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7.1 Viral

7.1.1 Cytomegalovirus


- British guidelines on the recommendations on the prophylaxis and treatment options of CMV in solid organ transplant.


- Guideline recommendations on the diagnosis and management of CMV infections in hematopoietic stem cell transplant patients


- The American Society of Transplantation practice guidelines for preventing and treating cytomegalovirus infection in solid organ transplant recipients.


- A report summarizes the recommendations of an international panel of experts who reconvened in October 2012 to revise and expand evidence and expert opinion-based consensus guidelines on CMV management


- A meta-analysis that included all studies evaluating valganciclovir 900 mg and 450 mg daily against controls as CMV prophylaxis in a direct comparison. Valganciclovir 900 mg showed no superiority efficacy compared to controls (ganciclovir or preemptive) and equivalent efficacy to VGC 450 mg for CMV universal prophylaxis. VGC 900 mg was significantly associated with 3 times increase in the risk of leukopenia and 2 times increase in the risk of rejection compared with VGC 450 mL

- A Meta-analysis that included 17 trials and 9 trials on universal prophylaxis and preemptive therapy, respectively, and evaluated the effectiveness of the various approaches in reducing the incidence of CMV disease.


- Meta-analysis included 11 articles which evaluated the impact of cytomegalovirus (CMV) immune globulin on CMV disease prevention and rejection.


- Systematic review of the literature included randomized clinical trials investigating clinical outcomes of prophylactic polyvalent immunoglobulin or cytomegalovirus (CMV)-specific immunoglobulin or plasma in patients undergoing HSCT. Clinical outcomes included overall survival, transplant-related mortality, CMV infection, CMV disease, graft-versus-host disease, interstitial pneumonitis/fibrosis and hepatic veno-occlusive disease


- An overview of the contemporary epidemiology, clinical presentation, diagnosis, prevention and treatment of CMV infection in solid organ transplant recipients


- Critical review based on relevant articles published about CMV infection in renal transplant elaborating on different clinical aspects, including resistance to ganciclovir


- A review article that discusses the management and prevention of CMV with elaborations on the new advances in the development of new antivirals, adoptive immunotherapy and DNA-CMV vaccines that might transform the management of CMV in the near future.


A randomized, international trial (VICTOR study), recipients with cytomegalovirus disease were treated with either 900 mg oral valganciclovir or 5 mg/kg i.v. ganciclovir twice daily for 21 days, followed by 900 mg daily valganciclovir for 28 days. A total of 321 patients were evaluated. Oral valganciclovir shows comparable safety and is not inferior to i.v. ganciclovir for treatment of cytomegalovirus disease in organ transplant recipients and provides a simpler treatment strategy.

- 1-year follow-up of VICTOR study, 321 SOT recipients with CMV disease were followed 1 year after treatment with either twice daily intravenous ganciclovir or oral valganciclovir (for 21 days) followed by once daily valganciclovir until day 49 in all patients


- The impact of valganciclovir as primary prophylaxis compared to preemptive therapy on rates of cytomegalovirus (CMV) infection and disease occurrence was evaluated in kidney transplant recipients who were of intermediate CMV risk.


- A prospective study that determined the safety and efficacy of valganciclovir for prevention of cytomegalovirus (CMV) in at-risk (donor positive/recipient negative [D+/R-] or R+) lung transplant recipients, and determined the length of prophylaxis required to significantly decrease both CMV infection and disease all in consecutive lung transplant recipients surviving >30 days. It showed that valganciclovir is safe and effective for prevention of CMV infection and disease in at-risk lung transplant recipients. The required length of prophylaxis was at least 180 days


- A single-center study on subset of patients whom were initially enrolled in a prospective, randomized, placebo-controlled study of CMV prevention in lung transplantation. The study aimed to determine if extended prophylaxis conferred a sustained long-term benefit and to assess its hematologic safety. It showed that extending valganciclovir prophylaxis to 12 months provides a durable long-term CMV protective benefit compared with short-course therapy, without increasing adverse hematologic effects

Multicenter Randomized, clinical trial involving 11 U.S. lung transplant centers, to determine whether extending prophylaxis with oral valganciclovir from the standard 3 months to 12 months after lung transplantation is efficacious. A beneficial effect with regard to prevention of CMV disease seems to extend at least through 18 months after transplantation.


Single-center, retrospective study that reports on its use in 17 transplant recipients with complex CMV syndromes who had failed or were intolerant to other therapies.


Placebo-controlled trial evaluating valacyclovir prophylaxis for prevention of cytomegalovirus disease in kidney transplant recipients.


Oral valganciclovir prophylaxis was compared to preemptive valganciclovir therapy for its pharmacoeconomic impact and occurrence of cytomegalovirus infection.


Preemptive valganciclovir therapy was compared to valacyclovir prophylaxis for their impact on cytomegalovirus disease and acute rejection at 12 months following kidney transplantation.


A study that test the role of IL-10 being an indicator for the risk of development of CMV infection after prophylaxis, and hence guiding the needed length of prophylaxis in kidney and liver transplant recipients.

- A case report on a 15-year-old boy with juvenile myelo-monocytic leukemia (JMML) received an allogeneic HSCT with bone marrow stem cells from a mismatched, unrelated donor. He who had refractory CMV infection despite the treatment with cidofovir. A rapid decline of his CMV-copy number and successful treatment was achieved with the combination foscarnet/leflunomide.


