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A Protocol for the Management of Alemtuzumab Induced Leukopenia in Kidney Transplant Recipients

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Purpose: Leukopenia is a common complication following alemtuzumab induction in kidney transplant recipients (KTR), often limiting its use. Our institution developed a protocol to manage this complication (Table 1). We sought to determine the incidence of leukopenia following alemtuzumab in KTR and to characterize the management of leukopenia and neutropenia per this protocol.

Methods: This was an IRB approved, single center, retrospective study of adult KTR between 11/2015 – 02/2017 who received alemtuzumab. We assessed baseline demographics, G-CSF administration, medication changes, white blood cell (WBC) count (leukopenia defined WBC < 4 x 10^3/microL; severe leukopenia defined as WBC ≤ 2.5 x 10^3/microL) and absolute neutrophil count (ANC) (neutropenia defined as ANC ≤ 1000/mm^3) at specified time points until 10 weeks post-transplant.

Results: During the study period, 98 KTR (77%) experienced leukopenia and 54 KTR (43%) developed severe leukopenia. Of the KTR with severe leukopenia, 3 required only medication changes and 19 required G-CSF after medication changes to resolve their severe leukopenia. Ten KTR received G-CSF outside the parameters of the protocol. In total, 29 KTR received G-CSF and 25 KTR had no intervention for their leukopenia. The median WBC for all patients declined from 9.7 x 10^3/microL immediately after transplant to 3.4 x 10^3/microL at the completion of follow-up (Figure 1).

Conclusion: Our study confirmed that centers should anticipate more than 40% of KTR receiving alemtuzumab will experience severe leukopenia. Providers, however, may take different approaches to the management of this complication. Our center's protocol offers a stepwise approach to the management of leukopenia in KTR who received alemtuzumab for induction.

Table 1. Alemtuzumab Induced Leukopenia Protocol

WBC/ANC	Intervention
WBC ≤ 2.5 x 10^3/microL	• Check CMV PCR • Hold SMX/TMP and valganciclovir (if not CMV mismatch) • Order ANC
ANC < 1000/mm3	• Decrease mycophenolic acid product by 50% if CNI therapeutic • Administer G-CSF
ANC < 500/mm3	• Hold mycophenolic acid product • Administer G-CSF • Initiate low dose prednisone if CNI sub-therapeutic and POD <60 or high risk for rejection

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Evaluation of Immunosuppression and Infection after Desensitization in Lung Transplantation

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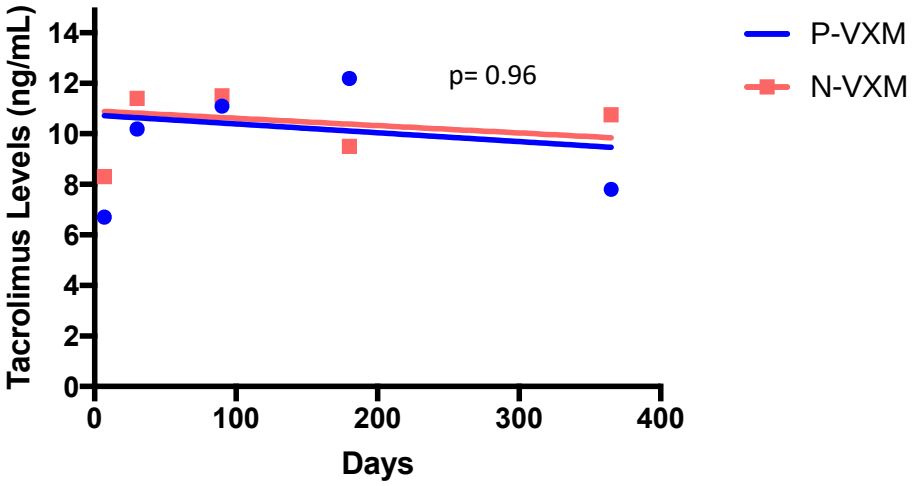
Purpose: To reduce waitlist time for sensitized lung transplant recipients (LTR), our center used peri-operative desensitization for LTR with a positive virtual crossmatch (P-VXM). We aimed to examine immunosuppression, infection and survival in our desensitized P-VXM LTR compared to negative virtual crossmatch (N-VXM) LTR.

