activation. We report a successful combined liver-kidney transplantation with perioperative plasma exchange and use of the humanized anti-C5 monoclonal antibody eculizumab.
Case diagnosis/treatment: An 11-month-old female presented with oliguric renal failure after 3 weeks of flu-like symptoms in the absence of diarrhea. Following the identification of Escherichia coli 0157:H7 in her stool, she was discharged home on peritoneal dialysis with a diagnosis of Shiga toxin-associated HUS. Three months later, she developed severe anemia, thrombocytopenia, and neurological involvement. aHUS was diagnosed and confirmed, and genetic testing revealed a mutation in CFH SCR20. Once donor organs became available, she received preoperative plasma exchange followed by eculizumab infusion with intra-operative fresh frozen plasma prior to combined liver-kidney transplant. At 19 months post-transplant, she continues to have excellent allograft and liver function without signs of disease recurrence.
Conclusion: Perioperative use of eculizumab in conjunction with plasma exchange during simultaneous liver-kidney transplant can be used to inhibit terminal complement activity, thereby optimizing successful transplantation by reducing the risk of graft thrombosis.

96. Kidney Transplantation in Patients With Atypical Hemolytic Uremic Syndrome Due to Complement Factor H Deficiency: Impact of Liver Transplantation
Kim S, Park E, Min S Il et al.
J Korean Med Sci. 2018 Jan 1;33(1):e4.

ABSTRACT

Background: Atypical hemolytic uremic syndrome (aHUS) is a rare disease that is often associated with genetic defects. Mutations of complement factor H (CFH) are the most common genetic defects that cause aHUS and often result in end-stage renal disease. Since CFH is mainly produced in the liver, liver transplantation (LT) has been performed in patients with defective CFH.
Methods: The clinical courses of four kidney allograft recipients who lost their native kidney functions due to aHUS associated with a CFH mutation were reviewed.
Results: Subject A underwent kidney transplantation (KT) twice, aHUS recurred and the allograft kidney failed within a few years. Subject B received a KT and soon experienced a recurrence of aHUS coinciding with infection. Her allograft kidney function has worsened, and she remains on plasma infusion therapy. Subject C underwent LT followed by KT. She is doing well without plasma infusion therapy after combined LT-KT for 3 years. Subject D received KT following LT and is now recurrence-free from aHUS.
Conclusion: In patients with aHUS associated with a CFH mutation, KT without LT was complicated with a recurrence of aHUS, which might lead to allograft loss. Conversely, LT was successful in preventing the recurrence of aHUS and thus might be another option for a recurrence-free life for aHUS patients associated with CFH mutation.

97. Preemptive Plasma Therapy Prevents Atypical Hemolytic Uremic Syndrome Relapse in Kidney Transplant Recipients

Aigner C, Bohmig G, Eskandary F et al.
Am. J. Transplant. 2018, 18, 793–794.

ABSTRACT

Background: Atypical hemolytic uremic syndrome (aHUS) frequently leads to renal failure, and kidney transplantation bears a high risk of disease recurrence and graft loss.
Methods: Patients who received a kidney graft in our center were retrospectively identified using our Vienna Thrombotic Microangiopathy Cohort. Since 2005, the majority of aHUS patients received perioperative plasma exchange (PE) followed by plasma infusions (PI). Patients were switched to eculizumab in case of plasma intolerance or failure. Those with no preemptive therapy served as controls. We used proportional Cox regression and logistic regression to examine predictors of graft survival.
Results: 19 aHUS patients received 32 grafts and had a follow-up > 1 year. Eight patients received preventive plasma therapy for eight transplants and 13 patients (including 2 patients who received plasma therapy for their last transplant) had no preventive therapy for 24 grafts. The median graft survival was 2.372 days in patients, that received preemptive therapy and 411 days in patients, that did not receive preemptive treatment (hazard ratio: 0.11; p= 0.03). Four patients were switched to eculizumab because of plasma intolerance or failure. Additionally, one patient, that was not transplanted according to the above-mentioned protocol, received eculizumab for aHUS relapse. Additionally, relapse of aHUS (p = 0.01) and year of transplantation (p<0.01) had an effect on graft failure.
Conclusions: This study shows that preemptive plasma therapy and eculizumab rescue in selected cases improve graft survival among kidney transplant recipients with aHUS.

98. Cost-effectiveness of Eculizumab Treatment After Kidney Transplantation in Patients With Atypical Haemolytic Uraemic Syndrome

Van den Brand JA, Verhave JC, Adang EM et al.

Nephrol Dial Transplant. 2017 Jan 1;32(suppl_1):i115-i122.

ABSTRACT

Background: Kidney transplantation in patients with atypical haemolytic uraemic syndrome (aHUS) is frequently complicated by recurrence of aHUS, often resulting in graft loss. Eculizumab prophylaxis prevents recurrence, improving graft survival. An alternative treatment strategy has been proposed where eculizumab is administered upon recurrence. We combined available evidence and performed a cost-effectiveness analysis of these competing strategies.

Methods: A cost-effectiveness analysis using a decision analytical approach with Markov chain analyses was used to compare alternatives for aHUS patients with end-stage renal disease (ESRD): (i) dialysis treatment, (ii) kidney transplantation, (iii) kidney transplantation with eculizumab therapy upon recurrence of aHUS, (iv) kidney transplantation with eculizumab induction consisting of 12 months of prophylaxis and (v) kidney transplantation with lifelong eculizumab prophylaxis. We assumed that all patients received a graft from a living donor and that recurrence probability was 28.4% within the first year of transplantation.

Results: At 8.34 quality-adjusted life years (QALYs) gained and a cost of €402 412, kidney transplantation without eculizumab was the least costly alternative. By comparison, dialysis was more costly and resulted in fewer QALYs gained. Eculizumab upon recurrence resulted in 9.55 QALYs gained at a cost of €425 097. The incremental cost-effectiveness ratio (ICER) was €18 748 per QALY. Both eculizumab induction and lifelong eculizumab were inferior to eculizumab upon recurrence, as both resulted in fewer QALYs gained and higher costs.

Conclusions: Kidney transplantation is more cost effective than dialysis to treat ESRD due to aHUS. Adding eculizumab treatment results in a substantial gain in QALYs. When compared with eculizumab upon recurrence, neither eculizumab induction nor lifelong eculizumab prophylaxis resulted in more QALYs, but did yield far higher costs. Therefore, eculizumab upon recurrence of aHUS is more acceptable.

F. PROFILAXIS VERSUS TRATAMIENTO ANTICIPADO

99. Targeted strategies in the prevention and management of atypical HUS recurrence after kidney transplantation.

Zuber J, Le Quintrec M, Morris H et al.

Transplant Rev (Orlando). 2013 Oct;27(4):117-25.

ABSTRACT

Atypical hemolytic and uremic syndrome (aHUS) is associated with a high rate of recurrence and poor outcomes after kidney transplantation. Fortunately, recent advances in the understanding of the pathogenesis of aHUS have permitted an individualized risk assessment of post-transplant recurrence. Acquired or inherited dysregulation of the alternative complement pathway, thought to be the driving force of the disease, is identified in most aHUS patients. Notably, depending on

the mutations involved, the risk of recurrence greatly varies, highlighting the importance of undertaking etiological investigations prior to kidney transplantation. In those with moderate to high risk of recurrence, the use of a prophylactic therapy, consisting in either plasmapheresis or eculizumab therapies, represents a major stride forward in the prevention of aHUS recurrence after kidney transplantation. In those who experience aHUS recurrence, a growing number of observations suggest that eculizumab therapy outperforms curative plasma therapy. The optimal duration of both prophylactic and curative therapies remains an important, yet unaddressed, issue. In this respect, the kidney transplant recipients, continuously exposed to endothelial-insulting factors, referred here as to triggers, might have a sustained high risk of recurrence. A global therapeutic approach should thus attempt to reduce exposure to these triggers.

100. Managing and preventing atypical hemolytic uremic syndrome recurrence after kidney transplantation.

Noris M, Remuzzi G.

Curr Opin Nephrol Hypertens. 2013 Nov;22(6):704-12.

ABSTRACT

Purpose of review: Several genetic and acquired abnormalities leading to abnormal activation of the alternative pathway of complement have been identified in patients with atypical hemolytic uremic syndrome (aHUS). The purpose of this review is to shed light on how advances in the understanding of aHUS pathogenesis have impacted on prevention and cure of aHUS recurrence after kidney transplantation.

Recent findings: Studies over the past decade have shown that the risk of posttransplant recurrence of aHUS depends on the underlying genetic abnormality. The risk is high in patients with mutations in genes encoding circulating complement proteins and regulators, whereas patients with mutations in membrane cofactor protein generally show good transplant outcome. Given the poor outcome associated with recurrence, isolated renal transplantation had been contraindicated in aHUS patients. Combined kidney-liver transplantation and prophylactic plasma exchange have been used to prevent posttransplant recurrences. More recent data have provided evidence about the efficacy of the anti-C5 monoclonal antibody eculizumab in the prevention and treatment of posttransplant aHUS recurrences.

Summary: This review summarizes recent advances on preventing and managing aHUS recurrence after kidney transplantation and discusses the issues that still need clarification.

101. Eculizumab use in kidney transplantation.

Johnson CK, Leca N.

Curr Opin Organ Transplant. 2015 Dec;20(6):643-51.

ABSTRACT

Purpose of review: Eculizumab suppresses the effector functions of the complement system and represents a therapeutic breakthrough for patients with paroxysmal nocturnal hemoglobinuria or atypical hemolytic uremic syndrome (aHUS). Safety monitoring is ongoing; so far, most notable is the expected increase in infection risk with encapsulated organisms. Despite potential applicability

in multiple complement-mediated disorders, the off-label use of eculizumab has been limited, mainly by its prohibitive cost. The purpose of this review is to summarize the current data relevant to the use of eculizumab in kidney transplantation.
Recent findings: In aHUS, prone to high rates of recurrence and allograft loss, eculizumab has made the most notable therapeutic impact. Further clarification of complement defects may help predict therapeutic responses and hopefully guide treatment duration. In C3 glomerulopathies, the clinical response to eculizumab appears more heterogeneous and less effective in processes mediated by upstream to C5 complement deregulation. A large clinical trial of eculizumab for prevention of delayed graft function is ongoing. In antibody-mediated rejection, the role of eculizumab is unclear as its use has been limited to very complex, mostly presensitized, patients in mixed combinations of therapeutic modalities.
Summary: Overall, eculizumab has raised awareness of complement-mediated disorders as an exciting, new therapeutic option with multiple potential applications in kidney transplantation. Further research is needed to develop a better understanding of eculizumab applicability, efficacy, and treatment monitoring and beyond, to future therapeutic tools targeting the complement.

102. Prophylactic Eculizumab Use in Kidney Transplantation: A Review of the Literature and Report of a Case with Atypical Hemolytic Uremic Syndrome.
Kasapoğlu U, Ruhi Ç, Tuğcu M et al.
Ann Transplant. 2015 Dec 1;20:714-9.

ABSTRACT
Background: Atypical hemolytic uremic syndrome (aHUS) is a very rare disease, which presents with microangiopathic hemolytic anemia, thrombocytopenia, and acute kidney injury. Progression to end-stage renal disease (ESRD) from acute kidney injury is observed in 60% of aHUS cases. The prognosis of aHUS patients who undergo kidney transplantation (Ktx) is generally poor, but these patients should be treated prophylactically with eculizumab to prevent recurrence after transplantation.
Case report: An 18-year-old man was referred to our center with a history of rapid progression to ESRD with unknown etiology. He had anemia, thrombocytopenia, high levels of LDH, and indirect bilirubin and creatinine on initial laboratory results. Our diagnosis was aHUS due to initial results, normal level of ADAMTS activity, and lack of predisposing factors seen in typical HUS. We planned to perform genetic analysis for the patient and the donor candidate (mother). The variations found on exon 7 of the CFH gene had not been reported previously. According to PolyPhen analysis, this mutation was reported as a potential cause for aHUS. We decided to perform Ktx under eculizumab prophylaxis. Weekly administration of prophylaxis was extended to 1 month. The graft functioned immediately after Ktx. The patient has completed his first year uneventfully in our follow-up, with a creatinine 0.79 mg/dl at his last control visit.
Conclusions: We found favorable results of an aHUS case successfully treated with kidney transplantation combined with short-term prophylactic eculizumab therapy.

103. Prevention and treatment of atypical haemolytic uremic syndrome after kidney transplantation.

Okumi M, Tanabe K.
Nephrology (Carlton). 2016 Jul;21 Suppl 1:9-13.

ABSTRACT
Atypical haemolytic uraemic syndrome is a rare disorder characterized by an over-activated, dysregulated alternative complement pathway due to genetic mutation and environmental triggers. Atypical haemolytic uraemic syndrome is a serious, life-threatening disease characterized by thrombotic microangiopathy, which causes haemolytic anaemia, thrombocytopaenia, and acute renal failure. Since recurrences of atypical haemolytic uraemic syndrome frequently lead to end-stage kidney disease even in renal allografts, kidney transplantation for patients with end-stage kidney disease secondary to atypical haemolytic uraemic syndrome has long been contraindicated. However, over the past several years, advancements in the management of atypical haemolytic uraemic syndrome have allowed successful kidney transplantation in these patients. The key factor of this success is eculizumab, a humanized anti-C5 monoclonal antibody, which inhibits terminal membrane-attack complex formation and thrombotic microangiopathy progression. In the setting of kidney transplantation, there are different possible triggers of post-transplant atypical haemolytic uraemic syndrome recurrence, such as brain-death related injury, ischaemia-reperfusion injury, infections, the use of immunosuppressive drugs, and rejection. Principal strategies are to prevent endothelial damage that could potentially activate alternative complement pathway activation and subsequently lead to atypical haemolytic uraemic syndrome recurrence in kidney allograft. Published data shows that prophylactic eculizumab therapy is highly effective for the prevention of post-transplant atypical haemolytic uraemic syndrome recurrence, and prompt treatment with eculizumab as soon as recurrence is diagnosed is important to maintain renal allograft function. Further study to determine the optimal dosing and duration of prophylactic therapy and treatment of post-transplant atypical haemolytic uraemic syndrome recurrence is needed.

104. An update for atypical haemolytic uraemic syndrome: diagnosis and treatment. A consensus document.
Campistol JM, Arias M, Ariceta G et al.
Nefrologia. 2015;35(5):421-47.

ABSTRACT
Haemolytic uraemic syndrome (HUS) is a clinical entity defined as the triad of nonimmune haemolytic anaemia, thrombocytopenia, and acute renal failure, in which the underlying lesions are mediated by systemic thrombotic microangiopathy (TMA). Different causes can induce the TMA process that characterizes HUS. In this document we consider atypical HUS (aHUS) a sub-type of HUS in which the TMA phenomena are the consequence of the endotelial damage in the microvasculature of the kidneys and other organs due to a disregulation of the activity of the complement system. In recent years, a variety of aHUs-related mutations have been identified in genes of the the complement system, which can explain approximately 60% of the aHUS cases, and a number of mutations and polymorphisms have been functionally characterized. These findings have stablished that aHUS is a consequence of the insufficient regulation of the activiation of the complement on cell surfaces, leading to endotelial damage mediated by C5 and the complement terminal pathway. Eculizumab is a monoclonal antibody that inhibits the activation of C5 and blocks

the generation of the pro-inflammatory molecule C5a and the formation of the cell membrane attack complex. In prospective studies in patients with aHUS, the use of Eculizumab has shown a fast and sustained interruption of the TMA process and it has been associated with significative long-term improvements in renal function, the interruption of plasma therapy and important reductions in the need of dialysis. According to the existing literature and the accumulated clinical experience, the Spanish aHUS Group published a consensus document with recommendations for the treatment of aHUs (Nefrologia 2013;33[1]:27-45). In the current online version of this document, we update the aetiological classification of TMAs, the pathophysiology of aHUS, its differential diagnosis and its therapeutic management.

105. An international consensus approach to the management of atypical hemolytic uremic syndrome in children.
Loirat C, Fakhouri F, Ariceta G et al.
Pediatr Nephrol. 2016 Jan;31(1):15-39.

ABSTRACT
Atypical hemolytic uremic syndrome (aHUS) emerged during the last decade as a disease largely of complement dysregulation. This advance facilitated the development of novel, rational treatment options targeting terminal complement activation, e.g., using an anti-C5 antibody (eculizumab). We review treatment and patient management issues related to this therapeutic approach. We present consensus clinical practice recommendations generated by HUS International, an international expert group of clinicians and basic scientists with a focused interest in HUS. We aim to address the following questions of high relevance to daily clinical practice: Which complement investigations should be done and when? What is the importance of anti-factor H antibody detection? Who should be treated with eculizumab? Is plasma exchange therapy still needed? When should eculizumab therapy be initiated? How and when should complement blockade be monitored? Can the approved treatment schedule be modified? What approach should be taken to kidney and/or combined liver-kidney transplantation? How should we limit the risk of meningococcal infection under complement blockade therapy? A pressing question today regards the treatment duration. We discuss the need for prospective studies to establish evidence-based criteria for the continuation or cessation of anticomplement therapy in patients with and without identified complement mutations.

106. Use of Highly Individualized Complement Blockade Has Revolutionized Clinical Outcomes after Kidney Transplantation and Renal Epidemiology of Atypical Hemolytic Uremic Syndrome.
Zuber J, Frimat M, Caillard S et al.
J Am Soc Nephrol. 2019 Dec;30(12):2449-2463.

ABSTRACT
Background: Atypical hemolytic uremic syndrome (HUS) is associated with high recurrence rates after kidney transplant, with devastating outcomes. In late 2011, experts in France recommended the use of highly individualized complement blockade-based prophylaxis with eculizumab to prevent post-transplant atypical HUS recurrence throughout the country.

Methods: To evaluate this strategy's effect on kidney transplant prognosis, we conducted a retrospective multicenter study from a large French nationwide registry, enrolling all adult patients with atypical HUS who had undergone complement analysis and a kidney transplant since January 1, 2007. To assess how atypical HUS epidemiology in France in the eculizumab era evolved, we undertook a population-based cohort study that included all adult patients with atypical HUS (n=397) between 2007 and 2016.
Results: The first study included 126 kidney transplants performed in 116 patients, 58.7% and 34.1% of which were considered to be at a high and moderate risk of atypical HUS recurrence, respectively. Eculizumab prophylaxis was used in 52 kidney transplants, including 39 at high risk of recurrence. Atypical HUS recurred after 43 (34.1%) of the transplants; in four cases, patients had received eculizumab prophylaxis and in 39 cases they did not. Use of prophylactic eculizumab was independently associated with a significantly reduced risk of recurrence and with significantly longer graft survival. In the second, population-based cohort study, the proportion of transplant recipients among patients with ESKD and atypical HUS sharply increased between 2012 and 2016, from 46.2% to 72.3%, and showed a close correlation with increasing eculizumab use among the transplant recipients.
Conclusions: Results from this observational study are consistent with benefit from eculizumab prophylaxis based on pretransplant risk stratification and support the need for a rigorous randomized trial.

107. Renal Transplantation in Patients With Atypical Hemolytic Uremic Syndrome: A Single Center Experience.
Alpay N, Ozçelik U.
Transplant Proc. 2019 Sep;51(7):2295-2297.

ABSTRACT
Purpose: Hemolytic uremic syndrome (HUS) is characterized by microangiopathic anemia, thrombocytopenia, and acute kidney injury. HUS is mostly associated with diarrhea (90%). However, 10% of cases are not associated with diarrhea and are thus called as atypical HUS (aHUS); these cases are usually caused by dysregulation of the complement system. Eculizumab, a monoclonal antibody against C5, is the drug of choice for treating aHUS. Herein we aimed to present 8 cases of renal transplantation performed on patients with aHUS.
Materials and methods: A total of 8 patients who had been diagnosed with aHUS between the years 2012 to 2018 were enrolled and underwent transplantations. All patients received induction treatment, standard immunosuppresive treatment (tacrolimus, mycophenolic acid, prednisolone), and eculizumab. Eculizumab was administered at a dosage of 900 mg/wk for the first month and 1200 mg every 2 weeks thereafter. Patients were followed up and recorded in terms of demographic features, serum creatinine, lactate dehydrogenase, acute rejection episodes, and allograft outcomes.
Results: Mean age was 34 ± 8 years (Male/Female: 6/2). One of the patients had a second transplantation. Median hemodialysis vintage (25%-75% interquartile range) was 37 (9-63) months. Four patients had pretransplant plasmapheresis and 2 patients had posttransplant plasmapheresis. Induction treatment was ATG in 7 patients, and basiliximab was used only in 1 patient. The median follow-up period was 25 (13-59) months. Mean serum creatinine levels were 1.9 ± .6, 1.2 ± .7, and

1 ± .1 mg/dL for the first day, first month, and last values, respectively. Mean lactate dehydrogenase levels were 286 ± 203, 239 ± 27, and 218 ± 86 U/L for first day, first month, and last values, respectively. None of the patients had an acute rejection episode. Currently, all patients have functioning allografts.
Conclusion: Patients with aHUS may be transplanted successfully with eculizumab with good allograft outcomes.

108. Living Donor Kidney Transplantation in Atypical Hemolytic Uremic Syndrome: A Case Series.
Duineveld C, Verhave JC, Berger SP et al.
Am J Kidney Dis. 2017 Dec;70(6):770-777.

Background: The development of complement inhibitors has greatly improved the outcome of patients with atypical hemolytic uremic syndrome (aHUS), making kidney transplantation a more feasible option. Although prophylactic eculizumab therapy may prevent recurrent disease after transplantation, its necessity for all transplant recipients is debated.
Study design: A case series.
Setting & participants: Patients with aHUS who underwent living donor kidney transplantation after 2011 at 2 university centers, prospectively followed up with a protocol of eculizumab therapy limited to only recipients with documented posttransplantation recurrent thrombotic microangiopathy. In addition, the protocol emphasized lower target level tacrolimus and aggressive treatment of high blood pressure.
Outcomes: Recurrence of aHUS, kidney function, acute kidney injury.
Results: We describe 12 female and 5 male patients with a mean age of 47 years. 5 patients had lost a previous transplant due to aHUS recurrence. 16 patients carried a pathogenic or likely pathogenic variant in genes encoding complement factor H, C3, or membrane cofactor protein, giving a high risk for aHUS recurrence. Median follow-up after transplantation was 25 (range, 7-68) months. One patient had aHUS recurrence 68 days after transplantation, which was successfully treated with eculizumab. 3 patients were treated for rejection and 2 patients developed BK nephropathy. At the end of follow-up, median serum creatinine concentration was 106 (range, 67-175) µmol/L and proteinuria was negligible.
Limitations: Small series and short duration of follow-up.
Conclusions: Living donor kidney transplantation in aHUS without prophylactic eculizumab treatment appears feasible.

109. Midterm Outcomes of 12 Renal Transplant Recipients Treated With Eculizumab to Prevent Atypical Hemolytic Syndrome Recurrence.
Levi C, Frémeaux-Bacchi V, Zuber J et al.
Transplantation. 2017 Dec;101(12):2924-2930.
ABSTRACT
Background: Atypical hemolytic uremic syndrome (aHUS) is an orphan disease with a high rate of recurrence after kidney transplantation. However, reports of successful prevention of posttransplant aHUS recurrence with eculizumab emerged a few years ago. To further delineate its

optimal use, we describe the largest series of kidney transplant recipients treated with prophylactic eculizumab.
Methods: Twelve renal transplant recipients with aHUS-related end-stage renal disease received eculizumab: 10 from day 0 and 2 at the time of recurrence (days 6 and 25). Clinical and histological features, complement assessment, and free eculizumab measurements were analyzed. The median follow-up was 24.6 months.
Results: Five patients had failed at least 1 previous renal transplant from aHUS. A genetic mutation was identified in 9 patients, anti-H antibodies were found in 2. No patient demonstrated biological recurrence of thrombotic microangiopathy under treatment. Three antibody-mediated rejections (AMRs) occurred without detectable C5 residual activity. AMR was associated with subclinical thrombotic microangiopathy in 2 patients. One patient lost his graft after several complications, including AMR. One patient experienced posttransplant C3 glomerulonephritis. The last median serum creatinine was 128.2 ± 40.8 µmol/L.
Conclusions: These data confirm that eculizumab is highly effective in preventing posttransplantation aHUS recurrence, yet may not fully block AMR pathogenesis.

110. Eculizumab for Atypical Hemolytic Uremic Syndrome Recurrence in Renal Transplantation.
Zuber J, Le Quintrec M, Kird S et al.
Am J Transplant. 2012 Dec;12(12):3337-54.

ABSTRACT
Eculizumab (anti-C5) has been sporadically reported as an efficient therapy for atypical hemolytic uremic syndrome (aHUS). However, the lack of series precludes any firm conclusion about the optimal use of anti-C5 for preventing or treating aHUS posttransplant aHUS recurrence. We thoroughly studied 22 renal transplant recipients with aHUS who received off-label therapy with anti-C5, including 12 cases, which have not been reported yet. Nine patients, all carrying a complement genetic abnormality associated with a high risk of aHUS recurrence, received prophylactic anti-C5 therapy to prevent posttransplant recurrence. Eight of them had a successful recurrence-free posttransplant course and achieved a satisfactory graft function, while the remaining patient experienced early arterial thrombosis of the graft. Thirteen renal transplant recipients were given anti-C5 for posttransplant aHUS recurrence. A complete reversal of aHUS activity was obtained in all of them. Importantly, the delay of anti-C5 initiation after the onset of the aHUS episode inversely correlated with the degree of renal function improvement. Three patients in whom anti-C5 was subsequently stopped experienced a relapse. Altogether these data suggest that long-term eculizumab is highly effective for preventing and treating posttransplant aHUS recurrence. Our study also indicates that anti-C5 should be promptly started if a recurrence occurs.

111. Prophylactic eculizumab prior to kidney transplantation for atypical hemolytic uremic syndrome.
Weitz M, Amon O, Bassler D et al.
Pediatr Nephrol. 2011 Aug;26(8):1325-9.

ABSTRACT
Atypical hemolytic uremic syndrome (aHUS) in childhood is a rare disease associated with high morbidity and mortality. Most cases progress to end-stage renal failure. In approximately 50% of affected patients, mutations in genes encoding complement proteins are causative of the impairment in the regulation of the complement alternative pathway. This leads to deficient host cell protection and inappropriate complement activation on platelets and endothelial cells, particularly in the kidneys. Complement factor H (FH) heterozygosity induces unregulated activation of the membrane attack complex (MAC) C5b-9. Present therapeutic strategies for aHUS include lifelong plasmapheresis and renal dialysis. Unfortunately, kidney transplantation is frequently an unsatisfactory intervention due to the high rate of post-transplantation HUS recurrence, particularly in patients with FH mutation. Combined liver-kidney transplantation is also associated with poor outcome, mostly as a result of premature liver failure secondary to uncontrolled complement activation. Eculizumab is a complement C5 antibody that inhibits complement factor 5a (C5a) and the formation of the MAC. Thus, this antibody may be a promising new agent for patients with an aHUS undergoing kidney transplantation. We present the first case of a young patient with aHUS who received eculizumab as prophylactic treatment prior to a successful kidney transplantation.

112. Pre-emptive eculizumab and plasmapheresis for renal transplant in atypical hemolytic uremic syndrome.
Nester C, Stewart Z, Myers D et al.
Clin J Am Soc Nephrol. 2011 Jun;6(6):1488-94.

ABSTRACT
The case of a 12-year-old with a hybrid CFH/CFHL1 gene and atypical hemolytic uremic syndrome (aHUS) that had previously developed native kidney and then renal allograft loss is reported. This case illustrates the relatively common occurrence of renal loss from the late presentation of aHUS. Also presented is a protocol for the pre-emptive use of eculizumab and plasmapheresis as part of a renal transplant plan for the treatment of aHUS in patients deemed at high risk for recurrent disease. This protocol was a result of a multidisciplinary approach including adult and pediatric nephrology, transplant surgery, transfusion medicine, and infectious disease specialists. This protocol and the justifications and components of it can function as a guideline for the treatment of a group of children that have waited in limbo for the first U.S. transplant to open the door to this type of definitive care for this devastating disease.

113. Anti-C5 as prophylactic therapy in atypical hemolytic uremic syndrome in living-related kidney transplantation.
Pelicano MB, de Córdoba SR, Diekmann F et al.
Transplantation. 2013 Aug 27;96(4):e26-9.

No abstract available

114. Eculizumab long-term therapy for pediatric renal transplant in aHUS with CFH/CFHR1 hybrid gene.

Román-Ortiz E, Mendizabal Oteiza S, Pinto S et al.
Pediatr Nephrol. 2014 Jan;29(1):149-53.

ABSTRACT
Background: Atypical hemolytic uremic syndrome (aHUS) is a form of thrombotic microangiopathy (TMA) caused by dysregulation of the complement system. Outcomes of kidney transplantation are poor owing to aHUS recurrence and loss of graft. Patients carrying CFH mutations or CFH/CFHR1 hybrid genes present a very high risk of recurrence despite preventive plasmapheresis. Evaluation of recent data suggests that prophylactic eculizumab pretransplant might be the preferred therapy if available.

Case-diagnosis/treatment: We report 3-year follow-up data in a 9-year-old boy with aHUS and successful renal transplant treated with prophylactic eculizumab without recurrence. He presented with aHUS at age 3, irreversible renal failure and uncontrolled severe hypertension with concentric left ventricular hypertrophy, recurrent acute pulmonary edema, and congestive heart failure despite five hypotensive agents and bilateral nephrectomy. Complement analysis demonstrated the presence of a CFH/CFHR1 hybrid gene inherited from his mother and a SNP risk CFH haplotype inherited from his father. Kidney transplant was performed with prophylactic eculizumab and subsequent fortnightly administration. Three years post-transplant, graft function remains stable (serum creatinine 0.9 mg/dl), hypertension is controlled, no left ventricular hypertrophy, no opportunistic infections, and negative clinical chemistry parameters for hemolysis.
Conclusion: Eculizumab is a safe and effective therapy for preventing TMA recurrence and provides long-term graft function in aHUS with the CFH/CFHR1 hybrid gene.

115. Living kidney transplantation in adult patients with atypical haemolytic uraemic syndrome.

Verhave JC, Westra D, van Hamersvelt HW et al.
Neth J Med. 2013 Sep;71(7):342-7.

ABSTRACT
Background: Dysregulation of complement activation is the most common cause of the atypical haemolytic uraemic syndrome (aHUS). Many patients with aHUS develop end-stage renal disease and consider kidney transplantation. However, the recurrence rate after transplantation ranges from 45-90% in patients with known abnormalities in circulating complement proteins. It was recently proposed that patients with aHUS should be treated prophylactically with plasma exchange or eculizumab to prevent recurrence after transplantation.
Methods: A case series describing the successful outcome of kidney transplantation without prophylactic therapy in four adult patients with aHUS and a high risk of disease recurrence. Patients received a living donor kidney and immunosuppression consisting of basiliximab induction, low-dose tacrolimus, prednisone and mycophenolate mofetil. Patients received a statin, and were targeted to a low blood pressure preferably using blockers of the renin-angiotensin system.
Results: After a follow-up of 16-21 months, none of the patients developed recurrent aHUS. Also, no rejection was observed.

Conclusions: Kidney transplantation in adult patients with aHUS can be successful without prophylactic eculizumab, using a protocol that minimises cold ischaemia time, reduces the risk of rejection and provides endothelial protection. Our data suggest that in patients with aHUS, controlled trials are needed to demonstrate the optimal strategy.

116. Successful living-related renal transplantation in a patient with factor H antibody-associated atypical hemolytic uremic syndrome.

Hofer J, Giner T, Cortina G et al.

Pediatr Transplant. 2015 Aug;19(5):E121-5

ABSTRACT

CFH-Ab-associated aHUS requires different diagnostic and therapeutic approaches and then the genetically defined aHUS forms. The risk of post-transplant recurrence with graft dysfunction in CFH-Ab aHUS is not well documented. It is suggested that recurrence can be expected if a significant CFH-Ab load persists at the time of transplantation. A pretransplant procedure to reduce CFH-Ab titer seems reasonable, but accurate recommendations are lacking. Whether further prophylactic interventions after transplantation are necessary has to be decided on an individual basis. We report the case of a late diagnosed CFH-Ab HUS with initial ESRD and a successful living-related renal transplantation over a post-transplant period of four and a half years on the basis of a prophylactic pretransplant IVIG admission.

117. Favorable four-yr outcome after renal transplantation in a patient with complement factor H antibody and CFHR1/CFHR3 gene mutation-associated HUS.

Grenda R, Jarmużek W, Rubik J, et al.

Pediatr Transplant. 2015 Sep;19(6):E130-4.

ABSTRACT

aHUS is a clinical challenge for successful renal transplantation.

Case report: A 14-yr-old girl lost her kidneys at the age of 7, due to CFH antibodies and CFH-related protein (CFHR1/CFHR3) homozygous deletion-associated aHUS. CFH, CFI, and MCP gene mutations were excluded. The patient was a candidate for renal transplantation despite persistent presence of CFH antibodies (up to 539 AU/mL). Treatment with MMF, IVIG, and repeated PF (n = 8) was introduced while being placed on urgent waiting list. Three years after aHUS onset, the patient underwent the deceased donor renal transplantation "under cover" of PF, as PF was performed directly prior to surgery and, then, PFs were repeated up to overall 14 sessions. Quadruple immunosuppression (basiliximab + tacrolimus + MMF + prednisolone) was used. Moderate symptoms of aHUS (hemolysis, low platelets, and low C3) were present within first seven days post-transplant and then normalized with PF therapy. The patient remained stable during four yr of further follow-up after transplantation.

Conclusion: Specific pre- and post-transplant management allowed successful renal transplantation in a CFH antibody-positive patient.

118. Prevention of recurrence of atypical hemolytic uremic syndrome post renal transplant with the use of higher-dose eculizumab.
Riddell A, Goodship T, Bingham C.
Clin Nephrol. 2016 Oct;86(10):200-2.

ABSTRACT
Eculizumab, a terminal complement inhibitor, has recently been used successfully to both prevent and treat the recurrence of atypical hemolytic uremic syndrome (aHUS) post renal transplantation. We describe a case that highlights the need to monitor the effects of eculizumab on the complement system and in this case alter the dosage. Despite taking the standard recommended dose of eculizumab for an adult, this aHUS patient developed a low-grade thrombotic microangiopathy on biopsy within months of renal transplantation. Complement assays (trough CH50) showed small amounts of residual terminal pathway activity suggesting inadequate complement blockade on 1,200 mg eculizumab every 2 weeks. Following an increase in the dose of eculizumab to 1,500 mg every 2 weeks, lactate dehydrogenase (LDH), proteinuria, and creatinine decreased, and CH50 assay showed 0%. His case emphasizes the need to monitor clinical parameters and complement activity to ensure that adequate therapeutic blockade is achieved.

119. Successful Renal Transplantation in a Patient with Atypical Hemolytic Uremic Syndrome Treated with Eculizumab in China.
Sun ZJ, Du X, Su LL et al.
Chin Med J (Engl). 2016 Jun 5;129(11):1379-81.

No abstract available

120. Renal Transplant Immunosuppression in Patients With Hemolytic Uremic Syndrome: Four Case Reports.
Galindo P, Ramirez M, Pérez Marfil A et al.
Transplant Proc. 2018 Mar;50(2):572-574

ABSTRACT
A high rate of recurrence has been described in atypical hemolytic uremic syndrome renal transplant recipients, favored by certain immunosuppressant drugs that can induce complement activation. We present four case series in which three patients were diagnosed pretransplantation and a fourth who had onset in the very early post-transplantation period. The patients received different immunosuppression schedules, and all had improvement after more than 2-years. We suggest the need to stratify the risk of atypical hemolytic uremic syndrome recurrence using genetic studies and the available drugs as the main factors that allow graft survival improvement today.

121. Successful kidney transplant with eculizumab, thymoglobulin and belatacept therapy in a highly-sensitised patient with atypical haemolytic uraemic syndrome due to factor H mutation.
Nieto-Ríos JF, Zuluaga-Quintero M, Bello-Márquez DC et al.

Nefrologia. 2018 Jul-Aug;38(4):433-437.

ABSTRACT
Atypical haemolytic uremic syndrome is a disease caused by complement regulation abnormalities that generally progresses to chronic end-stage renal disease with a high rate of recurrence in kidney transplantation and a high risk of graft loss. Anti-complement therapy has improved the prognosis of these patients, achieving disease remission in most cases, increasing the likelihood of a successful kidney transplant and increasing patient and graft survival. Drugs with low risk of induction of thrombotic microangiopathies such as belatacept and mycophenolate have also been used with satisfactory results. We present the case of a young patient at high immunological risk, with atypical haemolytic uraemic syndrome due to factor H mutation, who underwent a successful kidney transplantation with eculizumab, thymoglobulin, belatacept, mycophenolate and steroids, to date preserving excellent graft function without disease recurrence.

122. Atypical Hemolytic Uremic Syndrome After Kidney Transplantation: Lessons Learned From the Good, the Bad, and the Ugly. A Case Series With Literature Review.
Fayek SA, Allam SR, Martinez E et al.
Transplant Proc. 2020 Jan-Feb;52(1):146-152.

ABSTRACT
Atypical hemolytic uremic syndrome (aHUS) after kidney transplantation is rare and carries a grave outcome. We present a single-center experience of all aHUS cases since the program's inception. Six patients were diagnosed with aHUS, all after kidney transplants, except for 1 patient. All had nonreactive crossmatches. Delayed graft function (DGF) occurred in 2 patients. Five patients developed aHUS after transplant; 4 (80%) of these patients manifested aHUS ≤ 14 days. All were confirmed by allograft biopsy. Genetic testing was abnormal in all patients except for 1 patient. Actual patient and graft survival during the first year was 100% and 83.3%, respectively. A single graft was lost early in the study secondary to aHUS (eculizumab was not used in the treatment process). Prophylactic and therapeutic use of eculizumab salvaged all other cases. At 1 year, mean creatinine level was 1.9 mg/dL (range, 1.3-2.5). After 6 months of eculizumab treatment (halted in 2 cases) 1 patient had recurrence 2 months later and eculizumab was restarted. However, graft function continued to worsen, and the graft was ultimately lost at 20 months after kidney transplantation. High index of suspicion, prompt diagnosis, and utilization of eculizumab are key to successful salvage of allografts in cases of aHUS after kidney transplantation. aHUS can be prevented by prophylactic use of eculizumab. It still needs to be determined when and if eculizumab therapy can be safely discontinued.

123. Cost-effectiveness of eculizumab treatment after kidney transplantation in patients with atypical haemolytic uraemic syndrome.
van den Brand JA, Verhave JC, Adang EM et al.
Nephrol Dial Transplant. 2017 Jan 1;32(suppl_1):i115-i122.

ABSTRACT

Background: Kidney transplantation in patients with atypical haemolytic uraemic syndrome (aHUS) is frequently complicated by recurrence of aHUS, often resulting in graft loss. Eculizumab prophylaxis prevents recurrence, improving graft survival. An alternative treatment strategy has been proposed where eculizumab is administered upon recurrence. We combined available evidence and performed a cost-effectiveness analysis of these competing strategies.
Methods: A cost-effectiveness analysis using a decision analytical approach with Markov chain analyses was used to compare alternatives for aHUS patients with end-stage renal disease (ESRD): (i) dialysis treatment, (ii) kidney transplantation, (iii) kidney transplantation with eculizumab therapy upon recurrence of aHUS, (iv) kidney transplantation with eculizumab induction consisting of 12 months of prophylaxis and (v) kidney transplantation with lifelong eculizumab prophylaxis. We assumed that all patients received a graft from a living donor and that recurrence probability was 28.4% within the first year of transplantation.
Results: At 8.34 quality-adjusted life years (QALYs) gained and a cost of €402 412, kidney transplantation without eculizumab was the least costly alternative. By comparison, dialysis was more costly and resulted in fewer QALYs gained. Eculizumab upon recurrence resulted in 9.55 QALYs gained at a cost of €425 097. The incremental cost-effectiveness ratio (ICER) was €18 748 per QALY. Both eculizumab induction and lifelong eculizumab were inferior to eculizumab upon recurrence, as both resulted in fewer QALYs gained and higher costs.
Conclusions: Kidney transplantation is more cost effective than dialysis to treat ESRD due to aHUS. Adding eculizumab treatment results in a substantial gain in QALYs. When compared with eculizumab upon recurrence, neither eculizumab induction nor lifelong eculizumab prophylaxis resulted in more QALYs, but did yield far higher costs. Therefore, eculizumab upon recurrence of aHUS is more acceptable.

