ISSN 2380-0445

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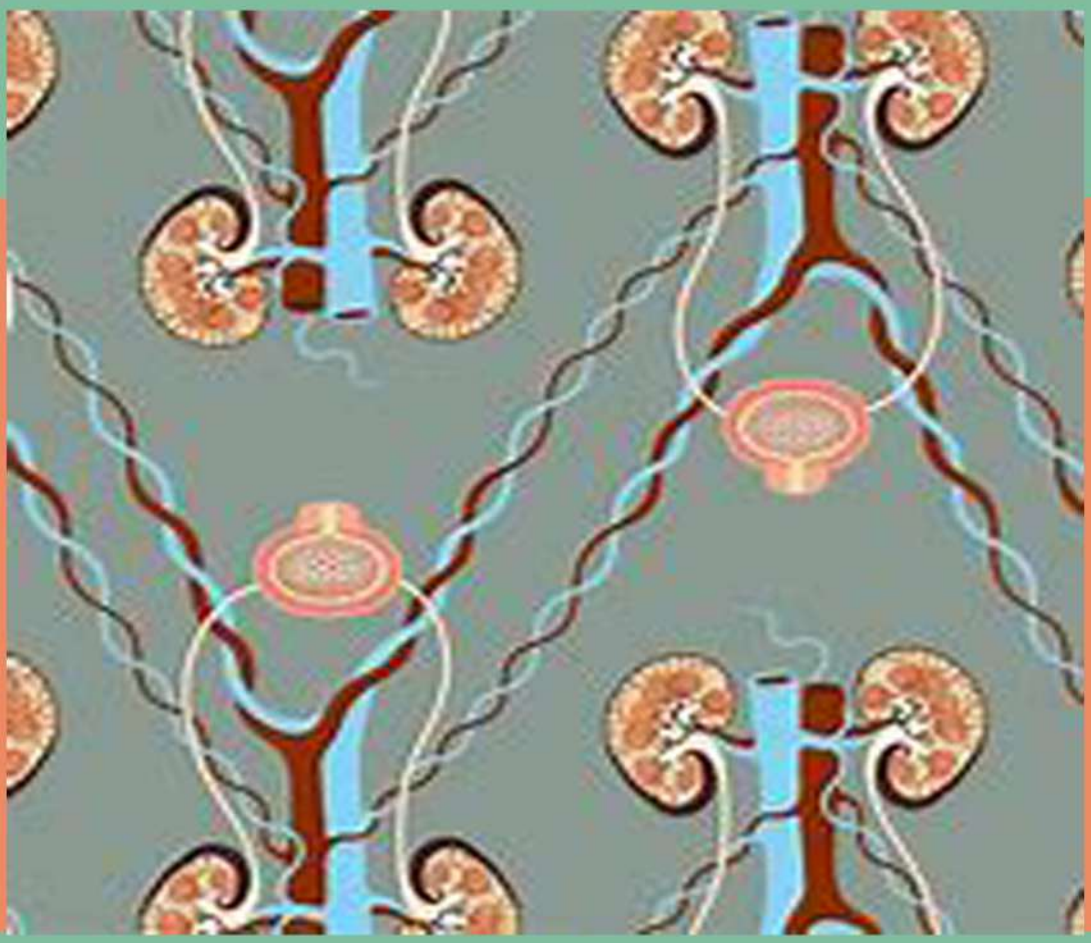
NEPHROLOGY

Open Journal

2020-2021, December | Volume 6, Issue 1



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Observational Study

Accuracy of Bioimpedance Modalities for Fluid Assessment in Hemodialysis Patients: A Randomized Observational Study

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Article Information
Received: July 28th, 2020; **Revised:** August 11th, 2020; **Accepted:** August 14th, 2020; **Published:** August 20th, 2020

Cite this article
John JC, Gipson GT, King CD, Bunchman TE, Karam O. Accuracy of bioimpedance modalities for fluid assessment in hemodialysis patients: A randomized observational study. *Nephrol Open J.* 2020; 6(1): 1-7. doi: 10.17140/NPOJ-6-124

ABSTRACT

Aim
Fluid overload is a major contributor to mortality in critically ill patients but is difficult to estimate clinically. Bioimpedance has been used to estimate fluid volumes with three different methods of analysis:1. single-frequency; 2. multi-frequency; 3. bioimpedance spectroscopy. The aim of this study is to assess the accuracy of different types of bioimpedance analysis in detecting changes in fluid volumes.

Methods
Prospective observational study, in end-stage renal disease patients requiring dialysis, in a tertiary care center. During hemodialysis, we assessed the correlation between change in estimated total body water volumes, as measured by all three methods of bioimpedance, and fluid volumes removed, as measured by changes in body weight.

Results
Twenty-four pediatric and adult patients were included in the study (median age 42.4 years) with a total of 30 study assessments performed. There was a weak correlation between change in body weight and change in estimated total body water volumes (R=0.15, 0.41, and 0.38, respectively). In the Bland-Altman analysis, the mean biases along with their associated 95% confidence limits of agreement were -0.23 L (-4.1 to 3.5 L) for single-frequency; -1.1 L (-4.1 to 1.9 L) for multi-frequency; and -0.6 L (-6.1 to 4.8 L) for bioimpedance spectroscopy.

Conclusion
In this study of end-stage renal disease patients requiring dialysis, the accuracy of bioimpedance measurement to evaluate fluid changes was poor, regardless of bioimpedance modality.

Keywords
Body composition/physiology; Body fluid/physiology; Electric impedance; Extracellular fluid/metabolism; Renal dialysis.

INTRODUCTION

Fluid overload is an independent risk factor for morbidity and mortality in both adult and pediatric critically ill patients.[1,2] However, measuring fluid overload is not consistent nor dependable. Gold standards for fluid overload assessment, such as air displacement plethysmography[3] or bromide and deuterium dilutions[4] are impractical in the clinical setting as they require specific devices, specific expertise, and are time-consuming, which has led to these techniques being mainly used for research purposes.

Weights and measurements of total fluid balance have been used as a surrogate marker; however, these are known to be inaccurate.[5] Specific physical exam findings (e.g. edema, mentation, capillary refill), static and dynamic vital signs (e.g. blood pressure, pulse, changes in variables with fluid administration or respiratory cycle), imaging modalities (e.g. echocardiography, lung ultrasound, chest X-ray), and laboratory data (e.g. fractional excretion of sodium/urea, blood lactate, mixed venous oxygen saturations) have been used for fluid evaluation but have large variability in assessments.[6]

Bioimpedance analysis (BIA) is a form of fluid assessment that has been used to evaluate total body water volume (V_{TBW}), intracellular water volume (V_{ICW}), and extracellular water volume (V_{ECW}) and has been studied for over the last 5 decades.[7] There are three major techniques of measuring BIA: Single Frequency (SF), Multi-frequency (MF), and Bioimpedance Spectroscopy (BIS). Each of these methodologies uses different equations and theories to derive fluid status, and therefore have inherent variations in fluid volume estimations.[8] The few who have evaluated their accuracy found strong inverse associations between estimated V_{TBW}(eV_{TBW}) as assessed by BIA and net ultrafiltration volume($V_{UF,net}$), with $V_{UF,net}$ explaining 92-99% of variability in V_{TBW} measurements.[9,10] Although studies have been performed that compare BIA to other existing technologies, there are few studies comparing various BIA methods with each other.[11] Most of these latter comparisons were associated with assessing nutritional status rather than fluid overload as their primary outcome.[11]

Our objective was to measure serial static body fluid volumes as estimated by each BIA modality, and then to explore the correlations between these derived volume changes and $V_{UF,net}$ or changes in body weight (ΔWt) thus assessing their validity in measuring changes in fluid status.

MATERIALS AND METHODS

Study Population

In order to accurately compare bioimpedance modalities, we required a patient population that demonstrate quantifiable fluid shifts over a short clinical period. End stage renal disease (ESRD) patients in general have difficulties with fluid accumulation and require discrete amounts of fluid removal to maintain euvolemia.

