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6.1. Induction therapy


- Retrospective single center analysis of basiliximab used in lung transplant recipients with acute kidney injury. No difference was found in rates of acute rejection or CLAD in those patients that received basiliximab vs those who did not, however more patients in the basiliximab group died at 1 year.

• Retrospective single center comparison of respiratory viral infections in pediatric lung transplant recipients receiving antithymocyte globulin or basiliximab induction therapy. There was no difference in infection rate or time to first infection between the groups.


• Retrospective single center analysis of all patients who received alemtuzumab as induction therapy. De novo DSAs developed in 17.7%, AMR diagnosed in 3.8%, and 5-year survival was worse in those who developed AMR.


• Retrospective single center analysis including 446 lung transplant recipients, 52% received alemtuzumab, 11% received antithymocyte globulin, and 37% received no induction therapy. The alemtuzumab group had the lowest rate of chronic kidney insufficiency and infection in the first year. Improved survival and low rates of ACR, lymphocytic bronchiolitis, and CLAD were found in the group receiving any induction therapy.


• Systematic review and meta-analysis of alemtuzumab in heart or lung transplant recipients. Alemtuzumab was associated with less acute cellular rejection compared to antithymocyte globulin and lower infection and acute rejection rates compared to basiliximab.


• Retrospective UNOS Registry study in 6117 lung transplant recipients demonstrating longer median survival for alemtuzumab and basiliximab versus no induction. Recipients of alemtuzumab had a lower incidence of BOS at 5 years.


• Retrospective comparison showed that alemtuzumab was associated with superior outcomes with biopsy score and lower incidence of grade 2 or higher rejection at 6 months but no difference in overall graft or patient survival between the 2 groups.

• Retrospective analysis of induction strategy in lung transplant recipients with CF at a single center. ATG induction was associated with a survival benefit at 1-3 and 5-years, lower rates of acute rejection, and no increased rate of infection versus no induction.


• Cochrane review of T-cell antibody induction (ATG, ALG, IL2RA, alemtuzumab, and OKT3) in lung transplant showed no clear benefit or harm of antibody induction compared to no induction or when comparing different types of antibody induction.


• Single-center retrospective comparison showing that alemtuzumab was associated with greater 5-year freedom from ACR, lymphocytic bronchiolitis, OB, and BOS.


• Single-center prospective study showing alemtuzumab induction with reduced dose maintenance IS was similar to no induction/standard dose IS in terms of ACR, death, and infection at 6 and 12 months.


• Single-center comparison of basiliximab and ATG showing no difference in ACR or infections in 37 lung transplant recipients.


• Prospective, single-center comparison of RATG and no induction showing no difference in graft survival, overall rejection, and infection, though there was a lower rate of early rejection with RATG.


• ISHLT registry study of 3970 adult lung transplant recipients suggesting that IL2RA and ATG are each associated with a survival benefit following lung transplant. Those treated with IL2RA had better graft survival than those treated with ATG and those who did not receive induction.

- Single-center retrospective review showing daclizumab was associated with significantly less acute rejection and bronchiolitis obliterans than those receiving ATG with a trend towards improved survival, though confounded by the use of MMF.

- Retrospective comparison showed that ATG associated with lower rate of acute rejection and BOS compared with basiliximab without increasing the risk for CMV.

- Prospective, randomized, single-center comparison of RATG (1.5 mg/kg/dose x 3 doses) versus no induction therapy + CSA/AZA/Pred; induction was associated with a lower rate of biopsy-proven grade II or greater rejection and a nonsignificant decrease in BOS with similar infection/malignancy occurrences.

6.2. Maintenance therapy

- Summary of currently available immunosuppression strategies including alternative routes of administration (intravenous, sublingual, inhaled) and use of generic immunosuppressants.

6.2.1 Calcineurin inhibitors

- Retrospective review of 494 lung transplant recipients within a single center to evaluate effect of clinical and pharmacogenetic predictors of tacrolimus-induced AKI. Overall, 60% of patients developed AKI between post-operative days 4-14. Trough levels greater than 12 ng/mL were most predictive of AKI development, and risk of AKI was predicted to increase 54% for each 5 ng/mL increase in average concentrations. Using concentration:dose ratios (CDR), the effect of various genotypes and clinical factors were evaluated. Greatest positive percent change in CDR was observed in patients with voriconazole exposure (+79.7, 95% CI 65.1 to 95.5) whereas greatest negative percent change in CDR was observed in CYP3A5 extensive metabolizers (-60.7, 95% CI -72.8 to -43.4).

- Single center, retrospective cohort study including 321 lung or heart-lung transplant recipients. Single nucleotide polymorphisms (SNPs) for the ABCB1, CYP3A4, and CYP45 genes were categorized for all patients. Linear models adjusted for subject characteristics.
CYP3A intermediate and extensive metabolizers spent less time in goal tacrolimus range compared to poor metabolizers. Patients with high ABCB1 function (carriers of ABCB1 CGC-CGC diplotype) has three times greater odds of developing KDIGO stage II or greater AKI as compared to TTT-TTT diplotype (P=.01). No differences in time to CLAD or death among ABCB1 genotypes or CYP3A genotypes.

- A single-center, observational, cross-sectional study of 292 lung transplant recipients looking at the effects of tacrolimus time-in-therapeutic range (TTR). Increasing TTR by 10% was associated with a significantly lower likelihood of high-burden ACR at 1 year (P < .001) and with lower rates of CLAD (P < .001) and mortality (P < .001) at 1 year.

- Prospective, randomized, multicenter, international, open-label investigation of tacrolimus (n = 124) compared to cyclosporine (n = 125) in combination with mycophenolate and prednisone. The primary endpoint of cumulative BOS incidence at three years was significantly lower in the tacrolimus group (P = 0.037). No significant difference in acute rejection or patient survival at one and three years. Incidences of infection were also similar, while development of renal dysfunction was more common in the tacrolimus group (P = 0.09).