124. Outcomes of Kidney Transplant Patients with Atypical Hemolytic Uremic Syndrome Treated with Eculizumab: A Systematic Review and Meta-Analysis.

Gonzalez Suarez ML, Thongprayoon C, Mao MA et al.

J Clin Med. 2019 Jun 27;8(7):919.

ABSTRACT

Background: Kidney transplantation in patients with atypical hemolytic uremic syndrome (aHUS) is frequently complicated by recurrence, resulting in thrombotic microangiopathy in the renal allograft and graft loss. We aimed to assess the use of eculizumab in the prevention and treatment of aHUS recurrence after kidney transplantation.
Methods: Databases (MEDLINE, EMBASE and Cochrane Database) were searched through February 2019. Studies that reported outcomes of adult kidney transplant recipients with aHUS treated with eculizumab were included. Estimated incidence rates from the individual studies were extracted and combined using random-effects, generic inverse variance method of DerSimonian and Laird. Protocol for this systematic review has been registered with PROSPERO (International Prospective Register of Systematic Reviews; no. CRD42018089438).
Results: Eighteen studies (13 cohort studies and five case series) consisting of 380 adult kidney transplant patients with aHUS who received eculizumab for prevention and treatment of post-transplant aHUS recurrence were included in the analysis. Among patients who received prophylactic eculizumab, the pooled estimated incidence rates of recurrent thrombotic

microangiopathy (TMA) after transplantation and allograft loss due to TMA were 6.3% (95%CI: 2.8-13.4%, I2 = 0%) and 5.5% (95%CI: 2.9-10.0%, I2 = 0%), respectively. Among those who received eculizumab for treatment of post-transplant aHUS recurrence, the pooled estimated rates of allograft loss due to TMA was 22.5% (95%CI: 13.6-34.8%, I2 = 6%). When the meta-analysis was restricted to only cohort studies with data on genetic mutations associated with aHUS, the pooled estimated incidence of allograft loss due to TMA was 22.6% (95%CI: 13.2-36.0%, I2 = 10%). We found no significant publication bias assessed by the funnel plots and Egger's regression asymmetry test ($p > 0.05$ for all analyses).
Conclusions: This study summarizes the outcomes observed with use of eculizumab for prevention and treatment of aHUS recurrence in kidney transplantation. Our results suggest a possible role for anti-C5 antibody therapy in the prevention and management of recurrent aHUS.

G. TRATAMIENTO DE LA RECIDIVA

125. Use of Highly Individualized Complement Blockade Has Revolutionized Clinical Outcomes after Kidney Transplantation and Renal Epidemiology of Atypical Hemolytic Uremic Syndrome.
Zuber J, Frimat M, Caillard S et al.
JASN December 2019, 30 (12) 2449-2463.

ABSTRACT
Background: Atypical hemolytic uremic syndrome (HUS) is associated with high recurrence rates after kidney transplant, with devastating outcomes. In late 2011, experts in France recommended the use of highly individualized complement blockade-based prophylaxis with eculizumab to prevent post-transplant atypical HUS recurrence throughout the country.
Methods: To evaluate this strategy's effect on kidney transplant prognosis, we conducted a retrospective multicenter study from a large French nationwide registry, enrolling all adult patients with atypical HUS who had undergone complement analysis and a kidney transplant since January 1, 2007. To assess how atypical HUS epidemiology in France in the eculizumab era evolved, we undertook a population-based cohort study that included all adult patients with atypical HUS (n=397) between 2007 and 2016.
Results: The first study included 126 kidney transplants performed in 116 patients, 58.7% and 34.1% of which were considered to be at a high and moderate risk of atypical HUS recurrence, respectively. Eculizumab prophylaxis was used in 52 kidney transplants, including 39 at high risk of recurrence. Atypical HUS recurred after 43 (34.1%) of the transplants; in four cases, patients had received eculizumab prophylaxis and in 39 cases they did not. Use of prophylactic eculizumab was independently associated with a significantly reduced risk of recurrence and with significantly longer graft survival. In the second, population-based cohort study, the proportion of transplant recipients among patients with ESKD and atypical HUS sharply increased between 2012 and 2016, from 46.2% to 72.3%, and showed a close correlation with increasing eculizumab use among the transplant recipients.
Conclusions: Results from this observational study are consistent with benefit from eculizumab prophylaxis based on pretransplant risk stratification and support the need for a rigorous randomized trial.

126. Atypical hemolytic uremic syndrome post-kidney transplantation: two case reports and review of the literature.

Alasfar S, Alachkar N.

Front Med (Lausanne). 2014 Dec 12;1:52.

ABSTRACT

Atypical hemolytic uremic syndrome (aHUS) is a rare disorder characterized by over-activation and dysregulation of the alternative complement pathway. Its estimated prevalence is 1-2 per million. The disease is characterized by thrombotic microangiopathy, which causes anemia, thrombocytopenia, and acute renal failure. aHUS has more severe course compared to typical (infection-induced) HUS and is frequently characterized by relapses that leads to end stage renal disease. For a long time, kidney transplantation for these patients was contraindicated because of high rate of recurrence and subsequent renal graft loss. The post-kidney transplantation recurrence rate largely depends on the pathogenetic mechanisms involved. However, over the past several years, advancements in the understanding and therapeutics of aHUS have allowed successful kidney transplantation in these patients. Eculizumab, which is a complement C5 antibody that inhibits complement factor 5a and subsequent formation of the membrane-attack complex, has been used in prevention and treatment of post-transplant aHUS recurrence. In this paper, we present two new cases of aHUS patients who underwent successful kidney transplantation in our center with the use of prophylactic and maintenance eculizumab therapy that have not been published before. The purpose of reporting these two cases is to emphasize the importance of using eculizumab as a prophylactic therapy to prevent aHUS recurrence post-transplant in high-risk patients. We will also review the current understanding of the genetics of aHUS, the pathogenesis of its recurrence after kidney transplantation, and strategies for prevention and treatment of post-transplant aHUS recurrence.

127. The use of eculizumab in renal transplantation

Barnet ANR, Asgari E, Chowdhury P et al.

Clin Transplant. May-Jun 2013;27(3):E216-29.

ABSTRACT

The complement system plays a vital role in mediating disease processes within renal allografts. Eculizumab is a humanized monoclonal antibody that targets complement protein C5, inhibiting cleavage into C5a and C5b, and therefore preventing formation of the membrane attack complex (MAC). It has been used primarily within renal transplantation to treat atypical hemolytic-uremic syndrome (aHUS) and antibody-mediated rejection (AMR) post-transplant, and also as prophylaxis in transplants at high risk for these conditions. Eculizumab appears to be effective in protecting renal allografts when post-transplant aHUS or AMR occur, although the published cases report relatively short follow-up. It is unclear how long treatment should continue (a particularly important issue given the expense of the drug), or whether eculizumab contributes to the development of accommodation in humans. When used for prophylaxis, eculizumab also appears to be effective. Some highly sensitized patients have developed either acute AMR or features of chronic AMR despite administration of the drug - this suggests that complement activation is not the only

mechanism responsible for AMR. All patients should receive vaccination against Neisseria meningitidis prior to receiving eculizumab. Clinical trials, predominantly in antibody-incompatible renal transplantation, are ongoing to determine the optimal use of C5 inhibition.

128. Ten-year Outcome of Eculizumab in Kidney Transplant Recipients With Atypical Hemolytic Uremic Syndrome- A Single Center Experience.

Kant S, Bhalla A, Alasfar S et al.

BMC Nephrol. 2020 May 20;21(1):189.

ABSTRACT

Background: Atypical hemolytic uremic syndrome (aHUS) can result in severe kidney dysfunction, secondary to thrombotic microangiopathy. Eculizumab has been used to treat this disorder, and has resulted in favourable outcomes in both, native and transplanted kidneys. There is limited long term follow up data in kidney transplant recipients (KTRs) who received prevention and treatment with Eculizumab. We report our long term follow up data from our center to address safety and efficacy of this therapy in KTRs.

Methods: We performed a retrospective analysis of KTRs between January 2009 and December 2018. Clinical diagnosis of aHUS established with presence of thrombotic microangiopathy, acute kidney injury, absence of alternate identifiable etiology. We reviewed clinical data, including genetic testing for complement factor mutations, post-transplant course, and response to therapy including therapeutic and prophylactic use of eculizumab.

Results: Nineteen patients with aHUS received a total of 36 kidney transplants; 10 of them had 2 or more prior kidney transplants. Median age at time of last transplant was 37 years (range 27-59), 72% were female (n = 14), 78% Caucasian (n = 15), with 61% had live donor transplant (n = 12) as the last transplant. Eculizumab prophylaxis was given to 10/19 (56%) at the time of transplantation, with no aHUS recurrence during the follow up. Median duration of follow up was 46 (range 6-237) months. Mean estimated glomerular filtration rate (eGFR) at the time of last follow up was 59.5 ml/min/m^2. No infections secondary to encapsulated organisms or other major infectious complications occurred during the follow up.

Conclusions: Eculizumab prophylaxis is safe and effective in KTRs with aHUS. Long term follow up demonstrates that it may be possible to discontinue prophylaxis carefully in selected patients with no evidence of complement mutations.

129. Complement Genes Strongly Predict Recurrence and Graft Outcome in Adult Renal Transplant Recipients With Atypical Hemolytic and Uremic Syndrome.

Le Quintrec M, Zuber J, Moulin B et al.

Am J Transplant. 2013 Mar;13(3):663-75.

ABSTRACT

Atypical hemolytic and uremic syndrome (aHUS) is a severe disease strongly associated with genetic abnormalities in the complement alternative pathway. In renal posttransplantation, few data are available on recurrence risk and graft outcome according to genetic background in aHUS patients. The aim of this study was to identify risk factors for recurrence and transplant outcome and, in

particular, the role of complement gene abnormalities. We retrospectively studied 57 aHUS patients who had received 71 renal transplants. A mutation in complement gene was identified in 39 (68%), in factor H (CFH), factor I (CFI), membrane cofactor-protein (MCP), C3 and factor B (CFB). At 5 years, death-censored graft survival was 51%. Disease recurrence was associated with graft loss ($p = 0.001$). Mutations in complement genes were associated with higher risk of recurrence ($p = 0.009$). Patients with CFH or gain of function (C3, CFB) mutations had a highest risk of recurrence. M-TOR inhibitor was associated with significant risk of recurrence ($p = 0.043$) but not calcineurin inhibitor immunosuppressive treatment ($p = 0.29$). Preemptive plasmatherapy was associated with a trend to decrease recurrence ($p = 0.07$). Our study highlights that characterization of complement genetic abnormalities predicts the risk of recurrence-related graft loss and paves the way for future genetically based individualized prophylactic therapeutic strategies.

130. Outcomes of patients with atypical haemolytic uraemic syndrome with native and transplanted kidneys treated with eculizumab: a pooled post hoc analysis.
Legendre CM, Campistol JM, Feldkamp T et al.
Transpl Int. 2017;30(12):1275-1283.

ABSTRACT
Atypical haemolytic uraemic syndrome (aHUS) often leads to end-stage renal disease (ESRD) and kidney transplantation; graft loss rates are high due to disease recurrence. A post hoc analysis of four prospective clinical trials in aHUS was performed to evaluate eculizumab, a terminal complement inhibitor, in patients with native or transplanted kidneys. The trials included 26-week treatment and extension periods. Dialysis, transplant and graft loss were evaluated. Study endpoints included complete thrombotic microangiopathy (TMA) response, TMA event-free status, haematologic and renal parameters and adverse events. Of 100 patients, 74 had native kidneys and 26 in the transplant subgroup had a collective history of 38 grafts. No patients lost grafts and only one with pre-existing ESRD received a transplant on treatment. Efficacy endpoints were achieved similarly in both subgroups. After 26 weeks, mean absolute estimated glomerular filtration rate increased from baseline to 61 and 37 ml/min/1.73 m^2 in native ($n = 71$; $P < 0.0001$) and transplanted kidney ($n = 25$; $P = 0.0092$) subgroups. Two patients (one/subgroup) developed meningococcal infections; both recovered, one continued therapy. Eculizumab was well tolerated. Eculizumab improved haematologic and renal outcomes in both subgroups. In patients with histories of multiple graft losses, eculizumab protected kidney function.

131. Atypical hemolytic uremic syndrome recurrence after kidney transplantation.
Matar D, Naqvi F, Racusen LC et al.
Transplantation. 2014;98(11):1205-1212.

ABSTRACT
Background: Atypical hemolytic uremic syndrome (aHUS) is a rare disease with a high recurrence rate after kidney transplantation. In most cases, aHUS are caused by genetic mutations of components of the complement alternative pathway. In this single-center series, we present our data of 12 consecutive patients with aHUS and the outcome after kidney transplantation.

Methods: In this 10-year retrospective study, we identified 12 patients with aHUS who were managed in our center since 2003. We reviewed clinical data, including genetic testing, posttransplant course and response to therapy including the prophylactic use of eculizumab.
Results: Overall, eight patients are women. Six of our patients have at least one genetic mutation causing aHUS, including 4 with complement factor H mutations. Nine patients had at least one previous kidney transplant that failed secondary to recurrent aHUS (75% of our patients). Three patients were treated with eculizumab and plasmapheresis for recurrent aHUS after kidney transplantation; two of them responded to the therapy. Four patients received prophylactic eculizumab; three of them received 6 months and one has been on life long therapy. No signs of recurrence have been observed in these 4 patients so far.
Conclusion: Genetic mutations of the complement alternative pathway were confirmed in half of our patients, most of those mutations are in CHF. We demonstrate that treatment or prophylaxis with eculizumab was effective in reversing or preventing aHUS whether or not genetic complement mutations were identified.

132. Long-term outcomes of the Atypical Hemolytic Uremic Syndrome after kidney transplantation treated with eculizumab as first choice.
de Andrade LGM, Contti MM, Nga HS et al.
PLoS One. 2017;12(11):e0188155.

ABSTRACT
Introduction: The treatment of choice for Atypical Hemolytic Uremic Syndrome (aHUS) is the monoclonal antibody eculizumab. The objective of this study was to assess the efficacy and safety of eculizumab in a cohort of kidney transplant patients suffering from aHUS.
Methods: Description of the prospective cohort of all the patients primarily treated with eculizumab after transplantation and divided into the therapeutic (onset of aHUS after transplantation) and prophylactic use (patients with previous diagnosis of aHUS undergoing kidney transplantation).
Results: Seven cases were outlined: five of therapeutic use and two, prophylactic. From the five cases of therapeutic use, there was improvement of the thrombotic microangiopathy in the 48 hours following the start of the drug and no patient experienced relapse during an average follow-up of 21 months in the continuous use of eculizumab (minimum of 6 and maximum of 42 months). One patient died at 6 months, due to Aspergillus infection. From the two cases of prophylactic use, one patient experienced relapsed thrombotic microangiopathy after 4 months and another patient remained asymptomatic after 16 months of follow-up, both on chronic treatment.
Discussion: The therapeutic use of eculizumab showed to be effective, with improvement of the microangiopathy parameters and persisting up to the end of the follow-up, without relapses. The additional risk of immunosuppression, leading to opportunistic infections, was well tolerated. The prophylactic use showed to be effective and safe; however, the doses and intervals should be individualized in order to avoid relapsed microangiopathy, especially in patients with factor H mutation.

133. Managing and preventing atypical hemolytic uremic syndrome recurrence after kidney transplantation.

Noris M, Remuzzi G.
Curr Opin Nephrol Hypertens. 2013;22(6):704-712.

ABSTRACT
Purpose of review: Several genetic and acquired abnormalities leading to abnormal activation of the alternative pathway of complement have been identified in patients with atypical hemolytic uremic syndrome (aHUS). The purpose of this review is to shed light on how advances in the understanding of aHUS pathogenesis have impacted on prevention and cure of aHUS recurrence after kidney transplantation.
Recent findings: Studies over the past decade have shown that the risk of posttransplant recurrence of aHUS depends on the underlying genetic abnormality. The risk is high in patients with mutations in genes encoding circulating complement proteins and regulators, whereas patients with mutations in membrane cofactor protein generally show good transplant outcome. Given the poor outcome associated with recurrence, isolated renal transplantation had been contraindicated in aHUS patients. Combined kidney-liver transplantation and prophylactic plasma exchange have been used to prevent posttransplant recurrences. More recent data have provided evidence about the efficacy of the anti-C5 monoclonal antibody eculizumab in the prevention and treatment of posttransplant aHUS recurrences.
Summary: This review summarizes recent advances on preventing and managing aHUS recurrence after kidney transplantation and discusses the issues that still need clarification.

134. Outcomes of Kidney Transplant Patients with Atypical Hemolytic Uremic Syndrome Treated with Eculizumab: A Systematic Review and Meta-Analysis.
Gonzalez Suarez ML, Thongprayoon C, Mao MA, Leeaphorn N, Bathini T, Cheungpasitporn W.
J Clin Med. 2019;8(7):919.

ABSTRACT
Background: Kidney transplantation in patients with atypical hemolytic uremic syndrome (aHUS) is frequently complicated by recurrence, resulting in thrombotic microangiopathy in the renal allograft and graft loss. We aimed to assess the use of eculizumab in the prevention and treatment of aHUS recurrence after kidney transplantation.
Methods: Databases (MEDLINE, EMBASE and Cochrane Database) were searched through February 2019. Studies that reported outcomes of adult kidney transplant recipients with aHUS treated with eculizumab were included. Estimated incidence rates from the individual studies were extracted and combined using random-effects, generic inverse variance method of DerSimonian and Laird. Protocol for this systematic review has been registered with PROSPERO (International Prospective Register of Systematic Reviews; no. CRD42018089438).
Results: Eighteen studies (13 cohort studies and five case series) consisting of 380 adult kidney transplant patients with aHUS who received eculizumab for prevention and treatment of post-transplant aHUS recurrence were included in the analysis. Among patients who received prophylactic eculizumab, the pooled estimated incidence rates of recurrent thrombotic microangiopathy (TMA) after transplantation and allograft loss due to TMA were 6.3% (95%CI: 2.8-13.4%, I^2 = 0%) and 5.5% (95%CI: 2.9-10.0%, I2 = 0%), respectively. Among those who received eculizumab for treatment of post-transplant aHUS recurrence, the pooled estimated rates of

allograft loss due to TMA was 22.5% (95%CI: 13.6-34.8%, I^2 = 6%). When the meta-analysis was restricted to only cohort studies with data on genetic mutations associated with aHUS, the pooled estimated incidence of allograft loss due to TMA was 22.6% (95%CI: 13.2-36.0%, I^2 = 10%). We found no significant publication bias assessed by the funnel plots and Egger's regression asymmetry test ($p > 0.05$ for all analyses).
Conclusions: This study summarizes the outcomes observed with use of eculizumab for prevention and treatment of aHUS recurrence in kidney transplantation. Our results suggest a possible role for anti-C5 antibody therapy in the prevention and management of recurrent aHUS.

135. Prevention and Treatment of Atypical Haemolytic Uremic Syndrome After Kidney Transplantation.
Okumi M, Tanabe K.
Nephrology (Carlton). 2016 Jul;21 Suppl 1:9-13.

ABSTRACT
Atypical haemolytic uraemic syndrome is a rare disorder characterized by an over-activated, dysregulated alternative complement pathway due to genetic mutation and environmental triggers. Atypical haemolytic uraemic syndrome is a serious, life-threatening disease characterized by thrombotic microangiopathy, which causes haemolytic anaemia, thrombocytopaenia, and acute renal failure. Since recurrences of atypical haemolytic uraemic syndrome frequently lead to end-stage kidney disease even in renal allografts, kidney transplantation for patients with end-stage kidney disease secondary to atypical haemolytic uraemic syndrome has long been contraindicated. However, over the past several years, advancements in the management of atypical haemolytic uraemic syndrome have allowed successful kidney transplantation in these patients. The key factor of this success is eculizumab, a humanized anti-C5 monoclonal antibody, which inhibits terminal membrane-attack complex formation and thrombotic microangiopathy progression. In the setting of kidney transplantation, there are different possible triggers of post-transplant atypical haemolytic uraemic syndrome recurrence, such as brain-death related injury, ischaemia-reperfusion injury, infections, the use of immunosuppressive drugs, and rejection. Principal strategies are to prevent endothelial damage that could potentially activate alternative complement pathway activation and subsequently lead to atypical haemolytic uraemic syndrome recurrence in kidney allograft. Published data shows that prophylactic eculizumab therapy is highly effective for the prevention of post-transplant atypical haemolytic uraemic syndrome recurrence, and prompt treatment with eculizumab as soon as recurrence is diagnosed is important to maintain renal allograft function. Further study to determine the optimal dosing and duration of prophylactic therapy and treatment of post-transplant atypical haemolytic uraemic syndrome recurrence is needed.

136. The long-acting C5 inhibitor, Ravulizumab, is effective and safe in adult patients with atypical hemolytic uremic syndrome naïve to complement inhibitor treatment.
Rondeau E, Scully M, Ariceta G et al.
Kidney Int. 2020 Jun;97(6):1287-1296.

ABSTRACT

Ravulizumab is a long-acting C5 inhibitor engineered from eculizumab with increased elimination half-life, allowing an extended dosing interval from two to eight weeks. Here we evaluate the efficacy and safety of ravulizumab in adults with atypical hemolytic uremic syndrome presenting with thrombotic microangiopathy. In this global, phase 3, single arm study in complement inhibitor-naïve adults (18 years and older) who fulfilled diagnostic criteria for atypical hemolytic uremic syndrome, enrolled patients received ravulizumab through a 26-week initial evaluation period. The primary endpoint was complete thrombotic microangiopathy response defined as normalization of platelet count and lactate dehydrogenase and 25% or more improvement in serum creatinine. Secondary endpoints included changes in hematologic variables and renal function. Safety was also evaluated. Ravulizumab treatment resulted in an immediate, complete, and sustained C5 inhibition in all patients. Complete thrombotic microangiopathy response was achieved in 53.6% of patients. Normalization of platelet count, lactate dehydrogenase and 25% or more improvement in serum creatinine was achieved in 83.9%, 76.8% and 58.9% of patients, respectively. Improvement in estimated glomerular filtration rate by one or more stage was achieved in 68.1% of patients by day 183. No unexpected adverse events were reported across a safety analysis set of 58 patients. Four deaths occurred (three within one month of study initiation, including one in a patient excluded based on eligibility criteria after the first dose) with none considered treatment-related by the study investigator. Thus, treatment with ravulizumab once every eight weeks resulted in rapidly improved hematologic and renal endpoints with no unexpected adverse events in adults with atypical hemolytic uremic syndrome.

137. Eculizumab Use for Kidney Transplantation in Patients With a Diagnosis of Atypical Hemolytic Uremic Syndrome.

Siedlecki AM, Isbel N, Walle JV et al.

Kidney Int Rep. 2018 Dec 3;4(3):434-446.

ABSTRACT

Introduction: Recurrence of atypical hemolytic uremic syndrome (aHUS) in renal allografts is common, leading to dialysis and graft failure. Pretransplant versus posttransplant initiation of eculizumab treatment in patients with aHUS has not been rigorously investigated. We hypothesized eculizumab pretransplant would reduce dialysis incidence posttransplant.

Methods: Of patients enrolled in the Global aHUS Registry (n = 1549), 344 had ≥1 kidney transplant. Of these, 188 had received eculizumab. Eighty-eight patients (47%) were diagnosed with aHUS and received eculizumab before, and during, their most recent transplant (group 1). A total of 100 patients (53%; group 2) initiated eculizumab posttransplantation. This second group was subdivided into those diagnosed with aHUS before (n = 52; group 2a) or after (n = 48; group 2b) their most recent transplant.

Results: Within 5 years of transplantation, 47 patients required dialysis; the risk of dialysis after transplantation was significantly increased in group 2b (hazard ratio [HR] 4.6; confidence interval [CI] 1.7-12.4) but not 2a (HR 2.3; CI 0.9-6.2). Graft function within 6 months of transplantation was significantly better in group 1 (median estimated glomerular filtration rate of 60.6 ml/min per 1.73 m^2) compared with 31.5 and 9.6 ml/min per 1.73 m^2 in groups 2a (P = 0.004) and 2b (P = 0.0001), respectively. One meningococcal infection (resolved with treatment) and 3 deaths (deemed unrelated to eculizumab) were reported.

Conclusions: Outcomes for transplant patients with aHUS treated with eculizumab were improved compared with previous reports of patients with aHUS not treated with eculizumab. Our findings suggest delayed aHUS diagnosis and therefore treatment is associated with an increased risk of dialysis posttransplantation and reduced allograft function.

138. Eculizumab for atypical hemolytic uremic syndrome recurrence in renal transplantation.
Zuber J, Le Quintrec M, Krid S, et al.
Am J Transplant. 2012;12(12):3337-3354.

ABSTRACT
Eculizumab (anti-C5) has been sporadically reported as an efficient therapy for atypical hemolytic uremic syndrome (aHUS). However, the lack of series precludes any firm conclusion about the optimal use of anti-C5 for preventing or treating aHUS posttransplant aHUS recurrence. We thoroughly studied 22 renal transplant recipients with aHUS who received off-label therapy with anti-C5, including 12 cases, which have not been reported yet. Nine patients, all carrying a complement genetic abnormality associated with a high risk of aHUS recurrence, received prophylactic anti-C5 therapy to prevent posttransplant recurrence. Eight of them had a successful recurrence-free posttransplant course and achieved a satisfactory graft function, while the remaining patient experienced early arterial thrombosis of the graft. Thirteen renal transplant recipients were given anti-C5 for posttransplant aHUS recurrence. A complete reversal of aHUS activity was obtained in all of them. Importantly, the delay of anti-C5 initiation after the onset of the aHUS episode inversely correlated with the degree of renal function improvement. Three patients in whom anti-C5 was subsequently stopped experienced a relapse. Altogether these data suggest that long-term eculizumab is highly effective for preventing and treating posttransplant aHUS recurrence. Our study also indicates that anti-C5 should be promptly started if a recurrence occurs.

139. Targeted Strategies in the Prevention and Management of Atypical HUS Recurrence After Kidney Transplantation.
Zuber J, Le Quintrec M, Morris H et al.
Transplant Rev (Orlando). 2013 Oct;27(4):117-25.

ABSTRACT
Atypical hemolytic and uremic syndrome (aHUS) is associated with a high rate of recurrence and poor outcomes after kidney transplantation. Fortunately, recent advances in the understanding of the pathogenesis of aHUS have permitted an individualized risk assessment of post-transplant recurrence. Acquired or inherited dysregulation of the alternative complement pathway, thought to be the driving force of the disease, is identified in most aHUS patients. Notably, depending on the mutations involved, the risk of recurrence greatly varies, highlighting the importance of undertaking etiological investigations prior to kidney transplantation. In those with moderate to high risk of recurrence, the use of a prophylactic therapy, consisting in either plasmapheresis or eculizumab therapies, represents a major stride forward in the prevention of aHUS recurrence after kidney transplantation. In those who experience aHUS recurrence, a growing number of observations

suggest that eculizumab therapy outperforms curative plasma therapy. The optimal duration of both prophylactic and curative therapies remains an important, yet unaddressed, issue. In this respect, the kidney transplant recipients, continuously exposed to endothelial-insulting factors, referred here as to triggers, might have a sustained high risk of recurrence. A global therapeutic approach should thus attempt to reduce exposure to these triggers.

H. DURACIÓN DEL TRATAMIENTO. CRITERIOS DE SUSPENSIÓN. RESULTADOS TRAS LA SUSPENSIÓN DEL TRATAMIENTO RIESGO DE REAPARICIÓN DEL CUADRO TRAS LA SUSPENSIÓN DEL TRATAMIENTO

140. Terminal complement inhibitor eculizumab in atypical hemolytic-uremic syndrome.
Legendre CM, Licht C, Muus P, et al.
N Engl J Med. 2013;368(23):2169-2181.

ABSTRACT
Background: Atypical hemolytic-uremic syndrome is a genetic, life-threatening, chronic disease of complement-mediated thrombotic microangiopathy. Plasma exchange or infusion may transiently maintain normal levels of hematologic measures but does not treat the underlying systemic disease.
Methods: We conducted two prospective phase 2 trials in which patients with atypical hemolytic-uremic syndrome who were 12 years of age or older received eculizumab for 26 weeks and during long-term extension phases. Patients with low platelet counts and renal damage (in trial 1) and those with renal damage but no decrease in the platelet count of more than 25% for at least 8 weeks during plasma exchange or infusion (in trial 2) were recruited. The primary end points included a change in the platelet count (in trial 1) and thrombotic microangiopathy event-free status (no decrease in the platelet count of >25%, no plasma exchange or infusion, and no initiation of dialysis) (in trial 2).
Results: A total of 37 patients (17 in trial 1 and 20 in trial 2) received eculizumab for a median of 64 and 62 weeks, respectively. Eculizumab resulted in increases in the platelet count; in trial 1, the mean increase in the count from baseline to week 26 was 73×10(9) per liter (P<0.001). In trial 2, 80% of the patients had thrombotic microangiopathy event-free status. Eculizumab was associated with significant improvement in all secondary end points, with continuous, time-dependent increases in the estimated glomerular filtration rate (GFR). In trial 1, dialysis was discontinued in 4 of 5 patients. Earlier intervention with eculizumab was associated with significantly greater improvement in the estimated GFR. Eculizumab was also associated with improvement in health-related quality of life. No cumulative toxicity of therapy or serious infection-related adverse events, including meningococcal infections, were observed through the extension period.
Conclusions: Eculizumab inhibited complement-mediated thrombotic microangiopathy and was associated with significant time-dependent improvement in renal function in patients with atypical hemolytic-uremic syndrome. (Funded by Alexion Pharmaceuticals; C08-002 ClinicalTrials.gov numbers, NCT00844545 [adults] and NCT00844844 [adolescents]; C08-003 ClinicalTrials.gov numbers, NCT00838513 [adults] and NCT00844428 [adolescents]).

141. Use of eculizumab for atypical haemolytic uraemic syndrome and C3 glomerulopathies.

Zuber J, Fakhouri F, Roumenina LT et al.
Nat Rev Nephrol 2012; 8: pp. 643-657.

ABSTRACT
In the past decade, a large body of evidence has accumulated in support of the critical role of dysregulation of the alternative complement pathway in atypical haemolytic uraemic syndrome (aHUS) and C3 glomerulopathies. These findings have paved the way for innovative therapeutic strategies based on complement blockade, and eculizumab, a monoclonal antibody targeting the human complement component 5, is now widely used to treat aHUS. In this article, we review 28 case reports and preliminary data from 37 patients enrolled in prospective trials of eculizumab treatment for episodes of aHUS involving either native or transplanted kidneys. Eculizumab may be considered as an optimal first-line therapy when the diagnosis of aHUS is unequivocal and this treatment has the potential to rescue renal function when administered early after onset of the disease. However, a number of important issues require further study, including the appropriate duration of treatment according to an individual's genetic background and medical history, the optimal strategy to prevent post-transplantation recurrence of aHUS and a cost-efficacy analysis. Data regarding the efficacy of eculizumab in the control of C3 glomerulopathies are more limited and less clear, but several observations suggest that eculizumab may act on the most inflammatory forms of this disorder.

142. Eculizumab use in kidney transplantation.
Johnson CK, Leca N.
Curr Opin Organ Transplant. 2015;20(6):643-651.

ABSTRACT
Purpose of review: Eculizumab suppresses the effector functions of the complement system and represents a therapeutic breakthrough for patients with paroxysmal nocturnal hemoglobinuria or atypical hemolytic uremic syndrome (aHUS). Safety monitoring is ongoing; so far, most notable is the expected increase in infection risk with encapsulated organisms. Despite potential applicability in multiple complement-mediated disorders, the off-label use of eculizumab has been limited, mainly by its prohibitive cost. The purpose of this review is to summarize the current data relevant to the use of eculizumab in kidney transplantation.
Recent findings: In aHUS, prone to high rates of recurrence and allograft loss, eculizumab has made the most notable therapeutic impact. Further clarification of complement defects may help predict therapeutic responses and hopefully guide treatment duration. In C3 glomerulopathies, the clinical response to eculizumab appears more heterogeneous and less effective in processes mediated by upstream to C5 complement deregulation. A large clinical trial of eculizumab for prevention of delayed graft function is ongoing. In antibody-mediated rejection, the role of eculizumab is unclear as its use has been limited to very complex, mostly presensitized, patients in mixed combinations of therapeutic modalities.
Summary: Overall, eculizumab has raised awareness of complement-mediated disorders as an exciting, new therapeutic option with multiple potential applications in kidney transplantation. Further research is needed to develop a better understanding of eculizumab applicability, efficacy, and treatment monitoring and beyond, to future therapeutic tools targeting the complement.

143. Atypical hemolytic uremic syndrome recurrence after kidney transplantation.
Matar D, Naqvi F, Racusen LC et al.
Transplantation. 2014;98(11):1205-1212.

ABSTRACT
Background: Atypical hemolytic uremic syndrome (aHUS) is a rare disease with a high recurrence rate after kidney transplantation. In most cases, aHUS are caused by genetic mutations of components of the complement alternative pathway. In this single-center series, we present our data of 12 consecutive patients with aHUS and the outcome after kidney transplantation.
Methods: In this 10-year retrospective study, we identified 12 patients with aHUS who were managed in our center since 2003. We reviewed clinical data, including genetic testing, posttransplant course and response to therapy including the prophylactic use of eculizumab.
Results: Overall, eight patients are women. Six of our patients have at least one genetic mutation causing aHUS, including 4 with complement factor H mutations. Nine patients had at least one previous kidney transplant that failed secondary to recurrent aHUS (75% of our patients). Three patients were treated with eculizumab and plasmapheresis for recurrent aHUS after kidney transplantation; two of them responded to the therapy. Four patients received prophylactic eculizumab; three of them received 6 months and one has been on life long therapy. No signs of recurrence have been observed in these 4 patients so far.
Conclusion: Genetic mutations of the complement alternative pathway were confirmed in half of our patients, most of those mutations are in CHF. We demonstrate that treatment or prophylaxis with eculizumab was effective in reversing or preventing aHUS whether or not genetic complement mutations were identified.

144. An update for atypical haemolytic uraemic syndrome: diagnosis and treatment. A consensus document.
Campistol JM, Arias M, Ariceta G, et al.
Nefrologia. 2013;33(1):27-45.

ABSTRACT
Haemolytic uraemic syndrome (HUS) is a clinical entity defined as the triad of nonimmune haemolytic anaemia, thrombocytopenia, and acute renal failure, in which the underlying lesions are mediated by systemic thrombotic microangiopathy (TMA). Atypical HUS (aHUS) is a sub-type of HUS in which the TMA phenomena are the consequence of decreased regulation of the alternative complement pathway on cell surfaces due to a genetic cause. aHUS is an extremely rare disease that, despite the administration of standard treatment with plasma therapy, often progresses to terminal chronic renal failure with a high associated rate of mortality. In recent years, research has established the key role that the complement system plays in the induction of endothelial damage in patients with aHUS, through the characterisation of multiple mutations and polymorphisms in the genes that code for certain complement factors. Eculizumab is a monoclonal antibody that inhibits the terminal fraction of the complement protein, blocking the formation of a cell membrane attack complex. In prospective studies in patients with aHUS, administering eculizumab produces a rapid and sustained interruption in the TMA process, with significant improvements in long-term renal function and an important decrease in the need for dialysis or plasma therapy. In this document, we

review and bring up to date the important aspects of this disease, with special emphasis on how recent advancements in diagnostic and therapeutic processes can modify the treatment of patients with aHUS.

145. Outcomes of Kidney Transplant Patients with Atypical Hemolytic Uremic Syndrome Treated with Eculizumab: A Systematic Review and Meta-Analysis.
Gonzalez Suarez ML, Thongprayoon C, Mao MA, Leeaphorn N, Bathini T, Cheungpasitporn W.
J Clin Med. 2019;8(7):919.

ABSTRACT
Background: Kidney transplantation in patients with atypical hemolytic uremic syndrome (aHUS) is frequently complicated by recurrence, resulting in thrombotic microangiopathy in the renal allograft and graft loss. We aimed to assess the use of eculizumab in the prevention and treatment of aHUS recurrence after kidney transplantation.
Methods: Databases (MEDLINE, EMBASE and Cochrane Database) were searched through February 2019. Studies that reported outcomes of adult kidney transplant recipients with aHUS treated with eculizumab were included. Estimated incidence rates from the individual studies were extracted and combined using random-effects, generic inverse variance method of DerSimonian and Laird. Protocol for this systematic review has been registered with PROSPERO (International Prospective Register of Systematic Reviews; no. CRD42018089438).
Results: Eighteen studies (13 cohort studies and five case series) consisting of 380 adult kidney transplant patients with aHUS who received eculizumab for prevention and treatment of post-transplant aHUS recurrence were included in the analysis. Among patients who received prophylactic eculizumab, the pooled estimated incidence rates of recurrent thrombotic microangiopathy (TMA) after transplantation and allograft loss due to TMA were 6.3% (95%CI: 2.8-13.4%, I^2 = 0%) and 5.5% (95%CI: 2.9-10.0%, I2 = 0%), respectively. Among those who received eculizumab for treatment of post-transplant aHUS recurrence, the pooled estimated rates of allograft loss due to TMA was 22.5% (95%CI: 13.6-34.8%, I^2 = 6%). When the meta-analysis was restricted to only cohort studies with data on genetic mutations associated with aHUS, the pooled estimated incidence of allograft loss due to TMA was 22.6% (95%CI: 13.2-36.0%, I^2 = 10%). We found no significant publication bias assessed by the funnel plots and Egger's regression asymmetry test ($p > 0.05$ for all analyses).
Conclusions: This study summarizes the outcomes observed with use of eculizumab for prevention and treatment of aHUS recurrence in kidney transplantation. Our results suggest a possible role for anti-C5 antibody therapy in the prevention and management of recurrent aHUS.

146. Midterm Outcomes of 12 Renal Transplant Recipients Treated With Eculizumab to Prevent Atypical Hemolytic Syndrome Recurrence.
Levi C, Frémeaux-Bacchi V, Zuber J, et al.
Transplantation. 2017;101(12):2924-2930.

ABSTRACT

Background: Atypical hemolytic uremic syndrome (aHUS) is an orphan disease with a high rate of recurrence after kidney transplantation. However, reports of successful prevention of posttransplant aHUS recurrence with eculizumab emerged a few years ago. To further delineate its optimal use, we describe the largest series of kidney transplant recipients treated with prophylactic eculizumab.
Methods: Twelve renal transplant recipients with aHUS-related end-stage renal disease received eculizumab: 10 from day 0 and 2 at the time of recurrence (days 6 and 25). Clinical and histological features, complement assessment, and free eculizumab measurements were analyzed. The median follow-up was 24.6 months.
Results: Five patients had failed at least 1 previous renal transplant from aHUS. A genetic mutation was identified in 9 patients, anti-H antibodies were found in 2. No patient demonstrated biological recurrence of thrombotic microangiopathy under treatment. Three antibody-mediated rejections (AMRs) occurred without detectable C5 residual activity. AMR was associated with subclinical thrombotic microangiopathy in 2 patients. One patient lost his graft after several complications, including AMR. One patient experienced posttransplant C3 glomerulonephritis. The last median serum creatinine was 128.2 ± 40.8 µmol/L.
Conclusions: These data confirm that eculizumab is highly effective in preventing posttransplantation aHUS recurrence, yet may not fully block AMR pathogenesis.

147. Eculizumab in atypical hemolytic uremic syndrome: strategies toward restrictive use.
Wijnsma KL, Duineveld C, Wetzels JFM et al.
Pediatr Nephrol. 2019 Nov;34(11):2261-2277..