Patients were recruited and enrolled at the Virginia Commonwealth University (VCU) Adult Chronic Dialysis Center and Pediatric Dialysis Center (Richmond, Virginia, USA), a tertiary care center which represents a medium-sized urban area population.

Inclusion criteria were patients with ESRD, age greater than 36-months, requiring at minimum two weekly sessions of dialysis, who are anticipated to require at least a month of dialysis, based on attending physician's assessment. ESRD was defined as requiring dialysis, but not based on a specific glomerular filtration rate. Exclusion criteria were 1) patients who refused to participate in the study; 2) patients with implanted medical devices such as pacemakers or defibrillators, as these could interfere with assessments; 3) patients who were pregnant at the time of enrollment (assessed by date of last menstrual period), 4) patients with limb amputations (not accounted for in equations for BIA); and 5) patients who have significant abrasions or dermatologic conditions not allowing proper placement of electrodes.

This protocol was approved by VCU's Institutional Review Board (HM20012398). As the BIA devices were not approved by the Food and Drug Administration (FDA) for clinical use in non-healthy populations, and some were not approved for use in children, we also obtained a non-significant risk (NSR) investigational device exemption (IDE). All patients signed informed consent.

Study Design

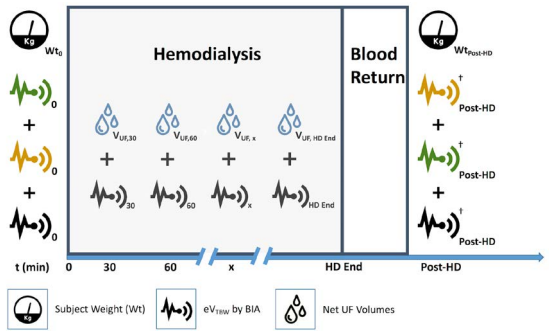
This is a single-center prospective observational study comparing estimated changes in volume before, during, and after dialysis as measured by three standard bioimpedance modalities, against fluid removal during scheduled hemodialysis sessions.

For each session we obtained a pre-dialysis weight, blood pressure, heart rate, and temperature. Ambulatory patients were weighed using a Scale-Tronix, 5702 Mobile Bariatric Standing Scale (Hillrom, Chicago, Il, USA). Immobile patients had weights obtained with a Hill-Rom, VersaCare Bed Scale (Hillrom, Chicago, IL, USA). Weights were expressed in kilograms (kg). Ambulatory patients had heights obtained using a stadiometer. Standard methods of weight and height measurement were used, shoes were taken off, and feet were placed together, with the patient's back against the wall. Immobile patients had heights obtained using a standardized 4 point measurement method[12]: measurements were obtained by adding the collective distances from vertex of the head to the medial end of the clavicle, lateral aspect of shoulder to anterior superior iliac spine, anterior superior iliac spine to lateral aspect of knee joint, and the lateral aspect of knee joint to sole of foot. Heights were expressed in centimeters (cm).

Patients were randomized for order of baseline BIA measurements with all three devices (loaned to us by the manufacturers), representing the three major modalities of BIA: 1) SF: Quantum V SF BIA (RJL Systems, Clinton, MI, USA), 2) MF: S10 BWA (In Body, Seoul, South Korea), 3) BIS: SFB7 BIS (ImpediMed, Brisbane, Australia). Sequence of measurements were randomized and predetermined prior to assessments by random number generation *via* Excel (Microsoft, Redmond, WA, USA), in a sealed envelope. All machines were used according to their manufacturer's specifications with patients in supine position if in a bed and patients in recumbent position if in a dialysis chair. Patients were made to maintain this position for at minimum 5 minutes prior to measurements. Placement of leads was standardized per manufacturer recommendations and research staff were trained on proper lead placement. Leads were removed between each measurement. Assessments took on average approximately 5 minutes each. The device that was randomized to be the third to be assessed was left on for the duration of the

dialysis run (Figure 1). We obtained measurements in 30 minute intervals during the dialysis run. As the machines require a weight input to calculate estimated volumes, initial BIA measures and all the interval measures are based on the initial weight. During the 30 minute intervals, hematocrit as assessed by Crit-line In-line Monitor (In-Line Diagnostics, Kaysville, UT, USA), clinical assessment of volume was assessed based off symptoms (cramping, nausea, dizziness, abdominal pain, etc.), interval V_{UF} and $V_{UF,net}$ were recorded, and routine vital signs were obtained. Post-dialysis weight, blood pressure, heart rate, and temperature were obtained. Post-dialysis BI measurements were obtained with all three devices, with another randomized order of assessment. Time from blood rinse-back to post dialysis BI measurements was recorded to ensure average times were similar (to balance the reduced error from prolonged equilibration). Measurements were obtained using manufacturer specifications in the same position as they were previously measured during the assessment. After the study enrollment period had finished, the data was reviewed, and two patients were found to have systematic errors during the interval measures (one for SF, the other for MF) and were thus excluded from the 30 minute interval analysis.

Figure 1. *Visual Protocol*



Patients were weighed prior to their initial analysis with all three methods. In this situation, the patient was randomized to bioimpedance device #3 for interval analysis.Volume measurements using device #1 and device #2 were performed, then device #3 was performed and left on for the duration of the hemodialysis run using the initial weight (Wt_0) input for the interval measurements. Ultrafiltration volumes were obtained for the corresponding time intervals ($V_{UF,t}$). Following hemodialysis, the three devices were reassessed based on predetermined, random order.

†Measurements with each BIA Methods were performed using $Wt_{Post\text{-}HD}$
1. Outcome, Net Changes: ΔWt vs total change in estimated total body water volume ($\Delta eV_{TBW,total}$).
2. Outcome, Interval Changes:$V_{UF,t}$ vs interval $\Delta eV_{TBW,t}$.

Outcomes

Our primary outcome was the change in bioimpedance by each modalitye V_{TBW} measured just before and just after dialysis, and ΔV_{TBW}, as measured by the $V_{UF,net}$, both measured in Liters.

Our secondary outcome was 30 minute interval ΔeV_{TBW}, as measured by BIA during dialysis and amount of $V_{UF,net}$ assessed every 30 minutes, all measured in Liters.

We also recorded the gender, age (in months), race, ethnicity, cause of ESRD, duration of ESRD, anuric status, and diuretic use.

Statistical Analysis

We report the ΔeV_{TBW}, ΔWt, and change in $V_{UF,net}$ as [final measure–initial measure].

The accuracy of the three BIA devices was assessed by three methods:

(1) The proportion of values where the difference between the ΔeV_{TBW} for each BIA modality and the ΔWt was a) less than 10%, and b) less than 20%.
(2) The correlation between the ΔeV_{TBW} for each BIA modality and the ΔWt; we considered, a priori, a good correlation defined by a Spearman R>0.8.
(3) A Bland-Altman plot, to report the mean bias and 95% confidence limits of agreement between the two methods.[13] For each device, we plotted the average between ΔeV_{TBW} and ΔWt, against the difference between ΔeV_{TBW} and ΔWt. We then applied a linear regression to evaluate for potential proportional errors.[14]

The accuracy of trends over 30 minute periods was assessed by plotting the ΔeV_{TBW} measures taken 30 minutes apart against the $V_{UF,net}$ during those same 30 minutes. The individual 30 minute interval measures should reside within standard graphical quadrant IV, thus indicating a decrease in V_{TBW} when the V_{UF} was positive. The percentage of data points that lie within these confines will be considered the minimum tolerable concordance (MTC). We used a linear regression model to adjust for the potential effect of the different times (e.g. 0 to 30 minutes *vs* 120 to 150 minutes).

Linear modeling analyses were performed with SAS version 14.3 for Windows (SAS, Cary, NC, USA). All other statistical analyses were performed with Statistical Package for the Social Sciences (SPSS) version 24 for Windows (SPSS, Chicago, IL, USA).