- Prospective, randomized study comparing tacrolimus (n = 66) and cyclosporine (n = 67) in combination with azathioprine and prednisone. Patients receiving tacrolimus experienced fewer acute rejection episodes per 100 patient days (P = 0.07) as well as significantly less BOS. The total incidence of infection was similar. However, bacterial pneumonia was more common the cyclosporine group and fungal infections were more common in the tacrolimus group. No differences in one and two-year survival were observed.

- Meta-analysis of 297 patients from randomized controlled trials comparing tacrolimus to cyclosporine. Mortality at 1 year or more was comparable between the treatment groups. Tacrolimus-treated patients experience fewer incidences of acute rejection (P=0.04), however they also experienced a higher rate of new-onset diabetes (P=0.003).

First of a two-part review, detailing the pharmacokinetics and therapeutic drug monitoring for calcineurin inhibitors in thoracic transplantation.


Retrospective review of 120 lung transplant recipients maintained on either cyclosporine and mycophenolate (n = 37) or tacrolimus and azathioprine (n = 83) in combination with prednisone and IL-2 receptor antagonist induction. Patients in the tacrolimus/azathioprine group had significantly better pulmonary function as measured by FEV1 and FVC at 12 months. No differences in acute rejection, BOS or survival were observed.


Prospective, randomized study comparing tacrolimus (n = 44) and cyclosporine (n = 46) in combination with azathioprine and prednisone. The primary endpoint (composite of cumulative acute rejection, lymphocytic bronchitis or BOS) occurred more in the cyclosporine group (P = 0.002). Cumulative acute rejection or lymphocytic bronchitis was also significantly less in the tacrolimus group and BOS stages 0-p and 1 trended towards higher incidence in the cyclosporine group. The incidence of CMV and community-acquired respiratory viruses was greater in the cyclosporine group; bacterial, fungal and total infections were similar.


Prospective, randomized, two-center investigation comparing tacrolimus (n = 37) and cyclosporine (n = 37) in combination with mycophenolate, prednisone and ATG induction. No significant differences in number of treated rejection episodes, freedom from acute rejection and BOS, or survival at 6 and 12 months were observed.


Prospective, randomized comparison of tacrolimus (n = 26) and cyclosporine (n = 24) in combination with mycophenolate, prednisone and rATG induction. The tacrolimus group had significantly fewer treated rejection episodes and rejection-free survival at 6 and 12 months was numerically greater for the tacrolimus group. Six and 12-month survival and incidences of infection were similar. Serum creatinine did not differ significantly between the groups. Cyclosporine-treated patients experienced more hypertension and hyperlipidemia requiring treatment, whereas as NODAT was only observed in the tacrolimus group.
### 6.2.2 Cell cycle inhibitors

- Retrospective cohort study that analyzed effect of known single nucleotide polymorphisms on outcomes such as survival, ≥ A2 or B2 acute rejections, and CLAD. SLCO1B3 SNPs rs4149117 and rs7311358 were associated with decreased 1 and 3-year survival, rejection, and shorter survival following CLAD diagnosis.

- Cohort study of mycophenolic acid (MPA) AUC0-12 between groups stratified based on outcomes including no events, infection, and CLAD. MPA AUC0-12 was significantly higher in the infection group and significantly lower in the CLAD group. Thresholds for these outcomes were established at 22 to 40 µg·h/mL for avoidance of infection and CLAD, respectively

- A review of data of 544 patients from the Dutch nationwide registry of histopathology (PALGA) looking at the incidence of squamous cell carcinoma (SCC) and associated risk factors. Sequential use of azathioprine and mycophenolate mofetil was associated with a lower risk of SCC compared with azathioprine use only.

- Prospectively collected data from 176 consecutive lung transplant recipients was compared to evaluate the use azathioprine and mycophenolate in combination with cyclosporine and prednisone. Patients in the mycophenolate group experienced fewer acute rejection episodes as well as decreased severity of rejection compared to azathioprine. Despite similar incidences of BOS, the mycophenolate group had significantly less graft loss due to BOS.

- Second component of comprehensive review, including pharmacokinetics and therapeutic drug monitoring for mycophenolate and mTOR inhibitors.

- Prospective, randomized, international, multicenter, open-label study comparing azathioprine and mycophenolate in combination with cyclosporine, prednisone and ATG
induction. No difference in the incidence of acute rejection at one or three years or time to acute rejection was observed. Additionally, no differences in incidence, severity, time to development of BOS or survival were detected at three years.

### 6.2.3 Mammalian target of rapamycin inhibitors


- Prospective, randomized, open label 12-month multicenter trial including lung transplant patients 3-8 months following transplant aimed at evaluating impact of low-CNI exposure regimens in patients with baseline renal dysfunction. Patients were stratified based on eGFR before randomization. The primary endpoint was eGFR after 12 months. Patients receiving quadruple low CNI regimens had superior renal function compared to the standard triple therapy group (64.5 ml/min vs 54.6 ml/min, p <0.001). BPAR, CLAD and death were similar between two groups.


- Retrospective cohort study of 9,019 lung transplant recipients who received either sirolimus plus tacrolimus or mycophenolate mofetil. The primary outcome was survival. A survival benefit was seen in patients receiving sirolimus plus tacrolimus without induction therapy when compared to mycophenolate mofetil plus tacrolimus with induction therapy (median survival 10.7 years, HR 0.48, 95% CI 0.31-0.76).


- A retrospective, single arm, exploratory study of groups of patients evaluating safety of using sirolimus early post-operatively. Early sirolimus administration was defined as administration within first 30 days post-transplantation. Thirteen patients received early sirolimus based immunosuppression along with cyclosporine and prednisone, as well as induction therapy. Thirty-day mortality was 0% and no anastomotic dehiscence was observed, even with administration as early as POD15. Four patients experienced severe acute cellular rejection within the first year following transplant. One patient developed bronchiolitis obliterans syndrome.