Methods: This was an IRB-approved, single-center retrospective study of LTR transplanted between 01/2015-05/2017. Multi-organ transplants or those with no virtual crossmatch available were excluded. Variables for analysis included induction agents, tacrolimus levels, mycophenolate mofetil daily doses, infections and patient survival.

Results: Seven LTR (20%) in the N-VXM group received induction, 6 of which received a lymphocyte depleting agent. Desensitization therapy for all P-VXM LTR included rabbit anti-thymocyte globulin (median total dose of 3 mg/kg, IQR 2.7-4.8), intravenous immunoglobulin G (median total dose of 1 g/kg, IQR 1-1) and plasmapheresis (3 sessions intra-op and a median of 4 sessions post-op, IQR 4-5) within 7 days of transplant. Maintenance immunosuppression appeared similar between groups, with no significant difference in tacrolimus trough levels (p=0.96) as shown in Figure 1. There were no significant differences in infections (Table 1) or patient survival (100% in the P-VXM group vs. 94% in the N-VXM group, p=0.26) at a median time to follow-up of 685 days (IQR 602-697) vs. 359 days (IQR 262-502), respectively; p= 0.008.

Conclusion: Our study has shown no differences in maintenance immunosuppressive regimens, infections and survival in P-VXM LTR who underwent desensitization when compared to N-VXM LTR, despite more use of lymphocyte depleting agents and plasmapheresis. Based off our single-center study, P-VXM LTR may be safely transplanted, although more studies are warranted.

Figure 1. Tacrolimus Trough Levels



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Desensitization in Lung Transplant Recipients with a Positive Virtual Crossmatch

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Purpose: Sensitized lung transplant recipients (LTR) are at an increased risk of acute rejection and mortality. Studies comparing outcomes between LTR with a positive virtual crossmatch (P-VXM) who undergo desensitization vs. LTR with a negative VXM (N-VXM) are limited. The purpose of this study is to compare the incidence of biopsy proven acute rejection (BPAR) between these groups.

Methods: This was an IRB-approved, single-center retrospective study of LTR transplanted between 01/2015 - 05/2017. Peri-operative desensitization for P-VXM patients included anti-thymocyte globulin, intravenous immunoglobulin G and plasmapheresis. Multi-organ transplants, or those with no VXM available were excluded. The primary outcome was incidence of BPAR. Secondary outcomes included time to BPAR, incidence of and time to a composite of BPAR or clinical rejection, incidence of infection and survival.

Results: There were 101 lung transplants performed during the study period. Based on inclusion criteria, 11 patients with a P-VXM and 35 patients with a N-VXM were analyzed. Baseline characteristics are shown in Table 1. There were no statistical differences in the incidence of or time to BPAR, the incidence of or time to the composite of BPAR or clinical rejection, incidence of infection and survival (Table 2). P-VXM patients had 100% survival at a median time to follow-up of 685 days.

Conclusion: LTR with a P-VXM who underwent peri-operative desensitization showed no difference in clinical outcomes compared to N-VXM LTR. Based on these limited data, P-VXM LTR may be transplanted with a standardized desensitization protocol.

Table 1. Baseline Characteristics

	P-VXM (n= 11)	N-VXM (n= 35)	p-value
Age at transplant, median years (IQR)	54 (51,59)	65 (56,69)	0.02
Male sex, n (%)	4 (36)	21 (60)	0.17
Race, n (%)			
Black	4 (36)	9 (26)	0.49
Non-Black	7 (64)	26 (74)	
Indication for transplant, n (%)			
IPF	8 (73)	14 (40)	0.16
COPD	2 (18)	11 (31)	
Other	1 (9)	10 (29)	
Lung transplant type, n (%)			
Double lung transplant	6 (55)	19 (54)	0.99
Length of hospitalization after transplant, median days (IQR)	22 (15,25)	15 (10,26)	0.46