Sample Size

As there is no preliminary data to allow for a sample size calculation, we based our calculations on an α of 0.05, a β of 0.1 (i.e. 90% power), and an anticipated R of 0.5, which allowed us to determine we needed a minimum 38 independent measures to demonstrate that the correlation coefficient differs from zero. As the three devices were loaned to us for a period of seven-months, we aimed to enroll as many patients as possible.

RESULTS

From September 1, 2018 to March 31, 2019, a total of 24 patients were enrolled in the study, with a total of 30 measures. The median age was 42.4 years-old (IQR 23.1; 58.7). Demographic data and associated summary statistics are presented in Table 1.

For each dialysis run, $V_{UF,net}$ was strongly correlated with the ΔWt, with a Spearman correlation coefficient of 0.94.

Table 1. *Patient Demographics and Summary Statistics*	
Gender	Male: 19/24 (79%)
Age	42.4 years (IQR 23.1; 58.7)
ESRD Duration	3.9 years (IQR 0.1; 4.9)
Anuric State	Yes: 11/24 (46%)
Diuretic Use	Yes: 5/25 (25%)
Ethnicity	Hispanic: 8/24 (33%)
	Non-Hispanic: 16/24 (67%)
Race	Caucasian: 5/24 (21%)
	African American: 12/24 (50%)
	Native American: 1/24 (4%)
	Other: 6/24 (25%)
ESRD, End Stage Renal Disease; IQR, Interquartile Range	

Overall Accuracy

We assessed the percentage of measures of ΔeV_{TBW} that were within a 10% margin of the ΔWt for each modality (SF, MF, BIS). These were 4%, 14%, and 4%, respectively. The percent of measures within a 20% margin of the ΔWt, were also performed and found to be 11 %, 18%, and 18%, respectively.

Correlations and Bland-Altman analyses were performed for ΔeV_{TBW} with each modality, SF, MF, and BIS respectively.

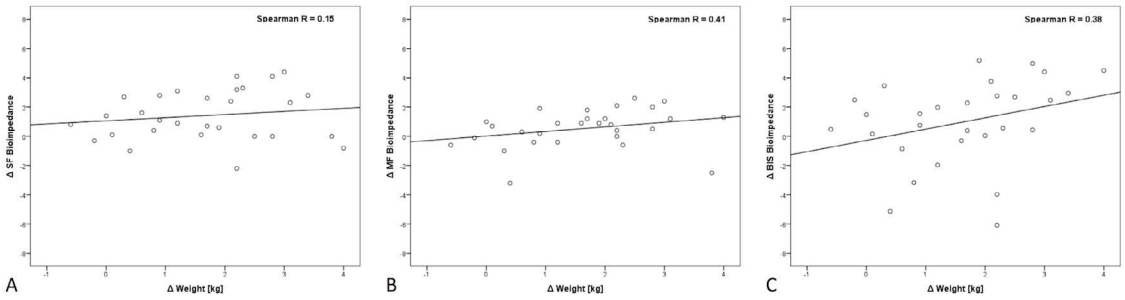
There was a poor correlation between ΔeV_{TBW} with each modality (SF, MF, BIS) and ΔWt with R=0.15, 0.41, and 0.38, respectively (Figure 2).

For the Bland-Altman analyses for SF, the mean bias was -0.23 L with a 95% confidence limit of agreement from -4.1 to 3.5 L (Figure 3A). A regression line was fit to assess for proportional error and was found to have a slope of 0.54. For MF, the mean bias was -1.1 L with a 95% confidence limit of agreement from -4.1 to 1.9 L (Figure 3B). The associated regression line for the data was found to have a slope of 0.17. For BIS, the mean bias was -0.6 L with a 95% confidence limit of agreement from -6.1 to 4.8 L (Figure 3C). The associated regression line for the data was found to have a slope of 0.88.

Accuracy over 30 minute intervals

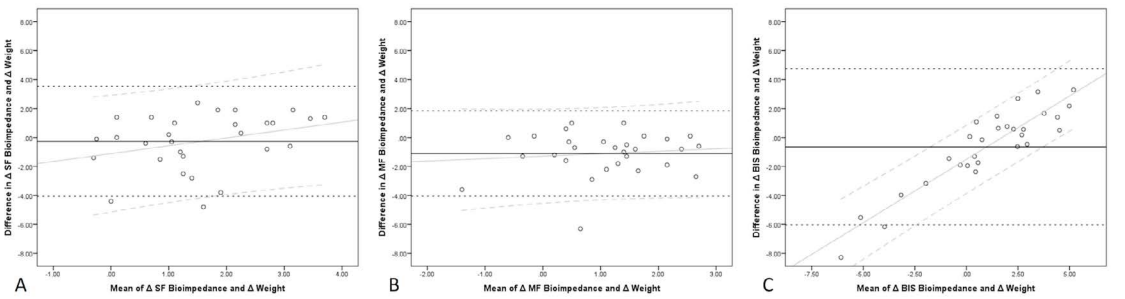
Concordance analysis was performed for 30 minute intervals comparing ΔeV_{TBW} and $V_{UF,net}$ (Figure 4). For SF, the correlation was very poor (R=0.004, p=0.97) for a total of 82 paired measures; the associated MTC was 63.4%. For MF, the correlation was very poor (R=-0.15, p=0.26) for a total of 58 paired measures; the

Figure 2. *Correlation between ΔWt and ΔeV_{TBW} as Measured by each Modality before and after Hemodialysis*



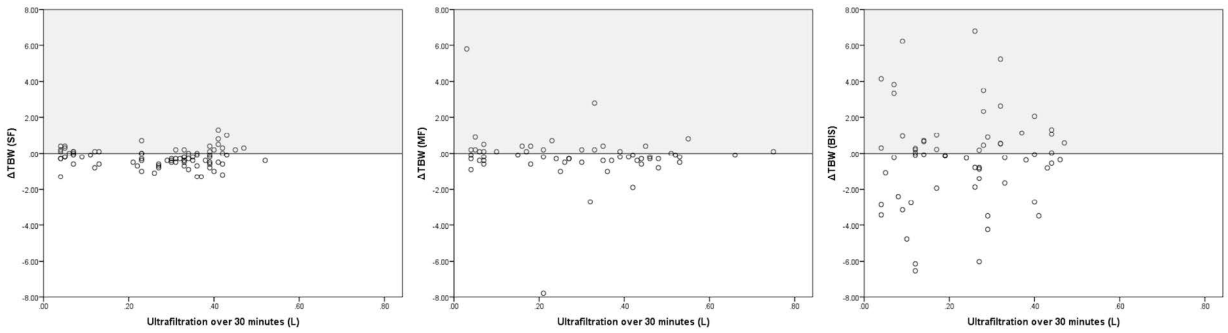
Panel A: SF (Single-Frequency), Panel B: MF (Multi-Frequency), Panel C: BIS (Bioimpedance Spectroscopy).

Figure 3. *Bland-Altman analysis for ΔWt and ΔeV_{TBW} as Measured by each Modality before and after Hemodialysis*



Panel A: SF (Single-Frequency), Panel B: MF (Multi-Frequency), Panel C: BIS (Bioimpedance Spectroscopy).

Figure 4. *Correlation between $V_{UF,net}$ and Δ eV_{TBW} as Measured by each Modality. $V_{UF,net}$ and Δ eV_{TBW} were Computed for Serial 30 min Intervals; thus, each Point Corresponds to One Interval*



Panel A: SF (Single-Frequency), Panel B: MF (Multi-Frequency), Panel C: BIS (Bioimpedance Spectroscopy).

associated MTC was 61.8%. For BIS, the correlation was very poor (R=0.09, p=0.51) for a total of 62 paired measures; the associated MTC was 53.6%. Overall trend of results remained unchanged when adjusting for the time-point using linear regression modeling.

Equilibration Times per Modality

The median time to measurements post blood return was 26.5 min overall with no significant difference with each type of modality (SF 25.9 min, MF 27.7 min, BIS 25.9 min, p=0.97).