- Randomized control trial in 190 lung transplant recipients assigned to either cyclosporine, prednisone, mycophenolate or cyclosporine, prednisone, everolimus 28 days after transplant. BOS-free survival was similar via the intention-to-treat analysis at two years. The per-protocol analysis demonstrated less incidence of BOS in the everolimus arm with less CMV infection, ACR, and lower respiratory infections, despite a more pronounced dropout rate.

- A multicenter, prospective, international, randomized open-label study of de novo enteric coated mycophenolate sodium (MPS) versus delayed-onset everolimus (RAD) in combination with cyclosporine and corticosteroids. Three-year ITT analysis found no significant difference between treatment arms in freedom from BOS but was underpowered to accept the null hypothesis that RAD and MPS have equivalent efficacy in preventing BOS, or death after lung transplantation.


- Twenty-four lung transplant recipients who were converted to an immunosuppression regimen consisting of tacrolimus, sirolimus and prednisone were compared to those on a regimen of tacrolimus, mycophenolate or azathioprine and prednisone. The sirolimus group was found to have a lower incidence of BOS and viral infections and improved survival.


- Retrospective review of 41 lung transplant recipients who were treated with everolimus and lower dose calcineurin inhibitors. Renal function preservation was greater when everolimus was initiated before CrCl deterioration or proteinuria development.


- Consensus document generated by experts representing Spanish lung transplant centers that summarizes everolimus pharmacokinetics, therapeutic drug monitoring and potential indications for use in lung transplantation.


- Report of a prospective, multicenter, randomized, controlled trial comparing azathioprine to sirolimus initiated at least three months post-transplant in combination with tacrolimus, prednisone and IL-2 receptor antagonist induction (n = 181). No differences in acute rejection, development of bronchiolitis obliterans syndrome (BOS) or survival at 12 and 36 months were observed. Significantly more patients in the azathioprine group experienced CMV infection, while significantly more in the sirolimus groups experienced significant adverse events and early discontinuation.

Prospective, randomized, international, multicenter, double-blind investigation comparing azathioprine (n = 112) to everolimus (n = 101) in combination with cyclosporine and prednisone. Everolimus was uniformly dosed 1.5 mg twice a day and not adjusted based on trough concentrations (median 6.6 ng/mL, 10th to 90th percentile: 2.8-11.8 ng/mL). The everolimus group experienced significantly less efficacy failure (composite endpoint including decline in FEV1 > 15%, graft loss, death or loss to follow up) as well as decline in FEV1 associated with BOS and acute rejection at 12 months. Elevated serum creatinine and discontinuation due to adverse events were more common in the everolimus group.


- Pilot study reporting bronchial anastomotic complications in three of four lung transplant recipients maintained on sirolimus, tacrolimus and prednisone immediately posttransplant. The average sirolimus trough concentration was 6.2 ± 1.2 ng/mL. Airway dehiscence developed in two patients, resulting in fatality for one patient. Although within the target range (4-10 ng/mL), the heart-lung transplant recipient had the lowest sirolimus trough concentrations and was the only subject that did not experience wound healing complications.


- Open-label, pilot investigation of 15 consecutive lung transplants receiving sirolimus in combination with tacrolimus and prednisone immediately post-transplant. Sirolimus trough concentrations were highly variable in the first week post-transplant, but, average levels were within or below the target range of 10-15 ng/mL and did not differ among those with and without dehiscence. Four patients experienced airway anastomotic dehiscence; three did not survive. When compared to historical controls, the sirolimus group had significantly worse survival.

6.2.4 Belatacept


- Case report of fatal acute respiratory distress syndrome in a single lung transplant recipient at 27 days after converting to belatacept from tacrolimus. The patient was stable prior to the conversion with no history of rejection or antibodies. Due to lack of involvement of the native lung, this manifestation was presumed to be due to rejection.


- Single center, retrospective case series including 11 adult lung transplant recipients before and after conversion to belatacept from a calcineurin inhibitor (CNI). Mean follow up was 246 days. There was no difference in acute cellular rejection, infections, or mean arterial
pressure. Estimated glomerular filtration rate was significantly higher after converting to belatacept. Progression of chronic lung allograft dysfunction occurred in 2 patients.


- Retrospective review of 8 patients with acute renal failure or refractory renal insufficiency who were initiated on belatacept therapy to reduce calcineurin inhibitor exposure. Glomerular filtration rate remained stable in 2 patients and increased in 5 and there was 1 patient death due to multisystem organ failure.

6.3 Desensitization therapy


- Two patient case series of successful desensitization using post-centrifugal plasma filtration in two heart and lung transplant recipients with multiple DSAs. This is the first report of using PCPF in cardiothoracic transplant recipients. Patients described in this series also received rituximab and/or bortezomib.


- This study evaluated a desensitization protocol (perioperative plasma exchange with or without the use of antithymocyte globulin or immune globulin) in sensitized lung transplant recipients in comparison to standard immunosuppression in unsensitized patients. Thirty-day survival and one-year graft survival were similar. Similar outcomes were seen between DSA-positive, PRA-positive/DSA-negative, and unsensitized patients.


- This retrospective study analyzed the efficacy of using a multi-modal desensitization therapy prior to lung transplantation in 18 candidates with cPRA ≥ 80%. Desensitization regimen included plasmapheresis, methylprednisolone, bortezomib, rituximab, followed by intravenous immunoglobulin. In 9 candidates who received a transplant, post-transplant survival was comparable to recipients with pretransplant HLA antibodies who did not undergo the desensitization protocol.


- Case report on two patients describing the impact of ECMO on PRA levels and the need of monitoring for anti-HLA sensitization while on ECMO

- An overview of acute lung allograft rejection, including clinical presentation, diagnosis, histopathologic features, and mechanisms of cellular and humoral rejection. It describes the clinical relevance for presence of HLA antibody and its association with humoral rejection.


- Retrospective analysis evaluating clinical impact of desensitization therapy with immune globulin and extracorporeal immunoadsorption in sensitized lung transplant recipients


- Retrospective review of clinical outcomes of a single center in sensitized (n= 18) and non-sensitized lung transplant recipients. No difference in acute rejection was observed, however there was an increased incidence of BOS in untreated sensitized recipients vs. unsensitized.