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A Quantitative approach to optimize levetiracetam dosing in critically ill patients undergoing continuous venovenous hemofiltration

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Background and Objectives: Limited data exist on the effect of continuous renal replacement therapy (CRRT) methods on antiepileptic drug pharmacokinetics (PK). Patients who undergo CRRT may experience refractory seizures from underexposure of therapy, while serious adverse effects may appear in those who are overexposed. Appropriately designed PK studies could potentially optimize dosing recommendations in patients undergoing CRRT. This study aims to assess the impact of continuous venovenous hemofiltration on key pharmacokinetic parameters in critically ill patients receiving levetiracetam. Individualized dosing recommendations based on key CRRT specific flow parameters will also be derived.

Methods: Nine patients receiving oral or intravenous levetiracetam and continuous venovenous hemofiltration (CVVH) in various intensive care units at a large academic medical center were enrolled to investigate the need for dosing adjustments. Pre-filter, post-filter, and ultrafiltrate samples were taken before dosing, after the completion of the infusion or 1 hours post oral dose, and 6 additional time points post-infusion or post oral administration. Plasma concentrations were determined using a validated HPLC-UV bioanalytical method. Blood and effluent flow rates and laboratory parameters were also collected at the time of sampling. Pharmacokinetic analysis was conducted using Phoenix WinNonlin® 7.1 (Pharsight Corporation).

Results: The average sieving coefficient (ratio of ultrafiltrate concentrations to prefilter plasma concentrations) was 0.90 ± 0.1 and the average volume of distribution was 0.75 ± 0.08 L/kg. Six out of the nine patients experienced concentrations outside the reported therapeutic range (12-46 mg/L) of levetiracetam. Average total drug clearance for patients taking 750 mg, 1000 mg, and 2000 mg were 3.27, 5.18, and 4.38 L/hr respectively, suggesting that differences in clearance can be attributed to differences in ultrafiltration flow rates. Individual dosing recommendations were based on matching exposures seen in subjects with normal renal function receiving a dose of 1000 mg.

Conclusion: Preset ultrafiltrate rates were different amongst patients and need to be taken into consideration when determining an appropriate dose. Patients with higher ultrafiltrate rates will have increased drug clearance and therefore will require higher doses in order to match exposures seen in patients with normal renal function. Therefore, individualized dosing recommendations should be based on CRRT flow parameters and drug specific sieving coefficients.

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Influence of parental asthma knowledge on child asthma control

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Purpose: Asthma is the most prevalent chronic disease state affecting children in the United States. Integrating self-management education is a main component for effective asthma control according to the 2007 National Heart, Lung and Blood Institute (NHLBI) Guidelines for Diagnosis and Management of Asthma. For pediatric patients, parental involvement regarding correct medication use, administration technique, environment control, and symptom assessment plays an important role in the child's asthma management, requiring parents to have knowledge of how each factor affects a child's asthma. The objectives of this study was to determine the correlation of parents' asthma knowledge and their child's asthma control.

Methods: This study has received approval from the University of Maryland Institutional Review Board. After obtaining informed consent, student pharmacists administered face-to-face surveys to parents of children diagnosed with asthma between the ages of 0 to17 years. Parents were recruited from an inner city, academic medical center general pediatric unit, two asthma clinics and local churches. Data was collected between April 2015 and September 2017. The 20-minute survey included questions regarding the parent demographics, general asthma knowledge and their child's asthma control. Parents' asthma knowledge was assessed using a validated 12-item consumer questionnaire, and was scored as 0 to 12 with 1 point given for each correct response. Parents were also asked to rate their child's asthma control. Additional questions regarding day and night symptoms, interference with normal activity, and usage of additional medications were included and used to categorize the child's asthma control using NHLBI asthma clinical practice guidelines as "well controlled", "not well controlled" or "very poorly controlled". Spearman's correlation was used to detect any correlations between parental asthma knowledge and child asthma control. In addition, one-way analysis of variance (ANOVA) was performed to detect differences in the mean asthma knowledge scores among asthma control categories.