DISCUSSION

Our results suggest that estimations of fluid volumes using bioimpedance regardless of modality are not accurate or precise in capturing true volumes removed during hemodialysis. Correlations between ΔeV_{TBW} and $V_{UF,net}$ were poor with the best being associated with MF BIA and having a Spearman R of only 0.41 (i.e. R squared=0.17), meaning that only 17% of the changes in BIA is explained by a change in fluid status.

Bland Altman analysis for each modality show moderate mean biases (least bias was for SF:-0.23 L) and poor limits of agreement (best limit of agreement was for MF:±2 L). On average all of the modalities underestimate the volume removed based on ΔWt during hemodialysis demonstrating lack of accuracy. Furthermore the 95% confidence limits of agreement are very large suggesting a significant lack of precision. Simple linear regression lines added to the Bland Altman analysis suggest that there was significant proportional error associated with BIS measurements.

Concordance analysis performed for the 30 minute intervals showed that all three devices lack clinical utility. For a given unit decrease in eV_{TBW}, there should be a correspondent unit of increase in $V_{UF,net}$ for any given time interval. Deviations from this pattern suggests problems with measurement technique or external sources of error (e.g. unaccounted fluid volumes being administered or removed from the system). All fluids consumed or lost were accounted for in interval $V_{UF,net}$ values, and insensible losses were deemed minimal over a 30 minute period. Therefore, we assume deviations are solely from failure of the instrument to measure the intended quantity or are due to measurement technique errors. The best MTC was only 63.4% for MF. Correlation coefficients also show poor fit, the best correlation being R=0.21 (for MF).

Other studies that have compared the three major modalities of BIA, with regards to fluid assessment, have had some inherent issues with nomenclature. Studies have grouped MF and BIS into one category.[15] Both of these modalities use multiple frequencies, however, the methods of analysis and equations to derive ECF and ICF are different. Studies have been performed that have compared the two modalities (MF and BIS), and have concluded that there are differences in the assessment techniques.[16]

Conversely, some authors have shown BIA to be a reliable tool to assess fluid overload. Torterüe et al has shown BIA to be more reflective of hydration status assessments on dialysis than IVC measurements with ultrasound assessment.[9] Hur et al has shown bioimpedance to more accurately assess dry weights in dialysis patients when compared to clinical assessments.[10] The use of BIA showed reductions of LVMI, average BP, and BP medication burden, without resultant issues of hypotension.[10] However, the lack of accuracy we report might be explained by our objective to identify small changes in fluid status, well-below the threshold to detect preload dependency[9] or change in vital signs.[10] Studies often citing the validity of bioimpedance as a method of measuring fluid status were not truly assessing the ability of the instruments to obtain repeated accurate evaluations. For example, Ho et al[10] assessed the validity of bioimpedance to measure fluid status in hemodialysis patients by comparing the change in bioimpedance measurements to deuterium dilutions during a single session.[17] Although they showed an absolute error of 5.9%, the denominator was the total body water as determined by deuterium dilution, not the fluid changes during dialysis. Most experts suggest using Bland-Altman Analysis to compare two measurement techniques, as this is the only way to assess systematic bias, accuracy, proportional errors, variation based on magnitude of measurements, while not being depended on individual measurement characteristics.[14] Other assessments are not adequately able to characterize these biases.

In addition, it is important to define the concept of precision, as some authors will use a large denominator (like Ho et al[10]), which will lead to a small error, while we used the proportional change from one time point to the other, which will unmask imprecision.

With regards to our findings, several limitations must be recognized. First, we were unable to enroll the number of patients required to achieve appropriate power. Given the significant discrepancies in measurements from BIA compared to V_{UF} and ΔWt, we would not expect that the addition of 14 patients would lead to a dramatic improvement in accuracy. Second, given that the instruments used for this study were supplied by the individual companies, there is always the concern for industry sponsored risk of bias. There was no financial support given by any of the companies involved in the study, devices were returned upon completion of the study, and the companies did not see the manuscript prior to publication. Third, concerns could arise from the fact that interval analysis was based off of the initial weight input. Clinically it is impractical to weigh patients during their dialysis sessions, and in many clinical settings outside of dialysis, there are often scenarios where it is not feasible to obtain serial weights for analysis. Other studies have reported interval changes with adjusted weight inputs based off cumulative ultrafiltration.[8] This dependence would suggest that the output is more reflective of the weight input than the intended measurements obtained from the machines further supporting that this method lacks clinical significance. Further research in other biometric parameters (BSA, BMI, Nutritional Status, etc.) to enhance BIA modeling could yield better results. And fourth, there are potential difficulties with appropriate fluid assessment after hemodialysis due to fluid shifts, which is why we reported total body water estimations. We also made sure there were no differences in the time between the end of the dialysis and the final measure for each modality.

CONCLUSION

In summary, this study demonstrates that the accuracy of bioimpedance analysis with regards to evaluating fluid status lacks precision and accuracy, regardless of modality used. Newer technological advances in the field could lead to improved measures, but at this time, the technology seems to be lacking clinical relevance.

ACKNOWLEDGMENTS

Devices were lent by manufacturers, who also provided the device-specific leads. However, the manufacturers were not involved in the design of the trial and were unaware of the results prior to publication.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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ISSN 2380-0445

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Original Research

Treatment of Acute Antibody-Mediated Rejection in Children Post-Kidney Transplantation: A Single Center's Experience

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Article Information
Received: November 21st, 2020; **Revised:** January 24th, 2021; **Accepted:** January 27th, 2020; **Published:** February 8th, 2021

Cite this article
Alhamoud I, Khin E, Huang R, McConnell L, Seikaly MG. Treatment of acute antibody-mediated rejection in children post-kidney transplantation: A single center's experience. *Nephrol Open J.* 2021; 6(1): 8-15 doi: 10.17140/NPOJ-6-125

ABSTRACT

Introduction

Acute antibody-mediated rejection (aAMR) can negatively impact renal allografts outcomes. To date, there has not been a consistent therapeutic approach to manage aAMR. The aim of the study is to evaluate the tolerance and efficacy of an institutional protocol of methylprednisolone, intravenous gamma globulin (IVIG), rituximab, and bortezomib used to treat aAMR in pediatric renal transplant recipients (pRTRs).

Methods

A retrospective chart review was performed on 10 pediatric renal transplant recipients (pRTRs) who were diagnosed with aAMR on a renal biopsy performed between January 2014 and November 2015.

Results

Over the study period, 9.5% of pRTRs had aAMR. Sixty percent of whom had concurrent acute cellular rejection (ACR). Renal allografts survival was 100% during the the first post-aAMR. At the time of diagnosis of aAMR, estimated glomerular filtration rate (eGFR) had decreased by 42% (mean at baseline eGFR=67.2±19.5 mL/min/1.73 m^2 *vs* mean at aAMR eGFR=38.9±14.2 mL/min/1.73 m^2; p=0.002). At 1-year post rejection, eGFR had increased by 26% as compared eGFR at the time of rejection (mean eGFR=49.0±13.2 mL/min/1.73 m^2; p=0.006). Immuno-dominant donor-specific anti-HLA antibody titers (iDSAs) class I and class II decreased by 69% and 15% at 6-month follow-up visit. No serious opportunistic infections nor malignancy were reported in our subjects.

Conclusion

Our study suggests that our protocol improved kidney function with 100% graft survival at 1-year post aAMR episode. The percentage decline in iDSAs class I titers was more significant than class II. Furthermore, our treatment protocol was well-tolerated with no life threatening complications.

Keywords

Acute antibody-mediated rejection (aAMR); Intravenous gamma globulin (IVIG); Pediatric renal transplant recipients (pRTRs).