6.4 Management of rejection


- Review article on diagnosis, staging, clinical presentation, and treatment strategies for acute rejection, AMR, and CLAD

6.4.1 Acute cellular rejection


- Retrospective single center cohort study that studied the efficacy and safety of pulse steroids in the absence of ACR as a treatment for a drop in FEV1 of ≥ 10%. A minority of patients (mostly those with BAL eosinophilia) responded to pulse steroid regimen of 500 mg IV methylprednisolone on day 1 followed by two doses of 100 mg IV methylprednisolone over the next two days. Severe complications associated with steroids occurred in 12% of patients.


- Retrospective single center cohort study including lung transplant recipients experiencing ACR. A1 rejection was treated with pulse prednisone or methylprednisolone 1 g depending on clinical presentation, A2 rejection was treated with methylprednisolone 1 g for 3 days followed by prednisone taper. 78.57% had resolution demonstrated by biopsy and 92.52% had symptomatic improvement, though no difference was noted in FEV1.
- Single center cohort study of 962 untreated spirometrically stable A1 rejection among consecutive lung transplant recipients. Compared to no ACR, there was no significant difference in risk of CLAD or death in the untreated A1 rejection group.

- Basiliximab administration prior to implantation of lung compared to administration immediately post-transplant was associated with a lower incidence of acute rejection, yet no differences in survival or bronchiolitis obliterans syndrome.

- Single-center study of 44 lung transplant recipients that investigated the impact of rabbit antithymocyte induction on the incidence of acute allograft rejection after lung transplant. There was a significant reduction in biopsy proven rejection with RATG induction vs. no induction with no observed difference in infections and malignancies.

- An analysis of outcomes of 16 untreated lung transplant patients with asymptomatic mild acute cellular rejection. Half of the patients with worsening function without intervention developed BOS relative to those in the spontaneously regressing group.

6.4.2 Antibody mediated rejection

- Case report of two patients treated with C1 esterase inhibitor as part of salvage therapy for probable or possible AMR with complement involvement. Initial therapy comprised plasma exchange, IVIG, rituximab, and pulsed steroids. Both patients were treated with 20 units/kg daily for three days followed by 20 units/kg twice a week for 6 months, and both received concurrent monthly IVIG while on C1 esterase inhibitor maintenance. One patient attained lasting improvement in respiratory function and the other achieved clinical stability for re-transplant.

- Retrospective review of successive immune globulin infusions for treatment of early donor specific antibodies (eDSA) in pediatric lung transplant patients, defined by authors as possible subclinical AMR. Patients received IVIG or IgGAM (enriched IgG, IgM, and IgA).
Over a 6 year period, 27 patients received immune globulin for eDSA and were compared against 38 patients with no eDSA. Notably, 14 (52%) of patients received plasma exchange and 25 (93%) received a single dose of rituximab along with immune globulin. Over median follow-up of 28 months, 25 (93%) had clearance of eDSA with 3 (12%) having recurrence of same DSA. Outcomes regarding graft survival, patient survival, biopsy proven rejection, and CLAD development were not statistically different.

- Review highlighting recently developed AMR diagnostic criteria in lung transplantation, potential mechanisms that mediate the development of AMR, and current and recent treatment strategies

- Single center, retrospective study of 8 lung transplant recipients who received combination therapy including rituximab. Two were classified as having clinically definite antibody medicated rejection. Three patients demonstrated decrease in intensity of DSA.

- Description of 14 lung transplant recipients undergoing AMR treatment with carfilzomib, plasma exchange, and IVIG. Median DSA C1q MFI dropped significantly after therapy and response was sustained at two weeks after therapy. Responders to carfilzomib had less chronic lung allograft dysfunction (CLAD) versus nonresponders.

- Consensus paper on the diagnostic criteria and definition of antibody-mediated rejection in lung transplant recipients.

- An evaluation of an institution-specific protocol for treating suspected antibody mediated rejection in sixteen lung transplant recipients with documented donor specific antibody (DSA) present and allograft dysfunction. A minority of patients had preserved lung function and cleared their DSAs at 6 months following treatment with protocol.

- A review of challenges with diagnosing antibody mediated rejection (AMR) and describes therapeutic options for treating AMR in lung transplant recipients.

- Case report describing a patient’s successful use of bortezomib therapy for recurrent AMR after lung transplant.


- A single center retrospective study that reviewed all lung transplant patients and identified those who had at least one marker of antibody mediated rejection to assess treatment therapies and outcomes.


- A single-center, retrospective study that identified patients with acute AMR and assessed their treatment regimens and other clinicopathological details to correlate clinical outcomes, including development of chronic lung allograft dysfunction, and survival.


- Case report of the first case with the successful use of bortezomib for antibody mediated rejection in a lung transplant recipient.


- Case report of a patient with successfully treated acute antibody-mediated rejection after lung transplantation with pulse-dose steroids, immune globulin, plasma exchange and rituximab.

### 6.4.3 Chronic lung allograft dysfunction


- Single center retrospective study that included double lung transplant recipients who received azithromycin prophylaxis and those who did not. Patients who received azithromycin had improved survival and baseline function compared to those who did not receive azithromycin. Rates of CLAD were not different.

- Single center retrospective study including lung transplant recipients in two groups: historical targeted antifungal prophylaxis and universal antifungal prophylaxis. There was no difference in freedom from CLAD at 3 years between universal vs targeted prophylaxis, nor based on antifungal agent selected.


- Investigator-initiated, randomized, open-label, multicenter trial in lung transplant recipients to assess the incidence of CLAD with once-daily tacrolimus-based vs cyclosporine-based maintenance immunosuppression. Enrollment is ongoing with expected follow up to complete 2022.


- Retrospective single center case series of eight consecutive lung transplant recipients treated with single subcutaneous alemtuzumab for CLAD. Rate of FEV1 decline significantly improved 3 months post vs 3 months prior to alemtuzumab. Mild to moderate infection occurred in four patients, severe infection occurred in one patient. Two patients died due to progressive CLAD.