Results: Sixty-six parents of children with asthma were included. Twelve (18.2 percent) patients' asthma were classified as "well controlled", 28 (42.4 percent) were "not well controlled" and 26 (39.4 percent) were "very poorly controlled". Parental asthma knowledge scores ranged between 4 and 11. No correlation (p equals 0.2) was found between asthma control and asthma knowledge. The mean asthma knowledge scores were similar among each asthma control category ("well controlled" 7.2 plus or minus 1.7, "not well controlled" 7.1 plus or minus 1.9, "very poorly controlled" 7.7 plus or minus 1.8, p equals 0.4). Similar knowledge questions were also missed among the three asthma control categories. Parents were unable to differentiate between preventer and reliever medications as most parents reported that both types of inhalers should be given to their children during asthma attacks. Other questions that many parents struggled with were pertaining to general triggers of asthma attacks.

Conclusion: No correlation was found between parental asthma knowledge and child asthma control. A very low level of asthma knowledge was identified in some parents. It is vital that pharmacists continue to educate parents and children on asthma and focus on the different types of asthma medication as well as triggers patients may encounter.

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Rates of off-label dosing of apixaban in end stage renal disease: a retrospective analysis of a large health-system

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Purpose: Apixaban is approved for stroke prophylaxis in patients with atrial fibrillation (AF) and for the treatment and secondary prevention of venothromboembolism (VTE). For thromboembolism, no dose adjustment is recommended regardless of renal function whereas for AF, 2 out of 3 parameters must be met: SCr > 1.5, age > 80 and weight < 60 kg. Whether these recommendations are followed in practice remains a concern, and consequences of off-label dosing are associated with worse outcomes. The purpose of this study was to evaluate apixaban dosing in patients with end stage renal disease (ESRD) admitted to a large academic hospital system.

Methods: This study was a retrospective chart review approved by the Institutional Review Board that included patients 18 years of age and older who carried a diagnosis of ESRD requiring intermittent hemodialysis who received at least one dose of apixaban while admitted to a hospital within a large academic hospital system between 11/2015 through 8/2017. Patients were excluded from the study if they received peritoneal dialysis. A total of 51 patients were included in the final analysis. The study's primary outcome was the composite rate of off-label doses of apixaban administered. The secondary outcome was the rate of underdosing, the rate of overdosing, the rate of off-label doses based on indication, and the rate of off-label doses by each hospital within the health system.

Results: Fifty-one patients were included in the study including 20 patients with AF, 24 patients with VTE, and 7 patients with an off-label indication. Of these patients, 33 received the correct dose (65%) and 18 received an off-label dose (35%). All 18 patients were underdosed; no patients were overdosed. Of the underdosed patients, five were on anticoagulation for AF, eleven for VTE, and two for an off-label indication. One-quarter (25%) of patients on anticoagulation for AF received an off-label dose while 45% of patients on anticoagulation for VTE received an off-label dose. Four patients received a dose change during hospitalization, leaving 15 inappropriately dosed patients at discharge. Three patients were switched to an appropriate dose, all of whom were on anticoagulation for AF, while one patient on anticoagulation for VTE was switched to an inappropriate dose. Seven patients were not on apixaban at discharge, leaving 44 patients including 19 patients with AF, 20 with VTE, and 5 with an off-label indication. Upon discharge, 11% of AF patients were prescribed an off-label dose and 55% of VTE patients were prescribed an off-label dose. Four hospitals were included in the analysis with rates of off-label dosing ranging from 17% to 42%.

Conclusion: A significant number of patients received an off-label dose of apixaban, a majority of whom were on anticoagulation for VTE. There appears to be a disconnect between the FDA recommended dose of apixaban in patients with ESRD and what is seen in practice, showing the importance of education and pharmacist intervention to ensure appropriate dosing.