- This study reviews the impact of pharmacist intervention adjusting valganciclovir dosing for CMV prophylaxis. The primary endpoint was CMV infection and ganciclovir resistance in a pre-intervention vs post-intervention group.


- Retrospective cohort of patients with CMV with U97 gene conferring ganciclovir resistance reviewing the treatment and clinical course patients experienced.


- Phase II clinical trial comparing CMV treatment with standard of care vs letermovir in kidney alone or kidney-pancreas transplant recipients with active CMV viral replication.

7.1.2 Epstein-Barr Virus and Lymphoproliferative disorder


- Evidence-based recommendations for diagnosis, prevention, prophylaxis and therapy of post-transplant lymphoproliferative disorders exclusively in the stem cell transplant setting.

- The American Journal of transplantation guidelines for management of Epstein-Barr Virus and Posttransplant Lymphoproliferative Disorder in Solid Organ Transplantation


- Clinical practice guidelines for the management of Epstein-Barr virus associated lymphoproliferative disease in solid organ transplant


- A multi-center trial assessing two different regimens and their effect on EBV replication. EBV D+/R- solid organ transplant recipients were randomized to receive either ganciclovir and placebo or ganciclovir and immunoglobulin (IG) for 3 months. No significant difference in EBV viral load suppression was observed when ganciclovir was compared with ganciclovir and IG in high-risk EBV D+/R-patients


- A randomized controlled trial of CMV-IVIG (cytomegalovirus-intravenous immunoglobulin) for prevention of Epstein Barr virus (EBV) posttransplant lymphoproliferative disease (PTLD) in pediatric liver transplantation (PLTx) recipients was begun in Pittsburgh and subsequently expanded to four additional sites. Patients were followed for 2 years post-LTx. No significant differences were seen in the adjusted 2-year EBV disease-free rate and PTLD-free rate between treatment and placebo groups at 2 years


- A multicenter retrospective study, analyzed the incidence of post-transplant non-Hodgkin lymphoma in 44 828 recipients of deceased-donor kidney transplants who were reported to the scientific registry of the Collaborative Transplant Study. Patients had received antiviral drugs (aciclovir or ganciclovir) or anti-CMV
immunoglobulin to prevent CMV infection according to the transplant centres’ protocols, or no CMV prophylaxis


- A multicenter retrospective study assessed the impact of rituximab on the outcome of PTLD. They examined the clinical features and outcomes among a large cohort of solid organ transplantation (SOT) patients with PTLD.


- A single, large-volume center assessed the incidence, predictors and outcomes of PTLD after liver transplantation. Suggested switching immunosuppression from calcineurin inhibitor to sirolimus may improve survival.

7.1.3 Herpes Simplex and Varicella-Zoster virus


- The American Journal of Transplantation guidelines on the management of herpes simplex virus in solid organ transplantation


- The American Journal of Transplantation guidelines on the management of varicella zoster virus in solid organ transplantation


- Evidence-based guidelines of the European Conference on Infections in Leukemia recommendations for managing of HSV, VZV and EBV infections in leukemia patients and in stem cell transplant recipients


- Section 13.4 relates to management of HSV/VZV, though guidelines are a bit older at this time


A double-blind controlled trial, 77 hematopoietic cell transplant recipients at risk for VZV reactivation were randomized to acyclovir 800 mg twice daily or placebo given from 1 to 2 months until 1 year after transplantation. VZV disease at 1 year was the primary end point. Arora A et al, (2008). Double-blind study comparing 2 dosages of valacyclovir hydrochloride for the treatment of uncomplicated herpes zoster in immunocompromised patients 18 years of age and older. Journal of Infectious Diseases, 197, 1289-1295. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/18422441


Famciclovir 500 mg three times a day was compared to acyclovir 800 mg five times a day showed no significant difference in new lesion formation, time to healing or duration of pain were observed. Macesin N et al (2017). Herpes simplex virus-2 transmission following solid organ transplantation: donor-derived infection and transplantation from prior organ recipients. Transplant Infectious Disease. 19 (5):1-8.

Report detailing 5 clusters of donor-derived HSV-2 infection in donor positive, recipient negative solid organ transplant, the treatment of HSV and clinical outcomes of infection.

### 7.1.4 Adenovirus infection


- A review on the management of pediatric patients with adenovirus infection post-transplant pediatric patients.

7.1.5 HBV prophylaxis and treatment


• Updated recommendations on when to treat, when to monitor, what patients should receive HBV therapy, and what drugs should be selected for each scenario.


• A recent review article discussing Strategies for prevention of HBV after LT.

• A review article that discusses the management of Chronic hepatitis B virus (HBV) infection post liver transplantation in the presence of newer more potent oral antiviral agents associated with less resistance (e.g., entecavir and tenofovir) for the treatment of CHB either in combination with HBIG or alone as a monotherapy.

• Another review article that discusses the management of chronic hepatitis B before and after liver transplantation.

• The prospective, open-label trial evaluates the strategies for preventing hepatitis B virus recurrence following liver transplantation. Patients received lamivudine in addition to hepatitis B immune globulin as combination therapy for the first month following transplant and were then randomized to receive either combination therapy for 17 months or lamivudine monotherapy for 17 months.

• An open-label, multicenter, international study that evaluated the impact of adefovir in pre- and post- liver transplant recipients on hepatitis B viral load was evaluated in patients with lamivudine-resistant hepatitis B.