- Case report of lung transplant recipient with bronchiolitis obliterans syndrome evolved to restrictive allograft syndrome treated with nintedanib 150 mg twice daily. Therapy was discontinued after four months due to gastrointestinal intolerance without clinical improvement.


- Single center retrospective case series of three lung transplant recipients with telomeropathies treated for CLAD with alemtuzumab. Alemtuzumab was safe in this patient population, however was associated with an increased incidence of neutropenia, thrombocytopenia, and anemia requiring transfusion compared to lung transplant recipients without telomeropathies.


- Retrospective single center case series including 12 lung transplant recipients treated for CLAD with extracorporeal photopheresis (ECP). 67% of patients responded to ECP therapy with a significantly improved mean decline in FEV1 post-treatment.

Consensus report with standardized definition and understanding of RAS.


Consensus report to standardize and refine nomenclature of CLAD and clinical phenotypes.


Retrospective single center study of lung transplant recipients with progressive CLAD, despite 3 months of azithromycin use, treated with montelukast. Montelukast associated with significantly improved FEV1 rate of decline at 3 and 6 months. Patients whose FEV1 improved or stabilized had significantly improved progression-free and overall survival.


Single-center retrospective cohort study of lung transplant recipients (n=108) treated with rATG for CLAD. Treatment with rATG was associated with reversal in the decline of lung function (increase of FEV1) in 40% of patients. Serum sickness, cytokine release syndrome, and infection after therapy developed in 22%, 15%, and 19% of patients, respectively.


Prospective feasibility study of allogeneic mesenchymal stem cell (MSC) therapy feasibility and safety in nine lung transplant recipients with bronchiolitis obliterans syndrome (BOS) refractory to standard therapy. Up to 1 month of follow up, there was no change in gas exchange, pulmonary function tests, or routine labs suggesting MSC therapy is safe. Further studies are needed to assess efficacy


Retrospective single center analysis of lung transplant recipients with CLAD who were treated with extracorporeal photopheresis (ECP), alemtuzumab, or no treatment. Rate of FEV1 decline was significantly improved after either treatment, however no difference in FVC was seen. There was no difference in infection rates or survival after treatment. Comparison with no treatment was limited due to significant clinical differences between groups, however no difference in mean FEV1 slope difference was identified.


Single center study assessing statin use and development of CLAD. Statin use was not associated with decreased risk of CLAD at 3 years but demonstrated decreased risk of death. At 3 years, patient survival was 81.7% in statin group and 68.3% in nonstatin group (P=.012)
- Analysis of a single center experience with methotrexate in five lung transplant recipients with steroid-resistant acute rejection episodes or in lung transplant patients with recurrent rejection or bronchiolitis obliterans syndrome.

6.5 Retransplant/graft failure

6.5.1 General retransplant/graft failure

- Single-center retrospective cohort study of lung transplantation recipients. Retransplant was associated with significantly higher mortality after 6 months post-transplant.

- Retrospective cohort study of adult lung retransplants identified a more complicated post-transplant course following retransplantation with longer ventilation time and ICU stay in addition to lower peak lung function. Quality of life, renal function, microbiology, and DSA formation were similar, and median survival was numerically shorter.

- Retrospective cohort study over 23 years of 233 lung transplant recipients in New Zealand were classified into two groups using a Deprivation Index Score. Socioeconomic status had no negative effect on rejection, CLAD, or patient survival.

- 50 lung transplant recipients underwent manometry and esophageal motility abnormalities were classified by the Chicago Classification v3.0. Esophagogastric junction outflow obstruction, incomplete bolus transit, and proximal reflux each increased risk of CLAD even though junction outflow obstruction was not associated with a greater number of reflux events. Esophageal dysmotility, more so than reflux alone, may be a risk for CLAD.

- Multicenter retrospective review demonstrated no significant difference in graft survival between recipients of retransplant with single or double lungs when stratified by previous transplant type.
- Single center retrospective review of lung retransplantion over a 19-year period. Survival was found to be significantly worse in retransplanted patients compared to primary transplant patients.

- A retrospective study that evaluated the association between lung donor age and primary graft dysfunction.

- This study reviewed patients with lung retransplant due to various indications. Results of retransplant data versus those of first-time lung transplant were no different.

- This study retrospectively reviewed patients with lung retransplantation due to BOS over a 14-year period. Endpoints for survival, causes of death, long-term functional status, and BOS recurrence rate had positive results following retransplantation.

- This multi-center study reviewed certain patient selection criteria and correlated it to retransplantation success.

### 6.5.2 Primary graft dysfunction

- Single-center retrospective study of lung transplant recipients. Patients requiring VA-ECMO had initial increased mortality, but comparable long-term survival.

- Five center prospective cohort study in Spain that enrolled all adult lung transplant patients with ICU readmissions after post-transplant ICU discharge. Graft rejection caused 10.8% of readmissions and pneumonia caused 36% of readmissions. Multivariate analyses identified bronchiolitis obliterans syndrome stage 2, restrictive allograft syndrome, and pneumonia at ICU readmissions as independent predictors of ICU mortality.
- Review article summarizing advances in understanding of PGD, updates in PGD classification and definition, and current controversies surrounding PGD

- A study over a 15-year period that assessed the use of ECMO for primary graft dysfunction post-transplant (within POD#7) and reviewed survival outcomes of that with patients who did not require ECMO.


6.6. Management of bronchiolitis obliterans syndrome

- Case report of a 63-year-old man who received a single right lung transplant who developed bronchiolitis obliterans syndrome which evolved into restrictive allograft disorder in 5 years. He was treated with nintedaninb 150 mg BID for 4 months without clinical benefit. The patient discontinued therapy due to GI intolerance.