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Evaluation of medication errors at the transition of care from an ICU to non-ICU location

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Background: Patients transferred between levels of care are vulnerable to medication errors. We hypothesized that medication errors occur at the transition of care (TOC) from an ICU to non-ICU location with multi-factorial causes.

Methods: This was a multicenter, retrospective, observational, 7-day point prevalence study. Adult patients transferred from an ICU to non-ICU location within a hospital were included. The primary outcome was the rate of medication errors occurring during TOC from an adult ICU to non-ICU location in a hospital. The secondary outcomes were types of and risk factors for medication errors occurring during TOC. Risk factors associated with medication errors were analyzed using a logistic regression.

Results: 985 patients were included from 58 ICUs. Among patients transferred, 45.7% had a medication error occur during TOC. Of 450 patients with a medication error, average 1.88 errors (SD: 1.30; range: 1-9) per patient occurred. The three most common types of errors were continuation of medication with an ICU-only indication (28%), indication with no pharmacotherapy (19%), and pharmacotherapy with no indication (12%). 94% of errors were severity category C or below with the majority of errors (75%) in severity category C, errors that reached the patient but did not cause harm. The occurrence of errors varied by type and size of the institution and ICUs. Requiring renal replacement therapy during ICU stay and number of medications ordered following transfer were identified as factors associated with the occurrence of an error (OR 2.90, 95% CI 1.42-5.95; OR 1.06, 95% CI 1.00-1.11, respectively). Orders for anti-infectives (OR 1.61, 95% CI 1.16-2.24), hematologic agents (1.79, 95% CI 1.20-2.67), and IV fluids, electrolytes or diuretics (OR 1.69, 95% CI 1.19-2.41) at time of transfer were associated with an increased odds of error occurrence. Factors associated with decreased odds of error occurrence included daily patient care rounds in the ICU (OR 0.14, 95% CI 0.07-0.29) and orders discontinued and rewritten at the time of transfer from the ICU (OR 0.44, 95% CI 0.22-0.85).

Conclusions: Nearly half of the patients transferred experienced medication errors at the time of TOC from ICU to non-ICU location within the same institution. Most errors reached the patient but did not cause significant harm. This study identified risk factors upon which risk mitigation strategies should be focused.

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Characterization of Vasopressin Use for Shock States

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Introduction/Hypothesis: Vasopressin has been used as an adjunctive vasopressor in shock states, including septic and vasoplegic shock. Studies evaluating vasopressin in shock states did not consistently demonstrate clinical benefit. In addition, the cost of vasopressin increased substantially. This study was conducted to characterize vasopressin use in a tertiary medical center.

Methods: It was a single- center, retrospective chart review of adult patients (>/= 18 years old) who received vasopressin infusion for shock between June 1 2016 to June 30 2016. Primary outcome is to describe dosing strategy of vasopressin (dose, duration, sequence of initiation and discontinuation in relation to catecholamine). Secondary outcomes include effect of vasopressin on catecholamine dose and incidence of hypotension after discontinuation of vasopressin. Baseline demographics were collected, including age, gender, location of patient and indication of vasopressin.

Results: Total of 81 patients were included in this evaluation, and majority of patients were in Medical ICU (25.9%) and Surgical ICU (24.7%). Most common indication for vasopressin was septic shock (64.5%). In most cases (84%), vasopressin was initiated after catecholamine infusion was started. The median dose of vasopressin was 0.04 units/min and duration was 36.1 hours (11.3-78.4). Addition of vasopressin did not lead to significant change in catecholamine requirement at 1 hour. Vasopressin was stopped first in 45.7% of patients. More patients developed hypotension if vasopressin was stopped first (37.8% vs. 14.7%) and required reinitiation of vasopressin (40.5% vs. 20.6%).

Conclusions: Majority of patients received vasopressin for septic shock, and vasopressin was often added after catecholamine infusion was started, with no change in catecholamine requirement after addition of vasopressin. With the high cost of vasopressin and inconsistent benefit seen, further studies should be done to confirm any clinical benefit. The sequence of discontinuation of vasoactives should also be evaluated.