• The prospective trial evaluates the use of adefovir dipivoxil in addition to lamivudine therapy for treating patients with chronic hepatitis B who developed a resistant strain of the hepatitis B virus. Hepatitis B viral load response to combination treatment was evaluated in patients with compensated as well as decompensated disease.

- The impact of long term antiviral therapies (lamivudine, tenofovir, adefovir) on hepatitis B virologic response and liver disease was evaluated in heart transplant recipients.


- The impact of entecavir, adefovir, and lamivudine therapy on virologic and biologic responses in hepatitis B surface antigen positive kidney transplant recipients is evaluated.


- Case series evaluating the use of entecavir or adefovir in kidney transplant recipients with hepatitis B virus infection resistant to lamivudine.

7.1.6 HCV prophylaxis and treatment


- World health organization guidelines for screening and treatment of chronic hepatitis C infection


- The American Association for the Study of Liver Diseases and the Infectious Diseases Society of America practice guidelines for testing and treating hepatitis C virus infection


- The American society for blood and marrow transplantation task force recommendations in the management of HCV in HSCT donors and recipients


- Review article of the data on direct acting antivirals combination therapies in transplantation, discuss the advantages and disadvantages of pre vs. post transplant HCV therapy and future directions

- A review article on the management of post liver transplant hepatitis C infection


- A review article that discusses the recent studies that have emerged on the use of NS5b polymerase inhibitor, sofosbuvir in combination with second generation protease inhibitor, simeprevir, fixed dose ledipasvir or daclatasvir with or without ribavirin in the treatment of post transplant rHCV infection


- An article that explores arguments for and against treating HCV in patients on the transplant list


- The FISSION (N=499) and NEUTRINO (N=327) trials evaluate the use of sofosbuvir and ribavirin with (NEUTRINO) or without (FISSION) peginterferon for 12 weeks in hepatitis C virus infected patients who did not previously receive treatment. In the NEUTRINO trial, sustained virologic response at 12 weeks following treatment (SVR 12) was 90% in patients with HCV genotype 1, 4, 5, or 6. In the FISSION trial, SVR 12 was 67% in patients with genotype 2 or 3.


- The POSITRON (N=278) and FUSION (N=201) trials evaluate the use of sofosbuvir and ribavirin for 12 weeks in hepatitis C virus infected patients with genotypes 2 or 3 who are either intolerant/had contraindication to peginterferon treatment (POSITRON) or failed peginterferon treatment (FUSION). Sustained virologic response 12 weeks following treatment was 78% and 50% in the POSITRON and FUSION trials, respectively.


- Prospective, randomized trial evaluating ledipasvir and sofosbuvir therapy with or without ribavirin therapy for 12 or 24 weeks in 440 previously treated patients with hepatitis C virus genotype 1. Sustained virologic response at 12 following treatment was high among all treatment groups with no significant differences seen between groups.

- Prospective, randomized trial evaluating ledipasvir and sofosbuvir with or without ribavirin therapy for 8 weeks or ledipasvir and sofosbuvir therapy for 12 weeks in 647 treatment-naïve patients with hepatitis C virus genotype 1. Sustained virologic response 12 weeks following treatment was high among all treatment groups with no significant differences seen between groups.


- Prospective, phase II trial evaluating simeprevir, ribavirin, and peginterferon combination therapy compared to ribavirin and peginterferon therapy in treatment-experienced patients with hepatitis C virus genotype 1. Simeprevir dosing (100mg vs. 150mg) and duration (12, 24, or 48 weeks) are evaluated with 48 weeks of peg-interferon and ribavirin therapy. Sustained virologic response 24 weeks following treatment was significantly higher in the simeprevir groups compared to the ribavirin and peginterferon group.


- A phase 2, open-label study of 61 patients with HCV of any genotype and cirrhosis to determine whether sofosbuvir and ribavirin treatment before liver transplantation could prevent HCV recurrence post-transplant


- A retrospective study examining the "real world" treatment of 170 patients with chronic HCV genotype 1 using the combination of SMV and SOF with or without ribavirin (RBV) for a fixed 12-week duration irrespective of prior interferon therapy, transplant status or fibrosis stage. The data confirm excellent SVR outcomes with favorable safety and tolerability profiles in patients who carry many traditional high-risk features for non-response, including post-LT recipients and patients with advanced liver disease


- The open-label ALLY-1 study assessed the safety and efficacy of a 60-mg once-daily dosage of daclatasvir (pan-genotypic NS5A inhibitor) in combination with sofosbuvir at 400 mg once daily (NS5B inhibitor) and ribavirin at 600 mg/day for 12 weeks with a 24-week follow-up in two cohorts of patients with chronic HCV infection of any genotype and either compensated/decompensated cirrhosis or post transplantation recurrence

- A prospective, observational study that evaluated the efficacy of sofosbuvir and simeprevir in patients with genotype 1 HCV post-liver transplant. Patients received sofosbuvir 400 mg plus simeprevir 150 mg daily for 12 wk without ribavirin. The primary end point was a sustained virologic response 12 wk after the end of therapy.


- A study that evaluated the efficacy and safety of sofosbuvir- and daclatasvir-based regimens. It analyzed data from 23 patients with Fibrosing cholestatic hepatitis who participated in a prospective cohort study in France and Belgium and the effects of antiviral agents in patients with recurrence of HCV infection after liver transplantation


- A prospective, multicenter, open-label pilot study that evaluated the efficacy and safety of an interferon-free regimen of the nucleotide polymerase inhibitor sofosbuvir combined with ribavirin for 24 weeks in treating post-transplantation HCV infection


- A report of efficacy and safety data for DCV-based all-oral antiviral therapy in liver transplantation (LT) recipients with severe recurrent HCV. DCV at 60 mg/day was administered for up to 24 weeks as part of a compassionate use protocol for a 97 infected patients.