INTRODUCTION

Kidney transplantation has significantly changed the quality of life of patients with advanced chronic kidney disease (CKD). Unfortunately, renal allografts have a finite longevity; this is despite significant advancements in post-renal transplant management. Long-term graft survival is often impacted by events such as rejection,recurrence of original disease, immunosuppression toxicity, non-adherence to antirejection therapy, and opportunistic infections. The incidence of acute antibody-mediated rejection (aAMR) in pediatric renal transplant recipients (pRTRs) has not been well defined.[1] This form of rejection is responsible for approximately 35.6% of renal allograft loss.[2-4] Histopathologic diagnostic criteria for aAMR have been recently redefined.[5,6]

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Currently, there has not been a collective approach to the management of patients with aAMR. Previously reported therapies to treat aAMR included: escalation of maintenance immunosuppressive agents, pulse methylprednisolone, intravenous gamma globulin (IVIG) to neutralize pathogenic circulating antibodies, rituximab to deplete B-lymphocytes, rabbit anti-thymoglobulin (rATG) to deplete T-cells, bortezomib to destroy mature plasma cells, apheresis to temporarily remove circulating antibodies, and recently eculizumab to block terminal complement pathway.[7] Those treatment options have been used individually or in combination with variable outcomes.[8]

METHODS

Study Design

A retrospective analysis was conducted on all pRTRs younger than 21-years-old who were diagnosed with aAMR between January 2014 and November 2015. Kidney biopsy (index biopsy) was performed for graft dysfunction (elevation of serum creatinine> 20% of baseline)using 2013 Banff criteria for AMR diagnosis.[5,6]

Primary endpoints included estimated glomerular filtration rate (eGFR) as well as graft survival at one year after aAMR. eGFR was estimated using bedside Schwartz equation.[9] Secondary endpoints involved iDSAs responseand treatment complications. Serum creatinineand serum iDSAs levels were monitored periodically to determine the response to treatment. The occurrence of opportunistic infections, malignancy, and bone marrow suppression parameters were monitored as markers of tolerance to therapy.

Baseline serum creatinine level to calculate eGFR was arbitrarily defined as the lowest serum creatinine level during thelast three months before the aAMR event. Baseline eGFR used the aforementioned baseline serum creatinine was calculated using bedside Schwartz equation.[9] As per our practice guidelines to manage aAMR, Immuno-dominant donor-specific anti-HLA antibody titers (iDSAs) titers were initially monitored every two weeks. The monitoring interval was then individualized based on the clinical and laboratory parameters.

Immunosuppression Regimen

Induction treatment for cadaveric kidney transplant recipients included rabbit anti-thymoglobulin (rATG) 1.5 mg/kg (total not to exceed 6 mg/kg) every other day till tacrolimus level is in therapeutic range (12-15 ng/mL), and methylprednisolone 10 mg/kg initially then tapered gradually. Living-donor kidney recipients receive basiliximab as an induction dose of 10 mg for weight <30 kg and 20 mg for weight >30 kg on day 0 and 4 after renal transplantation in addition to methylprednisolone as aforementioned. Once patient's serum creatinine level dropped to 50% of pre-transplant level, we started tacrolimus as a maintenance immunosuppressive therapy (initial dose 0.1 mg/kg/dose twice daily). Target level of tacrolimus had been maintained at 12-15 ng/mL during the first 4-weeks, 10-12 ng/mL in 5-12-weeks, 7-10 ng/mL in 13-16-weeks, 5-7 ng/mL in 17-24-weeks, and 3-5 ng/mL after 6-months of transplantation. Mycophenolate mofetil (MMF) 600 mg/m^2/day divided in two doses, and prednisone 15 mg daily between 1-3-months, 10 mg daily between 3-6-months, then gradually tapered till off over one year.

Treatment of aAMR

All aAMR subjects were treated with our institutional protocol. This protocol consisted of methylprednisolone 30 mg/kg for 5 doses (Max 1 gram/dose), IVIG 1 g/kg for 2 doses, rituximab 375 mg/m^2 for 2 doses (Max 1 gram/dose), and bortezomib 1.3 mg/m^2 for 4 doses (Max 2.5 mg/dose). The protocol was modified as deemed necessary by the primary nephrologist based on the clinical and laboratory parameters of recipients. One unresponsive patient received Eculizumab at the dose of 900 mg weekly for four-weeks then 1200 mg biweekly for two doses. Table 2 summarized our institutional protocol.

Maintenance immunosuppressive therapy was also intensified where tacrolimus level has been increased to be above the target level where rejection occurred, and mycophenolate mofetil dose has also been increased from 600 mg/m^2/day to 1200 mg/m^2/day divided in two doses. In some non-adherent recipients, tacrolimus was switched to intravascular. Belatacept infusion biweekly then monthly.

This study was approved by the Institutional Review Board (IRB # STU 112016081) at the University of Texas Southwestern Medical Center in Dallas, Texas, United States.

Table 2. *aAMR Protocol*

Medication/Dose	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10
Methylprednisolone											
30 mg/kg/dose (max 1 g/dose)	X	X	X	X	X						
IVIG											
1 g/kg/dose (max 70 g/dose)			X	X							
Bortezomib											
1.3 mg/m^2/dose (max 2.5 mg/dose)		X			X			X	X		
Rituximab											
375 mg/m^2/dose (max 1000 mg/dose)		X						X			

Statistical Methods

Descriptive analyses of the continuous and categorical data were performed using means, standard deviations, proportions and frequencies. Statistical testing of sub-groups included Chi-square test, Fisher's Exact test, two-sample t-test, and Wilcoxon Rank Sums test, as appropriate to the variable's level of measurement and distribution. Linear regression model was used to investigate relationship between single or multiple independent variables and outcome variable. The statistical analyses were performed with SAS 9.4.

RESULTS

Patient's Demographics

Over the study period, 10 of 105 pRTRs were diagnosed with aAMR (9.5%). All subjects were diagnosed at a median graft age of 43-months (range; 10-74 months). aAMRwas found predominantly in females (70%). The median patient's age was 15-years (range; 11-18-years). Therapeutic tacrolimus concentration was found in 6 patients (60%) with aAMR. Only one aAMR subject had high panel reactive antibodies (PRAs) prior to the second kidney transplantation and patient was desensitized using rituximab, bortezomib, and IVIG as per protocol. Demographic and clinical data of patients are summarized in Table 1.

Table 1. *Patient Demographics and Clinical Information*

	aAMR Subjects N=10
Patientage at Rejection (year) Median, range	15 (11-18)
Graftage at rejection date (months) Median, range	43 (10-74)
Female %, n	30% (3)
ESRD Cause	
Time on dialysis prior to transplant	70% (7)
Glomerular disease %, (n)	10% (1)
Others %, (n)	10% (1)
Time on Dialysis Prior to Transplant	
Pre-emptive %, (n)	0% (0)
≤12-months %, (n)	20% (2)
>12-months %, (n)	80% (8)
Dialysis Modality	
Pre-emptive %, (n)	0% (0)
Peritoneal dialysis %, (n)	80% (8)
Hemodialysis %, (n)	20% (2)
Transplant Type	
Deceased-Donor %, (n)	90% (9)
Living-Donor %, (n)	10% (1)
Prior transplant %, (n)	10% (1)
Pre-transplant PRA >20%	
Class I PRA %,(n)	10% (1)
Class II PRA %, (n)	10% (1)
Prior rejection %, (n)	10% (1)
Mismatch score/10 (mean, std)	8.2 (1)
Positive cross match %, (n)	0%, (0)
Pre-rejection Tacrolimus Level	
Therapeutic level %, (n)	60%, (6)
Non-therapeutic level %, (n)	40% (4)
1-year graft survival %, (n)	100% (10)
1-year patient survival %, (n)	100% (10)

ESRD: End Stage Renal Disease. CAKUT: Congenital Anomalies of Kidney and Urinary Tract

Histological Findings of aAMR

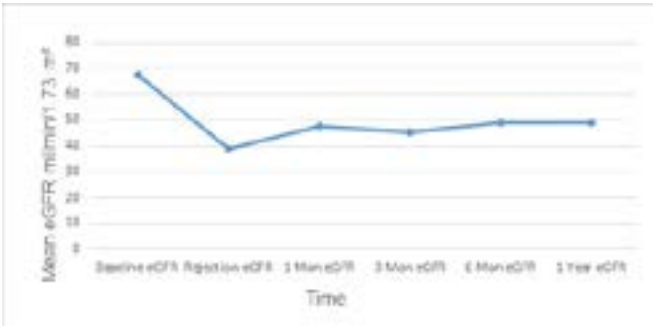
Acute cellular rejection (ACR) was concurrently diagnosed with aAMR in 6 patients out of 10 pRTRs as shown in Table 3. A C4d immunohistochemical stain was negative in 2 patients, focal in 5 patients (<50%), and diffuse in 3 patients (>50%). Allograft glomerulopathy was present in 2 grafts. The histopathological features of aAMR cases arepresented in Table 4.