ABSTRACT
With the introduction of the complement C5-inhibitor eculizumab, a new era was entered for patients with atypical hemolytic uremic syndrome (aHUS). Eculizumab therapy very effectively reversed thrombotic microangiopathy and reduced mortality and morbidity. Initial guidelines suggested lifelong treatment and recommended prophylactic use of eculizumab in aHUS patients receiving a kidney transplant. However, there is little evidence to support lifelong therapy or prophylactic treatment in kidney transplant recipients. Worldwide, there is an ongoing debate regarding the optimal dose and duration of treatment, particularly in view of the high costs and potential side effects of eculizumab. An increasing but still limited number of case reports and small cohort studies suggest that a restrictive treatment regimen is feasible. We review the current literature and focus on the safety and efficacy of restrictive use of eculizumab. Our current treatment protocol is based on restrictive use of eculizumab. Prospective monitoring will provide more definite proof of the feasibility of such restrictive treatment.

148. Current evidence on the discontinuation of eculizumab in patients with atypical haemolytic uraemic syndrome.
Macia M, de Alvaro Moreno F, Dutt T et al.
Clin Kidney J. 2017;10(3):310-319.

ABSTRACT

Background: Atypical haemolytic uraemic syndrome (aHUS) is a rare, life-threatening disorder for which eculizumab is the only approved treatment. Life-long treatment is indicated; however, eculizumab discontinuation has been reported.
Methods: Unpublished authors' cases and published cases of eculizumab discontinuation are reviewed. We also report eculizumab discontinuation data from five clinical trials, plus long-term extensions and the global aHUS Registry.
Results: Of six unpublished authors' cases, four patients had a subsequent thrombotic microangiopathy (TMA) manifestation within 12 months of discontinuation. Case reports of 52 patients discontinuing eculizumab were identified; 16 (31%) had a subsequent TMA manifestation. In eculizumab clinical trials, 61/130 patients discontinued treatment between 2008 and 2015. Median follow-up post-discontinuation was 24 weeks and during this time 12 patients experienced 15 severe TMA complications and 9 of the 12 patients restarted eculizumab. TMA complications occurred irrespective of identified genetic mutation, high risk polymorphism or auto-antibody. In the global aHUS Registry, 76/296 patients (26%) discontinued, 12 (16%) of whom restarted.
Conclusions: The currently available evidence suggests TMA manifestations following discontinuation are unpredictable in both severity and timing. For evidence-based decision making, better risk stratification and valid monitoring strategies are required. Until these exist, the risk versus benefit of eculizumab discontinuation, either in specific clinical situations or at selected time points, should include consideration of the risk of further TMA manifestations.

149. Eculizumab for atypical hemolytic uremic syndrome recurrence in renal transplantation.
Zuber J, Le Quintrec M, Krid S, et al.
Am J Transplant. 2012;12(12):3337-3354.

ABSTRACT
Eculizumab (anti-C5) has been sporadically reported as an efficient therapy for atypical hemolytic uremic syndrome (aHUS). However, the lack of series precludes any firm conclusion about the optimal use of anti-C5 for preventing or treating aHUS posttransplant aHUS recurrence. We thoroughly studied 22 renal transplant recipients with aHUS who received off-label therapy with anti-C5, including 12 cases, which have not been reported yet. Nine patients, all carrying a complement genetic abnormality associated with a high risk of aHUS recurrence, received prophylactic anti-C5 therapy to prevent posttransplant recurrence. Eight of them had a successful recurrence-free posttransplant course and achieved a satisfactory graft function, while the remaining patient experienced early arterial thrombosis of the graft. Thirteen renal transplant recipients were given anti-C5 for posttransplant aHUS recurrence. A complete reversal of aHUS activity was obtained in all of them. Importantly, the delay of anti-C5 initiation after the onset of the aHUS episode inversely correlated with the degree of renal function improvement. Three patients in whom anti-C5 was subsequently stopped experienced a relapse. Altogether these data suggest that long-term eculizumab is highly effective for preventing and treating posttransplant aHUS recurrence. Our study also indicates that anti-C5 should be promptly started if a recurrence occurs.

150. Outcomes of patients with atypical haemolytic uraemic syndrome with native and transplanted kidneys treated with eculizumab: a pooled post hoc analysis.

Legendre CM, Campistol JM, Feldkamp T et al.

Transpl Int. 2017;30(12):1275-1283.

ABSTRACT

Atypical haemolytic uraemic syndrome (aHUS) often leads to end-stage renal disease (ESRD) and kidney transplantation; graft loss rates are high due to disease recurrence. A post hoc analysis of four prospective clinical trials in aHUS was performed to evaluate eculizumab, a terminal complement inhibitor, in patients with native or transplanted kidneys. The trials included 26-week treatment and extension periods. Dialysis, transplant and graft loss were evaluated. Study endpoints included complete thrombotic microangiopathy (TMA) response, TMA event-free status, haematologic and renal parameters and adverse events. Of 100 patients, 74 had native kidneys and 26 in the transplant subgroup had a collective history of 38 grafts. No patients lost grafts and only one with pre-existing ESRD received a transplant on treatment. Efficacy endpoints were achieved similarly in both subgroups. After 26 weeks, mean absolute estimated glomerular filtration rate increased from baseline to 61 and 37 ml/min/1.73 m^2 in native ($n = 71$; $P < 0.0001$) and transplanted kidney ($n = 25$; $P = 0.0092$) subgroups. Two patients (one/subgroup) developed meningococcal infections; both recovered, one continued therapy. Eculizumab was well tolerated. Eculizumab improved haematologic and renal outcomes in both subgroups. In patients with histories of multiple graft losses, eculizumab protected kidney function.

151. Post-transplant recurrence of atypical hemolytic uremic syndrome in a patient with thrombomodulin mutation.

Sinibaldi S, Guzzo I, Piras R et al.

Pediatr Transplant. 2013;17(8):E177-E181.

ABSTRACT

HUS is characterized by hemolytic anemia, thrombocytopenia, and acute renal failure. While "typical" HUS is usually associated with Shiga toxin-producing Escherichia coli infections and recovers in the majority of cases, aHUS is caused by mutations of complement components or antibodies against CFH leading to uncontrolled activation of alternative complement pathway and often to ESRD. Recently, THBD gene mutations have been reported in aHUS. Theoretically, the risk of disease recurrence after renal transplantation should be low because THBD is primarily a membrane-bound protein expressed by endothelial cells; however, a small proportion of THBD is present as a soluble form in plasma. We report the case of a 19-yr-old man with aHUS secondary to a THBD mutation that relapsed twice after two renal transplantations performed 12 yr apart. Despite successful control of HUS with plasma exchange and eculizumab after the second transplantation, the graft was ultimately lost due to severe steroid-resistant cellular rejection. The present report suggests that THBD mutations may favor-relapse of aHUS after renal transplantation.

152. Eculizumab for the treatment of two recurrences of atypical hemolytic uremic syndrome in a kidney allograft.

Alachkar N, Bagnasco SM, Montgomery RA.
Transpl Int. 2012;25(8):e93-e95.

No abstract available

153. Efficacy of eculizumab in the treatment of recurrent atypical hemolytic-uremic syndrome after renal transplantation.
Larrea CF, Cofan F, Oppenheimer F et al.
Transplantation. 2010;89(7):903-904.

No abstract available

154. Eculizumab induces long-term remission in recurrent post-transplant HUS associated with C3 gene mutation.
Al-Akash SI, Almond PS, Savell VH Jr et al.
Pediatr Nephrol. 2011;26(4):613-619.

ABSTRACT
A 15-year-old male patient developed atypical hemolytic uremic syndrome (aHUS) at 16 months of age leading to end-stage renal disease. The family history was suggestive of autosomal dominant aHUS, and he was more recently found to have a C3 heterozygous gene mutation (1835C>T mutation in exon 14, which determines the amino-acidic substitution R570W) with no other complement abnormalities. He had two renal transplants, the first at 2.5 years, and the second at 8 years of age, but allograft dysfunction developed in both transplants leading to graft failure due to recurrent HUS at 5 years and 18 months post-transplantation respectively. At 15 years of age he received a third transplant from a deceased donor with pre-emptive plasmapheresis. He had immediate graft function and nadir serum creatinine was 1.3-1.4 mg/dl. Severe allograft dysfunction and hypertension developed 2 months after transplantation following influenza infection. Renal allograft biopsy showed thrombotic microangiopathy. He received plasmapheresis followed by eculizumab therapy. Allograft function returned to baseline 3 weeks after starting therapy, and post-treatment allograft biopsies showed improvement in thrombotic microangiopathy. He continues to receive eculizumab every 2 weeks with stable graft function 13 months after transplantation.

155. Successful long-term treatment of TMA with eculizumab in a transplanted patient with atypical hemolytic uremic syndrome due to MCP mutation.
Reuter S, Heitplatz B, Pavenstädt H et al.
Transplantation. 2013;96(10):e74-e76.

No abstract available

156. Managing and preventing atypical hemolytic uremic syndrome recurrence after kidney transplantation.

Noris M, Remuzzi G.

Curr Opin Nephrol Hypertens. 2013;22(6):704-712.

ABSTRACT

Purpose of review: Several genetic and acquired abnormalities leading to abnormal activation of the alternative pathway of complement have been identified in patients with atypical hemolytic uremic syndrome (aHUS). The purpose of this review is to shed light on how advances in the understanding of aHUS pathogenesis have impacted on prevention and cure of aHUS recurrence after kidney transplantation.

Recent findings: Studies over the past decade have shown that the risk of posttransplant recurrence of aHUS depends on the underlying genetic abnormality. The risk is high in patients with mutations in genes encoding circulating complement proteins and regulators, whereas patients with mutations in membrane cofactor protein generally show good transplant outcome. Given the poor outcome associated with recurrence, isolated renal transplantation had been contraindicated in aHUS patients. Combined kidney-liver transplantation and prophylactic plasma exchange have been used to prevent posttransplant recurrences. More recent data have provided evidence about the efficacy of the anti-C5 monoclonal antibody eculizumab in the prevention and treatment of posttransplant aHUS recurrences.

Summary: This review summarizes recent advances on preventing and managing aHUS recurrence after kidney transplantation and discusses the issues that still need clarification.

157. Long-term outcomes of the Atypical Hemolytic Uremic Syndrome after kidney transplantation treated with eculizumab as first choice.

de Andrade LGM, Contti MM, Nga HS et al.

PLoS One. 2017;12(11):e0188155.

ABSTRACT

Introduction: The treatment of choice for Atypical Hemolytic Uremic Syndrome (aHUS) is the monoclonal antibody eculizumab. The objective of this study was to assess the efficacy and safety of eculizumab in a cohort of kidney transplant patients suffering from aHUS.

Methods: Description of the prospective cohort of all the patients primarily treated with eculizumab after transplantation and divided into the therapeutic (onset of aHUS after transplantation) and prophylactic use (patients with previous diagnosis of aHUS undergoing kidney transplantation).

Results: Seven cases were outlined: five of therapeutic use and two, prophylactic. From the five cases of therapeutic use, there was improvement of the thrombotic microangiopathy in the 48 hours following the start of the drug and no patient experienced relapse during an average follow-up of 21 months in the continuous use of eculizumab (minimum of 6 and maximum of 42 months). One patient died at 6 months, due to Aspergillus infection. From the two cases of prophylactic use, one patient experienced relapsed thrombotic microangiopathy after 4 months and another patient remained asymptomatic after 16 months of follow-up, both on chronic treatment.

Discussion: The therapeutic use of eculizumab showed to be effective, with improvement of the microangiopathy parameters and persisting up to the end of the follow-up, without relapses. The

additional risk of immunosuppression, leading to opportunistic infections, was well tolerated. The prophylactic use showed to be effective and safe; however, the doses and intervals should be individualized in order to avoid relapsed microangiopathy, especially in patients with factor H mutation.

158. Ten-year outcome of Eculizumab in kidney transplant recipients with atypical hemolytic uremic syndrome- a single center experience.

Kant S, Bhalla A, Alasfar S et al.

BMC Nephrol. 2020;21(1):189.

ABSTRACT

Background: Atypical hemolytic uremic syndrome (aHUS) can result in severe kidney dysfunction, secondary to thrombotic microangiopathy. Eculizumab has been used to treat this disorder, and has resulted in favourable outcomes in both, native and transplanted kidneys. There is limited long term follow up data in kidney transplant recipients (KTRs) who received prevention and treatment with Eculizumab. We report our long term follow up data from our center to address safety and efficacy of this therapy in KTRs.

Methods: We performed a retrospective analysis of KTRs between January 2009 and December 2018. Clinical diagnosis of aHUS established with presence of thrombotic microangiopathy, acute kidney injury, absence of alternate identifiable etiology. We reviewed clinical data, including genetic testing for complement factor mutations, post-transplant course, and response to therapy including therapeutic and prophylactic use of eculizumab.

Results: Nineteen patients with aHUS received a total of 36 kidney transplants; 10 of them had 2 or more prior kidney transplants. Median age at time of last transplant was 37 years (range 27-59), 72% were female (n = 14), 78% Caucasian (n = 15), with 61% had live donor transplant (n = 12) as the last transplant. Eculizumab prophylaxis was given to 10/19 (56%) at the time of transplantation, with no aHUS recurrence during the follow up. Median duration of follow up was 46 (range 6-237) months. Mean estimated glomerular filtration rate (eGFR) at the time of last follow up was 59.5 ml/min/m^2. No infections secondary to encapsulated organisms or other major infectious complications occurred during the follow up.

Conclusions: Eculizumab prophylaxis is safe and effective in KTRs with aHUS. Long term follow up demonstrates that it may be possible to discontinue prophylaxis carefully in selected patients with no evidence of complement mutations.

159. Eculizumab for atypical hemolytic uremic syndrome recurrence in renal transplantation.

Zuber J, Le Quintrec M, Krid S et al.

Am J Transplant. 2012;12(12):3337-3354.

ABSTRACT

Eculizumab (anti-C5) has been sporadically reported as an efficient therapy for atypical hemolytic uremic syndrome (aHUS). However, the lack of series precludes any firm conclusion about the optimal use of anti-C5 for preventing or treating aHUS posttransplant aHUS recurrence. We thoroughly studied 22 renal transplant recipients with aHUS who received off-label therapy with

anti-C5, including 12 cases, which have not been reported yet. Nine patients, all carrying a complement genetic abnormality associated with a high risk of aHUS recurrence, received prophylactic anti-C5 therapy to prevent posttransplant recurrence. Eight of them had a successful recurrence-free posttransplant course and achieved a satisfactory graft function, while the remaining patient experienced early arterial thrombosis of the graft. Thirteen renal transplant recipients were given anti-C5 for posttransplant aHUS recurrence. A complete reversal of aHUS activity was obtained in all of them. Importantly, the delay of anti-C5 initiation after the onset of the aHUS episode inversely correlated with the degree of renal function improvement. Three patients in whom anti-C5 was subsequently stopped experienced a relapse. Altogether these data suggest that long-term eculizumab is highly effective for preventing and treating posttransplant aHUS recurrence. Our study also indicates that anti-C5 should be promptly started if a recurrence occurs.

160. A national specialized service in England for atypical haemolytic uraemic syndrome-the first year's experience.
Sheerin NS, Kavanagh D, Goodship TH et al.
QJM. 2016;109(1):27-33.

ABSTRACT
Background: In 2013 NHS England commissioned the use of eculizumab for both new patients with atypical haemolytic uraemic syndrome (aHUS) and those undergoing transplantation. This national service is delivered locally but coordinated by an expert centre at the Newcastle upon Tyne Hospitals NHS Foundation Trust.
Results: In the first year of service, 43 aHUS patients received eculizumab, 15 children and 28 adults. Twenty-three were new patients and 20 prevalent. Fifteen of the 23 new patients required dialysis before eculizumab was started, 8 of these recovered renal function. Twelve of the 20 prevalent patients who received eculizumab were transplant patients, 8 with prophylactic use and 4 for recurrent disease; the outcome in all was good. Eculizumab was withdrawn in 14 patients, 5 were patients who had not recovered renal function. In 3 of the 14 patients, it was necessary to reintroduce eculizumab because of recurrent disease (2 extra-renal and 1 renal). There were 2 deaths in the 43 patients, and neither was associated with use of eculizumab. There were no episodes of meningococcal disease.
Conclusions: The establishment of this national service has enabled aHUS patients in England to receive eculizumab when they need it for as long as they need it.

161. Atypical Hemolytic Uremic Syndrome After Kidney Transplantation: Lessons Learned From the Good, the Bad, and the Ugly. A Case Series With Literature Review.
Fayek SA, Allam SR, Martinez E et al.
Transplant Proc. 2020;52(1):146-152.

ABSTRACT
Atypical hemolytic uremic syndrome (aHUS) after kidney transplantation is rare and carries a grave outcome. We present a single-center experience of all aHUS cases since the program's inception.

Six patients were diagnosed with aHUS, all after kidney transplants, except for 1 patient. All had nonreactive crossmatches. Delayed graft function (DGF) occurred in 2 patients. Five patients developed aHUS after transplant; 4 (80%) of these patients manifested aHUS ≤ 14 days. All were confirmed by allograft biopsy. Genetic testing was abnormal in all patients except for 1 patient. Actual patient and graft survival during the first year was 100% and 83.3%, respectively. A single graft was lost early in the study secondary to aHUS (eculizumab was not used in the treatment process). Prophylactic and therapeutic use of eculizumab salvaged all other cases. At 1 year, mean creatinine level was 1.9 mg/dL (range, 1.3-2.5). After 6 months of eculizumab treatment (halted in 2 cases) 1 patient had recurrence 2 months later and eculizumab was restarted. However, graft function continued to worsen, and the graft was ultimately lost at 20 months after kidney transplantation. High index of suspicion, prompt diagnosis, and utilization of eculizumab are key to successful salvage of allografts in cases of aHUS after kidney transplantation. aHUS can be prevented by prophylactic use of eculizumab. It still needs to be determined when and if eculizumab therapy can be safely discontinued.

2. RECIDIVA DE LA GESF EN EL TRASPLANTE RENAL

A. ¿POR QUÉ TEMEMOS LA RECIDIVA DE LA GEFS EN EL INJERTO? ¿QUÉ RIESGOS CONLLEVA? CATEGORIZACIÓN DEL RIESGO SEGÚN DIAGNÓSTICO GENÉTICO, EVOLUCIÓN, CORTICORRESISTENCIA.

162. Recurrence of native kidney disease after kidney transplantation.
Yamamoto I, Yamakawa T, Katsuma A et al.
Nephrology (Carlton). 2018 Jul;23 Suppl 2:27-30.

ABSTRACT
The extent of recurrence of original kidney disease after kidney transplantation has been underestimated for several reasons. First, the duration of observation varies among studies. Second, the criteria used to schedule protocol and episode biopsies differ among institutions. And third, diagnostic modalities used for early detection of recurrent original kidney disease also vary.
Thus, rates of graft loss attributable to a recurrence of original kidney disease vary among institutions and are often underestimated. However, the recurrence of original disease is often thought to be less important than chronic rejection followed by loss of a functioning allograft. It is important to note that recent data have shown that in patients with certain limited primary kidney diseases (e.g., membranous proliferative glomerulonephritis [MPGN], IgA nephritis [IgAN], focal segmental glomerulonephritis [FSGS], and membranous nephropathy [MN]), the predominant (60%) cause of graft loss is the recurrence of original kidney disease. In addition, the rate of 5-year graft survival in patients with recurrent original kidney disease averages 45%. Thus, research must address the recurrence of original kidney disease. Here we focus on this recurrence and discuss diagnoses, preventive strategies, treatments, and future research directions.

163. Recurrence of FSGS After Kidney Transplantation in Adults.
Uffing A, Pérez-Sáez MJ, Mazzali M et al.
Clin J Am Soc Nephrol. 2020 Feb 7;15(2):247-256.

ABSTRACT
Background and objectives: FSGS recurrence after kidney transplantation is a major risk factor for graft loss. However, the natural history, clinical predictors, and response to treatment remain unclear because of small sample sizes and poor generalizability of single-center studies, and disease misclassification in registry-based studies. We therefore aimed to determine the incidence, predictors, and treatment response of recurrent FSGS in a large cohort of kidney transplant recipients.
Design, setting, participants, & measurements: The Post-Transplant Glomerular Disease (TANGO) project is an observational, multicenter, international cohort study that aims to investigate glomerular disease recurrence post-transplantation. Transplant recipients were screened for the diagnosis of idiopathic FSGS between 2005 and 2015 and details were recorded about the transplant, clinical outcomes, treatments, and other risk factors.

Results: Among 11,742 kidney transplant recipients screened for FSGS, 176 had a diagnosis of idiopathic FSGS and were included. FSGS recurred in 57 patients (32%; 95% confidence interval [95% CI], 25% to 39%) and 39% of them lost their graft over a median of 5 (interquartile range, 3.0-8.1) years. Multivariable Cox regression revealed a higher risk for recurrence with older age at native kidney disease onset (hazard ratio [HR], 1.37 per decade; 95% CI, 1.09 to 1.56). Other predictors were white race (HR, 2.14; 95% CI, 1.08 to 4.22), body mass index at transplant (HR, 0.89 per kg/m2; 95% CI, 0.83 to 0.95), and native kidney nephrectomies (HR, 2.76; 95% CI, 1.16 to 6.57). Plasmapheresis and rituximab were the most frequent treatments (81%). Partial or complete remission occurred in 57% of patients and was associated with better graft survival.
Conclusions: Idiopathic FSGS recurs post-transplant in one third of cases and is associated with a five-fold higher risk of graft loss. Response to treatment is associated with significantly better outcomes but is achieved in only half of the cases.

164. Renal Transplant Outcomes in Primary FSGS Compared With Other Recipients and Risk Factors for Recurrence: A National Review of the Irish Transplant Registry.
Cormican S, Kennedy C, O'Kelly P et al.
Clin Transplant. 2018 Jan;32(1).

ABSTRACT
Introduction: Primary focal segmental glomerular sclerosis (p-FSGS) is commonly complicated by recurrence (r-FSGS) post-transplantation. Our objective was to describe Irish outcomes for transplantation after end-stage renal disease (ESRD) due to p-FSGS, specifically rates of, and treatments for, r-FSGS.
Patients and methods: Irish patients with biopsy-proven FSGS were identified from the Irish National Kidney Transplant database (1982-2015). Medical record review was performed to identify predictors of r-FSGS and treatments for r-FSGS. Transplant outcomes were compared to outcomes in all renal transplants performed during the same time period using registry data. Demographic and clinical predictors of r-FSGS were identified. Statistical analysis was performed using Stata (version 13, College Station, TX, USA).
Results: Thirty-eight transplant recipients had biopsy-proven p-FSGS, 16 received a second transplant. A total of 3846 transplants formed the comparator group. r-FSGS complicated 60.5% (23/38) of first transplants. Eighty-six percent (10/12) of patients with previous r-FSGS developed recurrent disease after further transplantation. Patients with p-FSGS receiving a first renal transplant had higher rate of graft failure than those with another cause of ESRD (HR 1.9, 95% CI 1.152-3.139). Sixteen patients received immunotherapy for r-FSGS; 12 (86%) had at least partial response, but two (14%) developed significant complications.
Discussion: We demonstrate high rates of r-FSGS and describe modest success from with treatments for r-FSGS.

165. Facing the Vexing Problem of Recurrent FSGS After Kidney Transplantation.
Layafette R.
Clin J Am Soc Nephrol. 2020 Feb 7;15(2):171-173.

No abstract available

166. Long-Term Follow-up Results of Renal Transplantation in Pediatric Patients With Focal Segmental Glomerulosclerosis: A Single-Center Experience.
Bulut IJ, Taner S, Keskinoglu A et al.
Transplant Proc. 2019 May;51(4):1064-1069.

ABSTRACT
Introduction and aim: Focal segmental glomerulosclerosis (FSGS) is a common cause of end-stage renal disease in children. We analyzed the long-term outcome of pediatric patients with FSGS undergoing renal transplantation. The objective of the study is to report the experience of a single center and determine the incidence of recurrence, rejection, graft loss, and related risk factors.
Materials and method: This retrospective cohort study was performed between 1991 and 2018. Thirty patients with a pathologic diagnosis of primary FSGS were included in the study. The patients were diagnosed with FSGS according to histologic features in biopsies.
Results: Twenty-one of the donors were deceased (70%) and 9 were alive (30%). FSGS recurred in only 2 patients. Graft loss occurred in 6 patients (20%). The causes of graft loss were chronic rejection in 4 patients and acute rejection in 2. Our graft survival rate was 100% at 1 year, 91% at 5 years, 80% at 10 years, 70% at 15 years, and 42% at 20 years. Five- and 10-year graft survival rates were 83% and 83% in living donors and 94% and 79% in deceased donors, respectively. According to Kaplan-Meier analysis, there was no statistically significant difference in terms of graft survival between living and deceased donors.
Conclusion: This study, with its contribution to literature in terms of long follow-up of FSGS patients from childhood to adulthood, is important. However, further studies are required.

167. The Symptoms and Impact of Recurrent Focal Segmental Glomerulosclerosis in Kidney Transplant Recipients: A Conceptual Model of the Patient Experience.
English M, Hawryluk E, Krupnick R et al.
Adv Ther. 2019 Dec;36(12):3390-3408.

ABSTRACT
Introduction: We qualitatively examined the symptoms and impact of recurrent primary focal segmental glomerulosclerosis (rpFSGS) in kidney transplant recipients, compared with two related FSGS populations, to characterize the experience of patients with rpFSGS.
Methods: A literature review identified 58 articles concerning the experience of patients with pFSGS and/or rpFSGS in three groups: pre-transplant pFSGS, post-transplant rpFSGS, or post-transplant non-recurrent pFSGS. Literature findings were used to construct a preliminary conceptual model incorporating the symptoms and impact of rpFSGS, which was refined on the basis of qualitative interviews with clinicians. Twenty-five patients (rpFSGS: n = 15; pre-transplant pFSGS: n = 5; post-transplant non-recurrent pFSGS: n = 5) were interviewed to characterize the experience of patients with rpFSGS and compare it with other FSGS populations, and findings were used to finalize the conceptual model.

Results: The impact of pFSGS/rpFSGS described in the literature was diverse. Treatment-related symptoms, along with anxiety and depression, were considered important features of rpFSGS in addition to the findings from the literature review, according to clinicians. Patient-reported tiredness and swelling were the most common/disturbing symptoms associated with rpFSGS, while physical activity restrictions and adverse effects on work/social life were considered the most profound impact concepts. The collective disease experience was different for patients with rpFSGS and non-recurrent pFSGS, although psychological impact, including treatment-related anxiety and depression, were common to both groups.
Conclusions: Post-transplant recipients with rpFSGS display a greater symptom burden and experience a more diverse impact than those with non-recurrent pFSGS, highlighting the importance of effective patient monitoring and introducing effective treatments for the prevention and management of pFSGS recurrence.

168. Disease Recurrence-The Sword of Damocles in Kidney Transplantation for Primary Focal Segmental Glomerulosclerosis.
Kienzl-Wagner K, Waldegger S, Schneeberger S.
Front Immunol. 2019 Jul 17;10:1669.

ABSTRACT
A major obstacle in kidney transplantation for primary focal segmental glomerulosclerosis (FSGS) is the risk of disease recurrence. Recurrent FSGS affects up to 60% of first kidney grafts and exceeds 80% in patients who have lost their first graft due to recurrent FSGS. Clinical and experimental evidence support the hypothesis that a circulating permeability factor is the mediator in the pathogenesis of primary and recurrent disease. Despite all efforts, the causing agent has not yet been identified. Several treatment options for the management of recurrent FSGS have been proposed. In addition to plasma exchange, B-cell depleting antibodies are effective in recurrent FSGS. This indicates, that the secretion and/or activity of the postulated circulating permeability factor(s) may be B-cell related. This review summarizes the current knowledge on permeability factor(s) possibly related to the disease and discusses strategies for the management of recurrent FSGS. These include profound B-cell depletion prior to transplantation, as well as the salvage of an allograft affected by recurrent FSGS by transfer into a second recipient.

169. Clinical features and outcomes of kidney transplant recipients with focal segmental glomerulosclerosis recurrence.
Mansur JB, Sandes-Freitas TV, Kirsztajn GM et al.
Nephrology (Carlton). 2019 Nov;24(11):1179-1188.

ABSTRACT
Aim: Focal segmental glomerulosclerosis recurs in up to 30% and up to 80% of adult and pediatric kidney transplant recipients, respectively. There is no standard of care treatment. The purpose of this study was to evaluate clinical characteristics, treatments and outcomes of patients with focal segmental glomerulosclerosis recurrence (FSGSr).

Methods: This was a retrospective single-center cohort study including FSGSr patients treated with plasmapheresis (PP) and combinations of high dose steroids, cyclosporine and rituximab.
Results: Among 61 patients included in this analysis the median time to diagnosis was 19 days. The incidence of first biopsy-confirmed FSGSr was 18% reaching 52.4% with follow-up biopsies. During PP treatment 54% of the patients developed infectious complications. PP was discontinued in 37% of patients due to treatment failure (no remission or graft loss) and in 26% due to an adverse event. All patients who discontinued PP due to adverse event did not show clinical response or lost the allograft. The incidence of acute rejection was 34.4%. The incidences of partial and complete remissions were 16.4% and 27.8%, respectively. Overall 6-years patient and graft survivals were 90.7% and 64.5%, respectively.
Conclusion: This analysis confirms the low, variable and unpredictable rate of FSGSr remission, inconsistencies among available therapeutic options and its high rate of adverse events, and the negative impact on graft survival.

170. Recurrent focal segmental glomerulosclerosis after kidney transplantation.
Trachtman R, Sran SS, Trachtman H.
Pediatr Nephrol (2015) 30:1793–1802

ABSTRACT
Focal segmental glomerulosclerosis (FSGS) is an important cause of glomerular disease in children and adolescents and nearly 50 % of affected patients will progress to end-stage kidney disease over a 5 to 10-year period. Unfortunately, there is no established treatment for disease in the native kidney. Moreover, up to 55 % of patients develop recurrent disease after receiving a kidney transplant, with a substantially higher risk in patients who have already experienced recurrent disease in a prior transplant. A number of clinical and laboratory factors have been identified as risk factors for this complication. In addition, new investigations into podocyte biology and circulating permeability factors have shed light on the cause of recurrent the disease. While a number of novel therapeutic agents have been applied in the management of this problem, there still is no proven treatment. In this review, we summarize recent advances in the epidemiology, pathophysiology, and treatment of recurrent FSGS in pediatric patients who have received a kidney transplant.

B. ¿CÓMO DIAGNOSTICAR LA RECIDIVA DE GEFS?

a. ¿Es necesario un estudio genético pretrasplante en todos los casos de GEFS?

171. Genetic studies of focal segmental glomerulosclerosis: a waste of scientific time?
Howie AJ.
Pediatr Nephrol. 2020 Jan;35(1):9-16.

ABSTRACT
Many genetic causes of focal segmental glomerulosclerosis (FSGS) have been described. A paradox is that the science in the molecular biology, which generally appears of high quality, is not mirrored by a similarly critical analysis of the renal pathology. FSGS has been applied to such a wide range of

conditions that it can reasonably be said to have no useful meaning. Attempts to refine the term have been largely ignored. Study of 252 papers on genetic causes of FSGS found various clinical features. Many papers took the reported diagnosis without question. Few papers reported a pathological review, almost half reported FSGS and up to six other conditions caused by any particular gene, some reported FSGS with recognisable glomerular disorders, over 80% did not apply the Columbia classification, and in nearly all with photomicrographs, the images were not useful for refinement of FSGS. Some workers commented on a lack of genotype-phenotype correlation. One reason is a disregard of the principle that scientific investigation requires an unambiguous definition of the condition studied, to allow others to replicate or refute the findings. Genetic studies of FSGS should use a similarly rigorous approach to renal pathology to that used in molecular biology.

172. Application of next-generation sequencing technology to diagnosis and treatment of focal segmental glomerulosclerosis.
Harita Y.
Clin Exp Nephrol. 2018 Jun;22(3):491-500.

ABSTRACT
A broad range of genetic and non-genetic factors can lead to kidney injury that manifests as focal segmental glomerulosclerosis (FSGS), which can be classified into primary (idiopathic) and secondary forms. Previous genetic approaches to familial or sporadic cases of FSGS or steroid-resistant nephrotic syndrome identified causal mutations in a subset of genes. Recently, next-generation sequencing (NGS) approaches are becoming a part of a standard assessment in medical genetics. Current knowledge of the comprehensive genomic information is changing the way we think about FSGS and draws attention not only to identification of novel causal genes, but also to potential roles for combinations of mutations in multiple genes, mutations with complex inheritance, and susceptibility genes with variable penetrance carrying relatively minor but significant effects. This review provides an update on recent advances in the genetic analysis of FSGS and highlights the potential as well as the new challenges of NGS for diagnosis and mechanism-based treatment of FSGS.

173. Advances in molecular diagnosis and therapeutics in nephrotic syndrome and focal and segmental glomerulosclerosis.
Sharif B, Barua M.
Curr Opin Nephrol Hypertens. 2018 May;27(3):194-200.

ABSTRACT
Purpose of review: The widespread adoption of next-generation sequencing by research and clinical laboratories has begun to uncover the previously unknown genetic basis of many diseases. In nephrology, one of the best examples of this is seen in focal and segmental glomerulosclerosis (FSGS) and nephrotic syndrome. We review advances made in 2017 as a result of human and molecular genetic studies as it relates to FSGS and nephrotic syndrome.
Recent findings: There are more than 50 monogenic genes described in steroid-resistant nephrotic syndrome and FSGS, with seven reported in 2017. In individuals presenting with FSGS or nephrotic

syndrome before or at the age of 18 years, the commonest genes in which a mutation is found continues to be limited to only a few including NPHS1 and NPHS2 based on multiple studies. For FSGS or nephrotic syndrome that presents after 18 years, mutations in COl4A3/4/5, traditionally associated with Alport syndrome, are increasingly being reported. Despite the extensive genetic heterogeneity in FSGS, there is evidence that some of these genes converge onto common pathways.
There are also reports of in-vivo models exploring apolipoprotein 1 biology, variants in which account for part of the increased risk of nondiabetic kidney disease in African-Americans. Finally, genetic testing has several clinical uses including clarification of diagnosis and treatment; identification of suitable young biologic relatives for kidney donation; and preimplantation genetic diagnosis.
CRISPR gene editing is currently an experimental tool only, but the recent reports of excising mutations in embryos could be a therapeutic option for individuals with any monogenic disorder in the future.
Summary: Sequencing efforts are bringing novel variants into investigation and directing the efforts to understand how these lead to disease phenotypes. Expanding our understanding of the genetic basis of health and disease processes is the necessary first step to elaborate the repertoire of therapeutic agents available for patients with FSGS and nephrotic syndrome.

b. ¿Hay algún biomarcador fiable de recidiva de GEFS?

174. Identifying a Potential Biomarker for Primary Focal Segmental Glomerulosclerosis and Its Association With Recurrence After Transplantation.
Harel E, Shoji J, Abraham V et al.
Clin Transplant. 2019 Mar;33(3):e13487.

ABSTRACT
Background: We investigated circulating levels of individual soluble urokinase plasminogen activation receptor (suPAR) forms to determine if specific circulating fragments of suPAR (II-III) and (I) can better serve as clinical biomarkers for focal segmental glomerulosclerosis (FSGS) and the risk of recurrence after transplantation.
Materials and methods: Serum levels of intact suPAR and its cleaved forms were measured with two assays, ELISA and TR-FIA.
Results: suPAR levels in healthy controls were significantly lower than those who had glomerular diseases but were not significantly different between FSGS patients and glomerular controls. Intact suPAR (I-II-III) levels were noted to be elevated in glomerular diseases including FSGS. uPAR fragment (I) levels measured with the TR-FIA 4 assay were significantly higher in FSGS (695.4 + 91.29 pMol/L) than glomerular controls (239.1 + 40.45 pMol/L, P = 0.001). However, suPAR(I) levels were not significantly different between recurrent FSGS and nonrecurrent FSGS patients.
Conclusion: Our analysis of suPAR using the ELISA assay used in all previous studies does not appear to be a useful marker for FSGS nor serve as a predictor for its recurrence after transplantation. The TR-FIA assay results suggest that uPAR(I) is a potential biomarker for FSGS but not of its recurrence.

175. Identification of Glomerular and Podocyte-Specific Genes and Pathways Activated by Sera of Patients With Focal Segmental Glomerulosclerosis.

Otalora L, Chavez E, Watford D et al.

PLoS One. 2019 Oct 3;14(10):e0222948.

ABSTRACT

Focal segmental glomerulosclerosis (FSGS) accounts for about 40% of all nephrotic syndrome cases in adults. The presence of several potential circulating factors has been suggested in patients with primary FSGS and particularly in patients with recurrent disease after transplant. Irrespectively of the nature of the circulating factors, this study was aimed at identifying early glomerular/podocyte-specific pathways that are activated by the sera of patients affected by FSGS. Kidney biopsies were obtained from patients undergoing kidney transplantation due to primary FSGS. Donor kidneys were biopsied pre-reperfusion (PreR) and a subset 1-2 hours after reperfusion of the kidney (PostR). Thirty-one post reperfusion (PostR) and 36 PreR biopsy samples were analyzed by microarray and gene enrichment KEGG pathway analysis. Data were compared to those obtained from patients with incident primary FSGS enrolled in other cohorts as well as with another cohort to correct for pathways activated by ischemia reperfusion. Using an ex-vivo cell-based assay in which human podocytes were cultured in the presence of sera from patients with recurrent and non recurrent FSGS, the molecular signature of podocytes exposed to sera from patients with REC was compared to the one established from patients with NON REC. We demonstrate that inflammatory pathways, including the TNF pathway, are primarily activated immediately after exposure to the sera of patients with primary FSGS, while phagocytotic pathways are activated when proteinuria becomes clinically evident. The TNF pathway activation by one or more circulating factors present in the sera of patients with FSGS supports prior experimental findings from our group demonstrating a causative role of local TNF in podocyte injury in FSGS. Correlation analysis with clinical and histological parameters of disease was performed and further supported a possible role for TNF pathway activation in FSGS. Additionally, we identified a unique set of genes that is specifically activated in podocytes when cultured in the presence of serum of patients with REC FSGS. This clinical translational study supports our prior experimental findings describing a potential role of the TNF pathway in the pathogenesis of FSGS. Validation of these findings in larger cohorts may lay the ground for the implementation of integrated system biology approaches to risk stratify patients affected by FSGS and to identify novel pathways relevant to podocyte injury.

176. Apolipoprotein A-Ib as a Biomarker of Focal Segmental Glomerulosclerosis Recurrence After Kidney Transplantation: Diagnostic Performance and Assessment of Its Prognostic Value - A Multi-Centre Cohort Study.

Puig-Gay N, Jacobs-Cacha C, Sellarès J et al.

Transpl Int. 2019 Mar;32(3):313-322.

ABSTRACT

Recurrence of idiopathic focal segmental glomerulosclerosis (FSGS) is a serious complication after kidney transplantation. FSGS relapse is suspected by a sudden increase in proteinuria but there is not an accurate noninvasive diagnostic tool to confirm this entity or to detect patients at risk. We aimed to validate the diagnostic performance of ApoA-Ib to detect FSGS relapses by measuring

urinary ApoA-Ib in a retrospective cohort of 61 kidney transplanted patients (37 FSGS and 24 non-FSGS). In addition, to assess the ApoA-Ib predictive ability, ApoA-Ib was measured periodically in a prospective cohort of 13 idiopathic FSGS patients who were followed during 1 year after transplantation. ApoA-Ib had a sensitivity of 93.3% and a specificity of 90.9% to diagnose FSGS relapses, with a high negative predictive value (95.2%), confirming our previous results. In the prospective cohort, ApoA-Ib predated the recurrence in four of five episodes observed. In the nonrelapsing group (n = 9), ApoA-Ib was negative in 37 of 38 samples. ApoA-Ib has the potential to be a good diagnostic biomarker of FSGS relapses, providing a confident criterion to exclude false positives even in the presence of high proteinuria. It has also the potential to detect patients at risk of relapse, even before transplantation.

177. Further Evidence That the Soluble Urokinase Plasminogen Activator Receptor Does Not Directly Injure Mice or Human Podocytes.

Harel E, Shoji J, Abraham V et al.

Transplantation. 2020 Jan;104(1):54-60.