- The SOLAR-1 study was a large, multicenter, randomized controlled trial that included liver-transplant recipients (n=223) across a broad spectrum of histologic and clinical severity of recurrence. Study participants were randomly assigned to receive fixed-dose combination ledipasvir (90 mg) and sofosbuvir (400 mg) (hereafter ledipasvir/sofosbuvir) and weight-based ribavirin (1000 mg [<75 kg] to 1200 mg [≥ 75 kg]) for either 12 weeks or 24 weeks

- A phase 2, open-label study included enrolled 337 patients and assessed treatment with the NS5A inhibitor ledipasvir, the nucleotide polymerase inhibitor sofosbuvir, and ribavirin in patients infected with HCV genotypes 1 or 4


- A result of a study done with sofosbuvir (SOF) and ribavirin (RBV) on a compassionate-use basis to patients with severe recurrent hepatitis C, including those with fibrosing cholestatic hepatitis (FCH) and decompensated cirrhosis who had a life expectancy of 1 year or less. All patients received 24-48 weeks of SOF plus RBV. SOF and RBV provided high rates of SVR in patients with severe recurrent HCV, including patients with early severe recurrence, FCH, and cirrhosis.


- A phase 3, double-blind, placebo-controlled study involving untreated and previously treated patients with chronic HCV genotype 1, 2, 4, 5, or 6 infection, including those with compensated cirrhosis. Patients randomized to receive the nucleotide polymerase inhibitor sofosbuvir and the NS5A inhibitor velpatasvir in a once-daily, fixed-dose combination tablet or matching placebo for 12 weeks


- A phase 3, open-label study involving both previously treated and previously untreated patients infected with HCV genotypes 1 through 6 who had decompensated cirrhosis. Patients were randomly assigned to receive velpatasvir once daily for 12 weeks, sofosbuvir-velpatasvir plus ribavirin for 12 weeks, or sofosbuvir-velpatasvir for 24 weeks. The primary end point was a sustained virologic response at 12 weeks after the end of therapy


- This article describes the experience with DAAs in the treatment of posttransplant genotype (GT) 1 HCV from a consortium of community and academic centers (Hepatitis C Therapeutic Registry and Research Network [HCV-TARGET]). Twenty-one of the 54 centers contributing to the HCV-TARGET consortium participated in this study. Enrollment criteria included positive posttransplant HCV RNA before treatment, HCV GT 1, and documentation of use of a simprevir (SMV)/sofosbuvir (SOF) containing DAA regimen. Safety and efficacy were assessed. A total of 162 patients enrolled in HCV-TARGET started treatment with SMV+SOF with or without ribavirin (RBV) following LT.

- An ongoing, prospective, partially-randomised, phase 2, open-label study of once-daily SMV 150 mg + sofosbuvir 400 mg with and without ribavirin (RBV) 1000 mg (1200 mg for subjects ≥75 kg) in subjects with recurrent genotype 1 HCV post-orthotopic liver transplant


- The first multicenter included 123 patients that reported the efficacy, safety, and tolerability of this regimen in LT recipients


- Phase II, open label study investigating combination of simeprevir (SMV), daclatasvir (DCV), and ribavirin (RBV) administered for 24 weeks in 35 patients with recurrent HCV genotype 1b infection after orthotopic liver transplantation.


- Retrospective, single-center study of liver transplant recipients who received ledipasvir/sofosbuvir without ribavirin for treatment of recurrent hepatitis C.


- Retrospective, single-center, cohort analysis of kidney transplant recipients who received direct-acting antivirals for treatment of Hepatitis C. Endpoints included SVR at 12 weeks post completion of therapy and allograft function.


- The American Association for the Study of Liver Diseases and the Infectious Diseases Society of America practice guidelines for testing and treating hepatitis C virus infection.

● Consensus document regarding availability and use of Hepatitis C positive donor organs as well as transmission and payor concerns.


● Short communication reporting the use of increased risk donor organs. Describes a higher rate of use of increased risk donor organs compared to national rate of use.

7.1.7 Arenavirus and West Nile virus (WNV)


● Case series of WNV infection in kidney and pancreas transplant recipients that compared their outcomes with the general population and discussed the utility of U.S. plasma-derived IVIG as an adjuvant therapy for immunocompromised patients with complicated WNV infection. Arenavirus is mainly managed with supportive care with meticulous fluid balance and electrolyte infection. Intravenous ribavirin is the drug of choice for Lassa fever and should be considered for the treatment of Argentine and Bolivian hemorrhagic fever.


● Report two recipients of cadaveric kidneys from a single donor showed that organ recipients receiving immunosuppressive drugs may be at high risk for severe disease after WNV infection and blood transfusion was the probable source of the West Nile virus viremia in the organ donor.


● The primary treatment of WNV is supportive care such as hydration, hospitalization and use of ventilatory support, if needed. Temporary reduction in immunosuppression should be considered Intravenous immunoglobulin (IVIG) containing WNV specific antibodies has shown promise in the treatment of acute infection.