Outcomes of aAMR Treatment on Renal Allograft Function and Survival

Patient and graft survival was 100% at one-year of the observation period. At the time ofindexbiopsy, none of the patients needed dialysis. aAMR caused a decline in mean eGFR of 42% of baseline mean (mean baseline eGFR=67.2±19.5 mL/min/1.73 m^2 *versus* mean eGFR at rejection=38.9±14.2 mL/min/1.73 m^2; p=0.002).

Four-weeks post-treatment, eGFR increased by 22% in comparison to baseline eGFR (mean eGFR=47.4±8.9 mL/min/1.73 m^2 *vs* 38.9±14.2 mL/min/1.73 m^2. p=0.02). Despite not returning to baseline eGFR, 1-year eGFR had been stabilized and increased by 26% as compared to the rejection eGFR (mean eGFR=49.0±13.2 ml/min/1.73 m^2; p=0.001) as shown in Figure 1.

Figure 1. *Estimated GFR Change in pRTRs Treated for aAMR Over Time*



*Mean eGFR dropped significantly at the index biopsy 38.9 ml/min/1.73 m^2 vs baseline mean eGFR 67.2 ml/min/1.73 m^2; +p=0.002. However, mean eGFR increased significantly at 4-weeks (47.4 ml/min/1.73 m^2; *p=0.02), and had stayed stable (49.0 ml/min/1.73 m^2; *p=0.01) over a 1-year of observation period.*

A functional response (FR)of eGFR was determined as the ratio of a difference between eGFR at 1-month post-treatment and nadir eGFR level at the rejection time to the difference between the baseline eGFR and eGFR level at the rejection time.

Table 3. *Banff Classification of aAMR among Our pRTRs*

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10
Banff Score	aAMR ACR IA	aAMR ACR IB	aAMR ACR IIA	aAMR ACR IA	aAMR	aAMR	aAMR	aAMR ACR IB	aAMR	aAMR ACR IB

Table 4. *Histopathological Features of pRTRs Diagnosed with aAMR*

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10
Tubulitis (t)	1	3	3	2	1	0	0	3	0	3
Interstitial inflammation (i)	1	2	3	2	0	0	0	3	0	3
Glomerulitis (g)	1	2	0	2	1	0	2	1	0	1
Arterial hyaline thickening (ah)	0	0	0	1	0	0	1	0	0	0
Intimal arteritis (v)	0	0	1	0	0	0	0	0	0	0
C4d	1	2	0	3	2	0	3	1	3	0
Peritubular capillaritis (ptc)	2	2	3	2	1	2	2	2	2	2
Allograft glomerulopathy (cg)	0	Ia	0	Ia	0	0	0	0	0	0
Interstitial fibrosis (ci)	1	1	2	1	0	2	1	0	0	1
Tubular atrophy (ct)	1	1	2	1	0	2	1	0	1	1
Fibrous intimal thickening (cv)	0	0	2	0	0	0	0	0	0	1
Mesangial matrix increase (mm)	0	0	0	1	0	0	0	0	0	0

6 cases had concurrent AAMR and ACR (IA in 2 cases, IB in 3 cases, and IIA in one case). t: tubulitis. i: interstitial inflammation. g: glomerulitis. ah: arterial hyaline thickening. v: intimal arteritis. ptc: peritubular capillaritis. cg: allograft glomerulopathy. ci: interstitial fibrosis. ct: tubular atrophy. cv: fibrous intimal thickening. mm: mesangial matrix increase.

Table 5. *Donor-Specific Antibodies in aAMR Cases at Index Biopsy*

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10
DSA (MFI)	C4 (1435)	A29 (1053)	A1 (2475)	A29 (6342)	DQ2 (21697)	Neg	DQ4 (14878)	DRB5 (DR51-1671)	DQ2 (14489)	A31 (2889)
Interstitial inflammation (i)	DQ7 (5699)	B44 (1248)	A2 (2150)	B44 (3346)	DQ4 (21856)		DQ7 (13922)	DQ6 (6916)	DQ4 (15920)	A2 (1807)
Glomerulitis (g)		B50 (7258)	B13 (829)	B45 (5001)				DQ2/DQA2 (854)		B60 (437)
Arterial hyaline thickening (ah)		DQ5 (13125)	B51 (758)	C16 (2642)						DQ2 (8779)
Intimal arteritis (v)			DR7 (5251)	DR7 (2594)						DR7 (812)
C4d			DR-B4 (5028)	DR17 (7029)						
Peritubular capillaritis (ptc)			DQ (7446)	DQ2 (21531)						
Allograft glomerulopathy (cg)				DR-B3 ((DR52-1860)						
Interstitial fibrosis (ci)				DP0201 (2036)						

$$\text{Functional Response} = \frac{\text{eGFR@1 month post therapy-eGFR@aAMR}}{\text{Baseline eGFR-eGFR@aAMR}}$$

Functional graft response wass tratified as a complete response (CR) when the ratio had a value greater than 70%, an incomplete response (IR) when this ratio was between 30% and 70%, and no functional response if the ratio was less than 30%.[10] As a functional trend, none of aAMR cases had the complete response. However, the incomplete response (IR) at 4-weeks post-treatment was accomplished in 7 patients with aAMR. Three functional allografts were considered unresponsive to therapy.

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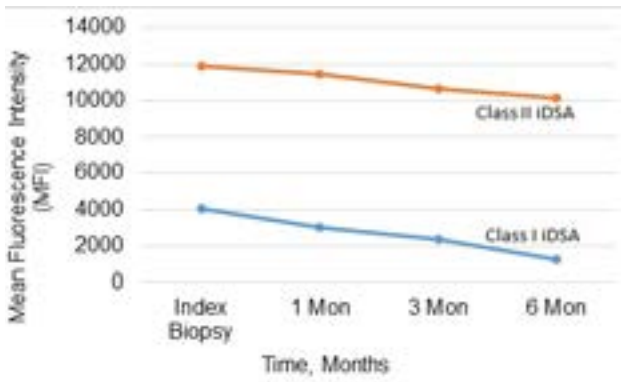
Outcomes of treatment on iDSAs

iDSAs were detected using the LabScreen Single Antigen Assay (Thermofisher, MA, USA). The method for calculating bead threshold has previously been published by Sullivan et al.[11] We considered the rise in iDSAs, quantified as mean fluorescence intensity (MFI), was significant if the level was above 1500 MFI. Donor-specific antibodies (DSAs) were detected in 9 patients, where 5 patients had both class I and II DSAs and 4 patients had only class II DSAs as illustrated in Table 5. Immuno-dominant DSAs class II were 3 folds higher than iDSAs class I. iDSA was mainly HLA-A for class I and HLA-DQ for class II.