ABSTRACT

Background: The role of the soluble urokinase plasminogen activator receptor (suPAR) in focal segmental glomerulosclerosis (FSGS) as the circulating factor or as a predictor of recurrence after transplantation remains controversial. Previously published studies in mice and isolated podocytes produced conflicting results on the effect of suPAR on podocyte injury, effacement of foot processes, and proteinuria. These discordant results were in part due to diverse experimental designs and different strains of mice. The aim of our study was to determine the reasons for the inconsistencies of the previous studies results with suPAR by using uniform methods and studies in different strains of mice.

Methods: We utilized a primary culture of human podocytes and 2 mouse models, the wild type (WT) and the urokinase plasminogen activator receptor (uPAR) KO (uPAR), in an attempt to resolve the reported conflicting results.

Results: In both WT and uPAR mouse models, injection of recombinant uPAR, even at a high dose (100 µg), did not induce proteinuria, effacement of podocytes, or disruption of the cytoskeleton. Injection of suPAR resulted in its deposition exclusively in the glomerular endothelial cells and not in the podocytes of WT mice and was not detected at the uPAR KO mice. Kidneys from patients with recurrent FSGS had negative immunostaining for uPAR. We also evaluated the effect of recombinant uPAR on primary culture of human podocytes. uPAR did not result in podocytes damage.

Conclusions: suPAR by itself is not the cause for direct podocyte injury, in vitro or in vivo. These findings suggest a more complex and still poorly understood role of suPAR in FSGS.

178. A Misprocessed Form of Apolipoprotein A-I Is Specifically Associated With Recurrent Focal Segmental Glomerulosclerosis.

Jacobs-Cachá C, Puig-Gay N, Helm D et al.

Sci Rep. 2020 Jan 24;10(1):1159.

ABSTRACT
Apolipoprotein A-Ib (ApoA-Ib) is a high molecular weight form of Apolipoprotein A-I (ApoA-I) found specifically in the urine of kidney-transplanted patients with recurrent idiopathic focal segmental glomerulosclerosis (FSGS). To determine the nature of the modification present in ApoA-Ib, we sequenced the whole APOA1 gene in ApoA-Ib positive and negative patients, and we also studied the protein primary structure using mass spectrometry. No genetic variations in the APOA1 gene were found in the ApoA-Ib positive patients that could explain the increase in its molecular mass. The mass spectrometry analysis revealed three extra amino acids at the N-Terminal end of ApoA-Ib that were not present in the standard plasmatic form of ApoA-I. These amino acids corresponded to half of the propeptide sequence of the immature form of ApoA-I (proApoA-I) indicating that ApoA-Ib is a misprocessed form of proApoA-I. The description of ApoA-Ib could be relevant not only because it can allow the automated analysis of this biomarker in the clinical practice but also because it has the potential to shed light into the molecular mechanisms that cause idiopathic FSGS, which is currently unknown.

179. Intrinsic Tumor Necrosis factor-α Pathway Is Activated in a Subset of Patients With Focal Segmental Glomerulosclerosis.
Chung CF, Kitzler T, Kachurina N et al.
PLoS One. 2019 May 16;14(5):e0216426.

ABSTRACT
Focal segmental glomerulosclerosis (FSGS) is frequently found in biopsies of patients with steroid resistant nephrotic syndrome (SRNS). The pathogenesis of SRNS/FSGS is often unknown and the disease will recur in up to 50% of patients post-transplant, indicating the presence of circulating podocyte-toxic factor(s). Several studies have reported clinical improvement after anti-TNFα therapy. However, prediction of the clinical outcome in SRNS/FSGS is difficult, and novel predictive biomarkers are needed. An image-based assay, which measures disassembly of focal adhesion complexes in cultured podocytes, was used to ascertain the presence of podocyte toxic activity in SRNS/FSGS sera. Expression of TNFα pathway genes was analysed in the Nephroseq FSGS cohort and in cultured podocytes treated with SRNS/FSGS sera. Podocyte toxic activity was detected in 48/96 SRNS/FSGS patients. It did not correlate with serum TNFα levels, age, sex, ethnicity or glomerular filtration rate. In ~25% of the toxic samples, the toxicity was strongly inhibited by blockade of TNFα signaling. Transcriptional profiling of human FSGS biopsies and podocytes treated with FSGS sera revealed significant increases in expression of TNFα pathway genes. We identified patients with serum podocyte toxic activity who may be at risk for FSGS recurrence, and those patients in whom serum podocyte toxicity may be reversed by TNFα blockade. Activation of TNFα pathway genes occurs in podocytes of FSGS patients suggesting a causative effect of this pathway in response to circulating factor(s). In vitro analyses of patient sera may stratify patients according to prognostic outcomes and potential responses to specific clinical interventions.

180. Circulating CASK Is Associated With Recurrent Focal Segmental Glomerulosclerosis After Transplantation.
Beaudreuil S, Zhang X, Herr F et al.

LoS One. 2019 Jul 29;14(7):e0219353.

ABSTRACT

Introduction: Focal and Segmental GlomeruloSclerosis (FSGS) can cause nephrotic syndrome with a risk of progression to end-stage renal disease. The idiopathic form has a high rate of recurrence after transplantation, suggesting the presence of a systemic circulating factor that causes glomerular permeability and can be removed by plasmapheresis or protein-A immunoadsorption.

Results: To identify this circulating factor, the eluate proteins bound on therapeutic immunoadsorption with protein-A columns were analyzed by comparative electrophoresis and mass spectrometry. A soluble form of calcium/calmodulin-dependent serine protein kinase (CASK) was identified. CASK was immunoprecipitated only in the sera of patients with recurrent FSGS after transplantation and not in control patients. Recombinant-CASK (rCASK) induced the reorganization of the actin cytoskeleton in immortalized podocytes, a redistribution of synaptopodin, ZO-1,vinculin and ENA. rCASK also induced alterations in the permeability of a monolayer of podocytes and increased the motility of pdodocytes in vitro. The extracellular domain of CD98, a transmembrane receptor expressed on renal epithelial cells, has been found to co-immunoprecipitated with rCASK. The invalidation of CD98 with siRNA avoided the structural changes of rCask treated cells suggesting its involvement in physiopathology of the disease. In mice, recombinant CASK induced proteinuria and foot process effacement in podocytes.

Conclusion: Our results suggest that CASK can induce the recurrence of FSGS after renal transplantation.

181. Diagnostic and Prognostic Value of Soluble Urokinase-type Plasminogen Activator Receptor (suPAR) in Focal Segmental Glomerulosclerosis and Impact of Detection Method.

Winnicki W, Sunder-Plassmann G, Sengölge G et al.

Sci Rep. 2019 Sep 24;9(1):13783.

ABSTRACT

The plasma soluble urokinase-type plasminogen activator receptor (suPAR) is a biomarker for focal segmental glomerulosclerosis (FSGS), but its value is under discussion because of ambiguous results arising from different ELISA methods in previous studies. The aim of this study was to compare diagnostic performance of two leading suPAR ELISA kits and examine four objectives in 146 subjects: (1) plasma suPAR levels according to glomerular disease (primary, secondary and recurrent FSGS after kidney transplantation, other glomerulonephritis) and in healthy controls; (2) suPAR levels based on glomerular filtration rate; (3) sensitivity and specificity of suPAR for FSGS diagnosis and determination of optimal cut-offs; (4) suPAR as prognostic tool. Patients with FSGS showed significant higher suPAR values than patients with other glomerulonephritis and healthy individuals. This applied to subjects with and without chronic kidney disease. Although both suPARnostic™ assay and Quantikine Human uPAR ELISA Kit exerted high sensitivity and specificity for FSGS diagnosis, their cut-off values of 4.644 ng/mL and 2.789 ng/mL were significantly different. Higher suPAR was furthermore predictive for progression to end-stage renal disease. In summary, suPAR values must be interpreted in the context of population and test methods used. Knowing test specific cut-offs makes suPAR a valuable biomarker for FSGS.

182. Development of a Novel Cell-Based Assay to Diagnose Recurrent Focal Segmental Glomerulosclerosis Patients.

Srivastava P, Solanki AK, Arif E et al.

Kidney Int. 2019 Mar;95(3):708-716.

ABSTRACT

Definitive diagnosis of glomerular disease requires a kidney biopsy, an invasive procedure that may not be safe or feasible to perform in all patients. We developed a noninvasive, accurate, and economical diagnostic assay with easy commercial adaptability to detect recurrent focal segmental glomerulosclerosis (rFSGS) after kidney transplant. Since FSGS involves podocyte damage and death, our approach involved mRNA profiling of cultured podocytes treated with plasma from patients with rFSGS to identify upregulated genes involved in podocyte damage. For concept validation, three upregulated pro-apoptotic candidate genes (IL1β, BMF, and IGFBP3) were selected, and their promoter regions were cloned into a luciferase-based reporter vector and transfected into podocytes to generate stable podocyte cell lines. Strikingly, when exposed to rFSGS patient plasma, these cell lines showed increased reporter activity; in contrast, no reporter activity was noted with plasma from patients with non-recurrent FSGS or membranous nephropathy. Area under the receiver operating characteristics curves (AUCs) for models discriminating between rFSGS and other nephropathies (non-recurrent FSGS and membranous nephropathy) and between rFSGS and non-recurrent FSGS ranged from 0.81 to 0.86, respectively. Estimated sensitivities and specificities for the diagnosis of rFSGS were greater than 80% for the IL1β and BMF cell lines, and were slightly lower for the IGFBP3 cell line. Importantly, the novel approach outlined here for the diagnosis of rFSGS is widely applicable to the design of sensitive and specific diagnostic/prognostic assays for other glomerular diseases.

183. Assessment of Increased Glomerular Permeability Associated With Recurrent Focal Segmental Glomerulosclerosis Using an in Vitro Model of the Glomerular Filtration Barrier.

Li M, Alfieri CM, Morello W et al.

J Nephrol. 2019 Dec 18. doi: 10.1007/s40620-019-00683-2.

ABSTRACT

The presence of circulating permeability factors (cPFs) has been hypothesized to be associated with recurrence of focal segmental glomerulosclerosis (rFSGS) in renal allografts. The available methods to detect cPFs are complex, not easily repeatable and inappropriate to represent the anatomical characteristics of the three-layer glomerular filtration barrier (GFB). Here we describe a novel method which measures the permeability to bovine serum albumin (BSA) through a three-layer device (3LD). The 3 layers comprise: (1) conditionally immortalized human podocytes (HCiPodo), (2) collagen type IV coated porous membrane and (3) human glomerular endothelial cells (HCiGEnC). Using this method, we found that sera from all rFSGS patients increased albumin permeability, while sera from non recurrent (nrFSGS) and genetic (gFSGS) forms of FSGS did not. The mechanisms underlying the increase of albumin permeability are probably due to endothelial cell damage as an initial event, which was demonstrated by the decrease of Platelet endothelial cell adhesion molecule (PECAM-1 or CD31), while the podocytes' expressions of synaptopodin and podocin were normal. Furthermore, we also found that the plasmapheretic treatment (PPT) eliminated the effect of

increasing BSA permeability in sera from rFSGS patients. These preliminary data suggest that our in vitro GFB model could not only be useful in predicting the recurrence of FSGS after renal transplantation (RTx), but also be a valuable in vitro model to study podocyte and endothelial cell biology.

c) ¿Es la proteinuria precoz diagnóstica?
d) ¿Es síntoma de recurrencia la disfunción precoz del injerto?
e) ¿Es útil la biopsia precoz del órgano? ¿Es imprescindible la microscopía electrónica?

184. Early Identification of Transplant Glomerulopathy in Pediatric Kidney Transplant Biopsies: A Single-Center Experience With Electron Microscopy Analysis.
Grodsky JD, Craver RD, Ashoor IF.
Pediatr Transplant. 2019 Aug;23(5):e13459.

ABSTRACT
Banff 2013 criteria recommend performing ultrastructural studies with electron microscopy (EM) in kidney transplant biopsies if the technology is available. We sought to determine the impact of EM on enhancing diagnostic findings in pediatric kidney transplant biopsies and the prognostic information gained from the additional findings. All kidney transplant biopsies since routine EM use started on June 1, 2014, until October 31, 2016, were reviewed. Primary outcome measures included the positive yield frequency of EM use defined as an upgraded diagnosis based on EM findings relative to light microscopy, and 12-month kidney allograft outcome of progression to ESRD or doubling of serum creatinine stratified by transplant glomerulopathy (TG) status on EM. Eighty unique kidney transplant biopsies were reviewed. EM studies were completed for 61 biopsies (76%). Complication rate was low (3.7%). In 61 biopsies where EM was completed, EM findings included foot process fusion (62%), endothelial cell swelling (38%), subendothelial lucencies (31%), and glomerular basement membrane duplication (41%). EM confirmed FSGS recurrence in three cases. In the remaining 58 cases, there was a positive yield of 31% where 18 biopsies were upgraded to a worse category after TG identification on EM. Kidney allograft outcome was poor regardless whether TG was detected early on EM or advanced on LM. Routine EM use in analyzing pediatric kidney transplant biopsies proved safe and provided valuable additional diagnostic information in almost one-third of cases. Additional studies are needed to determine if clinical interventions for early TG identified on EM can improve long-term outcomes.

185. Recurrence of Nephrotic Syndrome Following Kidney Transplantation Is Associated With Initial Native Kidney Biopsy Findings.
Pelletier JH, Kumar KR, Engen R et al.
Pediatr Nephrol. 2018 Oct;33(10):1773-1780.

ABSTRACT

Background and Objectives: Steroid resistant nephrotic syndrome (SRNS) due to focal segmental glomerulosclerosis (FSGS) and minimal change disease (MCD) is a leading cause of end stage kidney disease in children. Recurrence of primary disease following transplantation is a major cause of allograft loss. The clinical determinants of disease recurrence are not completely known. Our objectives were to determine risk factors for recurrence of FSGS/MCD following kidney transplantation, and factors that predict response to immunosuppression following recurrence.
Study Design: Multicenter study of pediatric patients with kidney transplants performed for ESKD due to SRNS between 1/2006–12/2015. Demographics, clinical course, and biopsy data were collected. Patients with primary-SRNS (PSRNS) were defined as those initially resistant to corticosteroid therapy at diagnosis, and patients with late-SRNS (LSRNS) as those initially responsive to steroids who subsequently developed steroid resistance. We performed logistic regression to determine risk factors associated with nephrotic syndrome (NS) recurrence.
Results: We analyzed 158 patients; 64 (41%) had recurrence of NS in their renal allograft. Disease recurrence occurred in 78% of patients with LSRNS compared to 39% of those with PSRNS. Patients with MCD on initial native kidney biopsy had a 76% recurrence rate compared with a 40% recurrence rate in those with FSGS. Multivariable analysis showed that MCD histology (OR; 95% CI: 5.6; 1.3–23.7) compared to FSGS predicted disease recurrence.
Conclusions: Pediatric patients with MCD and LSRNS are at higher risk of disease recurrence following kidney transplantation. These findings may be useful for designing studies to test strategies for preventing recurrence.

186. Glomerular C4d Deposition Can Precede the Development of Focal Segmental Glomerulosclerosis.

van de Lest NA, Zandbergen M, Wolterbeek R et al.
Kidney Int. 2019 Sep;96(3):738-749.

ABSTRACT

Recent studies suggest that complement plays a role in the pathogenesis of focal segmental glomerulosclerosis (FSGS). Moreover, co-localization of IgM and C3 deposits with FSGS lesions has frequently been reported. Here, we investigated whether glomerular complement deposition precedes the development of FSGS and whether it represents local complement activation. Renal biopsies from 40 patients with primary FSGS, 84 patients with minimal change disease, and 10 healthy individuals were stained for C4d, C1q, and mannose-binding lectin. C4d deposits were also measured in renal allograft biopsies from 34 patients with native primary FSGS, 18 of whom subsequently developed recurrent FSGS. Lastly, we measured C4d deposits in the Munich Wistar Frömter rat model of FSGS. The prevalence of C4d-positive glomeruli was significantly higher among patients with FSGS (73%) compared to patients with minimal change disease (21%) and healthy individuals (10%). Moreover, segmental sclerosis was absent in 42% of C4d-positive glomeruli. Glomerular C1q was significantly more prevalent in FSGS compared to minimal change disease or healthy individuals, while mannose-binding lectin was infrequently observed. C4d deposition was significantly more prevalent in recurrent FSGS (72%) before the development of sclerotic lesions compared to control transplant samples (27%). Finally, at the onset of albuminuria but before the development of FSGS lesions, Munich Wistar Frömter rats had a significantly higher percentage of C4d-positive glomeruli (31%) compared to control rats (4%). Thus, glomerular C4d deposition can

precede the development of FSGS, suggesting that complement activation may play a pathogenic role in the development of FSGS.

C. ¿ES POSIBLE HACER PROFILAXIS?: CUÁNDO Y CÓMO

187. The Effect of Peri-Transplant Plasmapheresis in the Prevention of Recurrent FSGS.
Verghese PS, Rheault MN, Jackson S et al.
Pediatr Transplant. 2018 May;22(3):e13154.

ABSTRACT
Many pediatric centers utilize a variety of protocols including preemptive plasmapheresis to prevent the recurrence of FSGS post-transplant. But the effectiveness of this expensive, time-consuming process of plasmapheresis in the prevention of FSGS recurrence is still unclear. We retrospectively reviewed all pediatric cases of FSGS in our center that received a kidney transplant and compared the transplant and patient outcomes of those transplanted after 2006 who received pretransplant plasmapheresis to those prior to 2006 who did not. Of the 57 children with FSGS, 31 and 26 were transplanted before and after 2006, respectively. The cohorts differed significantly in keeping with the center immunosuppression protocol changes, and prior to 2006, the recipients were significantly younger. All children with FSGS transplanted after 2006 underwent three and one sessions of 1.0 plasma volume/exchange plasmapheresis with fresh frozen plasma replacement prior to the transplant in living and deceased donors, respectively, in addition to five sessions of every other day post-transplant pheresis. The incidence (27% vs 26%, P = 1.0) and time to recurrence of FSGS in the kidney allograft (P = .22) were not significantly different in patients that did and did not undergo prophylactic plasmapheresis. We need to re-evaluate the role of preemptive plasmapheresis in the prevention of FSGS recurrence in a prospective multicenter study.

188. Effects of pretransplant plasmapheresis and rituximab on recurrence of focal segmental glomerulosclerosis in adult renal transplant recipients.
Park HS, Hong Y, Sun IO et al.
Korean J Intern Med. 2014 Jul;29(4):482-8.

ABSTRACT
Background/aims: Recurrent focal segmental glomerulosclerosis (FSGS) following renal transplantation is relatively common. However, the risk factors and optimal pretransplant treatment preventing recurrence of FSGS remain controversial.
Methods: We retrospectively reviewed 27 adult renal transplant recipients with FSGS over a period of 10 years. We first compared possible risk factors for FSGS recurrence between the recurrence and nonrecurrence groups. Then we evaluated the effect of pretransplant plasmapheresis (PP; n = 4) and PP with rituximab (PP + RTX; n = 5) on recurrence of FSGS after transplantation compared to control patients that were not treated with these modalities.
Results: There were seven recurrences in 27 patients (25.9%), but there were no significant differences in possible risk factors for FSGS recurrence between the two groups. Recurrence rates

between patients with pretransplant PP or PP + RTX and control patients were not significantly different (22.2% vs. 27.7%, p > 0.05). There was also no significant difference in recurrence between the pretransplant PP and PP + RTX groups (25% vs. 20%, p > 0.05).
Conclusions: Pretransplant PP or PP + RTX do not significantly decrease the recurrence of FSGS in adult renal transplant candidates.

D. ¿CÓMO Y CUÁNDO TRATAR LA RECIDIVA?

a. Terapias extracorpóreas

189. An update on LDL apheresis for nephrotic syndrome.
Raina R, Krishnappa V.
Pediatr Nephrol. 2019 Oct;34(10):1655-1669.

ABSTRACT
Low-density lipoprotein (LDL) apheresis has been used increasingly in clinical practice for the treatment of renal diseases with nephrotic syndrome (NS), specifically focal segmental glomerulosclerosis (FSGS). Persistent hyperlipidemia for prolonged periods is nephrotoxic and leads to chronic progressive glomerular and tubulointerstitial injury. Effective management of hyperlipidemia with HMG-CoA reductase inhibitors or LDL apheresis in drug-resistant NS patients may prevent the progression of renal disease and, in some patients, resolution of NS symptoms. Available literature reveals beneficial effects of LDL apheresis for NS refractory to drug therapy. Here we update on the current understanding of lipid nephrotoxicity and application of LDL apheresis to prevent progression of renal diseases.

190. LDL-apheresis-induced Remission of Focal Segmental Glomerulosclerosis Recurrence in Pediatric Renal Transplant Recipients.
Shah L, Hooper DK, Okamura D et al.
Pediatr Nephrol. 2019 Nov;34(11):2343-2350.

ABSTRACT
Background: Focal segmental glomerulosclerosis (FSGS) in pediatric patients is typically difficult to treat and will progress to end-stage renal disease (ESRD) in about 10% of cases. Following kidney transplantation, FSGS can recur in up to 56% of renal allografts-with a near 100% recurrence in subsequent transplants.
Methods: Four different pediatric centers across the USA and the UK employed a protocol using LDL-apheresis (LDL-A) and pulse solumedrol to treat recurrent FSGS after transplantation in seven patients. All the patients included in this series demonstrated immediate, or early, recurrence of FSGS, which clinically presented as nephrotic-range proteinuria within hours to days after implantation of the kidney.
Results: All patients experienced reductions in urinary protein to creatinine ratios resulting in partial or complete remission. All patients demonstrated improvements in their estimated GFRs at their most recent follow-up since LDL-A discontinuation.

Conclusions: This case series describes the successful treatment, across four different pediatric centers, of seven pediatric patients with recurrent post-transplant FSGS using the Liposorber® LA-15 in combination with pulse solumedrol.

191. Extracorporeal Therapies in the Treatment of Focal Segmental Glomerulosclerosis.
Raina R, Wang J, Sharma A et al.
Blood Purif. 2020 Feb 19;1-11.

ABSTRACT
Focal segmental glomerulosclerosis (FSGS) is one of the most frequent and severe glomerular kidney disease with frequent progression to end-stage renal disease and a high rate of recurrence in renal transplantations. Due to intolerance or resistance to the current immunomodulatory treatments, the management of FSGS is a therapeutic challenge. Over the last few years, development in extracorporeal therapies has shown potential beneficial outcomes in drug-resistant and recurrent FSGS patients. Thus, this study reviews the current literature on the use of extracorporeal therapies, such as plasma exchange therapy, immunoadsorption, and low-density lipoprotein apheresis, for the treatment of FSGS in the pediatric population.

192. Immunoadsorption for Recurrent Primary Focal Segmental Glomerulosclerosis on Kidney Allografts: A Single-Center Experience and Literature Review.
Bennani HN, Bonzi JY, Noble J et al.
Blood Purif. 2020;49(3):322-333.

ABSTRACT
Introduction: Primary focal and segmental glomerulosclerosis (FSGS) frequently reoccurs on kidney transplants and may lead to premature allograft loss. There are no guidelines for treating FSGS recurrence on allografts; treatment is based on apheresis (plasma exchange plasmapheresis [PP], semi-specific immunoadsorption [IA] with reusable columns) plus rituximab.
Objective: We aimed to assess the efficacy of IA to treat recurrent FSGS.
Methods: We report on 7 patients with recurrent FSGS on kidney allograft (proteinuria ≥3 g/g of urinary creatinine or ≥3 g/day); they all received IA. Our primary objective was to reduce proteinuria by >50%. Patients' mean age was 45 ± 10 years. Postoperative immunosuppression relied on steroids, mycophenolate mofetil, tacrolimus, with an induction therapy of basiliximab or antithymocyte globulins. Prophylaxis to prevent FSGS recurrence was either rituximab alone (n = 3), rituximab plus either PP or IA (n = 3), or no treatment (n = 1). Mean follow-up was 20 ± 13 months. There was a median of 72 (14-101) IA sessions per patient, that is, a mean of 14 ± 1 sessions per IA column.
Results: At 12 months after starting IA, all patients had partial (n = 6) or complete (n = 1) remission, and allograft survival was 100%. The mean reduction in proteinuria within an IA session was 45 ± 15%. At last follow-up, 2 patients are in remission without IA, 3 patients are in partial remission that is IA dependent, and 2 patients lost their allograft due to FSGS recurrence. The most frequent adverse event was cytomegalovirus reactivation (n = 13), which subsided after valganciclovir therapy.

Conclusions: We show that recurrence of FSGS can be controlled long term with IA plus rituximab. However, some patients remained dependent on IA.

193. Dextran-Sulfate Plasma Adsorption Lipoprotein Apheresis in Drug Resistant Primary Focal Segmental Glomerulosclerosis Patients: Results From a Prospective, Multicenter, Single-Arm Intervention Study

Raina R, Krishnappa V, Sanchez-Kazi C et al.
Front Pediatr. 2019 Dec 3;7:454.

ABSTRACT

Background: Focal segmental glomerulosclerosis (FSGS) causes end stage renal disease (ESRD) in significant proportion of patients worldwide. Primary FSGS carries poor prognosis and management of FSGS patients, refractory to standard treatments or resistant to steroids, remains a major challenge. Lipoprotein apheresis is a therapeutic approach for drug resistant primary FSGS and post-renal transplant primary FSGS recurrence.

Objectives: To examine the safety and probable benefit at 1, 3, 6, 12, and 24-months following completion of apheresis treatment using Liposorber® LA-15 system in patients with nephrotic syndrome (NS), due to refractory primary FSGS or primary FSGS associated NS, in post renal transplant children.

Material and Methods: Prospective, multicenter, single-arm intervention study using Liposorber® LA-15 system. Patients ≤21 years old with drug resistant or drug intolerant NS secondary to primary FSGS with glomerular filtration rate (GFR) ≥60 ml/min/1.73 m2 or post renal transplant patients ≤21 years old with primary FSGS associated NS were included in the study. Each patient had 12 dextran-sulfate plasma adsorption lipoprotein apheresis sessions over a period of 9 weeks. All patients were followed up at 1, 3, 6, 12, and 24-months following completion of treatment.

Results: Of 17 patients enrolled, six were excluded from the outcome analysis (protocol deviations). Of the remaining 11 patients, all but one have completed apheresis treatments. Three patients were lost to follow-up immediately after completion of apheresis and excluded from outcome analysis. At one-month follow-up, 1 of 7 patients (14.3%) attained partial remission of NS while 2 of 4 subjects (50%) and 2 of 3 subjects (66.7%) had partial/complete remission at 3- and 6-months follow-up, respectively. One of two patients followed up for 12 months had complete remission and one patient had partial remission of NS after 24 months. Improved or stable eGFR was noted in all patients over the follow-up period.

Conclusion: The results of our multicenter study showed improvement in the response rates to steroid or immunosuppressive therapy and induced complete or partial remission of proteinuria in some of the patients with drug resistant primary FSGS. The main limitation of our study is the small number of subjects and high dropout rate.

b. Ciclosporina / rituximab / ofatumumab / terapias combinadas

194. Combination of High-Dose Intravenous Cyclosporine and Plasma Exchange Treatment Is Effective in Post-Transplant Recurrent Focal Segmental Glomerulosclerosis: Results of Case Series.

Demir ME, Uyar M, Merhametsiz O.

Transplant Proc. 2020 Apr;52(3):843-849.

ABSTRACT
Background: Idiopathic focal segmental glomerulosclerosis (FSGS) commonly recurs in the early post-transplant period. The treatment protocols and results are conflictive in recurrent FSGS. We aimed to present the results of our treatment protocol and basic approach to the disease recurrences.
Methods: This prospective, single-center study was conducted between the years 2015 and 2018. Twelve patients who fit completely the diagnosis of idiopathic FSGS by clinical, laboratory, and biopsy findings were included. A specific treatment protocol which consists of plasma exchange and high dose intravenous cyclosporine was delivered to the patients independently of induction protocols. Twenty-four months of outcomes of graft functions were evaluated.
Results: Nine patients completed the treatment protocol and were documented for evaluation. All patients achieved a complete or partial remission in an average 24 months of follow-up period.
Conclusion: Idiopathic FSGS is more commonly recurrent than thought to be. The early detection of proteinuria is crucial because the administration of a plasma exchange-based treatment protocol can reverse proteinuria. We think our treatment protocol is a well-established, efficient, and safe choice for post-transplant recurrent FSGS in adults.

195. Combined Rituximab and Plasmapheresis or Plasma Exchange for Focal Segmental Glomerulosclerosis in Adult Kidney Transplant Recipients: A Meta-Analysis.

Hansrivijit P, Ghahramani N.

Int Urol Nephrol. 2020 Apr 18. doi: 10.1007/s11255-020-02462-6.

ABSTRACT
Purpose: To demonstrate the efficacy of combined rituximab and plasmapheresis (PP)/plasma exchange (PE) therapy for focal segmental glomerulosclerosis in transplanted kidneys (ptFSGS).
Methods: We searched MEDLINE, SCOPUS, and Cochrane Library for eligible publications. Only observational studies or clinical trials containing patients' age > 18 years were included for full-text extraction.
Results: A total of eight observational studies (n = 85) were included in meta-analyses. With a median follow-up of 18 months (IQR 4.4), combination therapy of RTX-PP/PE in patients with ptFSGS resulted in overall remission rate of 72.7% (95% CI 52.3-86.6%) with a significant reduction of proteinuria and serum creatinine levels. Complete remission was 41.0%, while partial remission was 31.7%. The mean difference of serum creatinine levels between pre- and post-treatment was - 0.65 mg/dL (95% CI - 1.15 to - 0.14). The mean difference of the degree of proteinuria between pre- and post-treatment was - 4.79 g/day (95% CI - 7.02 to - 2.56). Subgroup analyses were performed after adjusted for study year, type of intervention, and primary pre-transplant lesion. Patients with recurrent FSGS tended have lesser reduction in the degree of proteinuria compared to patients with de novo FSGS. Incidence of serious adverse events with combined RTX-PP/PE therapy was 0.12 event/year.
Conclusion: We conclude that combined RTX-PP/PE therapy may be considered as an alternative treatment of ptFSGS in achieving remission by lowering proteinuria and serum creatinine levels.

However, the efficacy of combined RTX-PP/PE therapy must be confirmed in randomized-controlled trials.

196. Rituximab and Therapeutic Plasma Exchange in Recurrent Focal Segmental Glomerulosclerosis Postkidney Transplantation.

Alasfar S, Matar D, Montgomery RA et al.

Transplantation. 2018 Mar;102(3):e115-e120.

ABSTRACT

Background: Focal segmental glomerulosclerosis (FSGS) is a common cause of end-stage renal disease with a high rate of recurrence after kidney transplantation. Several factors, such as white race, rapid progression, and previous allograft failure due to recurrence, were found to be risks of recurrence. Data are limited on the benefits of rituximab and/or therapeutic plasma exchange (TPE) in preventing recurrence. In this study, we sought to assess the efficacy of rituximab and TPE for the prevention and treatment of recurrent FSGS after kidney transplantation.

Methods: We enrolled 66 patients with FSGS in this prospective observational study and followed their outcomes. Patients with high risk for recurrence received preventative therapy with TPE and/or rituximab.

Results: Twenty-three (62%) of the 37 patients who received preventative therapy developed recurrence compared with 14 (51%) recurrences of the 27 patients who did not receive any therapy (P = 0.21). There was a trend for less relapse when rituximab was used as a therapy for recurrent FSGS (6/22 vs 9/18, P = 0.066). We used a clinical score of 5 values to assess the prediction of FSGS recurrence. A score of 3 or more had a predictive receiver operating characteristic curve of 0.72. Treatment with TPE and/or rituximab resulted in better allograft survival than historical studies. Allograft failure because of recurrent FSGS occurred in only 6 (9%) patients.

Conclusions: Preventative therapies do not decrease the recurrence rate of recurrent FSGS. However, prompt treatment of recurrence with these therapies may result in improved outcomes.

197. Ofatumumab Rescue Treatment in Post-Transplant Recurrence of Focal Segmental Glomerulosclerosis.

Colucci M, Labbadia R, Vivarelli M et al.

Pediatr Nephrol. 2020 Feb;35(2):341-345..

ABSTRACT

Background: Treatment of post-transplant focal segmental glomerulosclerosis (FSGS) recurrence is still debated. The use of the fully human anti-CD20 monoclonal antibody ofatumumab has been suggested.

Case-diagnosis/treatment: Two boys with FSGS received a kidney transplantation at the age of 15 years from a deceased and a living donor. Maintenance therapy consisted of calcineurin inhibitors, antiproliferative agents, and prednisone. Early post-transplant FSGS recurrence was observed after 2 and 3 days. Rituximab infusion and plasmapheresis sessions were performed with transient clinical improvement in the first patient, and no apparent response in the second patient. Both patients were treated with two ofatumumab infusions, which induced in patient #1 a complete and stable

remission for more than 12 months and in patient #2 a partial remission with a progressive reduction of proteinuria and normalization of serum protein levels.
Conclusions: Ofatumumab may be a therapeutic option for post-transplant FSGS recurrence in patients who respond poorly to rituximab.

198. Ofatumumab Treatment for Nephrotic Syndrome Recurrence After Pediatric Renal Transplantation.
Bernard J, Lalieve F, Sarlat J et al.
Pediatric Nephrology (2020) 35:1499–1506.

ABSTRACT
Background: Relapsing nephrotic syndrome (NS) after transplantation can be a challenge to treat. The result of the consequent long-lasting proteinuria is the loss of the graft. Disease recurrence after renal transplantation occurs in around half of cases, and the efficacy of therapeutic strategies is often limited. Recently, ofatumumab, a second-generation and fully human anti-CD20 monoclonal antibody, has been shown to be effective in severe situations.
Methods: We retrospectively collected data from the medical records of children with recurrence of NS after renal transplantation treated with ofatumumab in France, after failure of previous treatments.
Results: Six patients were included in this study in five centers with a median duration of follow-up of 10.5 months. Two different ofatumumab regimens were administered. The primary outcome was proteinuria at 6 months after the last dose of ofatumumab. No patient achieved a complete remission, 3/6 had a partial remission, and 3/6 had no response to ofatumumab. Four patients exhibited a minor allergic reaction with the first infusion. One patient died of infection, as a consequence of multiple factors. No malignancies were observed; however, the time of follow-up was not sufficient to see such disease.
Conclusions: Altogether, these results suggest ofatumumab has a poor efficacy in treating recurrence of NS after renal transplantation. However, it could be discussed in multidrug-resistant refractory NS, but infectious complications and overimmunosuppression have to be balanced. There is a need for further studies to confirm these findings and safety and to determine a standardized protocol in this indication.

199. Successful management of recurrent focal segmental glomerulosclerosis.
Kienzl-Wagner K, Rosales A, Scheidl S et al.
Am J Transplant. 2018 Nov;18(11):2818-2822.

ABSTRACT
Primary focal segmental glomerulosclerosis (FSGS) recurs in up to 55% of patients after kidney transplantation. Herein we report the successful management of recurrent FSGS. A 5-year-old boy with primary FSGS received a deceased donor renal transplant. Immediate and fulminant recurrence of FSGS caused anuric graft failure that was resistant to plasmapheresis and rituximab. After exclusion of structural or immunologic damage to the kidney by repeated biopsies, the allograft was retrieved from the first recipient on day 27 and transplanted into a 52-year-old second recipient

who had vascular nephropathy. Immediately after retransplantation, the allograft regained function with excellent graft function persistent now at 3 years after transplant. After 2 years on hemodialysis, the boy was listed for kidney retransplantation. To prevent FSGS recurrence, pretreatment with ofatumumab was performed. Nephrotic range proteinuria still occurred after the second transplantation, which responded, however, to daily plasma exchange in combination with ofatumumab. At 8 months after kidney retransplantation graft function is good. The clinical course supports the hypothesis of a circulating permeability factor in the pathogenesis of FSGS. Successful ofatumumab pretreatment implicates a key role of B cells. Herein we provide a description of successful management of kidney failure by FSGS, carefully avoiding waste of organs.

200. Rituximab for Recurrence of Primary Focal Segmental Glomerulosclerosis After Kidney Transplantation: Clinical Outcomes.
Cyril Garrouste, Canaud G, Büchler M et al.
Transplantation 2017;101: 649–656.

ABSTRACT
Background: Rituximab has shown encouraging results for the treatment of kidney transplantation recipients with focal segmental glomerulosclerosis (FSGS) recurrence. However, the correct, opportune, and safe use of rituximab for this indication remains to be determined.
Methods: This multicenter retrospective study reports on 19 new cases aged 35 (15-66) years who developed FSGS recurrence at 12 (1.5-27) days posttransplantation. Initial treatment consisted of plasma exchanges (PE), high doses of calcineurin inhibitors, and steroids. Rituximab was introduced either immediately (N = 6) or after failure of the initial treatment (N = 10) or failed attempted weaning from PE (N = 3).
Results: Overall, we observed 9 of 19 complete remissions and 3 of 19 partial remissions. Estimated glomerular filtration rates (Modification of Diet in Renal Disease 4) were significantly higher in the responding patients than in nonresponding patients at month (M)12, M36, and M60. Overall, kidney survival at 5 years was 77.4% (95% range, 41.9-92.7). The 5-year graft survival rates in the responding patients and the nonresponding patients were 100% and 36.5%, respectively (P = 0.01). A further course of rituximab was required for 4 patients as a result of FSGS relapse, with good results. During the first year after renal transplantation, 14 patients developed severe infections (16 bacterial, 4 viral, 1 parasitic).
Conclusions: In kidney transplantation recipients with recurrent FSGS, rituximab therapy may be a recommended treatment for cases that have failed either the initial treatment or weaning from PE.

201. The Factors That May Predict Response to Rituximab Therapy in Recurrent Focal Segmental Glomerulosclerosis: A Systematic Review.
Araya CE, Vikas RD.
J Transplant. 2011;2011:374213.

ABSTRACT
Recurrence of FSGS occurs in 30-40% of allografts. Therapies for recurrence are not well established. We retrieved all published reports depicting kidney transplant recipients with focal segmental

glomerulosclerosis (FSGS) recurrence, treated with rituximab, to determine factors associated with treatment response. We found 18 reports of 39 transplant recipients who received rituximab. By univariate analysis for two outcomes (no response versus any response), fewer rituximab infusions and normal serum albumin at recurrence were associated with treatment response. For 3 outcomes (no response, partial and complete remission), male gender, fewer rituximab infusions, shorter time to rituximab treatment, and normal serum albumin were associated with remission. Multivariate analysis for both models revealed that normal serum albumin at FSGS recurrence and lower age at transplant were associated with response. Rituximab for recurrence of FSGS may be beneficial for only some patients. A younger age at transplant and normal serum albumin level at recurrence diagnosis may predict response.

c. Otras terapias: ACTH, Abatacept, Galactosa, podocitos…

202. Protecting Podocytes: A Key Target for Therapy of Focal Segmental Glomerulosclerosis.
Campbell KN, Tumlin JA.
Am J Nephrol. 2018;47 Suppl 1(Suppl 1):14-29.

ABSTRACT
Background: Focal segmental glomerulosclerosis (FSGS) is a histologic pattern of injury demonstrated by renal biopsy that can arise from a diverse range of causes and mechanisms. It has an estimated incidence of 7 per 1 million and is the most common primary glomerular disorder leading to end-stage renal disease in the United States. This review focuses on damage to the podocyte and the consequences of this injury in patients with FSGS, the genetics of FSGS, and approaches to treatment with a focus on the effects on podocytes.
Summary: The podocyte is central to the glomerular filtration barrier and is particularly vulnerable because of its highly differentiated post-mitotic phenotype. The progressive structural changes involved in the pathology of FSGS include podocyte foot process effacement, death of podocytes and exposure of the glomerular basement membrane, filtration of nonspecific plasma proteins, expansion of capillaries, misdirected filtration at points of synechiae, and mesangial matrix proliferation. Although damage to and death of podocytes can result from single-gene disorders, evidence also suggests a role for soluble factors, such as soluble urokinase-type plasminogen activator receptor, cardiotrophin-like cytokine-1, and anti-CD40 antibodies, that promote FSGS recurrence post transplant. Several classes of medications, including corticosteroids, calcineurin inhibitors, endothelin receptor antagonists, adrenocorticotropic hormone, and rituximab, have been shown to be effective for the treatment of FSGS and have been demonstrated to have significant protective effects on podocytes. Key Messages: Greater understanding of podocyte biology is essential to the identification of new treatment targets and medications for the management of patients with FSGS.