● A review of 3 cases of kidney or pancreas transplants recipients who developed West Nile fever and had meningoencephalitis and review the literature on West Nile fever in organ transplant recipients


● Therapeutic strategies of donor-derived WNV infection based on these 4 cases included supportive care, reduction of immunosuppression, and frequent intravenous immunoglobulin and interferon.

7.1.8 BK Polyomavirus


● The American Society of Transplantation’s practice guidelines for preventing and treating BKV in solid organ transplant recipients.


● A systemic review evaluated 40 studies looking at immunosuppression reduction and antivirals for the management of BKV. There is no graft survival benefit to adding leflunomide or cidofovir to immunosuppression reduction for the management of BKV.


● The use of BK viral monitoring and immunosuppression reduction kidney transplant recipients following the identification of viremia was associated with resolution of viremia and absence of BK nephropathy.

● BKV plasma PCR was collected pre-transplant, weekly for 16 weeks, and then at months 5, 6, 9, and 12.

● At the time of BKV identification, the antiproliferative was discontinued. If viremia did not clear within 4 weeks, the calcineurin inhibitor dose was decreased by 20-25%.


● The use of everolimus to minimize calcineurin inhibitors was investigated in kidney transplant recipients. Over two years, a higher rate of CMV (infection, disease, and syndrome) and BKV was found in groups not receiving everolimus.

- From June 2004 – December 2008, 823 patients were retransplanted following BK nephropathy in prior kidney. Of these patients, 17.5% required treatment for BKV after retransplant.
- The 1 and 3 year Kaplan–Meier graft survival rates and median GFR were 98.5%, 93.6%, 65.5 and 68.4mL/min, respectively.


- Patients taking fluoroquinolones for one month after kidney transplant to prevent UTIs was associated with lower rates of BK viremia within 1-year post-transplant.


- Treating BKV in kidney transplant recipients with leflunomide alone or leflunomide plus cidofovir resulted in graft loss of 15% with a follow-up time of 6-40 months.
- The target leflunomide metabolite (A77 1726) trough was 50 – 100 mcg/mL; leflunomide trough values of < 40 mcg/mL did not clear the virus until cidofovir was added or adequate leflunomide drug levels were attained.


- Treating BKV in kidney transplant recipients with cidofovir 0.5–1.0 mg/kg weekly for 4-10 weeks with probenecid in addition to immunosuppression reduction resulted in renal function stabilization and no graft loss with a follow-up time of 8–41 months (median 24.8).


- Kidney transplant patients with BKV were managed with immunosuppression reduction with or without cidofovir 1.0 mg/kg weekly for up to 10 weeks without probenecid. The Kaplan-Meier graft survival at 6 years was significantly improved in patients who received cidofovir.


- Even after the Banff 2009 meeting, there is not an optimal histologic grading system for BK nephropathy. Based on a comparison of the 3 existing histologic
grading systems, the newest from the Banff Working Proposal 2009 needs to be modified to incorporate the degree of inflammation.

- Checking BKV DNA PCR in plasma from kidney transplant recipients is a sensitive (100%) and specific (88%) method for identifying viral nephropathy.

- From 2004 - 2006, 34, 937 kidney transplant patients were reviewed for the diagnosis of treated BK virus (TBKV) and risk factors. TBKV was found in 1.6% and 2.6% of patients at 6 months 1 year after transplant respectively.
- Risk factors for TBKV included advanced donor age, pediatric, African American and male recipients, HLA-mismatching, tacrolimus maintenance and Thymoglobulin induction as baseline immunosuppression.

- Kidney transplant patients received immunosuppression reduction and 2 g/kg of IVIG. After a mean follow-up of 15 months, 88% of patients still had functioning grafts.

- A retrospective evaluation of kidney transplant recipients diagnosed with BK viruria treated with ciprofloxacin course following the initial reduction in immunosuppression showed that ciprofloxacin may be a useful therapeutic tool for BKV infection refractory to conventional treatment.

- Leflunomide therapy in addition to a reduction of the immunosuppressive therapies resulted in a significant decline in the BK viral load without further deterioration of renal function.

- A 3-month course of levofloxacin early following transplantation did not prevent BK viruria, but was associated with an increased risk of adverse events such as bacterial resistance.
7.1.9 Human immunodeficiency virus


- The American journal of transplantation guidelines on the management of Human immunodeficiency virus in solid organ transplantation


- Infectious diseases society of America review management of CKD in patients with HIV


- Review renal transplantation in HIV-infected patients, focusing on clinical aspects, therapeutic strategies (immunosuppressive and antiretroviral treatments), ethical issues, comorbidity, and future challenges


- A review that provides a brief overview of the recent success of solid organ transplant in the HIV population, and an update on the pharmacokinetic and pharmacodynamic interactions between currently available cART and immunosuppressants in HIV-infected patients, who underwent transplantation


- Review current recommendations for preventing infections both before and after transplantation


- Review several emerging issues in the field such as eligibility criteria, selection of optimal immunosuppression agents and antiretroviral therapy in this population, and management of co-infection with Hepatitis B and Hepatitis C post-transplant

- A prospective, nonrandomized study of kidney transplantation in HIV-infected patients who had a CD4 T-cell count of 200 per cubic millimeter or higher and an undetectable plasma reported that the interaction between antiretroviral drugs and immunosuppressants introduced several challenges but showed that kidneys from HIV-positive deceased donors can be transplanted into carefully selected HIV-positive recipients.