- Single center retrospective analysis including lung transplant recipients with progressive BOS treated with total lymphoid irradiation (TLI). Treatment was associated with decreased rate of FEV1 decline, particularly in those with rapid decline. Overall patient survival was 44% at two years post-treatment. TLI was generally well-tolerated and may be useful as a bridge to redo transplant in select patients.

- Investigator-initiated, multicenter, randomized, controlled trial including lung transplant recipients with new onset progressive BOS assigned to pirfenidone or placebo for 6 months. Primary endpoint to be assessed is change in FEV1 over 6 months.
- Phase 2b trial in lung transplant recipients with BOS randomized to either inhaled liposomal cyclosporine (L-CsA) or standard-of-care (SOC) alone. Progression-free survival was non-significantly improved in the L-CsA group. L-CsA group also with improved median survival and stabilized change in FEV1 and FVC.

- Review of literature for ECP as part of BOS management in lung transplant recipients. The mechanism of action is described. Small studies suggest ECP therapy is associated with improved or stabilized lung function, decreased rate of functional decline, and is well-tolerated.

- Patients receiving montelukast for BOS did not have differences in graft loss at one year or in acute rejection, lymphocytic bronchiolitis, or respiratory infection rate. However, in a post-hoc subanalysis of stage 1 BOS patients, montelukast had a positive impact on FEV1 decline in the study period.

- Single-center retrospective cohort of patients treated with aerosolized antipseudomonals finding similar time to positive culture results in addition to incidence of culture positivity at one year. Aerosolized antipseudomonals were protective against recurrence in non-CF patients.

- Rescue alemtuzumab provides transient benefit for lung transplant recipients with BOS I, but recipients with advanced stage BOS seem not to improve with rescue alemtuzumab therapy.

- Analysis of UNOS data of approximately 6000 recipients demonstrated prolonged median survival with use of alemtuzumab or basiliximab compared to no induction. And a lower incidence of BOS at 5 years with alemtuzumab use.

A single-center study of bilateral lung transplant recipients that describes the factors influencing survival in patients with BOS – including timing and severity of BOS, and its concurrent treatment therapies.


An observational study that evaluated heart-lung or lung patients with refractory acute rejection (RAR) and BOS who failed therapy with steroid and antithymocyte globulin and received rescue alemtuzumab. Histological rejection scores were improved following alemtuzumab administration with freedom from BOS present in 65% of patients with RAR.


An open-label pilot trial involving 6 patients to determine the effect of azithromycin maintenance therapy on improvements in lung function in patients with BOS.


Single center retrospective study comparing the outcomes of lung transplant recipients prescribed statins vs those who did not receive HMG-CoA reductase inhibitors. Statin use was associated with a lower cumulative incidence of BOS relative to controls and may provide positive pulmonary effects post-transplant.


6.7 Lung diseases

6.7.1 Idiopathic pulmonary fibrosis


RCT of 177 patients with advanced IPF and either at risk for or with high probability of group 3 pulmonary hypertension treated with pirfenidone + placebo or pirfenidone + sildenafil. Patients were followed for 52 weeks for disease progression with a composite endpoint of decline in 6MWD, respiratory-related hospital admission, or all-cause mortality. Progression free survival was not improved with addition of sildenafil, and analysis of individual components of composite endpoint yielded no significant results.

- Retrospective review of adult lung transplant recipients in single center cohort. Of 611 evaluable patients in the study period, 28 patients (4.6%) developed EBV-associated neoplasia. Despite comprising 22.9% of overall LT population, IPF transplant recipients accounted for 12 (42.9%) of neoplasms. Multivariate Cox proportional hazards model suggested IPF (HR 3.51, 95% CI 1.33-8.21), EBV mismatch, and alemtuzumab induction were independent predictors of PTLD development. When evaluating for early vs late PTLD, diagnosis of IPF was only predictor of late PTLD after matching for age and sex.


- Review article discussing management of IPF comorbidities and the landscape of transplantation for patients with IPF


- Review article summarizing new therapeutic agents for IPF and potential future approaches


- 151 lung transplant recipients (2005-2017) were reviewed for overall, rejection-free, and BOS-free survival at 1 and 5 years. Differences in survival were not statistically significant although bilateral transplant recipients had longer ventilation duration and length of stay post-transplant.


- Analysis of UNOS data demonstrating no statistical difference in actuarial graft survival between patients undergoing single versus double lung transplant which suggests increased use of single lung transplant may increase the availability of organs to other candidates


- Case series of 9 patients receiving either pirfenidone or nintedanib demonstrated these medications may attenuate disease progression while awaiting a lung transplant.

• Phase 3 study that confirmed pirfenidone reduced disease progression (reflected by lung function, exercise tolerance, and progression-free survival) with idiopathic pulmonary fibrosis.

• Phase 3 trial demonstrating nintedanib reduces the decline in FVC and thus, slows disease progression.

• Phase II trial demonstrating pirfenidone, a new, effective anti-fibrotic agent, reduces deterioration in lung function in patients with idiopathic pulmonary fibrosis.

• Overall survival was evaluated in patients with idiopathic pulmonary fibrosis who received or did not receive lung transplantation.

• Review article describing the pathogenesis of idiopathic pulmonary fibrosis, diagnosis of disease, and treatment options.

• A retrospective review of outcomes in single and bilateral lung transplant recipients with idiopathic pulmonary fibrosis.

6.7.2 Primary pulmonary hypertension

• Retrospective analysis of single vs double lung transplant recipients, 12.3% due to primary pulmonary hypertension. 5-year survival amongst patients with primary pulmonary hypertension was significantly greater in those who received a double lung as compared to single lung transplant. Worst short-term survival of all indications was seen in the primary pulmonary hypertension group.

Retrospective, single center cohort study of children with pulmonary hypertension treated with sildenafil. 37% remained on sildenafil or tadalafil, 35% discontinued therapy due to improvement, 20% died, and 7% were lost to follow up. Overall sildenafil was well-tolerated.


Task force of World Symposium on Pulmonary Hypertension updates on definition, classification, diagnostics, and treatment of pediatric pulmonary hypertension.