203. Advanced Therapeutics in Focal and Segmental Glomerulosclerosis.
Liu Y, Shi Y, Ren R et al.
Nephrology (Carlton). 2018 Oct;23 Suppl 4:57-61.

ABSTRACT
Focal segmental glomerulosclerosis (FSGS) is a glomerulonephritis with podocyte injury. The renal prognosis of FSGS is relative poor. The overall remission rate of the FSGS patients with nephrotic syndrome to immunosuppressive treatments was reported as 47-66%, highlighting its therapeutic challenge-lacking in sufficient evidence-based interventions. In first-line treatment of nephrotic syndrome, daily oral prednisolone is a commonly used drug, whereas optimal treatment strategies, like indications and duration, remain controversial. Calcineurin inhibitor and cyclophosphamide are recommended in steroid-dependent/steroid-resistant patients. However, the high unmet need in effective immunosuppressive treatments calls for the development of new therapy methods. Rituximab, a monoclonal antibody targeting CD20 B-cells, could increase the complete or partial remission rate, and decrease the relapse rate based on several previous studies on FSGS. In addition, the using of rituximab could potentially help the FSGS patients to stop the concomitant therapy include steroid and immunosuppressive agents. Other treatment options like adalimumab or abatacept also showed potential therapeutic effect, but still required larger Randomized Controlled Trial study to determine its efficiency and safety. Besides, expanding understanding of the genetic basis of FSGS is necessary to investigate new therapeutic agents. With the unsatisfied patients' outcome under the current treatments, innovation should be encouraged on the treatment strategy based on Kidney Disease: Improving Global Outcomes guideline and international collaborations are required for the potential novel immunosuppressive or immunomodulatory therapies.

204. ACTH Gel in Resistant Focal Segmental Glomerulosclerosis After Kidney Transplantation.
Alhamad T, Dieck JM, Younus U et al.
Transplantation. 2019 Jan;103(1):202-209.

ABSTRACT
Background: Treatment of focal segmental glomerular sclerosis (FSGS) after kidney transplantation is challenging with unpredictable outcomes. The objective was to investigate the use of adrenocorticotropic hormone (ACTH) analogue gel in kidney transplant recipients with de novo or recurrent FSGS resistant to therapeutic plasma exchange (TPE) and/or rituximab.
Methods: We performed a retrospective review of cases of de novo or recurrent resistant FSGS at 2 large US transplant centers between April 2012 and December 2016. Proteinuria was measured by urine protein to creatinine ratio.
Results: We identified 20 cases of posttransplant recurrent and de novo FSGS resistant to conventional therapy with TPE and rituximab. Mean ± SD age was 49 ± 15.5 years, 14 (70%) were male, 13 (65%) were whites, and 8 (38%) had previous kidney transplants. Median (interquartile range) of recurrent and de novo FSGS was 3 (0.75-7.5) months posttransplant. The majority of patients, 15 (75%), received TPE as a treatment at the time of diagnosis and 10 (50%) received rituximab, which was started before the use of ACTH gel. There was a significant improvement of urine protein to creatinine ratio from a mean ± SD of 8.6 ± 7.6 g/g before ACTH gel to 3.3 ± 2.3 g/g after the use of ACTH gel (P = 0.004). Ten (50%) patients achieved complete or partial remission.

Conclusions: Although, the response varied among the recipients, ACTH gel might be an effective therapy for posttransplant resistant FSGS cases that fail to respond to TPE and rituximab.

205. Adrenocorticotropic Hormone in the Treatment of Focal Segmental Glomerulosclerosis Following Kidney Transplantation.
Grafals M, Sharfuddin A.
Transplant Proc. Jul-Aug 2019;51(6):1831-1837.

ABSTRACT
This retrospective study examined the effect of adrenocorticotropic hormone therapy on remission of recurrent focal segmental glomerulosclerosis (FSGS) in patients with history of kidney transplant (KT) treated at 2 transplant centers. Patients with biopsy-confirmed FSGS following KT who received Acthar Gel (Mallinckrodt ARD, Bedminster, New Jersey, United States) treatment for ≥1 month were eligible. A total of 14 patients with idiopathic FSGS were included. Acthar Gel treatment resulted in complete remission of FSGS in 3 patients and partial remission in 2 patients for a total treatment response rate of 36% (5/14) of patients. Among patients showing complete or partial remission, Acthar Gel treatment duration ranged from 6 months to 2 years and 60% (3/5 patients) had serum creatinine ≤ 2 mg/dL at the start of Acthar Gel treatment. Patient outcomes suggest Acthar Gel may be an effective and tolerable treatment for recurrent FSGS in patients with history of KT. Early initiation of Acthar Gel treatment and therapy duration of at least 6 months may be needed for optimal response to Acthar Gel in patients with history of KT and recurrent FSGS.

206. Successful Treatment With Abatacept in Recurrent Focal Segmental Glomerulosclerosis After Kidney Transplant.
Shah Y, Almeshari K, Aleid H et al.
Exp Clin Transplant. 2019 Jan;17(Suppl 1):178-180.

ABSTRACT
Primary focal segmental glomerulosclerosis recurrence occurs in 10% to 50% of recipients after kidney transplant and may affect both children and adults. Treatment after recurrence with plasma exchange and immunosuppression is quite variable and challenging, and those who do not respond usually progress to allograft failure. Podocyte injury and B7-1 expression and subsequently its blockade (abatacept) have been reported to be associated with complete remission of proteinuria in 4 patients with focal segmental glomerulosclerosis recurrence after kidney transplantation and in 1 patient with focal segmental glomerulosclerosis in native kidney. Here, we report our experience of successfully treating 3 consecutive patients with focal segmental glomerulosclerosis recurrence after kidney transplant with abatacept, which induced proteinuria remission.

207. Recurrence of focal and segmental glomerulosclerosis after transplantation.
Canaud G, Delville M, Legendre C.
Transplantation. 2016 Feb;100(2):284-7.

ABSTRACT
Focal segmental glomerulosclerosis, which is a common glomerular disorder, manifests clinically with a nephrotic syndrome and has a high propensity for recurrence after kidney transplantation. The pathophysiology is currently unknown, and podocytes appear to be the target of one or several circulating factor(s) that lead to the recurrence of proteinuria after kidney transplantation. Identifying these circulating factor(s) and cells involved in its synthesis remains elusive; however, recently, our research on podocyte cytoskeleton biology has opened a new era of treatment. This review will highlight recent progress in the physiopathology of focal segmental glomerulosclerosis recurrence after transplantation and its treatment.

E. ¿ES ACEPTABLE EL TRASPLANTE DE VIVO EN GEFS?, ¿ES FACTIBLE Y LO HACE MÁS ACONSEJABLE LA POSIBILIDAD DE TRANSFERENCIA DEL ÓRGANO SI RECIDIVA?

208. Risk Factors Associated With Allograft Failure in Pediatric Kidney Transplant Recipients With Focal Segmental Glomerulosclerosis.
Koh LJ, Martz K, Blydt-Hansen TD et al.
Pediatr Transplant. 2019 Aug;23(5):e13469.

ABSTRACT
Background: With improved outcomes for children transplanted with FSGS since previous NAPRTCS registry reports, this study re-evaluates the association of living donation, immunosuppression, and DGF on graft survival.
Setting: Patients transplanted between 2002 and 2016, comparing FSGS diagnosis vs other glomerular diseases.
Methods: Primary outcomes were allograft survival and FSGS recurrent-free graft survival. Potential risk factors were obtained at the time of transplant and up to 30 days post-transplantation. Analysis considered a priori that DGF may be a proxy for severe FSGS recurrence. Multivariable survival models for outcome were tested for sensitivity without/with DGF to determine features independent of recurrence.
Results: From the larger cohort of 3010 patients, 5-year graft survival in children with FSGS (n = 455) was worse (74.3%) compared with other glomerular diseases (87.1%, n = 690) (HR 1.45, P = 0.033). Modeling all glomerular diseases, survival risk was associated with deceased donor (HR 1.83, P = 0.002), re-transplantation (HR 1.58, P = 0.013), and recipient age (HR 1.06/y, P = 0.002). The living donor advantage was not confirmed in a FSGS model (HR 1.51 for deceased, P = 0.12). DGF was highly associated with graft failure (HR 4.39, P < 0.001) and independent of re-transplant history but not FSGS diagnosis. Induction agents or primary immunosuppression choices were not associated with survival.
Conclusion: Graft survival rates have improved since the previous report. Living donor did not predict graft failure, but there remains no survival advantage. DGF was the primary independent predictor for graft loss secondary to FSGS recurrence, consistent with DGF being a proxy for severe recurrent disease.

F. ¿HAY QUE MANTENER EN PROGRAMA DE TRASPLANTE TRAS VARIAS RECIDIVAS?

209. European Society of Pediatric Nephrology Survey on Current Practice Regarding Recurrent Focal Segmental Glomerulosclerosis After Pediatric Kidney Transplantation.

Bouts A, Veltkamp F, Tönshoff B et al.

Pediatr Transplant. 2019 May;23(3):e13385.

ABSTRACT

Introduction: Primary FSGS is an important cause of ESRD in children. FSGS recurrence after kidney transplantation is associated with early graft loss. No guidelines for treatment of FSGS recurrence exist. We conducted a survey to gain insight into variation of treatment between centers.

Methods: A survey was sent to all members of the ESPN on behalf of the "Renal Transplantation" and "Idiopathic Nephrotic Syndrome" working groups.

Results: Fifty-nine nephrologists from 31 countries responded, reporting 807 FSGS patients, with 241 (30%) FSGS recurrences after transplantation. Recurrence varied from 0% to 100% between respondents. Native nephrectomy before or during transplantation was performed, respectively, always (37%), never (39%), or on clinical indication (17%). Half of the respondents started preventive treatment before transplantation, using PF (n = 10); R (n = 4); PF or IA, plus R (n = 9); cyclosporine (n = 2); or unknown (n = 4). Immunosuppressive therapy for patients without known mutations consisted of a combination of steroids, tacrolimus/cyclosporine, and MMF, with or without IL-2R-blockade in, respectively, 61% and 86% of the respondents. Sixty-three percent applied a similar regimen to patients with known mutations. FSGS recurrence was treated with PF or IA, plus R by 66% of respondents; 54% observed no response. Complete remission in >50% of patients was reported by 41% of the respondents.

Discussion: FSGS recurrence after transplantation is common, but varies greatly between centers. We found great variability in preventive and therapeutic treatment regimens. Future research should focus on predisposing factors, including biopsy findings and genetic mutations, and standardized treatment.

3. RECIDIVA DE LA AMILOIDOSIS, GLOMERULOPATÍAS POR DEPÓSITO FIBRILAR NO AMILOIDE Y ENFERMEDAD POR DEPÓSITO DE CADENAS LIGERAS

A. RECIDIVA DE LA ENFERMEDAD POR DEPÓSITO DE CADENAS LIGERAS

210. Light Chain Deposition Disease After Kidney Transplantation With Long Graft Survival: Case Report

Kuppachi S, Holanda D, Thomas CP.
Transplant Proc Jan-Feb 2016;48(1):255-8.

ABSTRACT
Light Chain Deposition Disease (LCDD) is a monoclonal immunoglobulin deposition disease that commonly affects kidneys among other organs. It leads to end-stage renal disease and has a high disease recurrence rate after kidney transplantation. This has led some authors to advise against transplantation in view of the poor long-term graft and patient outcomes. Recent literature has shown improvement/stabilization of native kidney disease following the use of bortezomib. We present 2 cases of LCDD after transplantation with graft dysfunction. They were both treated with different therapeutic agents to induce remission. Because sustained remission was not achieved they received bortezomib following which they have experienced a prolonged period of stable renal function with no clinically detectable disease. These unique cases highlight the possibility to achieve long-term stable graft function and disease remission after renal transplantation for LCDD.

211. Long-term Outcome of Renal Transplantation in Light-Chain Deposition Disease

Leung N, Lager SJ, Gertz MA et al.
Am J Kidney Dis 2004 Jan;43(1):147-53.

ABSTRACT
Background: Light-chain deposition disease (LCDD) is a monoclonal gammopathy characterized by nonamyloid deposition of light chain in various organs. A small number of kidney transplantations have been performed on LCDD patients in whom end-stage renal disease (ESRD) developed.
Methods: The authors retrospectively reviewed the clinical and histologic findings and outcome of 7 patients with LCDD who underwent kidney transplantation at our institution.
Results: Renal insufficiency, hypertension, and proteinuria were present in all 7 patients. Proteinuria level was greater than 3.5 g/24 h in 3 patients. Three patients had microscopic hematuria. Monoclonal protein was detected in the serum in 3 patients, urine in 5, and was undetectable in 2. Median age at presentation was 42.7 (range, 33 to 58) years. The most common renal biopsy findings were mesangial expansion, mesangial nodules, tubular basement membrane thickening, and tubular atrophy. Kappa light chain was detected in all 7 renal biopsy results. Five patients were on dialysis before transplantation. LCDD recurred after a median of 33.3 (range, 2 to 45) months in 5 of the 7 patients. One patient remains on dialysis, whereas the other 4 have died. One patient died of progression of multiple myeloma 3 months after kidney transplantation without evidence of recurrence. Only 1 patient remains recurrence free after 13 years with normal renal allograft function.

Conclusion: Although long-term benefits are occasionally seen, renal allograft survival is reduced significantly in LCDD patients. Kidney transplantation should not be an option for LCDD patients unless measures have been taken to reduce light chain production.

212. Light Chain Deposition Disease and Proximal Tubulopathy in Two Successive Kidney Allografts

Drieux F, Loron MC, Francois A, et al.
Clin Nephrol 2015 Jun;83(6):351-6. doi: 10.5414/CN108319.

ABSTRACT

Light chain proximal tubulopathy (LCPT) is a rare kidney disease associated with plasma cell dyscrasias, characterized by light chain deposits in the proximal tubular cells, with or without crystal formation. We describe an exceptional case of LCPT without crystal formation in a kidney allograft, in a patient who underwent two renal transplants for a light chain deposition disease (LCDD) complicating smoldering myeloma. This is the first description of this association in successive kidney allografts. We concisely describe pathology of LCDD and LCPT and discuss potential pathophysiological mechanisms relating these two conditions.

213. Lambda Light Chain Deposition Disease in a Renal Allograft

Tanenbaum ND, Howell DN, Middleton JP, et al.
Transplant Proc 2005 Dec;37(10):4289-92.

ABSTRACT

Light chain deposition disease (LCDD) of the kidney is characterized by deposition of monoclonal light chains predominantly in glomeruli and in tubular basement membranes. The disease is frequently associated with a lymphoproliferative disorder, and the majority of cases are caused by deposition of kappa light chains. Although the occurrence of de novo multiple myeloma after renal transplantation is uncommon, there are several reports of LCDD involving renal allografts, either de novo or in patients with a diagnosis of LCDD prior to transplantation. To the best of our knowledge, all previously described cases in allografts have been in patients with kappa chain deposition. The relative importance of intrinsic properties of the kidney in predisposing to either kappa or lambda light chain deposition is not known. We present a case of LCDD caused by deposition of lambda light chains in a patient who received a cadaveric renal transplant.

214. Light Chain Deposition Disease Affecting the Gastrointestinal Tract in the Setting of Post-Living Donor Kidney Transplantation.

Jimenez-Zepeda VH , Vajpeyi R, John R et al.
Int J Hematol 2012 Jul;96(1):125-31.

ABSTRACT

Light chain deposition disease (LCDD) is an uncommon, clonal plasma cell proliferative disorder, in which monoclonal immunoglobulin light chains deposit in various tissues, resulting in organ dysfunction. Gastrointestinal (GI) involvement has been described in both primary and secondary amyloidosis, but has rarely been reported in LCDD, and only as an incidental finding. We report a case of LCDD in living related kidney transplant recipient presenting with severe GI dysmotility, weight loss and progressive allograft dysfunction. A diagnosis of LCDD was based on the kidney biopsy findings in the failing renal allograft, along with the presence of excess serum free kappa light chains and abnormal kappa:lambda ratio. Subsequent review of GI biopsies confirmed kappa light chain immunoglobulin deposition within the stomach. Further investigation suggested additional hepatic and cardiac involvement. The patient went on to receive bortezomib, achieving a biochemical response and stabilization of his advanced renal dysfunction; however, bortezomib was discontinued due to toxicity. The patient was subsequently treated with lenalidomide and dexamethasone, which were better tolerated. Further biochemical response and resolution of the GI symptoms was observed after 10 months of treatment. In summary, we present the first case of LCDD with symptomatic GI involvement, in which the diagnosis was established by intestinal biopsies. Our report also highlights the feasibility and effectiveness of lenalidomide in the treatment of LCDD.

215. Monoclonal Gammopathy of Renal Significance With Light-Chain Deposition Disease Diagnosed Postrenal Transplant: A Diagnostic and Therapeutic Challenge
Nambirajan A, Bhowmik D, Singh G et al.
Transpl Int 2015 Mar;28(3):375-9.

ABSTRACT
Patients with light-chain deposition disease (LCDD) frequently do not meet criteria for myeloma. In such cases, despite low tumor burden, the circulating monoclonal immunoglobulins cause renal damage, are responsible for post-transplant recurrence, and are rightly categorized as monoclonal gammopathy of renal significance (MGRS) requiring chemotherapy. A 65-year male with uncharacterized nodular glomerulopathy presented with proteinuria 3 years postrenal transplant. His allograft biopsies were diagnostic of light-chain deposition disease (likely recurrent), and in the absence of myeloma, he was labeled as MGRS. Based on the limited literature available, he was treated with bortezomib which resulted in normalization of serum-free light-chain ratios and resolution of proteinuria. He, however, later succumbed to complications of chemotherapy. This case highlights the diagnostic difficulties in LCDD, the importance of an accurate pretransplant diagnosis, and treatment of the malignant clone, in the absence of which post-transplant management of recurrence is challenging with poor outcomes.

216. Bortezomib Successfully Reverses Early Recurrence of Light-Chain Deposition Disease in a Renal Allograft: A Case Report.
Kaposztas Z , Kahan BD, Katz SM et al.
Transplant Proc 2009 Dec;41(10):4407-10.

ABSTRACT
Light-Chain Deposition Disease (LCDD) frequently recurs after renal transplantation, displaying a pernicious course. Herein we have described a 39-year-old Caucasian man with a history of immunoglobulin G-kappa multiple myeloma who failed two chemotherapy regimens, but ultimately responded to the combination of thalidomide, bortezomib, and dexamethasone followed by high-dose melphalan and autologous stem cell transplantation 3 years prior to transplantation, during which time he showed no evidence of persistent or recurrent disease. At 3 days following spousal living related renal transplantation, he displayed a rapid deterioration of renal function requiring dialysis therapy. This episode failed to respond to empiric antirejection therapy including anti-thymocyte globulin, plasmapheresis, and anti-CD20 monoclonal antibody. Increasing evidence suggested recurrence of LCDD, including positive immunofluorescence staining of basement membranes and vessels for kappa light chains as well as free kappa light chains in his urine and serum. Following suspension of sirolimus, he was initiated on and responded to bortezomib (1.3 mg/m(2)) with discontinuation of dialysis within 3 weeks and progressively improving renal function. His maintenance therapy, in addition to six 2-week-long cycles of bortezomib separated by 1-week rest periods, includes cyclosporine (50 mg twice daily), prednisone (10 mg daily), and curcumin (9 g daily). In sum, bortezomib rescue therapy salvaged a spousal renal transplant afflicted with recurrent LCDD.

217. De Novo Light-Chain Deposition Disease in a Cadaver Renal Allograft
Ecder T, Tbakhi A, Braun WE et al.
Am J Kidney Dis 1996 Sep;28(3):461-5.

ABSTRACT
The deposition of immunoglobulin (Ig) light chains after renal transplantation most commonly occurs as a manifestation of recurrent multiple myeloma or recurrent light chain nephropathy. We report the development of de novo light chain deposition disease (LCDD) in a cadaveric renal transplant recipient 16 years after transplantation with no evidence of prior multiple myeloma or LCDD and no current evidence of myeloma or lymphoproliferative malignancy.

218. Recurrence of Light-Chain Deposition Disease After Renal Transplantation
Larsen T, Hammer A, Jørgensen KA.
Scand J Urol Nephrol 2008;42(2):187-8.

ABSTRACT
A 51-year-old male with a history of chronic renal disease received a renal allograft, in which disease recurred. Light-chain deposition disease was confirmed through biopsies of the native kidney and graft, and detection of free kappa light chains in serum.

219. Long-term Outcome of Renal Transplantation in Light-Chain Deposition Disease
Leung N, Lager DJ, Gertz MA et al.
Am J Kidney Dis 2004 Jan;43(1):147-53.

ABSTRACT

Background: Light-chain deposition disease (LCDD) is a monoclonal gammopathy characterized by nonamyloid deposition of light chain in various organs. A small number of kidney transplantations have been performed on LCDD patients in whom end-stage renal disease (ESRD) developed.

Methods: The authors retrospectively reviewed the clinical and histologic findings and outcome of 7 patients with LCDD who underwent kidney transplantation at our institution.

Results: Renal insufficiency, hypertension, and proteinuria were present in all 7 patients. Proteinuria level was greater than 3.5 g/24 h in 3 patients. Three patients had microscopic hematuria. Monoclonal protein was detected in the serum in 3 patients, urine in 5, and was undetectable in 2. Median age at presentation was 42.7 (range, 33 to 58) years. The most common renal biopsy findings were mesangial expansion, mesangial nodules, tubular basement membrane thickening, and tubular atrophy. Kappa light chain was detected in all 7 renal biopsy results. Five patients were on dialysis before transplantation. LCDD recurred after a median of 33.3 (range, 2 to 45) months in 5 of the 7 patients. One patient remains on dialysis, whereas the other 4 have died. One patient died of progression of multiple myeloma 3 months after kidney transplantation without evidence of recurrence. Only 1 patient remains recurrence free after 13 years with normal renal allograft function.

Conclusion: Although long-term benefits are occasionally seen, renal allograft survival is reduced significantly in LCDD patients. Kidney transplantation should not be an option for LCDD patients unless measures have been taken to reduce light chain production.

220. Natural History and Outcome of Light Chain Deposition Disease

Sayed RH, Wechalekar AD, Gilbertson JA et al.

Blood 2015 Dec 24;126(26):2805-10.

ABSTRACT

Light chain deposition disease (LCDD) is characterized by the deposition of monotypic immunoglobulin light chains in the kidney, resulting in renal dysfunction. Fifty-three patients with biopsy-proven LCDD were prospectively followed at the UK National Amyloidosis Center. Median age at diagnosis was 56 years, and patients were followed for a median of 6.2 years (range, 1.1-14.0 years). Median renal survival from diagnosis by Kaplan-Meier analysis was 5.4 years, and median estimated patient survival was 14.0 years; 64% of patients were alive at censor. Sixty-two percent of patients required dialysis, and median survival from commencement of dialysis was 5.2 years. There was a strong association between hematologic response to chemotherapy and renal outcome, with a mean improvement in glomerular filtration rate (GFR) of 6.1 mL/min/year among those achieving a complete or very good partial hematologic response (VGPR) with chemotherapy, most of whom remained dialysis independent, compared with a mean GFR loss of 6.5 mL/min/year among those achieving only a partial or no hematologic response ($P < .009$), most of whom developed end-stage renal disease (ESRD; $P = .005$). Seven patients received a renal transplant, and among those whose underlying clonal disorder was in sustained remission, there was no recurrence of LCDD up to 9.7 years later. This study highlights the need to diagnose and treat LCDD early and to target at least a hematologic VGPR with chemotherapy, even among patients with advanced renal dysfunction, to delay progression to ESRD and prevent recurrence of LCDD in the renal allografts of those who subsequently receive a kidney transplant.

221. Recurrent Light and Heavy Chain Deposition Disease After Renal Transplantation
Alchi B, Nishi S, Iguchi S et al.
Nephrol Dial Transplant 2005 Jul;20(7):1487-91.

No abstract available

222. Late Recurrence of Light Chain Deposition Disease After Kidney Transplantation Treated With Bortezomib: A Case Report
Moiz A, Javed T, Garces J et al.
Ochsner J Fall 2014;14(3):445-9.

ABSTRACT
Background: Light chain deposition disease (LCDD) recurs frequently after renal transplantation with variable presentation.
Case report: We report the case of a 67-year-old Caucasian female with recurrence of LCDD after living-donor kidney transplantation. Bone marrow biopsy revealed kappa light chain-restricted population of plasma cells, and the patient met the criteria for multiple myeloma. Her renal function progressively worsened and she became dialysis dependent. She received 1 cycle of bortezomib along with intravenous dexamethasone. She was able to discontinue dialysis within 2 months, and at 1 year follow-up her renal function was stable.
Conclusion: Bortezomib has a role in the treatment of recurrent LCDD and multiple myeloma in kidney transplant patients. As opposed to traditional regimens, a short course may be beneficial.

223. Recurrence of Light Chain Deposit Disease After Renal Allograft Transplantation: Potential Role of Rituximab?
Kuypers DRJ, Lerut E, Claes K et al.
Transpl Int 2007 Apr;20(4):381-5.

ABSTRACT
Light chain deposit disease (LCDD) is a monoclonal plasma cell disorder characterized by tissue deposition of nonamyloid immunoglobulin light chains, predominantly kappa chains, causing renal insufficiency. LCDD reoccurs almost invariably after renal grafting, leading to early graft loss, usually within a time span of months to years. We describe a female patient with LCDD who lost her first living donor graft after 1 year due to extensive recurrence of kappa chain deposition. Rituximab was administered on the seventh day after her second transplantation with a graft from a deceased donor, in order to prevent early recurrence of LCDD. The 2-year protocol biopsy - similarly to the completely normal 1-year protocol biopsy - revealed persistent absence of light chain deposition on light microscopy but immunohistochemical staining and electron microscopy showed very mild recurrence of light chain deposits. A second 4-week course of rituximab was repeated because of these electron microscopic findings. Subsequently, free kappa light chain concentration decreased from 693 to 74 mg/l and remained low 4 months after completion of therapy. Rituximab could be considered for delaying early LCDD recurrence in patients in whom treatment of the underlying

bone marrow disorder failed or is contraindicated, but maintenance therapy is apparently necessary to consolidate this response.

224. Outcomes of Patients With Renal Monoclonal Immunoglobulin Deposition Disease
Kourelis TV, Nasr SH, Dispenzieri A et al.
Am J Hematol 2016 Nov;91(11):1123-1128. doi: 10.1002/ajh.24528. Epub 2016 Aug 29.

ABSTRACT
Recent reports suggest that deep hematologic responses to chemotherapy are associated with improved renal outcomes in monoclonal immunoglobulin deposition disease (MIDD). Here we describe the long term outcomes and identify prognostic factors after first line treatment of the largest reported series of patients with MIDD. Between March 1992 and December 2014, 88 patients with MIDD were seen at Mayo Clinic, MN. Renal responses were defined using criteria used for light chain amyloidosis (AL) or those used by the IMWG. Sixty-one (69%) patients had a GFR < 30 mL/min/1.73 m2 and 16 (18%) were on renal replacement therapy at diagnosis. The interval between albuminuria or elevation in creatinine and MIDD diagnosis was 12 months suggesting a delay in diagnosis. Thirty-seven patients (42%) had at least a hematologic CR/VGPR. Fifty-three (60%) received an autologous stem cell transplant (ASCT) or proteasome inhibitor (PI)-based treatments. Patients receiving ASCT or PI-based therapies were more likely to achieve at least a hematologic CR/VGPR compared to those receiving other therapies: 66% vs 2%, p < 0.0001. Patients that achieved a hematologic CR were more likely to achieve a renal response (53% vs 24%, p = 0.001). Five year overall and renal survival for the entire cohort was 67% and 57%, respectively. In multivariate analyses, a baseline GFR < 20 mL/min/1.73 m2 and a renal response (using AL or IMWG criteria) were independently predictive of progression to dialysis. This study confirms that deep hematologic responses, best achieved with ASCT or PI-based therapies, are a prerequisite to achieving renal responses. Am. J. Hematol. 91:1123-1128, 2016. © 2016 Wiley Periodicals, Inc.

B. RECIDIVA DE LA AMILOIDOSIS RENAL

225. Renal transplantation in amyloidosis and MIDD.
Stern L, Havasi A.
Front Biosci (Elite Ed). 2015 Jan 1;7:149-57.

ABSTRACT
Amyloidosis and monoclonal immunoglobulin deposition disease, though rare entities, can wreak havoc on the architecture and functioning of the kidneys. These diseases have a predilection to cause severe renal dysfunction leading to end stage renal disease (ESRD). In recent years, the available treatments for these diseases have expanded and afflicted patients are living longer, but with advanced kidney disease. Because of the complex nature of the pathophysiology and treatment of these diseases, it can be very challenging for a clinician to determine whether or not it is appropriate to refer an affected individual for kidney transplantation.

226. Comparative Analysis of Outcomes of Kidney Transplantation in Patients With AA Amyloidosis and Chronic Glomerulonephritis.

Sahutoglu T, Atay K, Caliskan Y et al.

Transplant Proc. 2016 Jul-Aug;48(6):2011-6. doi: 10.1016/j.transproceed.2016.04.015.

ABSTRACT

Background: Amyloid A (AA) amyloidosis is a multisystemic, progressive, and severe disease. Renal involvement is a prominent feature of the disease, and the outcome of patients on dialysis is poor. We aimed to analyze the outcomes of kidney transplantation in patients with AA amyloidosis in comparison with chronic glomerulonephritis (CGN).

Methods: Charts of patients who underwent kidney transplantation between 1988 and 2012 were reviewed; 41 patients with AA amyloidosis were identified, and 41 age- and sex-matched control patients with chronic CGN were included. Baseline characteristics, immunosuppressive regimens, and transplantation-related outcomes were retrieved using a standardized form.

Results: The mean follow-up period was 70.9 ± 44.9 months. The 10-year patient survival was found to be significantly worse in the AA amyloidosis group (62.5%) compared to CGN group (100%) (P = .008). During the follow-up period, three of the 41 patients (9.7%) died of sepsis and one patient died of cardiac complications in the amyloidosis group, whereas there was no patients were lost in the CGN group. The first-year, fifth-year, and tenth-year mean graft survival rates, acute and chronic rejections, and mean creatinine levels at last visits were not significantly different between the groups. Proteinuria >1 g/d, cytomegalovirus and tuberculosis infections, and rhabdomyolysis were recorded at a significantly higher rate in patients with amyloidosis.

Conclusion: As compared to patients with CGN, patients with AA amyloidosis had a lower patient survival; equal graft survival and rejection rates; and higher risks of developing proteinuria, cytomegalovirus and tuberculosis infections, and rhabdomyolysis.

227. Transthyretin amyloidosis and the kidney.

Lobato L, Rocha A.

Clin J Am Soc Nephrol. 2012 Aug;7(8):1337-46.

ABSTRACT

The amyloidoses are protein-misfolding disorders associated with progressive organ dysfunction. Immunoglobulin light chain is the most common, amyloid A the longest recognized, and transthyretin-associated amyloidosis (ATTR) the most frequent inherited systemic form. Although ATTR, an autosomal-dominant disease, is associated with at least 100 different transthyretin (TTR) mutations, the single amino-acid substitution of methionine for valine at position 30 is the most ABSTRACTcommon mutation. Each variant has a different organ involvement, although clinical differences attributed to environmental and genetic factors exist within the same mutation. Peripheral neuropathy and cardiomyopathy are broadly described, and insights into disease reveal that kidney impairment and proteinuria are also clinical features. This review combines clinical and laboratory findings of renal involvement from the main geographic regions of disease occurrence and for different mutations of TTR. Fifteen nephropathic variants have been described, but the TTR V30M mutation is the best documented. Nephropathy affects patients with late-onset neuropathy, low penetrance in the family, and cardiac dysrhythmias. Microalbuminuria can be the disorder's first

presentation, even before the onset of neuropathy. Amyloid renal deposits commonly occur, even in the absence of urinary abnormalities. The experience with renal replacement therapy is based on hemodialysis, which is associated with poor survival. Because TTR is synthesized mainly in the liver, liver transplantation has been considered an acceptable treatment; simultaneous liver-kidney transplantation is recommended to avoid recurrence of nephropathy. In addition, the kidney-safety profile of new drugs in development may soon be available.

228. Liver transplantation in transthyretin amyloidosis: Characteristics and management related to kidney disease.

Rocha A, Lobato L.

Transplant Rev (Orlando). 2017 Apr;31(2):115-120.

ABSTRACT

Orthotopic liver transplantation (LT) was implemented as the inaugural disease-modifying therapy for hereditary transthyretin (ATTR) amyloidosis, a systemic amyloidosis mainly affecting the peripheral nervous system and heart. The first approach to pharmacologic therapy was focused on the stabilization of the TTR tetramer; following that new advent LT was assumed as the second step of treatment, for those patients whose neuropathy becomes worse after a course of pharmacologic therapy. The renal disease has been ignored in hereditary ATTR amyloidosis. The low level of proteinuria or slight renal impairment does not suppose such a heavy glomerular and vascular amyloid deposition. Moreover, severity of renal deposits does not consistently parallel that of myelinated nerve fiber loss. These are pitfalls that limit the success of LT and suggest troublesome criteria for pharmacological therapy or LT. An algorithm of evaluation concerning renal disease and treatment options is presented and some bridges-to-decision are exposed. In stage 4 or 5 kidney disease, the approach remains to deliver combined or sequential liver-kidney transplantation in eligible patients. However, in the majority, hemodialysis is the only option even in the presence of a well-functioning liver graft. In this review, we highlight useful information to aid the transplant hepatologist in the clinical practice.

229. Long-term outcome of kidney transplantation in AL amyloidosis.

Angel-Korman A, Stern L, Sarosiek S et al.

Kidney Int. 2019 Feb;95(2):405-411.
Erratum in Kidney Int. 2019 Sep;96(3):796.
Comment in Kidney Int. 2019 Feb;95(2):258-260.

ABSTRACT

Therapies for AL amyloidosis have dramatically improved, leading to longer patient survival; however, more AL amyloidosis patients are reaching end-stage renal disease (ESRD). There are no clear guidelines regarding eligibility for kidney transplantation in patients with AL amyloidosis, and data on outcomes are limited. We evaluated the clinical and laboratory data of 49 patients who were followed in the Amyloidosis Center at Boston University and underwent kidney transplantation at a center in the United States between 1987-2017. During a median follow-up of 7.2 years (range 0-19), the median patient survival from diagnosis was 15.4 years, and from kidney transplantation

was 10.5 years. One, three, and five-year graft survival were 94%, 89%, and 81%, respectively. Patients with hematologic complete response or very good partial response prior to kidney transplantation had significantly better patient survival than patients with partial response or no response, and the median time to graft loss was 10.4 years versus 5.5 years, respectively. This is the largest published series of kidney transplantation in patients with AL amyloidosis, suggesting that kidney transplantation can have a good outcome in carefully selected patients, particularly in those who have achieved a complete response or very good partial response at the time of kidney transplantation.

230. LECT2 Amyloidosis in Kidney Transplantation: A Report of 5 Cases.
Mejia-Vilet JM, Cárdenas-Mastrascusa LR, Palacios-Cebreros EJ et al.
Am J Kidney Dis. 2019 Oct;74(4):563-566.

ABSTRACT
Leukocyte chemotactic factor 2 (LECT2) amyloidosis is a recently recognized entity that often affects the kidneys. Little information is available regarding kidney transplant outcomes in patients with LECT2 amyloidosis or who received kidney allografts containing LECT2 amyloid. We present clinical findings and allograft outcomes of 5 patients who received kidneys with donor-derived LECT2 amyloidosis. In all 5, LECT2 amyloidosis was discovered during protocol biopsies or in evaluation of suspected rejection. Less than 10% of kidney parenchyma was involved, with mostly interstitial and vascular deposits. Allograft function was not impaired and the amyloid deposits persisted for up to 8 years of follow-up. We conclude that kidneys with limited and localized LECT2 amyloid deposits that are otherwise suitable for transplantation need not be automatically discarded.

231 Hereditary transthyretin amyloidosis: a model of medical progress for a fatal disease.
Adams D, Koike H, Slama M et al.
Nat Rev Neurol. 2019 Jul;15(7):387-404.

ABSTRACT
Hereditary amyloidogenic transthyretin (ATTRv) amyloidosis with polyneuropathy (also known as familial amyloid polyneuropathy) is a condition with adult onset caused by mutation of transthyretin (TTR) and characterized by extracellular deposition of amyloid and destruction of the somatic and autonomic PNS, leading to loss of autonomy and death. This disease represents a model of the scientific and medical progress of the past 30 years. ATTRv amyloidosis is a worldwide disease with broad genetic and phenotypic heterogeneity that presents a diagnostic challenge for neurologists. The pathophysiology of the neuropathy is increasingly understood and includes instability and proteolysis of mutant TTR leading to deposition of amyloid with variable lengths of fibrils, microangiopathy and involvement of Schwann cells. Wild-type TTR is amyloidogenic in older individuals. The main symptoms are neuropathic, but the disease is systemic; neurologists should be aware of cardiac, eye and kidney involvement that justify a multidisciplinary approach to management. Infiltrative cardiomyopathy is usually latent but present in half of patients. Disease-modifying therapeutics that have been developed include liver transplantation and TTR stabilizers, both of which can slow progression of the disease and increase survival in the early stages. Most

recently, gene-silencing drugs have been used to control disease in the more advanced stages and produce some degree of improvement.

232. AA Amyloidosis After Renal Transplantation: An Important Cause of Mortality.
Sarihan I, Caliskan Y, Mirioglu S et al.
Transplantation. 2019 Oct 30. doi: 10.1097/TP.0000000000003043.

ABSTRACT
Background: There is limited data on the outcome of transplant recipients with familial Mediterranean fever (FMF)-associated AA amyloidosis. The aim of the present study is to evaluate demographic, clinical, laboratory, prognostic characteristics and outcome measures of these patients.
Methods: Eighty-one renal transplant recipients with FMF-associated AA amyloidosis (group 1) and propensity score-matched transplant recipients (group 2, n = 81) with nonamyloidosis etiologies were evaluated in this retrospective, multicenter study. Recurrence of AA amyloidosis was diagnosed in 21 patients (group 1a) and their features were compared with propensity score matched 21 recipients with FMF-amyloidosis with no laboratory signs of recurrence (group 1b).
Results: The risk of overall allograft loss was higher in group 1 compared to group 2 [25 (30.9%) vs. 12 (14.8%), p = 0.015 (HR 2.083; 95% CI 1.126 - 3.856)]. Patients in group 1 were characterized by an increased risk of mortality compared group 2 [11 (13.6%) vs 0%, p = 0.001 (HR 1.136; 95% CI 1.058 - 1.207)]. Kaplan Meier analysis revealed that 5-year and 10-year patient survival rates in group 1 (92.5% and 70.4%) were significantly lower than group 2 (100% and 100%; p = 0.026 and p = 0.023, respectively). Although not reaching significance, overall, 5-year and 10-year graft survival rates (57.1%, 94.7% and 53.8%, respectively) in group 1a were worse than group 1b (76.2%, 95% and 77.8%, respectively) (p = 0.19, p = 0.95 and p = 0.27, respectively).
Conclusions: AA amyloidosis is associated with higher risk of mortality after kidney transplantation. Inflammatory indicators should be monitored closely, and persistent high levels of acute phase reactants should raise concerns about amyloid recurrence in allograft.

233. Improved outcomes for kidney transplantation in AL amyloidosis: impact on practice.
Nuvolone M, Merlini G.
Kidney Int. 2019 Feb;95(2):258-260. doi: 10.1016/j.kint.2018.11.003.
Comment on Kidney Int. 2019 Feb;95(2):405-411.

ABSTRACT
Effective therapies for Ig light chain (AL) amyloidosis has led to an increasing proportion of patients with end-stage renal disease requiring renal replacement therapy, yet kidney transplantation is seldom performed in this setting due to concerns of renal and extrarenal disease progression. Angel-Korman et al. report unprecedented positive long-term outcomes in the largest series of kidney transplantation in AL amyloidosis providing the basis for a more proactive approach to this procedure.