- Retrospective analysis reported that Decreasing the dose of tacrolimus to 0.03–0.08 mg daily in patients with concomitant boosted PI therapy resulted in stable tacrolimus blood levels without alteration of PI drug levels.


- Thymoglobulin reverses acute rejection in HIV-infected kidney recipients, but produces profound and long-lasting suppression of the CD4+ T-cell count associated with increased risk of infections requiring hospitalization.

7.1.10 Human Parvovirus


- The American society of transplantation guidelines for management of Parvovirus in solid organ transplantation.


- A review of 91 cases describing the epidemiology and clinical spectrum of posttransplant PVB19 infection over 16 years period, with literature review.


- A review article that discusses the epidemiology, clinical manifestations, diagnosis and treatment of less common viruses (e.g.: West Nile virus,
Parvovirus and human T-cell lymphotrophic virus) in the setting of kidney transplantation.

7.1.11 RNA Respiratory Viruses


- A multicenter prospective trial on hematopoietic cell transplant recipients with respiratory syncytial virus infection of the upper airways investigates the safety and efficacy of aerosolized ribavirin in preventing disease progression


- A study that investigated the utility of intravenous (IV) ribavirin with steroids for the treatment of RSV infection after LTx. In 18 symptomatic patients


- Supportive care is recommended for respiratory syncytial virus and reduction of immune suppression should be considered, particularly in those with severe disease. The role of specific antiviral treatment is controversial.
- The use of IgIV and ribavirin are not associated with benefit in the management of parainfluenza virus infections in stem cell transplant recipients, ribavirin has in-vitro activity and has been used to treat lung transplant recipients with lower tract disease


- The mainstay of treatment of human metapneumovirus consist of intravenous ribavirin at a starting dose of 33 mg/kg/day for the first 24 hours, then 20 mg/kg/day thereafter. Duration of therapy was determined by resolution of clinical symptoms and sustained improvements in respiratory function

7.1.12 Measles

- This report summarizes exposure to measles through international travel and illustrates the potential for immunocompromised patients to encounter the virus despite common coverage with effective vaccine in the US.


- A review of published data on the efficacy and safety of live viral vaccines for measles, mumps, rubella, or varicella in post-transplant patients currently on immunosuppression


- Serologies of 18 children were reviewed 6 months post-transplant. Four of 18 (22.2%) and 2/18 (11.1%) lost immunity to measles and varicella, respectively.


- Broad-spectrum anti-infective drugs combined with IVIG should be given for Measles infection in pediatric liver transplant recipients.
7.2 Bacterial

7.2.1 Central venous catheter infections and treatment options


- Cochrane review of 30 studies comparing antimicrobial (antibiotic and non-antibiotic) lock solutions to standard sealing solutions (usually heparin) of the CVC for HD. Authors concluded that antibiotic antimicrobial and combined (antibiotic-non antibiotic) lock solutions decreased infections compared to control lock solutions, whereas non-antibiotic lock solutions reduced infections only for tunnelled CVC. The level of confidence of the conclusions is low.


- Guidelines for management of CVC infections, including recommended antibiotic therapies for specific pathogens.


- IDSA guidelines for prevention of catheter-related infections.


- Recommendations for management of catheter-related bloodstream infections in heart transplant patients. Recommends empiric coverage of Gram-positive and Gram-negative bacteria as well as Candida spp., and antimicrobial therapy for durations longer than would be used in other patients.


- Observational study in stem cell transplant patients showed a significant decrease in rates of catheter-related bloodstream infections after switching from isopropanol to chlorhexidine for disinfection of catheter connections.

- Prospective non-randomized study of antimicrobial-coated CVCs (n= 58) compared with uncoated (n= 49) uncoated CVCs. Significantly fewer fever days per 1,000 catheter days and positive blood cultures were observed in the antimicrobial covered CVC group.

7.2.2 Mycobacterium tuberculosis (new)


- IDSA guideline for drug susceptible TB


- Consensus statement that defines indications for treatment of latent TB in solid organ transplant recipients. This document also provides guidance in the treatment duration for TB in transplant recipients and how to manage drug interactions with immunosuppressive medications.


- Multicenter study that identified the incidence and risk factors for developing TB in solid organ transplant recipients.


- Review article that describes the incidence, diagnosis, and treatment of both latent and active TB in the solid organ transplant population.


- A literature on the use of TB prophylaxis in kidney transplant recipients

Consensus report on the potential for donor derived TB and how to manage recipients with potential donor exposure.

- Retrospective, observational study that attempted to identify risk factors for immune reconstitution syndrome in transplants patients being treated for TB.

7.2.3 Nontuberculosis Mycobacterium (new)


- IDSA guideline, update in progress as of 2018.


- Guideline covering mycobacterial species most commonly causing infection post-transplant. Includes recommendations for treatment, dosing and drug interactions to consider.


- Review of literature summarizing case reports of NTM infections in stem cell and solid organ transplant recipients.


- Review of mycobacterial species causing lung infection, epidemiology of infection, recommended treatment options.


- Review of 19 cases of NTM infection in renal transplant patients including treatment and outcomes.

● Retrospective study of 27 cases of mycobacterial infection after renal transplant of total of 1261 transplants. Seven patients were found to have infection with NTM organism. The article include description of clinical manifestations, treatment and outcomes.

7.2.4 Nocardia (new)


● The American Society of Transplantation guidelines for management of Nocardia infections in solid organ transplant recipients.