Monthly follow-up iDSAs data were available on 9 aAMR patients. Immuno-dominant DSA- class I titers had declined by 26% (3003±3745 MFI *vs* 4080±2560 MFI at rejection time) at 1 month, by 42% (3003±3745 MFI *vs* 4080±2560 MFI at rejection time) at 3-months, and by 69% (1265±1947 MFI *vs* 4080±2560 MFI at rejection time; p=0.04) at 6-months of follow-up. iDSAs class II had decreased by 4% (11468±6065 MFI *vs* 11930±5609 MFI) at 1-month and 10% (10629±6440 MFI *vs* 11930±5609 MFI) at 3-months, and by 15% (10130±7355 MFI *vs* 11930±5609 MFI: p>0.05) at 6-months of follow-up period as shown in Figure 2. IDSA class I became negative in 3 patients and iDSA class II became negative in one receipient.

Figure 2. *Mean Change Inimmuno-dominant DSA-HLA Class I and II Titers in Response to treatment of aAMR*



*MOf the 10 aAMR cases, 9 patients with functional graft had available DSA data over 6-12 months. One patient had aAMR with negative DSA. A significant decrease in iSDA-HLA class I occurred late 3-6 months post treatment (*paired t-test; p=0.04). Treatment effects on iDSA-HLA class II were minimal and did not reach statistical significance. No follow-up data of DSA were available for case 4.*

Safety Profile

Overall, the protocol was well-tolerated. No serious bacterial infections nor malignancywere reported in our subjects. Adverse effects on bone marrow parameters included lymphopenia (n=8), thrombocytopenia (n=3), and anemia (n=6).

Four patients developed opportunistic infectionswithin 4- months following the administration of our treatment protocol. These infections include: BK viremia (n=2), EBV viremia (n=1), CMV viremia (n=1), and herpes zoster infection (Shingles) (n=1). All infections were successfully treated without sequelae. Adverse effects occurring during drug administration included: Rituximab-related fever/chills (n=1), methylprednisolone-induced hypertension (n=2), IVIG-induced hypertension (n=1), Bortezomib-related paresthesia (n=1), and posterior reversible encephalopathy syndrome (PRES) (n=1).

DISCUSSION

Despite a considerable progress in the post-renal transplant management, aAMR remains an important event that threatens the short-and long-term outcomes of kidney transplantation. In the present case series, we investigated the outcomes of treatment of pRTRs who developed aAMR post-transplantation. Out of 10 cases, pure aAMR was diagnosed in 4 pRTRs, and 6 cases were combined aAMR and ACR. The incidence of aAMR without concurrent ACR was 3.8% of total pRTRs within our observation period, which is comparable to our previous case series as well as other reports in the literature.[1,12] In our cohort, the overall incidence of aAMR with ACR was up to 9.5%, which is also similar to some other reports.[13,14] aAMR in our population occurred late, beyond 1-year post-transplantation. Previous reports suggested that late aAMR heralds a poor response to conventional treatment and carries a high risk of graft loss.[15-19]

There is no consensus as to the treatment of aAMR in pRTRs[7,8] Most published data were derived from case reports or series, with variable approaches and inconsistent outcomes. Most regimens include inhibition of the B-Cells with monoclonal antibodies against cluster designation (CD20) with rituximab, destruction of antibody-secreting plasma cell (CD138) with bortezomib, antibodies removal and immunomodulation (plasma exchange, intravenous immunoglobulin, andcorticosteroids), and inactivation of antibody-mediated terminal complement activation (eculizumab). Despite the current plethora in the immunosuppressive agents, limited data are available to support any single agent or combined agents that offer clear advantages over others.[20]

Over the past few years, the use of bortezomib in pRTRs who developed aAMR has been rising with mixed outcomes.[1,21,22] Bortezomib, proteasome s26 inhibitor, causes apoptosis of mature plasma cells, B-cells and activated T-cells through complex series of interactions.[23-27] There are promising data of bortezomib in the treatment of aAMR in multiple case reports. Everly et al[22] reported that bortezomib therapy alone provides an effective treatment of AMR and ACR with minimal toxicity and provides a sustained reduction in iDSAs levels. However, the recent published randomized clinical trial failed to show that bortezomib alone prevents GFR loss, improves histologic features, or reduces DSA, with a potential for significant toxicity.[28]

In our cohort, the study subjects had a partial improvement in graft function (30-70% of baseline eGFR) in 7 patients with no response (<30% of baseline eGFR) in 3 patients at 4-week spost-treatment. None of the pRTRs among the study subjects fully regained baseline renal function. However, all aAMR

grafts had remained dialysis-free during the observation period. Our observation is in agreement with other studies that highlighted a role for bortezomib as a stabilizer of renal allografts function in conventional unresponsive late-aAMR.[13] The role of bortezomib-containing protocols should be further evaluated in randomized trials. Such trials should address strategies with regards to dosing, frequency, and duration of treatment. One limitation of our study is the use of combination therapyto treat aAMR. This does not allow us to define the role of the individual immunosuppressive agent.

Another putative predictor in aAMR prognosis is iDSAs. In our cohort, the decline in iDSAs class I (A) titer was more significant than iDSAs HLA class II (DQ) titer. As we mentioned above, regaining of renal function was independent of iDSAs response. Renal function in all grafts had stabilized without the need for renal replacement therapy. Furthermore, there had been no association between improvement in the graft function and the decrease in iDSAs titers. There was no correlation between the severity of aAMR and the decline in the allograft's eGFR nor the titers of iDSAs.

B-lymphocytes may also play a role in the development of aAMR since they have the potential to develop to mature antibody-secreting plasma cells, it seems to be prudent to target this type of cells in aAMR. B-cell depleting agents such as rituximab have been used off label in renal transplantation field including aAMR treatment. Several studies in pRTRs have demonstrated the beneficial effects of rituximab on graft function, graft survival, and histopathological reversibility in renal allografts with aAMR,[29-34] However, there was no consensus on the dosage and frequency of doses.[30,31] Furthermore, its utilization was limited due to a high risk of infectious complications.[35]

Other antitumoral therapies such as plasmapheresis and immunoadsorption have a limited role in the treatment of aAMR.[36,37] Plasmapheres is helps to remove preformed-abnormal circulating antibodies and enhances the effect of bortezomib on plasma cells and B-lymphocytes.[38,39]

IVIG has been used widely in aAMR treatment despite a limited-evidence of benefit.[40,41] Dual treatment with IVIG and plasmapheresis administration assists to substitute lost immunoglobulins and minimizes the risk of infections.[42-45] All aAMR cases received IVIG as per protocol. However, one receipient was given monthly IVIG 1 g/kg for six-months. iDSA class I and II in this subject had decreased substantially compared to other aAMR subjects.

It is common to diagnose ACR concurrently with aAMR. In our cohort, 60% of cases were mixed aAMR and ACR. A combined ACR and aAMR needs a multi-agent therapy as a single therapy is often not optimal. The role of T-cell depleting agents in pure aAMR treatment is not clear. Bortezomib therapy is reported to treat refractory ACR through a complex interactions on T-cell functions.[22]

In summary, our current study suggests that bortezomib-based protocol during a 1-year follow-up period resulted in 1) 100% graft survival with 26% increase eGFR from time of rejection 2) iDSAs class I antibodies declined more significantly than iDSAs class II antibodies and 3) our protocol was well-tolerated with no significant life-threatening infections nor malignancy were reported.