234. Patient and Kidney Allograft Survival in Recipients With End-Stage Renal Disease From Amyloidosis.

Sawinski D, Lim MA, Cohen JB et al.

Transplantation. 2018 Feb;102(2):300-309.

ABSTRACT

Background: Outcomes after kidney transplantation for patients with amyloidosis-associated end-stage renal disease (ESRD) have not been well characterized.

Methods: We performed a retrospective propensity score matched cohort study with Cox proportional hazards modeling using data from the United Network of Organ Sharing including patients transplanted from 1987 to 2015 (N = 310 629).

Results: Amyloidosis patients (N = 576) had higher rates of death (hazard ratio [HR], 1.58; 95% confidence interval [CI], 1.28-1.95) and graft loss (HR, 1.49; 95% CI, 1.19-1.87) compared with nonamyloidosis patients. The results were similar when the cohort was restricted to patients transplanted on or after 2001 (HR, 1.72; 95% CI, 1.31-2.26 for death; HR, 1.77; 95% CI, 1.35-2.33 for graft loss). However, there was no significant difference in risk of death or graft loss when amyloidosis patients were compared with those with diabetes-associated ESRD (mortality: HR, 0.99; 95% CI, 0.84-1.17; allograft loss: HR, 1.00; 95% CI, 0.84-1.20), or when compared with elderly patients (age, >65 years at the time of transplant) (mortality: HR, 0.99; 95% CI, 0.81-1.21; graft loss: HR, 1.02; 95% CI, 0.82-1.26).

Conclusions: For patients with amyloidosis-associated ESRD deemed suitable for transplantation, patient and graft survivals are diminished compared to kidney transplant recipients overall, but are comparable to other high-risk subgroups.

235. Kidney transplantation for end-stage renal disease secondary to familial Mediterranean fever.

Altindal M, Turkmen E, Yildirim T et al.

Clin Transplant. 2016 Jul;30(7):787-90.

ABSTRACT

Although kidney transplantation (KT) is widely used for treating renal amyloidosis secondary to familial Mediterranean fever (FMF), data concerning transplant outcome are limited and inconsistent. The aim of this study was to determine the long-term outcome of KT in patients with amyloidosis secondary to FMF. Kidney transplantation outcome in 24 patients with FMF was compared to that in 72 controls matched for age, gender of recipient, and type of the donor that underwent KT due to end-stage renal disease (ESRD) not caused by FMF. Mean follow-up time was 80.3 ± 55.1 months in the FMF group, vs. 86.5 ± 47.6 months in the control group. Death-censored graft survival at five and 10 yr in the FMF group was 95.8% and 78.4%, respectively, and was comparable to that in the control group. In the FMF group, five- and 10-yr patient survival (87.5 and 65.6%) was shorter than in the control group, but the difference was not statistically significant. The findings show that long-term outcome of KT in the patients with amyloidosis secondary to FMF was comparable to that in patients with ESRD not caused by FMF. Recurrence of amyloidosis in the allograft, gastrointestinal intolerance, and fatal infections remain as major complications during the post-transplant period.

236. Plasma cell neoplasia after kidney transplantation: French cohort series and review of the literature.

Kormann R, François H, Moles T et al.

PLoS One. 2017 Jun 21;12(6):e0179406.

ABSTRACT

Although post-transplant lymphoproliferative disorder (PTLD) is the second most common type of cancer in kidney transplantation (KT), plasma cell neoplasia (PCN) occurs only rarely after KT, and little is known about its characteristics and evolution. We included twenty-two cases of post-transplant PCN occurring between 1991 and 2013. These included 12 symptomatic multiple myeloma, eight indolent myeloma and two plasmacytomas. The median age at diagnosis was 56.5 years and the median onset after transplantation was 66.7 months (2-252). Four of the eight indolent myelomas evolved into symptomatic myeloma after a median time of 33 months (6-72). PCN-related kidney graft dysfunction was observed in nine patients, including six cast nephropathies, two light chain deposition disease and one amyloidosis. Serum creatinine was higher at the time of PCN diagnosis than before, increasing from 135.7 (±71.6) to 195.9 (±123.7) µmol/l (p = 0.008). Following transplantation, the annual rate of bacterial infections was significantly higher after the diagnosis of PCN, increasing from 0.16 (±0.37) to 1.09 (±1.30) (p = 0.0005). No difference was found regarding viral infections before and after PCN. Acute rejection risk was decreased after the diagnosis of PCN (36% before versus 0% after, p = 0.004), suggesting a decreased allogeneic response. Thirteen patients (59%) died, including twelve directly related to the hematologic disease. Median graft and patient survival was 31.7 and 49.4 months, respectively. PCN after KT occurs in younger patients compared to the general population, shares the same clinical characteristics, but is associated with frequent bacterial infections and relapses of the hematologic disease that severely impact the survival of grafts and patients.

237. Solid organ transplantation in AL amyloidosis.

Sattianayagam PT, Gibbs SD, Pinney JH et al.

Am J Transplant. 2010 Sep;10(9):2124-31.

ABSTRACT

Vital organ failure remains common in AL amyloidosis. Solid organ transplantation is contentious because of the multisystem nature of this disease and risk of recurrence in the graft. We report outcome among all AL patients evaluated at the UK National Amyloidosis Centre who received solid organ transplants between 1984 and 2009. Renal, cardiac and liver transplants were performed in 22, 14 and 9 patients respectively, representing <2% of all AL patients assessed during the period. One and 5-year patient survival was 95% and 67% among kidney recipients, 86% and 45% among heart recipients and 33% and 22% among liver recipients. No renal graft failed due to recurrent amyloid during median (range) follow up of 4.8 (0.2-13.3) years. Median patient survival was 9.7 years among 8/14 cardiac transplant recipients who underwent subsequent stem cell transplantation (SCT) and 3.4 years in six patients who did not undergo SCT (p = 0.01). Amyloid was widespread in all liver transplant recipients. Solid organ transplantation has rarely been performed in AL amyloidosis, but these findings demonstrate feasibility and support a role in selected patients.

238. Renal transplantation in systemic amyloidosis-importance of amyloid fibril type and precursor protein abundance.

Pinney JH, Lachmann HJ, Sattianayagam PT et al.

Am J Transplant. 2013 Feb;13(2):433-41.

ABSTRACT

Renal transplantation remains contentious in patients with systemic amyloidosis due to the risk of graft loss from recurrent amyloid and progressive disease. Outcomes were sought among all patients attending the UK National Amyloidosis Centre who received a renal transplant (RTx) between January 1978 and May 2011. A total of 111 RTx were performed in 104 patients. Eighty-nine percent of patients with end-stage renal disease (ESRD) due to hereditary lysozyme and apolipoprotein A-I amyloidosis received a RTx. Outcomes following RTx were generally excellent in these diseases, reflecting their slow natural history; median graft survival was 13.1 years. Only 20% of patients with ESRD due to AA, AL and fibrinogen amyloidosis received a RTx. Median graft survival was 10.3, 5.8 and 7.3 years in these diseases respectively, and outcomes were influenced by fibril precursor protein supply. Patient survival in AL amyloidosis was 8.9 years among those who had achieved at least a partial clonal response compared to 5.2 years among those who had no response ($p = 0.02$). Post-RTx chemotherapy was administered successfully to four AL patients. RTx outcome is influenced by amyloid type. Suppression of the fibril precursor protein is desirable in the amyloidoses that have a rapid natural history.

239. Kidney Transplantation in Systemic Amyloidosis.

Angel-Korman A, Havasi A.

Transplantation. 2020 Feb 11. doi: 10.1097/TP.0000000000003170..

ABSTRACT

The present review discusses current developments and outcomes of renal transplantation in systemic amyloidosis. Amyloidosis can wreak havoc on the architecture and functioning of the kidneys, leading to end stage renal disease (ESRD). In recent years, the available treatments, especially for AL amyloidosis but also for several of the underlying inflammatory diseases that cause AA amyloidosis have expanded leading to prolonged survival albeit frequently with renal failure. At the same time, there are also increasing numbers of patients diagnosed with 1 of the inherited forms of amyloidosis for which currently there is no targeted treatment available and, in some cases, renal failure is unavoidable. Due to the complex nature of the pathophysiology and treatment of these diseases, it can be very challenging for the clinician to determine whether or not it is appropriate to refer an affected individual for kidney transplantation. Determining eligibility criteria, as well as peritransplant and posttransplant management, requires a multidisciplinary approach with close monitoring and follow up.

240. Clinicopathologic Assessment of Monoclonal Immunoglobulin-Associated Renal Disease in the Kidney Allograft. A Retrospective Study and Review of the Literature.

Kamal J, Khairallah P, Crew RJ et al.

Transplantation. 2019 Oct 17. doi: 10.1097/TP.0000000000003010.

ABSTRACT

Background: Monoclonal immunoglobulin (MIg) associated renal disease (MIgARD) comprises a group of disorders caused by direct deposition of paraproteins in the kidney. Allograft MIgARD is infrequently encountered and poorly characterized.

Methods: First, we assessed our allograft biopsies diagnosed with MIgARD between 2007-2018. The cohort included 26 patients: proliferative glomerulonephritis with MIg deposits (PGNMID) (n=13), AL amyloidosis (n=5), light chain deposition disease (n=5), light chain proximal tubulopathy (n=2), and light chain cast nephropathy (n=1).Second, we conducted a literature review to evaluate the rare non-PGNMID entities. We identified 20 studies describing 29 patients that were added to our cohort (total n=42).

Results: Part-1: Patients' median age was 55, 31% were women, and 19% were blacks. Twelve patients (46%) lost their grafts at a median of 8 months after diagnosis. Compared to non-PGNMID, PGNMID patients had lower frequency of detectable paraproteins (31% vs. 92%, P=0.004) and hematologic neoplasms (23% vs. 77%, P=0.02). Within PGNMID group, 6 patients changed their apparent immunofluorescence phenotype between monotypic and polytypic while all 3 patients with hematologic neoplasms had substructure on electron microscopy.Part-2: Whereas light chain cast nephropathy occurred the earliest and had the worst graft survival, AL amyloidosis occurred the latest and had the best graft survival.

Conclusions: MIgARD in the kidney allograft is associated with poor prognosis. While posttransplant PGNMID can change its apparent clonality by immunofluorescence supporting oligoclonal immune responses, the presence of deposit substructure is an important indicator of underlying hematologic neoplasm. Non-PGNMID are often associated with hematologic neoplasms and varied prognosis.

241. The Clinical Presentation and Management of Systemic Light-Chain Amyloidosis in China.

Huang XH, Liu ZH.

Kidney Dis (Basel). 2016 Apr;2(1):1-9.

ABSTRACT

Background: Amyloidosis includes a group of diseases characterized by the extracellular deposition of various fibrillary proteins that can autoaggregate in a highly abnormal fibrillary conformation. The amyloid precursor protein of systemic light-chain (AL) amyloidosis is comprised of monoclonal light chains that are due to plasma cell dyscrasia. The clinical presentation of patients with AL amyloidosis varies from patient to patient. Current treatment strategies target the clone in order to decrease the production of the pathologic light chains. Recent advances in therapy have helped many patients with AL amyloidosis achieve hematologic and organ responses.

Summary: AL amyloidosis is the most common type of systemic amyloidosis in China with increasing morbidity and a high mortality rate. The clinical presentation of AL amyloidosis is variable, and the median overall survival was found to be 36.3 months. The disease prognosis and risk stratification are linked to serialized measurement of cardiac biomarkers and free light chains. The treatment of AL amyloidosis is mainly based on chemotherapy and autologous hematopoietic stem cell transplantation (ASCT). The use of novel agents (thalidomide, lenalidomide, and bortezomib) alone and in combination with steroids and alkylating agents has shown efficacy and continues to be explored.

Key messages: AL amyloidosis is the most common type of systemic amyloidosis in China with increasing morbidity and a high mortality rate. The lack of prospective clinical trials using the current therapies is a challenge for evidence-based decision making concerning the treatment of AL amyloidosis.
Facts from east and west: (1) AL amyloidosis is the most prevalent type of amyloidosis accounting for 65% of the amyloidosis-diagnosed patients in the UK and for 93% of the amyloidosis-diagnosed patients in China. The predisposition of men over women to develop AL amyloidosis might be higher in China than in Western countries (2:1 vs. 1.3:1). Both in the East and West, incidence increases with age. At the time of diagnosis, edema is twice as frequent and the proportion of renal involvement is higher in Chinese compared to Western patients. (2) Melphalan followed by ASCT is the current standard therapy but is restricted to eligible patients. The efficacy and safety of bortezomib combined with dexamethasone were proven in Western patients and recently confirmed in a Chinese cohort. Recent studies in China and the US indicate that bortezomib induction prior to ASCT increases the response rate. Thalidomide and lenalidomide have shown benefit, but toxicity and lack of clinical evidence exclude these agents from first-line therapy. The green tea extract epigallocatechin-3-gallate is under investigation as an inhibitor of AL amyloid formation and a compound that might dissolve amyloid.

242. Renal transplantation in patients with AA amyloidosis nephropathy: results from a French multicenter study.
Kofman T, Grimbert P, Canouï-Poitrine F et al.
Am J Transplant. 2011 Nov;11(11):2423-31.

ABSTRACT
Although end-stage renal disease related to AA amyloidosis nephropathy is well characterized, there are limited data concerning patient and graft outcome after renal transplantation. We performed a multicentric retrospective survey to assess the graft and patient survival in 59 renal recipients with AA amyloidosis. The recurrence rate of AA amyloidosis nephropathy was estimated at 14%. The overall, 5- and 10-year patient survival was significantly lower for the AA amyloidosis patients than for a control group of 177 renal transplant recipients (p = 0.0001, 0.028 and 0.013, respectively). In contrast, we did not observe any statistical differences in the 5- and 10- year graft survival censored for death between two groups. AA amyloidosis-transplanted patients exhibited a high proportion of infectious complications after transplantation (73.2%). Causes of death included both acute cardiovascular events and fatal septic complications. Multivariate analysis demonstrated that the recurrence of AA amyloidosis on the graft (adjusted OR = 14.4, p = 0.01) and older recipient age (adjusted OR for a 1-year increase = 1.06, p = 0.03) were significantly associated with risk of death. Finally, patients with AA amyloidosis nephropathy are eligible for renal transplantation but require careful management of both cardiovascular and infectious complications to reduce the high risk of mortality.

243. Characterization and outcomes of renal leukocyte chemotactic factor 2-associated amyloidosis.
Said SM, Sethi S, Valeri AM, et al.

Kidney Int. 2014 Aug;86(2):370-7..
Comment in Kidney Int. 2014 Aug;86(2):229-32.

ABSTRACT
Amyloidosis derived from leukocyte chemotactic factor 2 (ALECT2) is a recently described disease. Here, we report the characteristics and outcome of 72 patients with renal ALECT2, which included 19 who had another kidney disease on biopsy. Ninety-two percent of patients were Hispanics and over half were elderly. Three had other organ, but not cardiac, amyloidosis involvement. All patients without concurrent disease, except three, presented with chronic renal insufficiency. Proteinuria was variable and absent in a third, whereas nephrotic syndrome and hematuria were rare. After a median follow-up of 26 months, one-third developed end-stage renal disease (ESRD). The median renal survival was 62 months. Independent predictors of renal survival were serum creatinine at diagnosis, with a value of 2.0 mg/dl being the best cutoff for predicting ESRD, percentage global glomerulosclerosis, and presence of diabetes. Only four patients died and four had received chemotherapy for an erroneous diagnosis of immunoglobulin light chain-derived amyloidosis. Five patients underwent kidney transplantation; none had graft loss but one had disease recurrence. Patient survival is superior to renal immunoglobulin light chain-derived amyloidosis and reactive amyloidosis largely due to the absence of cardiac involvement. Thus, renal ALECT2 mainly affects elderly Hispanics who typically present with chronic renal insufficiency and bland urine sediment, with or without proteinuria.

244. Heavy Chain Fibrillary Glomerulonephritis: A Case Report.
Nasr SH, Sirac C, Bridoux F et al.
Am J Kidney Dis. 2019 Aug;74(2):276-280.

ABSTRACT
Heavy chain amyloidosis and heavy chain deposition disease are the only known kidney diseases caused by the deposition of truncated immunoglobulin heavy chains. Fibrillary glomerulonephritis typically results from deposition of DNAJB9 (DnaJ heat shock protein family [Hsp40] member B9) and polytypic immunoglobulin G (IgG). We describe a patient with monoclonal gammopathy (IgG with λ light chain) who developed DNAJB9-negative fibrillary glomerulonephritis leading to end-stage kidney disease, with recurrence in 2 kidney allografts. Pre- and postmortem examination showed glomerular deposition of Congo red-negative fibrillar material that was determined to be immunoglobulin heavy chain. We propose the term "heavy chain fibrillary glomerulonephritis" to describe this lesion, which appears to be a rare kidney complication of monoclonal gammopathy. The diagnosis should be suspected when the kidney biopsy shows fibrillary glomerulonephritis with negative staining for immunoglobulin light chains and DNAJB9; the diagnosis can be confirmed using immunochemical and molecular studies.

245. Kidney transplantation in AL Amyloidosis: is it time to maximize access?
Sathick IJ, Rosenbaum CA, Gutgarts V et al.
Br J Haematol. 2020 Feb;188(3):e1-e4.

No abstract available

246. AA amyloidosis in the renal allograft: a report of two cases and review of the literature.
Rojas R, Josephson MA, Chang A et al.
Clin Kidney J. 2012 Apr;5(2):146-149.

ABSTRACT
AA amyloidosis is a disorder characterized by the abnormal formation, accumulation and systemic deposition of fibrillary material that frequently involves the kidney. Recurrent AA amyloidosis in the renal allograft has been documented in patients with tuberculosis, familial Mediterranean fever, ankylosing spondylitis, chronic pyelonephritis and rheumatoid arthritis. De novo AA amyloidosis is rarely described. We report two cases of AA amyloidosis in the renal allograft. Our first case is a 47-year-old male with a history of ankylosing spondylitis who developed end-stage renal disease reportedly from tubulointerstitial nephritis from non-steroidal anti-inflammatory agent use. A biopsy was never performed. One year after transplantation, AA amyloidosis was identified in the femoral head and 8 years post-transplantation, AA amyloidosis was identified in the renal allograft. He was treated with colchicine and adalimumab and has stable renal function at 1 year-follow-up. Our second case is a 57-year-old male with a long history of intravenous drug use and hepatitis C infection who developed end-stage kidney disease due to AA amyloidosis. Our second patient's course was complicated by renal adenovirus, pulmonary aspergillosis and hepatitis C with AA amyloidosis subsequently being identified in the allograft 2.5 years post-transplantation. Renal allograft function remains stable 4-years post-transplantation. These reports describe clinical and pathologic features of two cases of AA amyloidosis presenting with proteinuria and focal involvement of the renal allograft.

247. Kidney Transplantation After Hematopoietic Cell Transplantation in Plasma Cell Dyscrasias: Case Reports.
Domínguez-Pimentel V, Rodríguez-Muñoz A, Froment-Brum M et al.
Transplant Proc. 2019 Mar;51(2):383-385.

ABSTRACT
The plasma cell dyscrasias (PCDs) include a number of entities such as multiple myeloma, primary amyloidosis, and monoclonal immunoglobulin deposition disease. Hematopoietic cell transplant (HCT) is the only cure for a variety of hematologic and oncologic diseases. Clinically significant renal impairment is a common feature in plasma cell myeloma, affecting 20% to 55% of patients at initial diagnosis; 2% to 3% of patients present with failure sufficiently severe to require hemodialysis. This circumstance is associated with a high early mortality. The necessity for immunosuppression after HCT could complicate its management and may precipitate the development of complications. In some patients an effective alternative could be kidney transplant (KT); however, the presence of 2 transplants will require optimal adjustment of immunosuppression and management of complications. At present, there are few published cases of KT after HCT, and the experience of managing 2 transplants is limited. We would like to describe our experience with 4 patients who had a PCD and initially received HCT and received subsequent KT. In our experience the progress

and outcome of KT after HCT were optimal. We would like to address that a higher incidence of cytopenia associated with the combination of immunosuppression (lenalidomide, tacrolimus, mycophenolate, etc.) and other drugs (ie, valganciclovir) should be considered together with an increased risk of opportunistic infections and PCD relapse.

248. De novo AL amyloidosis in the kidney allograft.
Qian Q, Nasr SH, Fidler ME et al.
Am J Transplant. 2011 Mar;11(3):606-12.

ABSTRACT
We report four cases of de novo amyloidosis occurring after 16, 18, 28 and 31 years following kidney transplantation. These patients presented with proteinuria and progressive allograft dysfunction. Kidney biopsy showed AL amyloidosis in all compartments of the allograft kidney. Serum immunofixation studies revealed monoclonal lambda light chains in all four cases. Bone marrow examination showed 10% plasma cells in one case, 5-10% in two cases and less than 5% in one case. Two patients died unexpectedly within 3 months and 1 year of the diagnosis of allograft AL amyloidosis. Of the remaining two, one underwent autologous stem cell transplant that resulted in complete hematologic remission. However, the patient relapsed within 2 years and also developed progressive kidney allograft failure. The patient received a second autologous stem cell transplant with complete hematologic response, followed by a second kidney transplant, which showed no evidence of amyloid at 1-year posttransplant. The remaining case was treated with prednisone and bortezomib, which has stabilized kidney function in the short term. In conclusion, this study shows that AL amyloidosis is an uncommon but important cause of late onset proteinuria in the kidney allograft that results in kidney allograft failure.

249. Short-term complications after renal transplantation in AFibE526V (p.Glu545Val) amyloidosis.
Tavares I, Silvano J, Moreira L et al.
Amyloid. 2019;26(sup1):162-163.

No abstract available

250. Hereditary lysozyme amyloidosis -- phenotypic heterogeneity and the role of solid organ transplantation.
Sattianayagam PT, Gibbs SD, Rowczenio D et al.
J Intern Med. 2012 Jul;272(1):36-44.

ABSTRACT
Objectives: Lysozyme amyloidosis (ALys) is a form of hereditary systemic non-neuropathic amyloidosis, which is inherited in an autosomal dominant fashion. Lysozyme, which is the amyloidogenic precursor protein in ALys, is a ubiquitous bacteriolytic enzyme synthesized by

hepatocytes, polymorphs and macrophages. The aim of this study is to describe the phenotype and outcome of patients with ALys including the role of solid organ transplantation.
Design: Retrospective evaluation of patients with ALys.
Setting: UK National Amyloidosis Centre.
Patients: All 16 patients with ALys followed at the centre.
Results: A family history of amyloidosis was present in every affected individual. Although the phenotype was broadly similar amongst those from the same kindred, there were marked phenotypic differences between kindreds who possessed the same amyloidogenic mutation. Symptomatic gastrointestinal (GI) amyloid was prevalent, and macroscopically visible amyloidotic lesions were present in nine of 10 patients who underwent GI endoscopy. All symptomatic ALys individuals had hepatic amyloid. Four patients received orthotopic liver transplants (OLT), three for spontaneous hepatic rupture and one case, who had extensive hepatic amyloid and a strong family history of hepatic rupture, pre-emptively. All of the liver grafts were functioning at censor 1.7, 5.8, 9.0 and 11.0 years after OLT. Five patients had progressive amyloidotic renal dysfunction culminating in end-stage renal failure, three of whom underwent renal transplantation (RTx). There was no evidence of renal allograft dysfunction at censor 6.6, 1.8 and 0.8 years after RTx.
Conclusions: Lysozyme amyloidosis is a disease of the GI tract, liver and kidneys, which has a slow natural history. There was a clear family history in all cases within this cohort, demonstrating a high clinical penetrance in the presence of an amyloidogenic lysozyme mutation. There is currently no amyloid-specific therapy for the condition which is managed symptomatically. OLT and RTx appear to be successful treatments for patients with liver rupture or end-stage renal disease, respectively, with excellent outcomes in terms of medium-term graft function and patient survival.

251. Long-term outcome of renal transplantation in patients with familial Mediterranean fever amyloidosis: a single-center experience.
Abedi AS, Nakhjavani JM, Etemadi J.
Transplant Proc. 2013;45(10):3502-4.

ABSTRACT
Introduction: Familial Mediterranean fever (FMF) is an autosomal-recessive disorder, affecting multiple organs. The AA type of amyloidosis is most common and serious complication cause nephropathy and end-stage renal disease (ESRD). Renal transplantation (RTX) remains treatment of choice for ESRD. We aimed to investigate long-term results of RTX in patients with FMF amyloidosis.
Patients and methods: We compared the outcomes of 18 patients (12 men and 6 women) with FMF amyloidosis among 601 (2.9%) transplants with 200 control patients. Demographic data and gene analysis were evaluated.
Results: In our study the 1-year graft and patient survivals were 94.44% and 100%, respectively. At 5 years after RTX, they were 94.73% and 88.88%, respectively, in the FMF group without difference from controls. Mean creatinine level at 1 and 5 years were 1.43 ± 0.54 and 1.73 ± 0.89, respectively. The results of MEFV mutation analyses were: M694V/M694V homozygote in 1 patient, M694V/EQ148 in 3, M694V/V726A in 2, 680M-I/E148Q in 3, M694V/M680I in 5, R202Q/M680I in 2, and M694V/R202Q in 2. Recurrence was noticed in 1 patient with M694V/M680I. One patient died because of graft loss and cardiac complications with M694V/M680I gene analysis. Colchicine was reduced in 4 patients owing to side effects.

Conclusion: Long-term outcomes of transplantation in patients with amyloidosis secondary to FMF is similar to that in the general transplant population and maintenance colchicine, even after decreasing its dose, effectively prevents recurrence of amyloidosis in the allograft.

252. Familial Mediterranean Fever Is Associated With Increased Mortality After Kidney Transplantation-A 19 Years' Single Center Experience.

Green H, Lichtenberg S, Rahamimov R et al.

Transplantation. 2017 Oct;101(10):2621-2626.

ABSTRACT

Background: Current data regarding the outcome of kidney transplantation in patients with familial Mediterranean fever (FMF) who reach end-stage renal disease (ESRD) due to reactive amyloidosis A (AA) are scarce and inconclusive.

Methods: The outcomes of 20 patients with FMF and biopsy-proven AA amyloidosis that were transplanted between 1995 and 2014 were compared with 82 control patients (32 with diabetes mellitus and 50 with nondiabetic kidney disease). Major outcome data included overall patient and graft survivals.

Results: During a mean overall follow-up of 116.6 ± 67.5 months 11 patients (55%) with FMF died versus 26 patients (31%) in the control group. Median time of death for patients with FMF was 61 months (range, 16-81) after transplantation. Estimated 5-year, 10-year, and actuarial 15-year overall patients survival rates were 73%, 45%, and 39%, respectively, for patients with FMF, versus 84%, 68% and 63%, respectively, for the control group (P = 0.028). FMF was associated with more than twofold increased risk for death after transplantation, and with a threefold increased risk for hospitalization because of infections during the first year. Infections and cardiovascular disease were the cause of death in the majority of patients with FMF. Overall graft survival was similar between the groups. Recurrence of AA amyloidosis was diagnosed in 2 patients during the first year after transplantation.

Conclusions: FMF is associated with increased risk of mortality after kidney transplantation.

253. Long-term outcome of kidney transplantation in AL amyloidosis.

Angel-Korman A, Stern L, Sarosiek S, et al.

Kidney Int. 2019 Sep;96(3):796.

Erratum for Kidney Int. 2019 Feb;95(2):405-411.

No abstract available

254. Long-term outcomes of patients with light chain amyloidosis (AL) after renal transplantation with or without stem cell transplantation.

Herrmann SM, Gertz MA, Stegall MD et al.

Nephrol Dial Transplant. 2011 Jun;26(6):2032-6.

Comment in Nephrol Dial Transplant. 2011 Jun;26(6):1766-8.

ABSTRACT

Background: Recent advances in the treatment of immunoglobulin light chain amyloidosis (AL) have dramatically improved survival. Kidney transplantation (KTx) has become more common but the long-term outcomes remain unknown and it is the objective of this study.

Methods: Nineteen patients with AL underwent living (n = 18) or deceased (n = 1) KTx at our institution from 1999 to 2008 (median age 57 years, six women). The primary end points were patient and kidney allograft survival and recurrence of AL in the allograft. The secondary end point was kidney transplant rejection. Outcome data were stratified according to three treatment modalities: renal transplantation followed by autologous stem cell transplantation (ASCT) (Group 1, n = 8), ASCT followed by renal transplantation (Group 2, n = 6) and renal transplantation after complete remission achieved with nonmyeloablative therapy (Group 3, n = 5).

Results: The median follow-up was 41.4 months. At the time of study, 79% were still alive. Median graft survival did not differ from median overall survival. There was no difference in survival rates between the treatment groups. Five patients had a cellular rejection. Two of the three patients with a rejection in Group 1 died but neither patient with rejection in Groups 2 and 3. Recurrent amyloidosis was diagnosed by biopsy in one patient in Group 2 (preceding ASCT) and in another patient in Group 3.

Conclusions: KTx can be successfully performed in AL patients in complete hematologic response and meet the usual KTx selection criteria. Outcomes appear similar whether hematologic response was achieved with ASCT or by nonmyeloablative therapy.

255. Recurrent AA amyloidosis in a kidney transplant.

Sethi S, El Ters M, Vootukuru S et al.

Am J Kidney Dis. 2011 Jun;57(6):941-4.

ABSTRACT

Recurrent AA amyloidosis in a kidney transplant is rare, especially when the underlying inflammatory condition is controlled. We present a 59-year-old man who underwent a living donor kidney transplant 17 years ago for kidney failure due to AA amyloid nephropathy in the setting of long-standing Crohn disease. His Crohn disease was quiescent before and after the kidney transplant. Transplant function had been stable until a month before presentation, when he developed worsening proteinuria and decreased kidney function. A transplant biopsy showed recurrent AA amyloidosis despite excellent clinical and histologic control of Crohn disease.

256. Liver Transplantation for Hereditary Transthyretin Amyloidosis: After 20 Years Still the Best Therapeutic Alternative?

Ericzon BG, Wilczek HE, Larsson M et al.

Transplantation. 2015 Sep;99(9):1847-54.

ABSTRACT

Background: Until recently, liver transplantation (Ltx) was the only available treatment for hereditary transthyretin (TTR) amyloidosis; today, however, several pharmacotherapies are tested.

Herein, we present survival data from the largest available database on transplanted hereditary TTR patients to serve as a base for comparison.
Methods: Liver transplantation was evaluated in a 20-year retrospective analysis of the Familial Amyloidosis Polyneuropathy World Transplant Registry.
Results: From April 1990 until December 2010, data were accumulated from 77 liver transplant centers. The Registry contains 1940 patients, and 1379 are alive. Eighty-eight Ltx were performed in combination with a heart and/or kidney transplantation. Overall, 20-year survival after Ltx was 55.3%. Multivariate analysis revealed modified body mass index, early onset of disease (<50 years of age), disease duration before Ltx, and TTR Val30Met versus non-TTR Val30Met mutations as independent significant survival factors. Early-onset patients had an expected mortality rate of 38% that of the late-onset group ($P < 0.001$). Furthermore, Val30Met patients had an expected mortality rate of 61% that of non-TTR Val30Met patients ($P < 0.001$). With each year of duration of disease before Ltx, expected mortality increased by 11% ($P < 0.001$). With each 100-unit increase in modified body mass index at Ltx, the expected mortality decreased to 89% of the expected mortality ($P < 0.001$). Cardiovascular death was markedly more common than that observed in patients undergoing Ltx for end-stage liver disease.
Conclusions: Long-term survival after Ltx, especially for early-onset TTR Val30Met patients, is excellent. The risk of delaying Ltx by testing alternative treatments, especially in early-onset TTR Val30Met patients, requires consideration.

257. Lysozyme amyloidosis - a case report and review of the literature.
Pleyer C, Flesche J, Saeed F.
Clin Nephrol Case Stud. 2015 Dec 28;3:42-45.

ABSTRACT
Lysozyme amyloidosis is an exceedingly rare hereditary autosomal dominant amyloidosis, which is characterized by the precipitation of lysozyme protein within the body, leading to multi-organ dysfunction. Herein, we present the case of a U.S. family affected by lysozyme amyloidosis. In particular, we report pericardial disease involvement leading to recurrent pericardial effusion, which to our knowledge has not been described yet. To our knowledge, we have also for the first time identified the amyloidogenic component of lysozyme amyloidosis via laser microdissection and mass spectrometry from a bone marrow biopsy. The diagnosis of this disease remains challenging as it can be easily mistaken for primary amyloidosis, which also presents with similar symptoms. Immunohistochemical staining of tissue for specific amyloidogenic proteins allows for an accurate diagnosis and should be performed in all amyloidosis patients in order to spare patients from potentially futile or harmful therapy. The widespread systemic involvement of lysozyme amyloidosis currently provides limited options for treatment, although kidney and/or liver transplantation appear to be promising palliative treatments. Practicing clinicians and researchers need to collect more information about this rare entity to further characterize the behavior of this disease and develop new potential treatment strategies.

258. Kidney Transplant in a Patient With Tumor Necrosis Factor Receptor-1 Syndrome (TRAPS): Case Report and Review of the Literature.

Rodziewicz N, Bhushan S, Avasia A et al.
Transplant Proc. 2016 Jan-Feb;48(1):265-6.

ABSTRACT
Tumor necrosis factor receptor -1-associated periodic syndrome (TRAPS) is a rare disease that may result in chronic kidney disease due to secondary amyloidosis. We report a case of a patient with a history of TRAPS who received a kidney transplant 11 years ago and still has functioning kidney transplant despite recurrence of amyloidosis and proteinuria.

259. The clinical implication of monoclonal gammopathies: monoclonal gammopathy of undetermined significance and of renal significance.
Batko K, Malyszko J, Jurczyszyn A et al.
Nephrol Dial Transplant. 2019 Sep 1;34(9):1440-1452. doi: 10.1093/ndt/gfy259.

ABSTRACT
Monoclonal gammopathy of renal significance (MGRS) has introduced a new perspective to several well-known disease entities impacting nephrology, haematology and pathology. Given the constantly changing disease spectrum of these entities, it is clinically imperative to establish diagnostic and treatment pathways supported by evidence-based medicine. MGRS is a disease of the kidney, secondary to plasma cell clonal proliferation or immune dysfunction, requiring therapeutic intervention to eradicate the offending clone. To fully understand the disease(s), it is prerequisite to determine the significance of the findings. The diagnostic work up should be extensive due to the wide heterogeneity of clinical presentation, ultimately necessitating kidney biopsy. Particular patient profiles such as AL amyloidosis, which may be diagnosed through biopsies of other tissues/organs, may be an exception. Treatment decisions should be formulated by multi-disciplinary consensus: nephrologists, haematologists and pathologists. The ultimate goal in managing MGRS is eradication of the offending plasma cell clone which requires targeted chemotherapy and, in eligible cases, haematopoietic stem cell transplantation. We present a review of diagnostic procedures, treatment options and advances in the last few years in the management of MGRS in an effort to acquaint specialists with this new face of several older diseases.

260. The Role of Kidney Transplantation in Monoclonal Ig Deposition Disease.
Angel-Korman A, Stern L, Angel Y et al.
Kidney Int Rep. 2020 Mar 9;5(4):485-493.

ABSTRACT
Introduction: Monoclonal Ig deposition disease (MIDD) frequently leads to kidney failure, and a large proportion of these patients would greatly benefit from kidney transplantation. However, data on kidney transplantation outcomes in MIDD are limited.
Methods: This was a retrospective analysis of long-term renal outcomes of 23 patients with MIDD, including 6 patients who underwent kidney transplantation.
Results: The 1-, 5-, and 10-year overall survival (OS) from diagnosis were 95%, 78%, and 65%, respectively. Approximately half of the patients (n = 12) progressed to end-stage renal disease

(ESRD) with a median time from diagnosis to ESRD of 3.4 years. The 1-, 5-, and 10-year renal survival from diagnosis were 77%, 48%, and 29% respectively. Renal response was observed only in 5 patients (22%), all of them after achieving hematologic complete response. Median OS from diagnosis was significantly better for those who underwent kidney transplantation versus those who remained on dialysis (19.8 years vs. 8.3 years, P = 0.016). Among patients who underwent kidney transplantation, the shortest survival from MIDD diagnosis was 13.7 years and the longest was 27.8 years. Of the 3 patients with kidney transplants who died, the time from the first kidney transplantation to death was 7.4, 18.8, and 20.4 years. Graft loss due to disease recurrence occurred at 4 months and 3.8 years after kidney transplantation in 2 patients who either were not treated or did not respond to treatment.
Conclusion: As treatments for MIDD have dramatically improved, more patients are achieving sustained hematologic responses with longer patient and graft survival after kidney transplantation.

261. Renal transplantation in AA amyloidosis associated with Whipple's disease.
Rocha S, Lobato L, Carvalho MJ et al.
Amyloid. 2011 Dec;18(4):240-4.

ABSTRACT
Whipple's disease (WD) is a chronic infection caused by Thropheryma whipplei that usually manifests with intestinal, articular, pulmonary, neurological and cardiac abnormalities. Rarely, WD has been associated with renal AA amyloidosis.We report a 50 year-old male with nephrotic syndrome and renal failure whose renal biopsy revealed extensive AA amyloidosis. Amyloid was not found in other organs, namely in gastrointestinal tract and bone marrow. There was no evidence of chronic inflammatory disease, and despite detailed investigation, the diagnosis of the underlying disease remained obscure. Eight months after referral he started peritoneal dialysis. Three years later he developed anorexia, weight loss, anemia, and recurrent attacks of non-bloody diarrhea. A biopsy of the small intestine showed typical histological findings of WD and PCR was positive for T. whipplei. He was treated with ceftriaxone followed by co-trimoxazole, with remission of complaints and histological features. Three years later the patient underwent successful cadaveric kidney transplantation. In this case, AA amyloidosis preceded the manifestations of WD. To the best of our knowledge, this is the first report of kidney transplantation in a patient with amyloidosis due to WD. Recurrence of amyloidosis in renal graft is not expected.

262. Transplantation within the era of anti-IL-1 therapy: case series of five patients with familial Mediterranean fever-related amyloidosis.
Özçakar ZB, Keven K, Çakar N et al.
Transpl Int. 2018 Oct;31(10):1181-1184.

No abstract available

263. Recurrence from primary and secondary glomerulopathy after renal transplant.
Canaud G, Audard V, Kofman T et al.
Transpl Int. 2012 Aug;25(8):812-24.

ABSTRACT
Glomerulonephritis is the primary cause of end-stage renal failure in 30-50% of kidney transplant recipients and recurrence of the initial disease is an important determinant of long-term graft outcome after transplantation. Although renal transplantation remains the best treatment option for patients with end stage renal diseases in most cases, diagnosis and management of recurrences of glomerulopathies are critical for the optimization and improvement of long-term kidney transplant graft survival and provide a unique opportunity to explore the pathogenesis of native kidney disease. This review aims to update knowledge for a large panel of recurrent primary and secondary glomerulonephritis after kidney transplantation, excluding diabetic nephropathy including primary focal and segmental glomerulosclerosis, membranous nephropathy, IgA nephropathy, membranoproliferative glomerulonephritis, lupus, vasculitis but also less usual secondary nephropathy related to sarcoidosis, AA and AL amyloidosis, monoclonal immunoglobulin deposition disease, and fibrillary glomerulonephritis.

264. Amyloidosis Diagnosed in Solid Organ Transplant Recipients.
Sharpley FA, Fontana M, Gilbertson JA et al.
Transplantation. 2020 Feb;104(2):415-420.