● Ten-year retrospective evaluation of the epidemiology and identification of Nocardia isolates submitted to the CDC for antimicrobial susceptibility testing.

7.3 Fungal

7.3.1 PJP


● Thirty-five clinical trials including those that compared prophylactic regimens to placebo, different doses of prophylactic agents, and different prophylactic regimens were analyzed to identify ideal medications and their respective doses to prevent pneumocystis carinii pneumonia.


● Multicenter, open-label trial that evaluated atovaquone daily (N=536) compared to dapsone daily (N=521) as prophylaxis for the development of pneumocystis carinii pneumonia in human immunodeficiency virus positive patients who were intolerant to sulfamethoxazole-trimethoprim. The incidence of pneumocystis carinii pneumonia was similar among both study groups.

A retrospective analysis evaluating atovaquone 1500mg daily (N=25) compared to trimethoprim-sulfamethoxazole single-strength daily (N=160) for preventing pneumocystis carinii pneumonia within one year following kidney transplantation. No cases of pneumocystis carinii pneumonia were seen in either study group.


A retrospective analysis evaluating clindamycin/primaquine, trimethoprim-sulfamethoxazole, and dapsone prophylaxis for preventing pneumocystis carinii pneumonia in 206 patients with advanced human immunodeficiency virus infection. The rate of pneumocystis carinii pneumonia was lowest in patients receiving trimethoprim-sulfamethoxazole, followed by dapsone, then clindamycin/primaquine.


The American Society of Transplantation’s practice guidelines for preventing and treating pneumocystis carinii pneumonia in solid organ transplant recipients.


Retrospective review evaluating pneumocystis jirovecii pneumonia (PCP) and Nocardia occurrence in 1352 kidney transplant recipients receiving trimethoprim-sulfamethoxazole prophylaxis for one month following transplant. The incidence of PCP and Nocardia was low in this patient population.


Retrospective review evaluating pneumocystis jirovecii pneumonia (PCP) occurrence in kidney (N=657), kidney/pancreas (N=44), liver (N=436), lung or heart/lung (N=104) transplant recipients receiving trimethoprim-sulfamethoxazole prophylaxis for 6 months in kidney/pancreas, 12 months in lung, and no prophylaxis in liver transplant recipients. The overall incidence of PCP was low with the highest frequency seen in lung transplant recipients and all episodes occurring more than two years following transplant.


Systematic review on the use of adjunctive corticosteroid therapy in AIDS patients with PCP pneumonia. Identified that steroid therapy was most beneficial in patients with arterial O2 pressures < 70 mmHg, alveolar arterial gradient > 35 mmHg on room air, and when started with 72 hr of PCP treatment.

- Retrospective chart review that compared the efficacy of Bactrim, dapsone, and inhaled pentamidine for PCP prophylaxis in 200 HIV patients.

7.3.2 Aspergillus (new)


- IDSA guidelines for aspergillosis.


- Review article on aspergillosis in solid organ transplant recipients.


- Retrospective, case control series that identified risk factors for developing aspergillosis infections in solid organ transplant recipients.


- Non-inferiority trial comparing the efficacy of isavuconazole to voriconazole for the treatment of invasive mold infections. Majority of the study population had hematological malignancies and had infections caused by Aspergillus. Isavuconazole was found to be non-inferior to voriconazole for the treatment of invasive mould infections and was associated with decreased adverse effects. However, therapeutic drug monitoring for voriconazole was not utilized in this trial.


- Randomized trial in patients with hematological malignancies with invasive aspergillosis infections treatment with voriconazole monotherapy or combination therapy with voriconazole and anidulafungin. Combination antifungal therapy was found to have a survival benefit compared to monotherapy, but this trial was not powered to make superiority claims.

- A prospective, randomized trial comparing amphotericin B lipid complex and amphotericin B deoxycholate inhalations for prophylaxis of aspergillosis in lung transplant recipients. Both agents were associated with low rates of invasive fungal infections, but the lipid formulation was associated with decreased adverse effects.


- A retrospective study that aimed to characterize Aspergillus infections in lung transplant recipients. Patients that are pre-colonized with Aspergillus infections prior to lung transplant may benefit from systemic antifungal prophylaxis after transplant.


- Meta-analysis to determine the accuracy of serum galactomannan assays for diagnosing aspergillosis infections in immunocompromised patients. For solid organ transplant recipients, galactomannan assays were found to have a sensitivity of 0.22 and specificity of 0.84.

  7.3.3 Cryptococcus (new)


  - Treatment guidelines for cryptococcal disease in HIV-infected individuals, organ transplant recipients, and non-HIV-infected nontransplant hosts. Includes recommendations for other unique populations and those with Cryptococcus gattii infection.


  - The American Society of Transplantation guidelines for management of Cryptococcosis in solid organ transplant recipients.


  - In 79 patients with central nervous system cryptococcosis, lipid formulations of amphotericin B were associated with lower mortality when compared to amphotericin B deoxycholate.


  - Prospective, cohort study of patients with C. neoformans showed that lack of flucytosine induction is an independent risk factor for mycotic failure at two weeks.
7.3.4 Invasive Candidiasis (new)


- The American Society of Transplantation guidelines for management of donor-derived fungal infections in solid organ transplant recipients.


- The American Society of Transplantation guidelines for management of Candida in solid organ transplant recipients.


- Review of risk factors, prevention, diagnosis, and treatment of invasive fungal infections in SOT recipients (focus on candidiasis and aspergillosis).