Retrospective case-control study of lung transplant recipients with idiopathic pulmonary hypertension assessing perioperative death. Highest risk of death was associated with high frequencies of syncope, hyponatremia, lower cardiac index, inner diameter of left ventricle, and RV/LV ratio.


Safety and tolerability of selexipag following treprostinil. The study included 34 patients, and 32 were successfully transitioned to selexipag with 28 of those patients meeting criteria for continued therapy. Three patients discontinued therapy due to adverse effects.


Guideline for pharmacologic therapy for adult patients with PAH as informed by available evidence.


Treatment algorithm focusing on 3 areas: 1) general measures, supportive therapy, referral strategy, acute vasoreactivity testing and chronic treatment with calcium channel blockers; 2) initial therapy with approved PAH drugs; and 3) clinical response to the initial therapy, combination therapy, balloon atrial septostomy, and lung transplantation.


Retrospective, single center review of all patients transplanted for pulmonary arterial hypertension.

• Review article discussing indications for transplant, preparation for transplant and listing, operative issues, and outcomes for patients with pulmonary arterial hypertension.


• Review article describing molecular, environmental, and genetic causes for pulmonary hypertension.


• Review article describing treatment alternatives according to the various pathophysiologic mechanisms involved with pulmonary arterial hypertension.

6.7.3 Alpha-1 antitrypsin deficiency


  o Retrospective review of UNOS data on lung transplants between March 1992 and September 2019. Patients transplanted for AATD had similar long-term survival compared to all other transplant recipients (HR 0.96, 95% CI 0.9-1.02, p=0.19). When adjusting for age, overall survival was improved with AATD patients relative to those with non-AATD related COPD (HR 0.59, CI 0.555-0.64, p<0.001), but risk of death from infection or multi-organ failure was higher in AATD patients. Median survival was better in patients with double lung transplant compared to single lung transplant (7.7 years vs 4.4 years, p < = 0.001).


  • Retrospective review of 222 lung transplant recipients with COPD and AATD . Primary endpoint of incidence of post-transplant complications. Early bronchial anastomotic complications and late bowel complications were observed only in AATD patients.


  • UNOS database study which demonstrated patients with A1AD who received a single lung transplant had reduced 1 year survival. For patients who received a bilateral lung transplants there was no significant difference in survival by diagnosis


  • Single center retrospective cohort study of 385 patients who underwent lung transplant for COPD with or without alpha-1 antitrypsin deficiency (A1AD). A1AD patients were found to
have worse short-term complications, but improved long-term survival compared to COPD patients.


- Systematic review of A1AD treatment categorized studies into four groups: COPD medical, COPD surgical, A1AD specific, and other treatments. Concluded that only intravenous augmentation is the only disease-specific therapy in A1AD and can slow emphysema as determined by CT density. Other treatments lack data, and usual COPD treatments may not be effective.


- This study evaluated survival and health benefits in individuals receiving lung transplant for alpha-1 antitrypsin deficiency (A1AT) matched with A1AT patients who did not receive lung transplant. Lung transplant improved quality of life, but did not improve 5-year survival.


- This study evaluated survival after lung transplant between alpha-1 antitrypsin deficient (A1AT) individuals with chronic obstructive pulmonary disease (COPD) compared to those without A1AT-related COPD. A significant difference in survival was seen between the two groups at six and twelve years.


- Evaluated number of years of life gained and expense per year of life gained in patients receiving augmentation therapy. Augmentation therapy was associated with increase in life years gained with gender and smoking status impacting years of life gained.


- This study evaluated survival benefit in patients with alpha-1 antitrypsin deficiency and emphysema receiving lung transplantation and compared outcomes to patients who did not receive lung transplant and continued medical therapy. Lung transplantation was found to significantly improve survival.


- The article introduces a case vignette and further discusses the pathogenesis of genetic predisposition to alpha1-antitrypsin deficiency, diagnosis of disease, potential treatment options, and areas for research.
6.7.4 Cystic fibrosis

- Multicentre, parallel group, open-label, randomized controlled trial in 72 cystic fibrosis that found that treatment with IV ceftazidime for 14 days did not yield better outcomes than 12 weeks of oral ciprofloxacin (both regimens in combination with 12 weeks of inhaled colistimethate).

- Consensus guideline summarizing the definition and care of patients with advanced CF.

- Single center retrospective study of lung transplant recipients with CF who underwent endoscopic sinus surgery at least 1 year after transplant. Antibiotic use in the 6 months after surgery compared to the 6 months prior was significantly decreased, with no difference in other outcomes such as hospitalizations.

- Review article encompassing the pharmacologic and non-pharmacologic care of critically ill patients with CF.

- Phase 3, double-blind, placebo-controlled trial to assess the CFTR modulator elexacaftor-tezacaftor-ivacaftor in CF patients at least 12 years of age. Treatment demonstrated statistically significant improvements in all endpoints compared to placebo, including the primary endpoint of FEV1 change from baseline at week 4.

- Review article detailing updates in pharmacologic management of CF as well as non-pulmonary manifestations and management.

- Prospective cohort study of lung transplant recipients, stratified by CF vs non-CF, compared to control non-transplant group. Posaconazole tablets resulted in therapeutic trough levels in all groups, however levels in CF lung transplant recipients were significantly lower. The
authors also report the effect of posaconazole on immunosuppression drug levels and the effect of concomitant PPI use.

- Summary of lung transplant in cystic fibrosis including patient characteristics and overall survival post-transplantation.

- Over 30,000 lung transplant recipients were included with 17% having a CF diagnosis. This group had greater incidence of PTLD in addition to higher EBV and CMV mismatches.

- Randomized, double-blind, placebo-controlled trial in CF patients with at least one G551D-CFTR mutation of ivacaftor for 48 weeks. Estimated mean change from baseline at 24 weeks in FEV1 was significantly greater in the ivacaftor group. Effect was maintained through week 48. There were fewer pulmonary exacerbations, higher respiratory symptoms domain scores, greater weight gain, and decreased sweat chloride.