ABSTRACT
Background: Development of amyloidosis post solid-organ transplantation has not been reported, although plasma cell neoplasms are a rare form of posttransplant lymphoproliferative disorder, which could be complicated by light chain amyloidosis (AL) amyloidosis.
Methods: We searched our database of 5112 patients seen between 1994 and 2018 with a diagnosis of amyloidosis post solid-organ transplant. Patients were excluded if the amyloid diagnosis preceded the transplant date. The indication and type of organ transplant were recorded in addition to the amyloidosis type, organs involved, treatment given, and survival.
Results: Thirty patients were identified. The median age at diagnosis with amyloidosis was 52 years (range 33-77). The median time from transplantation to diagnosis was 10.5 years (0.58-36). The grafts were kidney (N = 25, 83.3%), liver (N = 2, 6.7%), heart (N = 2, 6.7%), and combined heart, lung, and kidney (N = 1, 3.3%). The type of amyloidosis was systemic AL (N = 14, 47%), serum amyloid A amyloidosis (AA) (N = 11, 37%), localized AL (N = 3, 10%), wild-type transthyretin amyloidosis (ATTR) (N = 1, 3.3%), and amyloid of uncertain type (N = 1, 3.3%). Renal graft dysfunction was seen in 11 of 25 (44%) cases. Median graft survival was 185 months (96-269), and median survival from diagnosis with amyloidosis was 45 months (2-89); median survival by amyloidosis type was localized AL: 64 months (20-67), systemic AL: 23.5 months (0-95), ATTR amyloidosis: 17 months, and AA, 15 months (0-77).
Conclusions: This series is the first description of amyloidosis post solid-organ transplant; 30 cases among 5112 amyloid patients >24 years suggests that amyloidosis may occur post solid-organ transplantation with an overall poor survival.

265. Defining the role of renal transplantation in the modern management of multiple myeloma and other plasma cell dyscrasias.

Bansal T, Garg A, Snowden JA et al.

Nephron Clin Pract. 2012;120(4):c228-35.

ABSTRACT

Plasma cell dyscrasias (PCD) are due to an abnormal proliferation of a single clone of plasma or lymphoplasmacytic cells leading to secretion of immunoglobulin (Ig) or an Ig fragment, causing the dysfunction of multiple organs. Median survival of these patients has significantly improved over the last decade due to availability of treatment options such as high-dose melphalan with autologous stem cell transplantation and novel anti-myeloma agents. Renal transplantation has not traditionally been considered in these patients due to the previously limited prognosis, along with concerns relating to disease recurrence affecting the renal allograft and increased infection susceptibility following renal transplant due to immunosuppression and the PCD itself. However, with the increasing range of effective treatment options, renal transplantation could now be considered, especially in young patients with good performance status. It is therefore timely to reappraise the potential role of renal transplantation in end-stage renal disease due to multiple myeloma and other PCD. This review summarizes the literature relating to renal transplantation in PCD, including multiple myeloma, monoclonal Ig deposition disease and systemic AL amyloidosis, to attempt to identify patients who may benefit most from this approach and to explore areas for further development.

266. End-stage renal failure due to amyloidosis: outcomes in 490 ANZDATA registry cases.

Tang W, McDonald SP, Hawley CM et al.

Nephrol Dial Transplant. 2013 Feb;28(2):455-61.

ABSTRACT

Background: There are few reports regarding the long-term renal replacement therapy (RRT) outcomes of amyloidosis.

Methods: In this retrospective, multi-centre, multi-country registry analysis, all patients with and without amyloidosis who commenced RRT for end-stage renal failure (ESRF) in Australia and New Zealand between 1963 and 2010 were included.

Results: Of 58 422 patients who underwent RRT during the study period, 490 (0.8%) had ESRF secondary to amyloidosis. The median survival of amyloidosis patients on dialysis (2.09 years, 95% CI 1.85-2.32 years) was significantly inferior to that of patients with other causes of ESRF (4.45 years, 95% CI 4.39-4.51 years) (log-rank score 242, $P < 0.001$). The survival of amyloidosis patients receiving peritoneal dialysis (1.9 years, 95% CI 1.58-2.22) was comparable with those receiving haemodialysis (2.17 years, 95% CI 1.89-2.45) ($P = 0.18$). Fifty-three (13.8%) amyloidosis patients died of amyloidosis complications. Forty-six patients underwent renal transplantation with first graft survival rates of 45% at 5 years and 26% at 10 years. Nine (16.4%) patients experienced amyloidosis recurrence in their allografts, which led to graft failure in six patients. ESRF patients with amyloidosis experienced inferior median first renal allograft survival (4.55 years, 95% CI 1.96-7.15 versus 10.7 years, 95% CI 10.5-11.0, $P = 0.001$) and transplant patient survival (6.03 years, 95% CI 2.71-9.36 versus 16.8 years,

95% CI 16.4-17.1, P < 0.001) compared with patients with other causes of ESRF. Respective 10-year patient survival rates were 37 and 69%.
Conclusions: Amyloidosis was associated with poor patient survival following dialysis and/or renal transplantation, poor renal allograft survival and a significant incidence of disease recurrence in the allograft. An appreciable proportion of amyloid ESRF patients died of amyloidosis-related complications.

267. Recurrence of amyloidosis in a kidney transplant.
Sethi S, Fervenza FC, Miller D et al.
Am J Kidney Dis. 2010 Aug;56(2):394-8.

No abstract available

268. Renal transplantation in light chain amyloidosis: coming out of the cupboard.
Bridoux F, Ronco P, Gillmore J et al.
Nephrol Dial Transplant. 2011 Jun;26(6):1766-8.
Comment on Nephrol Dial Transplant. 2011 Jun;26(6):2032-6.

No abstract available

269. Characterization of end-stage renal disease after liver transplantation in transthyretin amyloidosis (ATTR V30M).
Rocha A, Lobato L, Silva H et al.
Transplant Proc. 2011 Jan-Feb;43(1):189-93.

ABSTRACT
Transthyretin (TTR) amyloidosis, an autosomal-dominant disease, is characterized by peripheral and autonomic neuropathy--familial amyloidotic polyneuropathy (FAP). End-stage renal disease (ESRD) occurs at 10 years after the onset of neuropathy. Orthotopic liver transplantation (OLT) is the usual treatment of choice. We evaluated FAP patients, ATTR V30M, before and after OLT who started dialysis within 3 months after surgery. The 11 patients had an age at the onset of neuropathy of 31.9 ± 6.3 years with a mean evolution of disease to OLT of 4.54 ± 2.5 years. The glomerular filtration rate was <60 mL/min in 2 patients, 2 displayed nephrotic range proteinuria, and 3 had microalbuminuria. Elective pacemaker implantation was necessary in 8 subjects. Post-OLT 3 patients developed proteinuria, 2 of whom showed increasing nephrotic syndrome. Dysautonomia worsened leading to bladder catheterization in 6. In patients with previous normal renal function and proteinuria <3 g/d, the evolution of neuropathy to the first dialysis was 14.6 ± 4.2 years versus 7.5 ± 1.1 among the other subjects. Overall, dialysis was implemented at 7.4 ± 4.9 years after surgery. There was no liver graft dysfunction. The heart evaluation post-OLT showed the following: 3 patients with de novo dysrhythmias requiring pacemaker implantation and 3 with N-terminal pro-natriuretic peptide levels >10,000 pg/mL. Death occurred in 4 subjects at an average of 26 months after initiation of dialysis. Concerning ESRD, there was no clear benefit of transplantation in the early

stages. Patients with normal renal function and lower levels of proteinuria showed slower progression to ESRD, irrespective of their duration of neuropathy.

270. Recurrence of secondary glomerular disease after renal transplantation.
Ponticelli C(1), Moroni G, Glassock RJ.
Clin J Am Soc Nephrol. 2011 May;6(5):1214-21.

ABSTRACT
The risk of a posttransplant recurrence of secondary glomerulonephritis (GN) is quite variable. Histologic recurrence is frequent in lupus nephritis, but the lesions are rarely severe and usually do not impair the long-term graft outcome. Patients with Henoch-Schonlein nephritis have graft survival similar to that of other renal diseases, although recurrent Henoch-Schonlein nephritis with extensive crescents has a poor prognosis. Amyloid light-chain amyloidosis recurs frequently in renal allografts but it rarely causes graft failure. Amyloidosis secondary to chronic inflammation may also recur, but this is extremely rare in patients with Behcet's disease or in those with familial Mediterranean fever, when the latter are treated with colchicine. Double organ transplantation (liver/kidney; heart/kidney), chemotherapy, and autologous stem cell transplantation may be considered in particular cases of amyloidosis, such as hereditary amyloidosis or multiple myeloma. There is little experience with renal transplantation in light-chain deposition disease, fibrillary/immunotactoid GN, or mixed cryoglobulinemic nephritis but successful cases have been reported. Diabetic nephropathy often recurs but usually only after many years. Recurrence in patients with small vessel vasculitis is unpredictable but can cause graft failure. However, in spite of recurrence, patient and graft survival rates are similar in patients with small vessel vasculitis compared with those with other renal diseases. Many secondary forms of GN no longer represent a potential contraindication to renal transplantation. The main issues in transplantation of patients with secondary GN are the infectious, cardiovascular, or hepatic complications associated with the original disease or its treatment.

271. End-stage renal failure due to transthyretin amyloidosis after liver transplantation: outcomes in 19 registry cases.
Rocha A, Beirão I, Pessegueiro H et al.
Amyloid. 2017 Mar;24(sup1):85-86.

No abstract available

272. ALECT2 amyloidosis: a new type of systemic amyloid highly prevalent in the Hispanic population.
Jiménez-Zepeda VH, Leung N.
Rev Invest Clin. 2014 May-Jun;66(3):269-73.

ABSTRACT

Amyloidosis results from extracellular deposition of fibril-forming proteins and currently ~30 different proteins have been found to be amyloidogenic. Recently, a novel type of amyloidosis with a high incidence on Hispanic population has been described to be derived from leukocyte chemotactic factor 2 (ALECT2). The objective of the present article is to raise awareness on the presence of this entity for the medical community in México. ALECT2 is a clinical entity characterized by deposition of the LECT2 protein mainly on liver and kidney. Renal ALECT2 affects elderly Hispanics who present with chronic renal insufficiency and bland urine sediment, not always associated to proteinuria. No treatment guidelines are reported for this disease but support measures including organ transplantation when required are recommended. Further genetic and clinical characterization of this entity is needed to help understanding the mechanisms by which this protein becomes amyloidogenic and how to prevent organ damage related to its deposition.

273. Monoclonal Gammopathies After Renal Transplantation: A Single-center Study.
Bhasin B, Szabo A, Wu R et al.
Clin Lymphoma Myeloma Leuk. 2020 Mar 7:S2152-2650(20)30116-6.

ABSTRACT
Introduction: Plasma cell disorders (PCDs) are clonal plasma cell disorders that include conditions such as monoclonal gammopathy of undetermined significance (MGUS), monoclonal gammopathy of renal significance (MGRS), multiple myeloma (MM), smoldering MM (SMM), solitary plasmacytoma, and light-chain (AL) amyloidosis. The risk factors associated with and the clinical course of PCDs after renal transplantation is not well established although immunosuppressive protocols may impact the incidence and natural history of PCDs posttransplant.
Patients and methods: This single-center retrospective study evaluated patients with a history of renal transplant who developed a PCD between January 1, 2014-December 31, 2018.
Result: A total of 41 patients met the inclusion criteria including 29 with MGUS and 12 with symptomatic PCD (4 with MM, 2 with SMM, 4 with MGRS, 1 with AL amyloidosis, and 1 with solitary plasmacytoma). The median follow-up of survivors was 41.6 months. Three patients (1 with MGUS and 2 with MGRS) progressed to MM during the follow-up period. There was a male preponderance in both groups. There was no correlation between the donor and immunosuppressive regimen and the development of a PCD. Patients with symptomatic PCD had higher serum creatinine and M-protein levels at diagnosis and higher free light chain ratio and plasma cell burden. There was also a higher percentage of allograft failure noted in the symptomatic PCD subset 50% (n = 6), whereas only 23% (n = 7) of patients had allograft failure in the MGUS group.
Conclusion: This study shows the importance of considering monoclonal gammopathy in the differential of renal dysfunction after kidney transplant and the need to follow these patients closely to monitor for progression to symptomatic PCD.

274. Outcomes of Canakinumab Treatment in Recipients of Kidney Transplant With Familial Mediterranean Fever: A Case Series
Sendogan DO, Saritas H, Kumru G et al.
Transplant Proc 2019 Sep;51(7):2292-2294.

ABSTRACT
Familial Mediterranean fever (FMF) is an important and preventable cause of chronic kidney disease due to secondary amyloidosis. Although colchicine is the first-line therapy in patients with FMF with 60% to 65% complete remission rates, 5% to 10% of patients are colchicine-resistant and 5% to 10% of them are intolerant to the therapy. Anti-interleukin-1 agents, such as anakinra and canakinumab, are safe and efficient therapeutic options in patients with colchicine resistance or intolerance. However, the data on management of these targeted agents is limited in recipients of kidney transplant (RKT). In this case series, we aim to share our experience on canakinumab therapy of 4 RKTs with FMF-related amyloidosis, who were followed up in our clinic between 2010 and 2017. All of the 4 patients with end-stage renal disease were colchicine- resistant and on other alternative therapies, which provided poor disease control. For efficient control of secondary amyloidosis, canakinumab therapy was initiated in 1 of the patients before the renal transplant, and for the remaining patients after renal transplant. Any serious adverse effect, development of proteinuria, or graft dysfunction has not been observed in any of the patients. Under the canakinumab treatment, complete clinical responses, prevent typical familial Mediterranean fever attacks with fever and arthritis and abdominal pain, normalized serum amyloid A and C-reactive protein levels were achieved in all patients. Canakinumab treatment is a safe and effective therapeutic option for RKTs with FMF who are resistant or intolerant to colchicine and anakinra.

275. Inotersen: New Promise for the Treatment of Hereditary Transthyretin Amyloidosis
Mathew V, Wang AK.
Drug Des Devel Ther 2019 May 6;13:1515-1525.

ABSTRACT
Hereditary transthyretin amyloidosis is a fatal autosomal dominant disorder characterized by deposition of transthyretin amyloid into the peripheral nervous system, heart, kidney, and gastrointestinal tract. Previous treatments using liver transplantation and small molecule stabilizers were not effective in stopping disease progression. Inotersen, a 2'-O-methyoxyethyl-modified antisense oligonucleotide, which acts by reducing the production of transthyretin, was recently demonstrated to improve disease course and quality of life in early hereditary transthyretin amyloidosis polyneuropathy in a 15-month Phase III study.

276. Recent Advances in the Diagnosis, Risk Stratification, and Management of Systemic Light-Chain Amyloidosis
Vaxman I, Gertz M.
Acta Haematol 2019;141(2):93-106.

ABSTRACT
The term amyloidosis refers to a group of disorders in which protein fibrils accumulate in certain organs, disrupt their tissue architecture, and impair the function of the effected organ. The clinical manifestations and prognosis vary widely depending on the specific type of the affected protein. Immunoglobulin light-chain (AL) amyloidosis is the most common form of systemic amyloidosis, characterized by deposition of a misfolded monoclonal light-chain that is secreted from a plasma

cell clone. Demonstrating amyloid deposits in a tissue biopsy stained with Congo red is mandatory for the diagnosis. Novel agents (proteasome inhibitors, immunomodulatory drugs, monoclonal antibodies, venetoclax) and autologous stem cell transplantation, used for eliminating the underlying plasma cell clone, have improved the outcome for low- and intermediate-risk patients, but the prognosis for high-risk patients is still grave. Randomized studies evaluating antibodies that target the amyloid deposits (PRONTO, VITAL) were recently stopped due to futility and currently there is an intensive search for novel treatment approaches to AL amyloidosis. Early diagnosis is of paramount importance for effective treatment and prognosis, due to the progressive nature of this disease.

C. RECIDIVA DE LA ENFERMEDAD POR DEPÓSITO GLOMERULAR FIBRILAR NO AMILOIDE EN EL TRASPLANTE RENAL.

277. Heavy Chain Fibrillary Glomerulonephritis: A Case Report
Nasr SH , Sirac C, Bridoux F et al.
Am J Kidney Dis 2019 Aug;74(2):276-280.

ABSTRACT
Heavy chain amyloidosis and heavy chain deposition disease are the only known kidney diseases caused by the deposition of truncated immunoglobulin heavy chains. Fibrillary glomerulonephritis typically results from deposition of DNAJB9 (DnaJ heat shock protein family [Hsp40] member B9) and polytypic immunoglobulin G (IgG). We describe a patient with monoclonal gammopathy (IgG with λ light chain) who developed DNAJB9-negative fibrillary glomerulonephritis leading to end-stage kidney disease, with recurrence in 2 kidney allografts. Pre- and postmortem examination showed glomerular deposition of Congo red-negative fibrillar material that was determined to be immunoglobulin heavy chain. We propose the term "heavy chain fibrillary glomerulonephritis" to describe this lesion, which appears to be a rare kidney complication of monoclonal gammopathy. The diagnosis should be suspected when the kidney biopsy shows fibrillary glomerulonephritis with negative staining for immunoglobulin light chains and DNAJB9; the diagnosis can be confirmed using immunochemical and molecular studies.

278. DNAJB9 Is a Specific Immunohistochemical Marker for Fibrillary Glomerulonephritis
Nasr SH, Vrana JA, Dasari S.
Kidney Int Rep 2017 Aug 8;3(1):56-64.

ABSTRACT
Introduction: Fibrillary glomerulonephritis (FGN) is a rare disease with unknown pathogenesis and a poor prognosis. Until now, the diagnosis of this disease has required demonstration of glomerular deposition of randomly oriented fibrils by electron microscopy that are Congo red negative and stain with antisera to Igs. We recently discovered a novel proteomic tissue biomarker for FGN, namely, DNAJB9.

Methods: In this work, we developed DNAJB9 immunohistochemistry and tested its sensitivity and specificity for the diagnosis of FGN. This testing was performed on renal biopsy samples from patients with FGN (n = 84), amyloidosis (n = 21), a wide variety of non-FGN glomerular diseases (n = 98), and healthy subjects (n = 11). We also performed immunoelectron microscopy to determine whether DNAJB9 is localized to FGN fibrils.
Results: Strong, homogeneous, smudgy DNAJB9 staining of glomerular deposits was seen in all but 2 cases of FGN. The 2 cases that did not stain for DNAJB9 were unique, as they had glomerular staining for IgG only (without κ or λ) on immunofluorescence. DNAJB9 staining was not observed in cases of amyloidosis, in healthy subjects, or in non-FGN glomerular diseases (with the exception of very focal staining in 1 case of smoking-related glomerulopathy), indicating 98% sensitivity and > 99% specificity. Immunoelectron microscopy showed localization of DNAJB9 to FGN fibrils but not to amyloid fibrils or immunotactoid glomerulopathy microtubules.
Conclusion: DNAJB9 immunohistochemistry is sensitive and specific for FGN. Incorporation of this novel immunohistochemical biomarker into clinical practice will now allow more rapid and accurate diagnosis of this disease.

279. Long-term Outcome of Kidney Transplantation in a Patient With Coexisting Lipoprotein Glomerulopathy and Fibrillary Glomerulonephritis
Cheung CY, Chan AOK, Chan GPT et al.
Clin Kidney J 2014 Aug;7(4):396-8.

No abstract available

280. End-Stage Kidney Disease Due to Fibrillary Glomerulonephritis and Immunotactoid Glomerulopathy - Outcomes in 66 Consecutive ANZDATA Registry Cases
Mallett A, Tang W, Hart G et al.
Am J Nephrol 2015;42(3):177-84.

ABSTRACT
Background: Fibrillary glomerulonephritis (FGN) and immunotactoid glomerulopathy (IG) are uncommon and characterised by non-amyloid fibrillary glomerular deposits. The aim of this study was to investigate characteristics and outcomes of patients undergoing renal replacement therapy (RRT) for end-stage kidney disease (ESKD) secondary to FGN and IG.
Methods: All ESKD patients who commenced RRT in Australia and New Zealand 1 January 1990 to 31 December 2010 were included. Outcomes were assessed by Kaplan-Meier, multivariate logistic-regression analysis and multivariable Cox proportional-hazards survival analysis.
Results: Of 45,216 individuals with ESKD, 55 (0.12%) had FGN and 11 (0.02%) had IG. The median survival of FGN patients on dialysis (5.63 years, 95% CI 3.31-7.96) was not significantly different from patients with other ESKD causes (median 4.01 years, 95% CI 4.34-4.47; log-rank 1.32, p = 0.25), but was significantly longer than that of IG patients (median 2.93 years, 95% CI 0.00-6.17; log-rank 4.8, p = 0.03). Thirteen (24%) FGN patients received 13 renal-allografts, 4 (36%) IG patients received 4 renal-allografts and 11,528 (26%) other ESKD patients received 12,278 renal-allografts. FGN patients experienced comparable outcomes to other ESKD patients for both 10-year patient survival (100 vs.

84%, p = 0.93) and renal-allograft survival (67 vs. 76%, p = 0.06). For IG, the median follow-up was 3.66 years with 75% patient survival and 100% renal-allograft survival. One (8%) FGN patient and 1 (25%) IG patient experienced recurrent FGN and IG respectively in their allograft.
Conclusion: Patients with FGN have comparable dialysis and renal transplant outcomes to patients with other causes of ESKD. IG patients have inferior survival on dialysis, although renal transplant outcomes are acceptable. Disease recurrence in renal-allografts was low for both FGN and IG.

281. Long-term Outcome of Kidney Transplantation in Patients With Fibrillary Glomerulonephritis or Monoclonal Gammopathy With Fibrillary Deposits

Czarnecki PG, Lager DJ, Leung N et al.
Kidney Int 2009 Feb;75(4):420-7.

ABSTRACT

To determine the outcome of kidney transplantation in patients with fibrillary glomerulonephritis (FGN), a rare glomerular disease, we followed 12 patients, 5 with FGN and 7 patients with monoclonal gammopathy and fibrillary deposits (MGFD), who underwent 15 kidney transplants since 1988 with a median follow-up of 52 months. Recurrent disease did not arise in any of the patients with FGN but developed in 5 patients with MGFD. Seven allografts failed: 1 in the FGN group and 6 in the MGFD group. Median allograft survival for patients with MGFD was 37 months but had not been reached in FGN patients. One patient with FGN had primary allograft failure secondary to graft thromboembolism. Three patients with MGFD were re-transplanted and one lost the second allograft to recurrent disease, but the other two died from hematological malignancy. Another patient was diagnosed with MPGN type III and did not have detectable fibrillary material 22 months after transplantation. One patient with MGFD had stable allograft function 6 months post-transplant but another, with recurrent disease, underwent peripheral blood stem cell transplantation and regained stable allograft function. Our study shows that kidney transplantation appears safe in patients with FGN with little risk of recurrence. However, patients with MGFD have a significant risk for disease recurrence. Whether the development of hematological malignancies following transplantation in this group is related to their original disease or was coincidental requires further studies.

282. Fibrillary Glomerulonephritis and Pulmonary Hemorrhage in a Patient With Renal Transplantation

Ginesta JC, Torras A, Ricart MJ et al.
Clin Nephrol 1995 Mar;43(3):180-3.

ABSTRACT

Fibrillary glomerulonephritis is an unusual kidney disease characterized by the deposition of immunoglobulins in a fibrillar pattern. Until recently it has been considered to involve the kidneys alone. We describe a patient who underwent renal transplantation and developed fibrillary glomerulonephritis with rapidly progressive renal failure and severe pulmonary hemorrhage two years and a half after transplantation. Nephropathy prior to transplantation was thought to be focal and segmental glomerulosclerosis. Diagnosis of fibrillary glomerulonephritis in renal allograft was confirmed by postmortem examination. 50% of the glomeruli with extracapillary crescents were

observed on light microscopy. By immunofluorescence main deposition of IgA was detected in the glomerular capillar walls and the mesangium. Electron microscopy showed fibrillo-reticular deposits in the same place. Lung histology showed both old and recent areas of alveolar hemorrhage. Granular staining for IgA was observed in the alveolar walls by immunofluorescence. Ultrastructural analysis of the lung made evident fibrillo-reticulary deposits in the interstitium, similar than those observed in the glomeruli. The presence of these deposits in both renal and pulmonary tissues indicates the possibility of systemic involvement in fibrillary glomerulonephritis. In our case it could be related to the recurrence of this glomerulopathy in renal allograft.

283. Fibrillary and Immunotactoid Glomerulonephritis: Distinct Entities With Different Clinical and Pathologic Features

Rosenstock JL, Markowitz GS, Valeri AM et al.
Kidney Int 2003 Apr;63(4):1450-61.

ABSTRACT

Background: Controversy surrounds the relatedness of fibrillary glomerulonephritis (FGN) and immunotactoid glomerulonephritis (IT).

Methods: To better define their clinicopathologic features and outcome, we report the largest single center series of 67 cases biopsied from 1980 to 2001, including 61 FGN and 6 IT. FGN was defined by glomerular immune deposition of Congo red-negative randomly oriented fibrils of < 30 nm (mean, 20.1 +/- 0.4 nm). IT was defined by glomerular deposition of hollow, stacked microtubules of > or = 30 nm (mean, 38.2 +/- 5.7 nm).

Results: FGN comprised 0.6% of total native kidney biopsies and IT was tenfold more rare (0.06%). Deposits in FGN were immunoglobulin G (IgG) dominant and polyclonal in 96%. IgG subtype analysis in 19 FGN cases showed monotypic deposits in four (two IgG1 and two IgG4) and oligotypic deposits in 15 (all combined IgG1 and IgG4). In IT, deposits were IgG dominant in 83% and monoclonal in 67% (three IgG1 kappa and one IgG1 lambda). FGN patients were a mean age of 57 years, 92% were Caucasian, and 39% were male. At biopsy, FGN patients had the following clinical characteristics (mean, range): creatinine 3.1 mg/dL (0.5 to 14), proteinuria 6.5 g/day (0.8 to 25), 60% microhematuria, and 59% hypertension. Histologic patterns of FGN were diverse, including diffuse proliferative glomerulonephritis (DPGN) (nine cases), membranoproliferative glomerulonephritis (MPGN) (27 cases), mesangial proliferative/sclerosing (MES) (13), membranous glomerulonephritis (MGN) (four), and diffuse sclerosing (DS) (eight). The more proliferative (MPGN and DPGN) and sclerosing (DS) forms presented with a higher creatinine and greater proteinuria compared to MES and MGN. Median time to end-stage renal disease (ESRD) was 24.4 months for FGN and mean time to ESRD varied by histologic subtype: DS 7 months, DPGN 20 months, MPGN 44 months, compared to MES 80 months and MGN 87 months. There was no statistically significant effect of immunosuppressive therapy (given to 36% of FGN patients). By Cox regression (hazard ratio, confidence interval, P value), independent predictors of progression to ESRD were creatinine at biopsy [2.05 (1.55 to 2.72) P < 0.001] and severity of interstitial fibrosis [2.01 (1.05 to 3.85) P = 0.034]. Although IT had similar presentation, histologic patterns, and outcome compared to FGN, it had a greater association with monoclonal gammopathy (P = 0.014), underlying lymphoproliferative disease (P = 0.020), and hypocomplementemia (P = 0.032).

Conclusion: FGN is an idiopathic condition characterized by polyclonal immune deposits with restricted gamma isotypes. Most patients present with significant renal insufficiency and have a poor outcome despite immunosuppressive therapy, and outcome correlates with histologic subtype. By contrast, IT often contains monoclonal IgG deposits and has a significant association with underlying dysproteinemia and hypocomplementemia. Differentiation of FGN from the much more rare entity IT appears justified on immunopathologic, ultrastructural, and clinical grounds.

284. Recurrence of DNAJB9-Positive Fibrillary Glomerulonephritis After Kidney Transplantation: A Case Series

El Ters M, Bobart SA, Cornell LD et al.

Am J Kidney Dis 2020 May 12;S0272-6386(20)30571-0.

ABSTRACT

Rationale & objective: Fibrillary glomerulonephritis (FGN) is a rare glomerular disease that often progresses to kidney failure requiring kidney replacement therapy. We have recently identified a novel biomarker of FGN, DnaJ homolog subfamily B member 9 (DNAJB9). In this study, we used sequential protocol allograft biopsies and DNAJB9 staining to help characterize a series of patients with native kidney FGN who underwent kidney transplantation.

Study design: Case series.

Setting & participants: Between 1996 and 2016, kidney transplantation was performed on 19 patients with a reported diagnosis of FGN in their native/transplant kidneys. Using standard diagnostic criteria and DNAJB9 staining, we excluded 5 patients (4 atypical cases diagnosed as possible FGN and 1 donor-derived FGN). Protocol allograft biopsies had been performed at 4, 12, 24, 60, and 120 months posttransplantation. DNAJB9 immunohistochemistry was performed using an anti-DNAJB9 rabbit polyclonal antibody. Pre- and posttransplantation demographic and clinical characteristics were collected. Summary statistical analysis was performed, including nonparametric statistical tests.

Observations: The 14 patients with FGN had a median posttransplantation follow-up of 5.7 (IQR, 2.9-13.8) years. 3 (21%) patients had recurrence of FGN, detected on the 5- (n=1) and 10-year (n=2) allograft biopsies. Median time to recurrence was 10.2 (IQR, 5-10.5) years. Median levels of proteinuria and iothalamate clearance at the time of recurrence were 243mg/d and 56mL/min. The remaining 11 patients had no evidence of histologic recurrence on the last posttransplantation biopsy, although the median time of follow-up was significantly less at 4.4 (IQR, 2.9-14.4) years. 3 (21%) patients had a monoclonal protein detectable in serum obtained pretransplantation; none of these patients had recurrent FGN.

Limitations: Small study sample and shorter follow-up time in the nonrecurrent versus recurrent group.

Conclusions: In this series, FGN had an indolent course in the kidney allograft in that detectable histologic recurrence did not appear for at least 5 years posttransplantation.

285. New Developments in the Diagnosis of Fibrillary Glomerulonephritis

Nasr SH, Fogo AB.

Kidney Int 2019 Sep;96(3):581-592.

ABSTRACT

Fibrillary glomerulonephritis is a glomerular disease historically defined by glomerular deposition of Congo red-negative, randomly oriented straight fibrils that lack a hollow center and stain with antisera to immunoglobulins. It was initially considered to be an idiopathic disease, but recent studies highlighted association in some cases with autoimmune disease, malignant neoplasm, or hepatitis C viral infection. Prognosis is poor with nearly half of patients progressing to end-stage renal disease within 4 years. There is currently no effective therapy, aside from kidney transplantation, which is associated with disease recurrence in a third of cases. The diagnosis has been hampered by the lack of biomarkers for the disease and the necessity of electron microscopy for diagnosis, which is not widely available. Recently, through the use of laser microdissection-assisted liquid chromatography-tandem mass spectrometry, a novel biomarker of fibrillary glomerulonephritis, DnaJ homolog subfamily B member 9, has been identified. Immunohistochemical studies confirmed the high sensitivity and specificity of DnaJ homolog subfamily B member 9 for this disease; dual immunofluorescence showed its colocalization with IgG in glomeruli; and immunoelectron microscopy revealed its localization to individual fibrils of fibrillary glomerulonephritis. The identification of this tissue biomarker has already entered clinical practice and undoubtingly will improve the diagnosis of this rare disease, particularly in developing countries where electron microscopy is less available. Future research is needed to determine whether DnaJ homolog subfamily B member 9 is an autoantigen or just an associated protein in fibrillary glomerulonephritis, whether it can serve as a noninvasive biomarker, and whether therapies that target this protein are effective in improving prognosis.

286. Long-term Kidney Disease Outcomes in Fibrillary Glomerulonephritis: A Case Series of 27 Patients

Javaugue V, Karras A, Glowacki F et al.

Am J Kidney Dis 2013 Oct;62(4):679-90.

ABSTRACT

Background: Fibrillary glomerulonephritis (GN) is a rare disorder with poor renal prognosis. Therapeutic strategies, particularly the use of immunosuppressive drugs, are debated.

Study design: Case series.

Setting & participants: 27 adults with fibrillary GN referred to 15 nephrology departments in France between 1990 and 2011 were included. All patients were given renin-angiotensin system blockers and 13 received immunosuppressive therapy, including rituximab (7 patients) and cyclophosphamide (3 patients).

Outcomes & measurements: Clinical and histologic features of patients and kidney disease outcome. Renal response was defined as a >50% decrease in 24-hour proteinuria with <15% decline in estimated glomerular filtration rate (eGFR).

Results: All patients presented with proteinuria, associated with nephrotic syndrome (41%), hematuria (73%), and hypertension (70%). Baseline median eGFR was 49 mL/min/1.73 m(2). Eight patients had a history of autoimmune disease and none had evidence of hematologic malignancy during follow-up. Light microscopic studies showed mesangial GN (70%), predominant pattern of membranous GN (19%), or membranoproliferative GN (11%). By immunofluorescence, immunoglobulin G (IgG) deposits (IgG4, 15/15; IgG1, 9/15) were polyclonal in 25 cases. Serum IgG

subclass distribution was normal in the 6 patients tested. After a median 46-month follow-up, renal response occurred in 6 of 13 patients who received immunosuppressive therapy with rituximab (5 patients) or cyclophosphamide (1 patient). Of these, 5 had a mesangial or membranous light microscopic pattern, and median eGFR before therapy was 76 mL/min/1.73 m(2). In contrast, chronic kidney disease progressed in 12 of 14 patients who were not given immunosuppressive therapy, 10 of whom reached end-stage renal disease.
Limitations: Number of patients, retrospective study, use of multiple immunosuppressive regimens.
Conclusions: The therapeutic approach in fibrillary GN remains challenging. The place of immunosuppressive therapy, particularly anti-B-cell agents, needs to be assessed in larger collaborative studies.

287. Fibrillary Glomerulonephritis: An Apparent Familial Form?
Ying T, Hill P, Desmond M et al.
Nephrology (Carlton) 2015 Jul;20(7):506-9.

ABSTRACT
Fibrillary glomerulonephritis is a rare cause of glomerulonephritis characterized by non-amyloid fibrillary deposits of unknown aetiology. It is generally considered idiopathic but may be associated with secondary causes such as monoclonal gammopathy, hepatitis B and C infections, autoimmune diseases and malignancies. We report two Australian families with apparent familial fibrillary glomerulonephritis inherited in an autosomal dominant pattern, and postulate the existence of a primary familial entity. Family 1 consists of an affected father and daughter; the daughter progressed to end-stage renal failure within 18 months of diagnosis, despite immunosuppressive therapy. The father, however, remains stable at 10 months follow up. Family 2 comprises an affected mother and son; the mother commenced haemodialysis 5 years after diagnosis and subsequently underwent successful renal transplantation. The son is presently stable at last follow-up after 5 years. A further review of the second family history reveals a third family member (maternal father) dying of 'Bright's disease'. We describe their histopathology, clinical progression and treatment outcomes, and provide a review of the current understanding of this heterogeneous condition that is associated with poor renal outcomes.

288. Outcome of Renal Transplantation in Fibrillary Glomerulonephritis
Samaniego M, Nadasdy GM, Laszik Z et al.
Clin Nephrol 2001 Feb;55(2):159-66.

ABSTRACT
Fibrillary glomerulonephritis (FGN) is a rare but progressive glomerular disease usually with end-stage renal disease (ESRD) developing within months or few years following the diagnosis. Little is known about the outcome of renal transplantation in patients with ESRD due to FGN. We report four patients with FGN who received renal allografts. Two patients developed recurrent FGN in their grafts. One patient was diagnosed to have recurrent FGN 9 years post-transplant, and lost his graft 4 years thereafter. Another patient had recurrent disease 2 years post-transplant but has stable graft function after 7 years. One patient died with normal renal allograft function 7 years following

transplantation. The fourth patient has chronic transplant nephropathy 34 months post-transplant without evidence of recurrent FGN. A literature review revealed 10 additional patients who received 11 renal allografts due to ESRD caused by FGN. Four of these 10 patients had biopsy-proven recurrence (one patient in two subsequent grafts), but this caused graft loss only in 2 patients 56 months and 7 years post-transplant, respectively. The earliest recurrence was diagnosed 2 years post-transplant. We conclude that although the recurrence rate of FGN in renal transplants is high (around 50%), the recurrent disease has a relatively benign course and prolonged graft survival is possible.

289. Recurrence of Fibrillary Glomerulonephritis in a Renal Transplant Recipient
Mitwalli A, Shah I, Hammad D et al.
Int Urol Nephrol 2013 Oct;45(5):1527-32.

ABSTRACT
Fibrillary glomerulonephritis (FGN) is a rare glomerular deposition disease and a rare cause of nephrotic syndrome. The patients usually present with renal insufficiency, nephrotic range proteinuria and microscopic hematuria. The electron microscopy study is the only means of diagnosis. The clinical course of the disease is generally unpredictive and the patients inevitably progress to ESRD. Here, we describe a case of FGN, which presented with nephrotic syndrome and impaired renal function. Renal biopsy showed that 26 out of 30 glomeruli were completely sclerosed. Remaining showed mesangial expansion and double contour consistent with a membranoproliferative pattern, with 70 % interstitial fibrosis and tubular atrophy. Immunofluorescence revealed C3 (2+) diffuse mesangial deposits. Electron microscopic showed subendothelial dense deposits with organized tubular structures. During follow-up, the patient underwent renal transplantation from a living unrelated kidney donor. Later on, as the renal allograft function showed deterioration, renal biopsy was performed and showed recurrence of FGN in the renal allograft.

290. A Recurrent Fibronectin Glomerulopathy in a Renal Transplant Patient: A Case Report
Otsuka Y, Takeda A, Horike K et al.
Clin Transplant 2012 Jul;26 Suppl 24:58-63.

ABSTRACT
Fibronectin glomerulopathy (FNG) is a rare, autosomal dominant renal disease with massive mesangial, and subendothelial fibronectin deposits. It presents proteinuria, often in the nephrotic range in the third to fourth decade, and slow progression to end-stage renal disease. The risk of recurrent disease in renal allograft is uncertain. A Japanese female with end-stage renal disease because of unknown origin received a renal transplant and was referred with proteinuria and mild deterioration of renal function four months after transplantation. Five allograft biopsies were underwent from one h to 12 months after the transplantation, including a biopsy 19 d after the transplantation, which revealed dense deposits suggesting fibronectin. A biopsy 134 d after the transplantation showed a feature of lobular glomerulonephritis corresponding FNG. The diagnosis was confirmed by IST4 positive and IST9 negative immunostaining together with typical fibrillary

dense deposits in the mesangium and subendothelial spaces in electron microscopy. This is the first report of recurrent FNG in Japan.

291. Fibrillary Glomerulonephritis: Early Diagnosis Associated With Steroid Responsiveness
Dickenmann M, Schaub S, Nickeleit V et al.
Am J Kidney Dis 2002 Sep;40(3):E9.

ABSTRACT
Patients with fibrillary glomerulonephritis usually present with nephrotic proteinuria, microscopic hematuria, impaired renal function, and hypertension; 50% develop end-stage renal disease within a few years. There is no known effective therapy for fibrillary glomerulonephritis. We describe three patients with biopsy-proven fibrillary glomerulonephritis, in whom pathognomonic fibrillar deposits of 20-nm diameter were seen by electron microscopy. All patients had nephrotic syndrome and normal renal function at the time of diagnosis. They were treated initially with prednisone, 1 mg/kg body weight, then tapered individually according to the clinical course. Additional therapy consisted of an angiotensin-converting enzyme inhibitor and diuretics. Proteinuria disappeared in two of three patients after 9 and 12 months of therapy. In one patient, proteinuria was reduced from 7.49 mg/mg creatinine to 0.63 mg/mg creatinine after 6 months of treatment. The kidney function remained normal in all three cases. Two patients are now free of steroid therapy for 9 and 6 months. They show no signs of recurrence of kidney disease and have normal renal function without significant proteinuria. Steroid therapy in patients with biopsy-proven fibrillary glomerulonephritis, starting with prednisone, 1 mg/kg body weight, and tapered individually according to the clinical course, is a promising strategy. Early start of treatment in patients with preserved renal function seems to be crucial for a favorable outcome.

292. Fibrillary Glomerulonephritis in a Renal Allograft
Palanichamy V, Saffarian N, Jones B et al.
Am J Kidney Dis 1998 Nov;32(5):E4.

ABSTRACT
Fibrillary glomerulonephritis is an uncommon disease seen in approximately 1% of all native kidney biopsy specimens. We present here a case of a 40-year-old white woman with the rapid loss of graft function secondary to fibrillary glomerulonephritis within 7 days of receiving a living-related renal allograft. This case emphasizes the values of combining urinalysis with prompt allograft kidney biopsy in recipients with an elevated serum creatinine posttransplantation. When one encounters rapidly progressing glomerulonephritis or a pulmonary-renal syndrome in the immediate posttransplantation period, fibrillary glomerulonephritis must be considered in the differential diagnosis. Because of a high recurrence rate and no available treatment to modify a potentially malignant course of this disease, we recommend caution when considering these patients for transplantation.