- Retrospective review of liver transplant recipients to assess the feasibility and efficacy of tiered, targeted fungal prophylaxis. Intra-abdominal candidiasis was the most common fungal infection (73%); invasive fungal infections occurred in 6% of high-risk transplants who received prophylaxis versus 4% in low risk transplant who did not receive prophylaxis.


- IDSA guidelines for treatment of candidiasis.


- CDC MMWR report with a review of C. auris and description of reported cases in the U.S.
7.3.5 Histoplasmosis (new)

https://academic.oup.com/cid/article/45/7/807/541502

- IDSA guidelines for treatment of histoplasmosis.


- The American Society of Transplantation guidelines for management of endemic fungal infections in solid organ transplant recipients.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3814825/

- Retrospective review of 152 cases of histoplasmosis across 24 centers to identify risk factors and characterize infections. The average time to onset was 27 months, with the first year being the highest risk time frame. Ten percent of patients died, usually within the first month. In patients that survived one month after diagnosis, amphotericin followed by 12 months of an azole was usually successful.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5664161/

- Prospective surveillance study of 70 patients (64 SOT recipients) across 15 centers to characterize endemic infections in these patients.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5753102/

- Review of the epidemiology, clinical presentation, and treatment strategies for Histoplasmosis and Blastomycosis in SOT recipients.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4946023/

- “VITAL” study: Open-label nonrandomized phase 3 trial evaluating efficacy and safety of isavuconazole in treatment of rare invasive fungal diseases. Seven of the patients were treated for histoplasmosis, with 1 having complete success, 3 with partial success, 1 with stable disease, and 2 with progression of disease.
Median isavuconazole levels ranged from 3.2 ng/mL to 4.01 ng/mL and it was overall well tolerated.

7.4 Other

7.4.1 Timing of post-transplant infections (including donor-derived infections- new)


- This is a review article focusing on the epidemiology of infections after transplant categorized into three time frames- the first month, second through sixth month, and greater than six months.


- This is a review article that addresses patterns of infections post-transplant and the management of transplantation associated infections.


- This review article presents a timeline for infections post-transplant.


- This article reviews risk factors for and patterns of infections post-transplant.


- This article examines risk factors that contribute to infections in transplant patients as well as the timing of infections post-transplant.


- This article provides definitions for infections in transplant patients to be used during clinical trials assessing immunosuppressive therapy and also provides recommendations for monitoring for infections.

Retrospective review analyzing the transmission rates and 30-day graft and patient survival outcomes for recipients of organs procured from bacteremic donors.


Retrospective review of solid organ transplant recipients who developed cryptococcosis post-transplant, including nine who developed infection within 30 days which could indicate unrecognized pretransplant or donor-derived cryptococcosis.

7.4.2 Infectious exposure management

7.4.2.1 Measles


This report summarizes exposure to measles through international travel and illustrates the potential for immunocompromised patients to encounter the virus despite common coverage with effective vaccine in the US.


Serologies of 18 children were reviewed 6 months post-transplant. Four of 18 (22.2%) and 2/18 (11.1%) lost immunity to measles and varicella, respectively.

7.4.2.2 Varicella


No differences in median time to full healing of HSV rash were detected among patients receiving valacyclovir 1 gram TID versus 2 grams TID.

- Acyclovir limited cutaneous dissemination as well as abbreviated duration of positive cultures, pain associated with lesions, postulation of lesions, crusting of lesions and complete healing of lesions.


- Famciclovir 500 mg three times a day was compared to acyclovir 800 mg five times a day and no significant differences in new lesion formation, time to healing or duration of pain were observed


- Review article on the management of varicella zoster in solid organ transplant recipients.

7.4.2.3 Influenza


- Description of infection control and oseltamivir prophylaxis in an outbreak of 12 patients in a group of immunocompromised patients.

7.4.2.4 Tuberculosis


- CDC guidelines for evaluating patients at risk for developing TB after an exposure. Includes as section specifically regarding immunocompromised hosts that suggests considering them as “high priority” when evaluating potential contacts of a TB infected person.

7.4.2.5 Bacterial meningitis


- Guidelines for management of meningococcal outbreaks. There are no specific recommendations for immunocompromised patients.

7.4.3 Immunizations

- Comprehensive review of data surrounding vaccination pre- and post-transplant with useful summary table by the AST Infectious Diseases Community of Practice.


- Most recently published recommendations from the CDC regarding vaccination in the United States. Immunocompromised conditions highlighted in recommendations with helpful chart outlining specific timing/indication for each vaccine.


- Recommendations 88 through 104 pertain to vaccination pre/post solid organ transplant. Contains references to the individually relevant trials in this area of study and highlights where recommendations vary from CDC guidelines.


- Recommendations regarding administration of specific travel vaccines as well as standard of care vaccines post-transplant by the AST Infectious Diseases Community of Practice.

7.4.4 Toxoplasmosis prophylaxis and treatment (new)


- Summary of literature discussing chemoprophylaxis of toxoplasmosis infection.


- Review article discussing the relative risk of toxoplasmosis infection, timing of infection and prophylaxis options in solid organ and hematopoietic stem cell transplant recipients.

- Multicenter study of cases of toxoplasmosis with details including diagnosis, manifestations and outcomes.


- Single center study of the effect of T. gondii donor and recipient serostatus on heart transplant outcomes including 5 year mortality and rates of CAV comparing results to previous studies of association of toxoplasmosis serostatus to outcomes.