6.8 Miscellaneous

6.8.1 Hypogammaglobulinemia

- This study evaluated pre and posttransplant IgG levels and incidence of infection, rejection, antibiotic use, and immunosuppression use in lung transplant recipients. Of 133 patients, severe hypogammaglobulinemia (IgG <400 mg/dL) was highest at the time of transplant (32.4%) while at 3, 6, 9, and 12 months posttransplant the prevalence was 7.4%, 7.5%, 8.9%, and 6.3%, respectively. Additionally, severe hypogammaglobulinemia was associated with ≥2 pneumonias (P=0.0006) and increased number of antibiotic courses (P=0.003) when compared to other lung transplant recipients.

- This retrospective single-center cohort study compared use of intravenous Immunoglobulin-G (IVIG) in lung transplant recipients with hypogammaglobulinemia (IgG <700 mg/dL, n=216)) to those with hypogammaglobulinemia but remained untreated (n=192) and those without hypogammaglobulinemia (n=76) up to 300 days post-transplant and found that hypogammaglobulinemia was independently associated with death (HR 2.44, 95% CI 1.34-4.47), with death significantly different between groups at 2 years (35% vs. 19% vs. 16%, respectively). A-grade cellular rejection (ACR) was significantly different at 5 years with a
composite rejection standardization score (CRSS) of 0.5 vs. 0.4 vs. 0.3 between groups, respectively. Additionally, gram-negative pneumonias occurred more often in those who received IVIG (P=0.04).

- Single-center retrospective chart review evaluating occurrence of community-acquired respiratory viruses (CARVs) among patients with normal and hypogammaglobulinemia (defined as IgG <700 mg/dL) found that of 263 lung transplant recipients, incidence of CARV was 27% in patients with normal IgG titers versus 23.4% in patients with hypogammaglobulinemia (P=0.62).

- Single-center retrospective chart review evaluating quantitative total and subclass IgG levels found of 57 lung transplant recipients, 34 (60%) had IgG levels <700 mg/dL, of which 8 (14%) had severe hypogammaglobulinemia defined as IgG <400 mg/dL with females vs males (25% vs 0%, P=0.07). Additionally, emphysema and BOS were additional risk factors for severe hypogammaglobulinemia. Severe hypogammaglobulinemia was associated with increased risk of pneumonia (P=0.01) and worse survival (P=0.04).

- Single-center retrospective chart review evaluating post-transplant humoral immune status survey including total immunoglobulin levels (IgG, IgM, IgA) and IgG subclasses (IgG1-4) found of 67 lung transplant recipients, 47 (70%) had IgG levels <600 mg/dL, of which 25 (37%) had IgG levels <400 mg/dL, and 22 (33%) had IgG levels 400-600 mg/dL. Infections were significantly more common in patients with IgG <400 mg/dL and more common in patients with IgG 400-600 mg/dL versus patients with normal IgG levels with infections including: number of pneumonias (P=0.0006), bacteremias (P=0.02), total bacterial infections (P=0.002), tissue-invasive cytomegalovirus (P=0.01), invasive aspergillosis (P=0.001), total fungal infections (P=0.001), and total infections (P=0.006). Additionally, survival was poorest in patients with IgG levels <400 mg/dL.

6.8.2 Hyperammonemia

- Case report a patient who experienced hyperammonemia secondary to shock liver post re-do double lung transplant. The patient’s ammonia level was persistently > 250 ug/dL despite conventional therapy. Ammonia levels returned to baseline after initiation plasmapheresis but the patient unfortunately still passed away.

- Case report of 2 patients with acute hyperammonemic encephalopathy after lung transplantation managed with an extracorporeal liver support system.

- Review article detailing the pathophysiology, diagnostics, and management of hyperammonemia in the lung transplant patient population.

- Single center retrospective cohort study of lung transplant recipients who underwent Ureaplasma spp testing pre-transplant in donor and recipient. 8.3% of recipients and 13.3% of donors had positive screening tests. Patients with positive donor organs who received empiric therapy with levofloxacin and azithromycin did not develop hyperammonemia syndrome.

- Single center retrospective study of lung transplant recipients with symptomatic hyperammonemia managed with two different formulas: Ammonul or Buphenyl. All patients improved with no recurrence, suggesting Buphenyl as an appropriate alternative to Ammonul.

- Case report of lung transplant recipient with hyperammonemia empirically treated with doxycycline in addition to ammonia‐lowering therapies. The patient improved and Ureaplasma species later identified via PCR and BAL culture.

- This retrospective cohort series of lung transplant recipients (n=807) who developed hyperammonemia syndrome, defined as symptoms of encephalopathy and plasma ammonia level >200 umol/L, occurred in 8 patients postoperatively with a median time to onset 9 days, median peak ammonia level 370 umol/L. All patients were treated with hemodialysis, 7 of 8 patients were also treated with bowel decontamination, and 5 of 8 patients were treated with nitrogen scavenging agents. 6 of 8 patients died.

- This case series of lung transplant recipients (n=3) who developed hyperammonemia early postoperatively reports aggressive ammonia reduction with early initiation of hemodialysis, prolonged daily intermittent hemodialysis, high dialysis dose, and overnight slow low-efficiency dialysis improves survival.
- This retrospective cohort study evaluated the incidence of hyperammonemia in lung transplant recipients postoperatively. Of 145 lung transplant recipients, 6 developed hyperammonemia within 26 days of transplant. The 30 day post-transplantation mortality rate was 67% for patients with hyperammonemia versus those without (17%, P=0.01). Development of major gastrointestinal complications (P=0.03) and use of total parenteral nutrition (P=0.045) were associated with the development of hyperammonemia.

- This case report of two lung transplant recipients who developed fatal hyperammonemia following transplant determined that activity of hepatic glutamine synthetase was markedly reduced (in patient 1, 12% of the mean value in controls; in patient 2, 28% of the mean value in controls), with a concomitant reduction in amount of glutamine synthetase protein also observed.