293. Clinical Features, Predictors of Disease Progression and Results of Renal Transplantation in fibrillary/immunotactoid Glomerulopathy

Pronovost PH, Brady HR, Gunning ME et al.

Nephrol Dial Transplant 1996 May;11(5):837-42.

ABSTRACT

Background: The clinical manifestations of fibrillary-immunotactoid glomerulopathy are still being appreciated. It is unclear whether fibrillary-immunotactoid glomerulopathy actually represents two distinct clinicopathological entities, fibrillary glomerulopathy (FG) and immunotactoid glomerulopathy (ITG), or a single disease with different ultrastructural variants.

Methods: To address these issues, we analysed the clinical features of 186 patients with fibrillary-immunotactoid glomerulopathy referred to our institutions (25 patients) or reported in the literature (161 patients). In separate analyses, patients were subclassified as having either fibrillary glomerulopathy (FG) or immunotactoid glomerulopathy (ITG) according to fibril diameter (FG<=30nm, ITG>30 nm) or arrangement (FG, random; ITG, focally organized).

Results: Proteinuria (FG approximately 100%, ITG approximately 100%), nephrotic syndrome (FG approximately 71%, ITG approximately 82%), haematuria (FG approximately 71%, ITG approximately 64%), hypertension (FG approximately 67%, ITG approximately 45%), and renal insufficiency (FG approximately 54%, ITG approximately 42%) were frequent clinical correlates of both FG and ITG, irrespective of the ultrastructural criteria for diagnosis. Twenty-five patients presenting to our institutions (24 FG, 1 ITG) were divided into three groups based on rate of decline of GFR (mean slope of 1/serum creatinine versus time: group 1 -0. 103+/-0.238; group 2 0.121+/-0.040; group 3 0.466+/-0.318) in an attempt to identify clinical predictors of progression at presentation. Rapid progressors (Group 3) had an increased incidence of nephrotic syndrome and tended to have higher blood pressure than patients with milder disease, but did not differ from other groups in age, prevalence of haematuria or degree of renal insufficiency. The number of patients requiring dialysis was 0/10 in group 1, 2/6 in group 2, and 2/4 in group 3 over a follw-up period 47+/-46, 55+/-32, and 19+/-19 months respectively; two predialysis deaths being recorded in group 3. Four patients received five renal allografts (one patient being transplanted twice) and were followed for 4-11 years. Whereas recurrence of FG was documented in three allografts undergoing post-transplant biopsy, the rate of deterioration of GFR was invariably slower in allografts than native kidneys (mean slope of 1/Cr versus time: 0.036+/-0.01 versus 0. 0301+/-0.18 respectively). The strength of association between FG-ITG and lymphoproliferative malignancy varied depending on whether patients with monoclonal-gammopathy-associated fibrillary deposits were included or excluded from the analysis.

Conclusions: We contend that patients presenting with Congo-red-negative fibrillary deposits on renal biopsy should be evaluated carefully for monoclonal-gammopathy and cryoglobulins, but there is insufficient published data, as yet, to justify subclassification of FG and ITG as distinct clinical entities. Indeed, we argue that it remains to be determined if FG-ITG represents a unique condition or a forme fruste of cryoglobulin- or gammopathy-associated renal disease. Although the optimal treatment for FG-ITG has not been determined, renal transplantation appears an attractive option in patients with end-stage renal failure.

294. Immunotactoid Glomerulopathy
Korbet SM, Schwartz MM, Lewis EJ.
Am J Kidney Dis 1991 Mar;17(3):247-57.

ABSTRACT
During the past 10 years, immunotactoid glomerulopathy has become recognized with increasing frequency. The lesion is characterized histologically by highly organized ultrastructural deposits that appear to be composed of immunoglobulin and complement and are negative for amyloid by Congo red stain. Clinically and/or serologically, patients have no evidence of cryoglobulinemia, amyloidosis, systemic lupus erythematosus, or a paraproteinemia, disorders associated with glomerular deposits, which also have a highly organized tactoidal or fibrillar characteristic. Immunotactoid glomerulopathy does not appear to be a multisystemic disease process and thus may represent a primary glomerulopathy. Patients with immunotactoid glomerulopathy present with proteinuria (nephrotic range in more than 60%) and over half of the patients have hypertension, hematuria, and renal insufficiency. Progression to end stage renal disease has occurred in more than 40% of patients reported to date. The experience in treating this disorder using prednisone and/or immunosuppression is limited and has not been impressive. Four patients have successfully undergone renal transplantation, but proteinuria recurred in two and was associated with the recurrence of immunotactoid glomerulopathy in the renal allograft. Although we have gained insight into the clinical course and histopathology of this disorder over the past few years, we still know little about its pathogenesis, an area for further research.

295. Immunotactoid Glomerulopathy (ITGP): A Not Fully Defined Clinicopathologic Entity
Monga G, Mazzucco G, Motta M et al.
Ren Fail 1993;15(3):401-5.

ABSTRACT
Immunotactoid glomerulopathy is characterized by the ultrastructural finding of fibrillary or microtubular deposits in patients without systemic diseases such as SLE, diabetes, paraproteinemias, cryoglobulinemia, or amyloidosis. These deposits correspond in most (but not all) cases to immunoglobulin and complement deposits as shown by immunohistochemical techniques. Different light microscopic patterns (mesangioproliferative, membranous, membranoproliferative, and crescentic) have been reported. Clinical presenting feature is characterized by proteinuria (often of nephrotic range), hematuria, and hypertension in most cases. Chronic renal failure requiring hemodialysis or transplantation is described in more than half the patients. Pathogenesis has not yet been elucidated and only some speculative hypotheses have so far been suggested. At present there is no clear evidence that we are dealing with a new pathologic entity, but larger series must be collected and studied in order to find a correct taxonomic collocation of this glomerulopathy.

296. Glomerulopathies With Organized Monoclonal Immunoglobulin Deposits
Touchard G, Bridoux F, Goujon JM.
Nephrol Ther 2016 Feb;12(1):57-65.

ABSTRACT
The spectrum of glomerular disorders with organized immunoglobulin (Ig) deposits is heterogeneous. It encompasses 2 mains categories: glomerulopathies with fibrillary deposits are mostly represented by immunoglobulinic amyloidosis (most commonly AL amyloidosis, characterized by monoclonal light chain deposits often of the lambda isotype), and pseudo-amyloid fibrillary glomerulonephritis in which deposits predominantly contain polyclonal IgG4. Glomerulopathies with microtubular deposits include cryoglobulinemic glomerulonephritis (type I and type II, with or without detectable serum cryoglobulin) and glomerulonephritis with organized microtubular monoclonal Ig deposits (GOMMID) also referred to as immunotactoid glomerulopathy. Pathological diagnosis requires meticulous studies by light microscopy (with systematic Congo red staining), immunofluorescence with specific conjugates, and electron microscopy. Ultrastructural studies are required to differentiate amyloid fibrils (8 to 10 nm in external diameter), pseudo-amyloid fibrils (15-20 nm) and microtubules (10 to 50 nm in external diameter, with a central hollow core). Glomerular deposits in type I cryoglobulinemic glomerulonephritis are arranged into parallel straight microtubules similar to those observed in GOMMID, but with different topography that allows distinction between the two entities. Glomerular substructures composed of circulating Igs should be distinguished from collagen fibrils that are commonly observed in glomerular disorders with or without deposition of monoclonal or polyclonal Igs.

297. A Case of Recurrent Immunotactoid Glomerulopathy in an Allograft Treated With Rituximab
Sathyan S, Khan FN, Ranga KV.
Transplant Proc 2009 Nov;41(9):3953-5.

ABSTRACT
Immunotactoid glomerulopathy is a glomerular disorder typified by hollow cylindrical and sometimes spherical microtubular deposits, with a diameter of 30-40 nm, but up to 90 nm, often in a parallel arrangement or in intersecting bundles. These patients frequently end up receiving kidney transplants due to progressive renal insufficiency. Known to recur in renal transplant recipients with variable outcomes, its treatment options are limited. Classically steroids, cyclophosphamide, mycophenolate mofetil, and plasma exchanges have been used to treat these recurrences. More recently, rituximab has been suggested as a treatment and has demonstrated improved outcomes in other glomerular diseases. Herein we describe a case of a middle-aged female renal transplant recipient for end-stage renal disease secondary to immunotactoid glomerulopathy, who experienced a recurrence of this condition in the transplanted kidney. Following a failure of conventional therapy we administered a course of rituximab, resulting in a reduction and stabilization of her serum creatinine level while her proteinuria persisted.

298. De Novo Immunotactoid Glomerulopathy of the Renal Allograft: Possible Association With Cytomegalovirus Infection
Rao KV, Hafner GP, Crary GS et al.
Am J Kidney Dis 1994 Jul;24(1):97-103.

ABSTRACT

A 59-year-old man with end-stage renal failure from systemic vasculitis developed de novo immunotactoid glomerulopathy of the renal allograft, with clinical evidence of hematuria, proteinuria, and acute renal failure 6 weeks after cadaveric renal transplantation. The morphologic lesion of immunotactoid glomerulopathy and the clinical renal disease resolved during the following 2 weeks. The disease had not recurred in the subsequent 20 months of posttransplant follow-up. During the same period, the patient also developed systemic cytomegalovirus (CMV) infection with viremia, acute hepatitis, and bone marrow suppression. The clinical manifestations of CMV illness and the renal disease have subsided following the withdrawal of immunosuppressive agents and simultaneous treatment with ganciclovir. Although there is no direct proof that CMV infection was responsible for the development of immunotactoid glomerulopathy, the circumstantial evidence in this patient strongly suggests that these two disease were temporally linked. To our knowledge, the association between CMV infection and immunotactoid glomerulopathy has not been documented previously.

299. Successful Treatment of Recurrence of Immunotactoid Glomerulopathy in a Kidney Allograft Recipient
Carles X, Rostaing L, Modesto A et al.
Nephrol Dial Transplant 2000 Jun;15(6):897-900.

No abstract available

300. Course of Renal Transplantation in Immunotactoid Glomerulopathy
Korbet SM, Rosenberg BF, Schwartz MM et al.
Am J Med 1990 Jul;89(1):91-5. doi: 10.1016/0002-9343(90)90104-l.

No abstract available

301. Fibrillary Glomerulonephritis: A Report of 66 Cases from a Single Institution
Nasr SH, Valeri AM, Cornell LD et al.
Clin J Am Soc Nephrol 6: 775–784, 2011.

ABSTRACT
Background and objectives: Fibrillary glomerulonephritis (FGN) is a rare primary glomerular disease. Most previously reported cases were idiopathic. To better define the clinical-pathologic spectrum and prognosis, we report the largest single-center series with the longest follow-up.
Design, setting, participants, & measurements: The characteristics of 66 FGN patients who were seen at Mayo Clinic, Rochester, between 1993 and 2010 are provided.
Results: The mean age at diagnosis was 53 years. Ninety-five percent of patients were white, and the female: male ratio was 1.2:1. Underlying malignancy (most commonly carcinoma), dysproteinemia, or autoimmune disease (most commonly Crohn's disease, SLE, Graves' disease, and idiopathic thrombocytopenic purpura), were present in 23, 17, and 15% of patients, respectively. Presentation included proteinuria (100%), nephrotic syndrome (38%), renal insufficiency (66%),

hematuria (52%), and hypertension (71). The most common histologic pattern was mesangial proliferative/sclerosing GN followed by membranoproliferative GN. During an average of 52.3 months of follow-up for 61 patients with available data, 13% had complete or partial remission, 43% had persistent renal dysfunction, and 44% progressed to ESRD. The disease recurred in 36% of 14 patients who received a kidney transplant. Independent predictors of ESRD by multivariate analysis were older age, higher creatinine and proteinuria at biopsy, and higher percentage of global glomerulosclerosis.
Conclusions: Underlying malignancy, dysproteinemia, or autoimmune diseases are not uncommon in patients with FGN. Prognosis is poor, although remission may occur in a minority of patients without immunosuppressive therapy. Age, degree of renal impairment at diagnosis, and degree of glomerular scarring are predictors of renal survival.

302. Fibrillary Glomerulonephritis: An Update
Rosenstock JL, Markowitz GS.
Kidney Int Rep 2019 Apr 29;4(7):917-922.

ABSTRACT
Fibrillary glomerulonephritis (FGN) is a rare proliferative form of glomerular disease characterized by randomly oriented fibrillar deposits with a mean diameter of 20 nm. By immunofluorescence (IF), the deposits stain for IgG, C3, and κ and λ light chains, suggesting that the fibrils may be composed of antigen-antibody immune complexes. A recent major advance in our understanding of the pathogenesis of FGN resulted from the discovery that a major component of the fibrils is DNA-J heat-shock protein family member B9 (DNAJB9), and immunohistochemical staining for DNAJB9 now makes it possible to diagnose FGN in the absence of ultrastructural evaluation. FGN has a poor prognosis, treatment options are currently limited, and transplant recurrence is not uncommon.

4. HIPEROXALURIA Y TRASPLANTE RENAL

303. Primary hiperoxaluria.
Niaudet P.
UpToDate. Waltham, Mass.: UpToDate, 2020.
https://www.uptodate.com/contents/primary-hyperoxaluria. Consultado el 5 de julio de 2020.

No abstract available

304. Stiripentol for the treatment of primary hyperoxaluria and calcium oxalate nephropathy.
Wyatt CM, Drüeke TB.
Kidney Int. 2020;97(1):17-19.

No abstract available

305. Patients With Primary Hyperoxaluria Type 2 Have Significant Morbidity and Require Careful Follow-Up.
Garrelfs SF, Rumsby G, Peters-Sengers H, Erger F et al.
Kidney Int. 2019 Dec;96(6):1389-1399.

ABSTRACT
Primary hyperoxaluria type 2 is a rare inherited disorder of glyoxylate metabolism causing nephrocalcinosis, renal stone formation and ultimately kidney failure. Previously, primary hyperoxaluria type 2 was considered to have a more favorable prognosis than primary hyperoxaluria type 1, but earlier reports are limited by low patient numbers and short follow up periods. Here we report on the clinical, genetic, and biochemical findings from the largest cohort of patients with primary hyperoxaluria type 2, obtained by a retrospective record review of genetically confirmed cases in the OxalEurope registry, a dataset containing 101 patients from eleven countries. Median follow up was 12.4 years. Median ages at first symptom and diagnosis for index cases were 3.2 years and 8.0 years, respectively. Urolithiasis was the most common presenting feature (82.8% of patients). Genetic analysis revealed 18 novel mutations in the GRHPR gene. Of 238 spot-urine analyses, 23 (9.7%) were within the normal range for oxalate as compared to less than 4% of 24-hour urine collections. Median intra-individual variation of 24-hour oxalate excretion was substantial (34.1%). At time of review, 12 patients were lost to follow-up; 45 of the remaining 89 patients experienced chronic kidney disease stage 2 or greater and 22 patients had reached stage 5. Median renal survival was 43.3 years, including 15 kidney transplantations in 11 patients (1 combined with liver transplantation). Renal outcome did not correlate with genotype, biochemical parameters or initially present nephrocalcinosis. Thus, primary hyperoxaluria type 2 is a disease with significant morbidity. Accurate diagnosis by 24-hour urine analysis and genetic testing are required with careful follow-up.

306. Targeting Kidney Inflammation as a New Therapy for Primary Hyperoxaluria?
Martin-Higueras C, Ludwig-Portugall I, Hoppe B et al.
Nephrol Dial Transplant. 2019 Jun 1;34(6):908-914.

ABSTRACT
The primary hyperoxalurias (PHs) are inborn errors of glyoxylate metabolism characterized by endogenous oxalate overproduction in the liver, and thus elevated urinary oxalate excretion. The urinary calcium-oxalate (CaOx) supersaturation and the continuous renal accumulation of insoluble CaOx crystals yield a progressive decline in renal function that often ends with renal failure. In PH Type 1 (AGXT mutated), the most frequent and severe condition, patients typically progress to end-stage renal disease (ESRD); in PH Type 2 (GRHPR mutated), 20% of patients develop ESRD, while only one patient with PH Type 3 (HOGA1 mutated) has been reported with ESRD so far. Patients with ESRD undergo frequent maintenance (haemo)dialysis treatment, and finally must receive a combined liver-kidney transplantation as the only curative treatment option available in PH Type 1. In experimental models using oxalate-enriched chow, CaOx crystals were bound to renal tubular cells, promoting a pro-inflammatory environment that led to fibrogenesis in the renal parenchyma by activation of a NACHT, LRR and PYD domains-containing protein 3 (NALP3)-dependent inflammasome in renal dendritic cells and macrophages. Chronic fibrogenesis progressively impaired renal function. Targeting the inflammatory response has recently been suggested as a therapeutic strategy to treat not only oxalate-induced crystalline nephropathies, but also those characterized by accumulation of cystine and urate in other organs. Herein, we summarize the pathogenesis of PH, revising the current knowledge of the CaOx-mediated inflammatory response in animal models of endogenous oxalate overproduction. Furthermore, we highlight the possibility of modifying the NLRP3-dependent inflammasome as a new and complementary therapeutic strategy to treat this severe and devastating kidney disease.

307. Combined and Sequential Liver-Kidney Transplantation in Children.
Grenda R, Kaliciński P.
Pediatr Nephrol. 2018 Dec;33(12):2227-2237.

ABSTRACT
Combined and sequential liver-kidney transplantation (CLKT and SLKT) is a definitive treatment in children with end-stage organ failure. There are two major indications: - terminal insufficiency of both organs, or - need for transplanting new liver as a source of lacking enzyme or specific regulator of the immune system in a patient with renal failure. A third (uncommon) option is secondary end-stage renal failure in liver transplant recipients. These three clinical settings use distinct qualification algorithms. The most common indications include primary hyperoxaluria type 1 (PH1) and autosomal recessive polycystic kidney disease (ARPKD), followed by liver diseases associated with occasional kidney failure. Availability of anti-C5a antibody (eculizumab) has limited the validity of CLKT in genetic atypical hemolytic uremic syndrome (aHUS). The liver coming from the same donor as renal graft (in CLKT) is immunologically protective for the kidney and this provides long-term rejection-free follow-up. No such protection is observed in SLKT, when both organs come from different donors, except uncommon cases of living donation of both organs. Overall long-term

outcome in CLKT in terms of graft survival is good and not different from isolated liver or kidney transplantation, however patient survival is inferior due to complexity of this procedure.

308. Bilateral Native Nephrectomy to Reduce Oxalate Stores in Children at the Time of Combined Liver-Kidney Transplantation for Primary Hyperoxaluria Type 1.
Lee E, Ramos-Gonzalez G, Rodig N et al.
Pediatr Nephrol. 2018 May;33(5):881-887.

ABSTRACT
Objective: Primary hyperoxaluria type-1 (PH-1) is a rare genetic disorder in which normal hepatic metabolism of glyoxylate is disrupted resulting in diffuse oxalate deposition and end-stage renal disease (ESRD). While most centers agree that combined liver-kidney transplant (CLKT) is the appropriate treatment for PH-1, perioperative strategies for minimizing recurrent oxalate-related injury to the transplanted kidney remain unclear. We present our management of children with PH-1 and ESRD on hemodialysis (HD) who underwent CLKT at our institution from 2005 to 2015.
Methods: On chart review, three patients (2 girls, 1 boy) met study criteria. Two patients received deceased-donor split-liver grafts, while one patient received a whole liver graft. All patients underwent bilateral native nephrectomy at transplant to minimize the total body oxalate load. Median preoperative serum oxalate was 72 µmol/L (range 17.8-100). All patients received HD postoperatively until predialysis serum oxalate levels fell <20 µmol/L. All patients, at a median of 7.5 years of follow-up (range 6.5-8.9), demonstrated stable liver and kidney function.
Conclusions: While CLKT remains the definitive treatment for PH-1, bilateral native nephrectomy at the time of transplant reduces postoperative oxalate stores and may mitigate damage to the renal allograft.

309. Recurrence of oxalate nephropathy after isolated kidney transplantation for primary hyperoxaluria type 2.
Del Bello A, Cointault O, Delas A et al.
Am J Transplant. 2018 Feb;18(2):525-526.

No abstract available

310. An Investigational RNAi Therapeutic Targeting Glycolate Oxidase Reduces Oxalate Production in Models of Primary Hyperoxaluria.
Liebow A, Li X, Racie T et al.
J Am Soc Nephrol. 2017 Feb;28(2):494-503.

ABSTRACT
Primary hyperoxaluria type 1 (PH1), an inherited rare disease of glyoxylate metabolism, arises from mutations in the enzyme alanine-glyoxylate aminotransferase. The resulting deficiency in this enzyme leads to abnormally high oxalate production resulting in calcium oxalate crystal formation and deposition in the kidney and many other tissues, with systemic oxalosis and ESRD being a

common outcome. Although a small subset of patients manages the disease with vitamin B6 treatments, the only effective treatment for most is a combined liver-kidney transplant, which requires life-long immune suppression and carries significant mortality risk. In this report, we discuss the development of ALN-GO1, an investigational RNA interference (RNAi) therapeutic targeting glycolate oxidase, to deplete the substrate for oxalate synthesis. Subcutaneous administration of ALN-GO1 resulted in potent, dose-dependent, and durable silencing of the mRNA encoding glycolate oxidase and increased serum glycolate concentrations in wild-type mice, rats, and nonhuman primates. ALN-GO1 also increased urinary glycolate concentrations in normal nonhuman primates and in a genetic mouse model of PH1. Notably, ALN-GO1 reduced urinary oxalate concentration up to 50% after a single dose in the genetic mouse model of PH1, and up to 98% after multiple doses in a rat model of hyperoxaluria. These data demonstrate the ability of ALN-GO1 to reduce oxalate production in preclinical models of PH1 across multiple species and provide a clear rationale for clinical trials with this compound.

311. The primary hyperoxalurias: A practical approach to diagnosis and treatment.
Hulton SA.
Int J Surg. 2016;36(Pt D):649-654.

ABSTRACT
Although the primary hyperoxalurias (PH) are rare disorders, they are of considerable clinical importance in relation to calcium oxalate urolithiasis and as a cause of renal failure worldwide. Three distinct disorders have been described at the molecular level. The investigation of any child or adult presenting with urinary tract stones or nephrocalcinosis, must exclude PH as an underlying cause. This paper provides a practical approach to the investigation and diagnosis of PH, indicating the importance of distinguishing between the PH types for the purposes of targeting appropriate therapy. Conservative management is explored and the various transplant options are discussed.

312. Combined Liver and Kidney Transplantation and Kidney After Liver Transplantation in Children: Indication, Postoperative Outcome, and Long-Term Results.
Büscher R, Büscher AK, Cetiner M et al.
Pediatr Transplant. 2015 Dec;19(8):858-65.

ABSTRACT
CLKT and sequential KALT are decided on a case-by-case basis in children for special indications such as ARPKD or PH1. We report on 21 children who underwent CLKT or KALT at our hospital between 1998 and 2013. Eleven children were diagnosed with PH1 and six with ARPKD. Other diagnosis were Joubert syndrome (n = 1), nephronophthisis (n = 1), CF (n = 1), and hepatocellular carcinoma (n = 1). Children (12 males, nine females) were aged 7.8 ± 6.2 yr (range, 10 months to 18 yr) at time of transplantation. Average wait time was 1.9 ± 0.9 yr (range, four months to 2.3 yr). Fifteen patients received dialysis prior to transplantation. In PH1 patients, four children received CLKT, five received KALT, and two infants have received only an LTx, whereas all six patients with ARPKD received CLKT. In patients with other indications, CLKT was performed in three cases and KALT in one girl. Cumulative 10-yr survival of all 21 patients was 78.4%. At the time of transfer into adult care, 13

patients retained stable liver and kidney function. Regardless the underlying diagnosis, CLKT and KALT can be performed in children with good surgical outcomes and long-term survival.

313. The merits of sequential transplantation for hyperoxaluria type I.
Filler G.
Pediatr Transplant. 2015 Feb;19(1):5-7.

No abstract available

314. Primary hyperoxalurias: diagnosis and treatment.
Ben-Shalom E, Frishberg Y.
Pediatr Nephrol. 2015 Oct;30(10):1781-91.

ABSTRACT
Primary hyperoxalurias (PH) comprise a group of three distinct metabolic diseases caused by derangement of glyoxylate metabolism in the liver. Recent years have seen advances in several aspects of PH research. This paper reviews current knowledge of the genetic and biochemical basis of PH, the specific epidemiology and clinical presentation of each type, and therapeutic approaches in different disease stages. Potential future specific therapies are discussed.

315. Long-term results of combined liver-kidney transplantation for primary hyperoxaluria type 1: the French experience.
Compagnon P, Metzler P, Samuel D et al.
Liver Transpl. 2014 Dec;20(12):1475-85.

ABSTRACT
Primary hyperoxaluria type 1 (PH1) is a hepatic metabolic defect leading to end-stage renal failure. The posttransplant recurrence of kidney disease can suggest a need for combined liver-kidney transplantation (LKT). However, the risk of LKT is theoretically far higher than the risk of kidney-alone transplantation (KAT). An unselected consecutive series of 54 patients with PH1 was analyzed according to the type of transplantation initially performed between May 1979 and June 2010 at 10 French centers. The duration of dialysis, extrarenal lesions, age, and follow-up were similar between the groups. Postoperative morbidity and mortality did not differ between the groups, and 10-year patient survival rates were similar for the LKT (n = 33) and KAT groups (n = 21; 78% versus 70%). Kidney graft survival at 10 years was better after LKT (87% versus 13%, P < .001) . Four patients (12.1%) lost their first kidney graft in the LKT group, whereas 19 (90%) did in the KAT group (P < .001). The recurrence of oxalosis occurred in 11 renal grafts (52%) in the KAT group but in none in the LKT group (P < .001). End-stage renal failure resulting from rejection was also higher in the KAT group (19% versus 9%, P < 0.0001). A second kidney transplant was performed for 15 patients (71%) in the KAT group versus 4 patients (12%) in the LKT group (P < 0.001). In conclusion, LKT for PH1 provides better kidney graft survival, less rejection, and similar long-term patient survival and is not

associated with an increased short-term mortality risk. LKT must be the first-line treatment for PH1 patients with end-stage renal disease.

316. Two-step transplantation for primary hyperoxaluria: a winning strategy to prevent progression of systemic oxalosis in early onset renal insufficiency cases.
Sasaki K, Sakamoto S, Uchida H et al.
Pediatr Transplant. 2015 Feb;19(1):E1-6.

ABSTRACT
Several transplant strategies for PH1 have been proposed, and LT is performed to correct the metabolic defects. The patients with PH1 often suffer from ESRD and require simultaneous LKT, which leads to a long wait due to the shortage of suitable organ donors. Five patients with PH1 underwent LDLT at our institute. Three of the five patients were under dialysis before LDLT, while the other two patients were categorized as CKD stage 3. An isolated LDLT was successfully performed in all but our first case, who had complicated postoperative courses and consequently died due to sepsis after retransplantation. The renal function of the patients with CKD stage 3 was preserved after LDLT. On the other hand, our second case with ESRD underwent successful LDKT six months after LDLT, and our infant case is waiting for the subsequent KT without any post-LDLT complications after the early establishment of PD. In conclusion, a two-step transplant strategy may be needed as a life-saving option for patients with PH1 and may be possible even in small infants with systemic oxalosis. While waiting for a subsequent KT, an early resumption of PD should be considered from the perspective of the long-term requirement of RRT.

317. Vitamin B6 in primary hyperoxaluria I: first prospective trial after 40 years of practice.
Hoyer-Kuhn H, Kohbrok S, Volland R et al.
Clin J Am Soc Nephrol. 2014 Mar;9(3):468-77.

ABSTRACT
Background and objectives: Primary hyperoxaluria type I (PH I) is caused by deficiency of the liver-specific enzyme alanine-glyoxylate:aminotransferase (AGT). Many mutations are known to perturb AGT protein folding. Vitamin B6 (B6) is the only specific drug available for treatment. Although B6 has been used for >40 years, controlled data on B6 efficacy are lacking. Therefore, this study investigated the absolute and relative change of urinary oxalate (Uox) excretion under increasing dosages of B6, the first prospective trial to do so.
Design, setting, participants, & measurements: B6 response was studied in 12 patients (7 male patients) with genetically confirmed PH I (3 Gly170Arg homozygous, 5 compound Gly170Arg and/or Phe152Ile heterozygous, and 4 negative for Gly170Arg and/or Phe152Ile mutations) and noncompromised renal function. Efficacy was defined as a 30% relative reduction in Uox excretion. B6 was administered orally starting at 5 mg/kg body weight per day and given in increments of 5 mg/kg every 6 weeks, up to a final dosage of 20 mg/kg per day at week 24. Uox and serum B6 levels were measured every 6 weeks.

Results: Mean relative Uox reduction was 25.5%. Uox declined from 2.09±0.55 (mean±SD) at baseline to 1.52±0.60 mmol/1.73 m(2) per day (P=0.01) at week 24. Serum B6 levels increased from 22.5±8.7 to 1217±776 ng/ml (P<0.001). Six patients showed a ≥30% relative reduction of Uox at week 24.
Conclusion: This first prospective trial confirmed B6 efficacy in 50% of patients (three of three homozygous, one of five heterozygous, and two of four patients negative for the Gly170Arg and/or Phe152Ile mutations). Interestingly, no complete biochemical remission was observed, even in the homozygous Gly170Arg study participants. Future trials are necessary to learn more about genotype-related B6 response and B6 metabolism.

318. Primary hyperoxaluria.
Rumsby G, Cochat P.
N Engl J Med. 2013 Nov 28;369(22):2163.

No abstract available

319. Primary Hyperoxaluria Type 1: Indications for Screening and Guidance for Diagnosis and Treatment
Cochat P, Hulton S-A, Acquaviva C et al.
Nephrol Dial Transplant. 2012 May;27(5):1729-36.

ABSTRACT
Primary hyperoxaluria Type 1 is a rare autosomal recessive inborn error of glyoxylate metabolism, caused by a deficiency of the liver-specific enzyme alanine: glyoxylate aminotransferase. The disorder results in overproduction and excessive urinary excretion of oxalate, causing recurrent urolithiasis and nephrocalcinosis. As glomerular filtration rate declines due to progressive renal involvement, oxalate accumulates leading to systemic oxalosis. The diagnosis is based on clinical and sonographic findings, urine oxalate assessment, enzymology and/or DNA analysis. Early initiation of conservative treatment (high fluid intake, pyridoxine, inhibitors of calcium oxalate crystallization) aims at maintaining renal function. In chronic kidney disease Stages 4 and 5, the best outcomes to date were achieved with combined liver-kidney transplantation.

320. Characteristics and Outcomes of Children With Primary Oxalosis Requiring Renal Replacement Therapy
Harambat J, van Stralen KJ, Espinosa L et al.
Clin J Am Soc Nephrol. 2012 Mar;7(3):458-65.

ABSTRACT
Background and objectives: Primary hyperoxaluria (PH) as a cause of ESRD in children is believed to have poor outcomes. Data on management and outcomes of these children remain scarce.

Design, setting, participants, & measurements: This study included patients aged <19 years who started renal replacement therapy (RRT) between 1979 and 2009 from 31 countries providing data to a large European registry.
Results: Of 9247 incident patients receiving RRT, 100 patients had PH. PH children were significantly younger than non-PH children at the start of RRT. The median age at RRT of PH children decreased from 9.8 years in 1979-1989 to 1.5 years in 2000-2009. Survival was 86%, 79%, and 76% among PH patients at 1, 3, and 5 years after the start of RRT, compared with 97%, 94%, and 92% in non-PH patients, resulting in a three-fold increased risk of death over non-PH patients. PH and non-PH patient survival improved over time. Sixty-eight PH children received a first kidney (n=13) or liver-kidney transplantation (n=55). Although the comparison was hampered by the lower number of kidney transplantations primarily derived from the earlier era of RRT, kidney graft survival in PH patients was 82%, 79%, and 76% at 1, 3, and 5 years for liver-kidney transplantation and 46%, 28%, and 14% at 1, 3, and 5 years for kidney transplantation alone, compared with 95%, 90%, and 85% in non-PH patients.
Conclusions: The outcomes of PH children with ESRD are still poorer than in non-PH children but have substantially improved over time.

321. Primary Hyperoxaluria Type 1: Strategy for Organ Transplantation
Cochat P, Fargue S, Harambat J.
Curr Opin Organ Transplant. 2010 Oct;15(5):590-3.

ABSTRACT
Purpose of review: Primary hyperoxaluria type 1, the most common form of primary hyperoxaluria, is an autosomal recessive disorder caused by a deficiency of the liver-specific enzyme alanine: glyoxylate aminotransferase. This results in increased synthesis and subsequent urinary excretion of the metabolic end-product oxalate and the deposition of insoluble calcium oxalate in the kidney and urinary tract. As glomerular filtration rate decreases due to progressive renal involvement, oxalate accumulates and results in systemic oxalosis.
Recent findings: Diagnosis is still often delayed. It is mainly established on the basis of clinical and sonographic findings, urinary oxalate ± glycolate assessment, and DNA analysis.
Summary: Following specific conservative measures, the ultimate management is based on organ transplantation. Correction of the enzyme defect by liver transplantation should be planned before systemic oxalosis develops to optimize outcomes and may be either simultaneous (immunological benefit) or sequential (biochemical benefit) liver-kidney transplantation depending on disease staging, facilities, and access to deceased or living donors. Allograft and patient survival currently approaches that of transplant patients with kidney transplantation alone and with other diseases requiring combined liver-kidney transplantation. In addition, this strategy has also provided significant improvement in both quality of life and statural growth.

322. Liver transplantation in oxalosis prior to advanced chronic kidney disease.
Scheinman JI.
Pediatr Nephrol. 2010 Nov;25(11):2217-22.

ABSTRACT
While curative of the disease, combined kidney and liver transplantation (K/LTx) for primary hyperoxaluria type 1 (PH1) continues to carry with it a risk for patient death of 15-25%, which over time may not differ from that of kidney transplantation alone (KTx). In this editorial, survival data are reviewed as well as the limited data available for kidney graft function, which may favor K/LTx in the short term but is more uncertain in the longer term. The window of opportunity that favors preemptive K/LTx is relatively narrow and is likely even narrower for preemptive isolated LTx. Capability and experience in the medical management of such patients, and the opportunities available, as well as likely patient compliance, so far without supporting data, may be the most important determination of the best strategy for management.

323. Preemptive liver transplantation for primary hyperoxaluria (PH-I) arrests long-term renal function deterioration.
Perera MT, Sharif K, Lloyd C et al.
Nephrol Dial Transplant. 2011 Jan;26(1):354-9.

ABSTRACT
Background: Primary hyperoxaluria-I (PH-I) is a serious metabolic disease resulting in end-stage renal disease. Pre-emptive liver transplantation (PLT) for PH-I is an option for children with early diagnosis. There is still little information on its effect on long-term renal function in this situation.
Methods: Long-term assessment of renal function was conducted using Schwartz's formula (estimated glomerular filtration rate-eGFR) in four children (Group A) undergoing PLT between 2002 and 2008, and a comparison was done with eight gender- and sex-matched controls (Group B) having liver transplantation for other indications.
Results: All patients received a liver graft from a deceased donor. Median follow-up for the two groups was 64 and 94 months, respectively. One child in Group A underwent re-transplantation due to hepatic artery thrombosis, while acute rejection was seen in one. A significant difference was seen in eGFR at transplant (81 vs 148 mL/min/1.73 m(2)) with greater functional impairment seen in the study population. In Group A, renal function reduced by 21 and 11% compared with 37 and 35% in Group B at 12 and 24 months, respectively. At 2 years post-transplantation, there was no significant difference in eGFR between the two groups (72 vs 100 mL/min/1.73 m(2), respectively; P = 0.06).
Conclusions: Renal function remains relatively stable following pre-emptive LTx for PH-I. With early diagnosis of PH-I, isolated liver transplantation may prevent progression to end-stage renal disease and the need for renal transplantation.

324. Transplantation outcomes in primary hyperoxaluria.
Bergstralh EJ, Monico CG, Lieske JC et al.
Am J Transplant. 2010;10(11):2493-2501.

ABSTRACT
Optimal transplantation strategies are uncertain in primary hyperoxaluria (PH) due to potential for recurrent oxalosis. Outcomes of different transplantation approaches were compared using life-

table methods to determine kidney graft survival among 203 patients in the International Primary Hyperoxaluria Registry. From 1976-2009, 84 kidney alone (K) and combined kidney and liver (K + L) transplants were performed in 58 patients. Among 58 first kidney transplants (32 K, 26 K + L), 1-, 3- and 5-year kidney graft survival was 82%, 68% and 49%. Renal graft loss occurred in 26 first transplants due to oxalosis in ten, chronic allograft nephropathy in six, rejection in five and other causes in five. Delay in PH diagnosis until after transplant favored early graft loss (p = 0.07). K + L had better kidney graft outcomes than K with death-censored graft survival 95% versus 56% at 3 years (p = 0.011). Among 29 year 2000-09 first transplants (24 K + L), 84% were functioning at 3 years compared to 55% of earlier transplants (p = 0.05). At 6.8 years after transplantation, 46 of 58 patients are living (43 with functioning grafts). Outcomes of transplantation in PH have improved over time, with recent K + L transplantation highly successful. Recurrent oxalosis accounted for a minority of kidney graft losses.

325. Effect of conservative treatment on the renal outcome of children with primary hyperoxaluria type 1.

Fargue S, Harambat J, Gagnadoux MF et al.

Kidney Int. 2009 Oct;76(7):767-73.

ABSTRACT

Primary hyperoxaluria type 1 results from alanine: glyoxylate aminotransferase deficiency. Due to genotype/phenotype heterogeneity in this autosomal recessive disorder, the renal outcome is difficult to predict in these patients and the long-term impact of conservative management in children is unknown. We report here a multicenter retrospective study on the renal outcome in 27 affected children whose biological diagnosis was based on either decreased enzyme activity or identification of mutations in the patient or his siblings. The median age at first symptoms was 2.4 years while that at initiation of conservative treatment was 4.1 years; 6 children were diagnosed upon family screening. The median follow-up was 8.7 years. At diagnosis, 15 patients had an estimated glomerular filtration rate (eGFR) below 90, and 7 children already had stage 2-3 chronic kidney disease. The median baseline eGFR was 74, which rose to 114 with management in the 22 patients who did not require renal replacement therapy. Overall, 20 patients had a stable eGFR, however, 7 exhibited a decline in eGFR of over 20 during the study period. In a Cox regression model, the only variable significantly associated with deterioration of renal function was therapeutic delay with a relative risk of 1.7 per year. Our study strongly suggests that early and aggressive conservative management may preserve renal function of compliant children with this disorder, thereby avoiding dialysis and postponing transplantation.

326. Clearance and removal of oxalate in children on intensified dialysis for primary hyperoxaluria type 1.

Illies F, Bonzel KE, Wingen AM et al.

Kidney Int. 2006;70(9):1642-1648.

ABSTRACT

Patients with end-stage renal failure owing to primary hyperoxaluria type 1 (PH1) receive dialysis while waiting for transplantation. So far, dialysis has not been shown to overcome the problem of ongoing oxalate production and deposition at extrarenal sites. We report on six children with PH1 who had to be dialyzed for a median period of 2.5 years while awaiting liver transplantation. Aiming at preventing oxalate tissue accretion, oxalate mass transfer was studied and dialysis intensified accordingly. Mean plasma oxalate concentration was between 51 and 137 micromol/l. In three of the six patients with a urinary output between 630 and 3140 ml, urinary removal of oxalate was between 5.6 and 12.4 mmol/week/1.73 m^2. Hemodialysis (HD) in five of the six patients demonstrated a mean oxalate dialysance between 158 and 444 l/week/1.73 m2. Peritoneal dialysis (PD) in two of the six patients showed mean oxalate clearances of 66 and 103 l/week/1.73 m^2. One patient received HD and PD. By adding all modes of elimination, a mean total oxalate mass between 10.1 and 24.1 mmol/week/1.73 m^2 was removed. Dialysis is still necessary as a temporary therapy for a number of patients with PH1. Dialysis should be instituted pre-emptively and maximally exploited by intensified HD/PD treatment protocols, without, however, cutting back urinary output.

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