CONCLUSION

In conclusion, our study suggests a beneficial role for the combined therapy in the management of pRTRs who develop aAMR. However, confirmatory results should come from larger scale, longitudinal, multicenter study, which would allow for better understanding of efficacy and safety of our protocol.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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ISSN 2380-0445

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Editorial

Living Well with Kidney Disease by Patient and Care-Partner Empowerment: Kidney Health for Everyone Everywhere

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Article Information

Received: January 2nd, 2021; **Accepted:** January 27th, 2021; **Published:** February 11th, 2021

Cite this article

Kalantar-Zadeh K, Li P K-T, Tantisattamo E, et al. Living well with kidney disease by patient and care-partner empowerment: Kidney health for everyone everywhere. *Nephrol Open J.* 2021; 6(1): e1-e6. doi: 10.17140/NPOJ-6-e012

ABSTRACT

Living with chronic kidney disease (CKD) is associated with hardships for patients and their care-partners. Empowering patients and their care-partners, including family members or friends involved in their care, may help minimize the burden and consequences of CKD related symptoms to enable life participation. There is a need to broaden the focus on living well with kidney disease and re-engagement in life, including an emphasis on patients being in control. The World Kidney Day (WKD) Joint Steering Committee has declared 2021 the year of "Living Well with Kidney Disease" in an effort to increase education and awareness on the important goal of patient empowerment and life participation. This calls for the development and implementation of validated patient-reported outcome measures to assess and address areas of life participation in routine care. It could be supported by regulatory agencies as a metric for quality care or to support labelling claims for medicines and devices. Funding agencies could establish targeted calls for research that address the priorities of patients. Patients with kidney disease and their care-partners should feel supported to live well through concerted efforts by kidney care communities including during pandemics. In the overall wellness program for kidney disease patients, the need for prevention should be reiterated. Early detection with a prolonged course of wellness despite kidney disease, after effective secondary and tertiary prevention programs, should be promoted. WKD 2021 continues to call for increased awareness of the importance of preventive measures throughout populations, professionals, and policymakers, applicable to both developed and developing countries.

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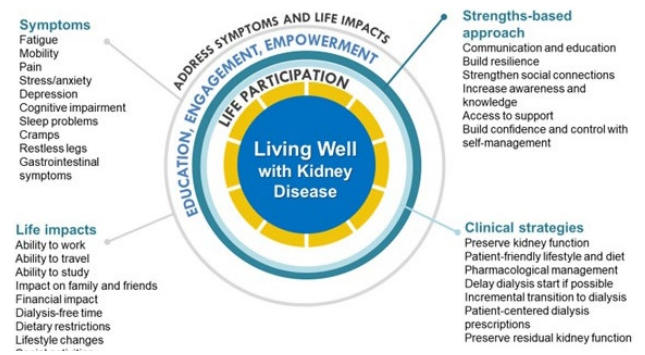
PATIENT PRIORITIES FOR LIVING WELL: A FOCUS ON LIFE PARTICIPATION

Chronic kidney disease (CKD), its associated symptoms, and its treatment, including medications, dietary and fluid restrictions, and kidney replacement therapy can disrupt and constrain daily living, and impair the overall quality of life of patients and their family members. Consequently, this can also impact treatment satisfaction and clinical outcomes.[1] Despite this, the past several decades have seen limited improvement in the quality of life of people with CKD.[1] To advance research, practice, and policy, there is increasing recognition of the need to identify and address patient priorities, values, and goals.[1]

Several regional and global kidney health projects have addressed these important questions including the Standardised Outcomes in Nephrology (SONG) with more than 9,000 patients, family members, and health professionals from over 70 countries.[2,3] Across all treatment stages, including CKD, dialysis and transplantation, SONG participating children and adults with CKD consistently gave higher priority to symptoms and life impacts than health professionals.[2,3] In comparison, health professionals gave higher priority to mortality and hospitalization than patients and family members. The patient-prioritized outcomes are shown in Figure 1. Irrespective of the type of kidney disease or treatment stage, patients wanted to be able to live well, maintain their role and social functioning, protect some semblance of normality, and have a sense of control over their health and well-being.

Figure 1. *Conceptual Framework of "Living WellwithKidney Disease" Based on Patient Centeredness and Empowering Patient with Focus on Effective Symptom Management and Life Participation*



Life participation, defined as the ability to do meaningful activities of life including, but not limited to, work, study, family responsibilities, travel, sport, social, and recreational activities, was established a critically important outcome across all treatment stages of CKD.[1,2] The quotations from patients with kidney disease provided in Box 1 demonstrates how life participation reflects the ability to live well with CKD.[4] According to the World Health Organization (WHO), participation refers to "*involvement in a life situation*".[5] This concept is more specific than the broader construct of quality of life. Life participation places the life priorities and values of those affected by CKD and their family at the center of decision making. The World Kidney Day Steering Committee calls for the inclusion of life participation, a key focus in the care of patients with CKD, to achieve the ultimate goal of living well with kidney disease. This calls for the development and implementation of validated patient-reported outcome measures, that could be used to assess and address areas of life participation in routine care. Monitoring of life participation could be supported by regulatory agencies as a metric for quality care or to support labelling claims for medicines and devices. Funding agencies could establish targeted calls for research that address the priorities of patients, including life participation.

Box 1. *Quotations from Patients with CKD Related to Priorities for Living Well*

"*I don't want to think about dying from my disease. I want to be able to live well with my disease.*" – Patient with CKD
"*Life participation is most important because without it, you can't do anything.*" – Child with CKD
"*Maybe it's as simple as asking patients whether, how well they are able to participate in the life that they want to lead because it's going to be different for different people*" – Kidney transplant recipient
"*Everyone has to face death, what I would like to have is a good quality of life rather than to face death.*" – Kidney transplant recipient
"*So, it doesn't actually really matter what the numbers say, and some of my numbers should have suggested that I should be feeling a lot worse than what I actually was, it's about how much I feel I can do and participate in my life and feel normal.*" – Patient with CKD
"*I'm still living. I get out of bed, and I'm still living and still breathing. As long as I can do that, I'm going to carry on and be positive because life is short.*" Patient with CKD
"*I put life participation because I know that looking from the outside, I know [his kidney disease] stops [him] from thinking bigger. . .Although that's really big, there's this life that has to happen at the same time.*" – Family member
"*Amazed at comments from professional(sic) about travel, free time, etc they seem to think the mechanics of dialysis far more important. Dialysis is a treatment which keeps us alive to live a life, not just to wait for death.*" – Patient receiving dialysis
"*I prefer to be above ground, then below ground. So why not enjoy life whilst being above ground.*" – Adam Martin
"*Over the years, I have learned to worry less, control my emotions, and not fear death. I keep my mind active. I follow the advice of the philosopher-emperor Marcus Aurelius to 'love the hand that fate (has dealt me) and play it as (my) own'. Living well with CKD means to live the best life I can in the time I have available….Living well with CKD is the same as living well.*" – Tess Harris
"*While CKD brings me some limitations, I can maximize the possibility to live well. I kept working when I was doing hemodialysis. After transplant, I could live: study, work, travel, marry, have children, and service the community.*" – Maggie Ng
**Personal communication; quotations are identified by name with permission*

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PATIENT EMPOWERMENT, PARTNERSHIP AND A PARADIGM SHIFT TOWARDS A STRENGTHS-BASED APPROACH TO CARE

Patients with CKD and their family members including care-partners should be empowered to achieve the health outcomes and life goals that are meaningful and important to them. The WHO defines patient empowerment as "*a process through which people gain greater control over decisions or actions affecting their health*",[6] which requires patients to understand their role, to have knowledge to be able to engage with clinicians in shared decision-making, skills, and support for self-management. For patients receiving dialysis, understanding the rationale for a lifestyle change, having access to practical assistance and family support promoted patient empowerment, while feeling limited in life participation undermined their sense of empowerment.[7]

The World Kidney Day Steering Committee advocates for strengthened partnership with patients in the development, implementation, and evaluation of interventions for practice and policy settings, that enable patients to live well with kidney diseases. This needs to be supported by consistent, accessible, and meaningful communication. Meaningful involvement of patients and family members across the entire research process, from priority setting and planning the study through to dissemination and implementation, is now widely advocated.[8] There have also been efforts, such as the Kidney Health Initiative, to involve patients in the development of drugs and devices to foster innovation.[9]

We urge for greater emphasis on a strengths-based approach as outlined in Table 1, which encompasses strategies to support patient resilience, harness social connections, build patient awareness and knowledge, facilitate access to support, and establish confidence and control in self-management. The strengths-based approach is in contrast to the medical model where chronic disease is traditionally focussed on pathology, problems, and failures.[10] Instead, the strengths-based approach acknowledges that each individual has strengths and abilities to overcome the problems and challenges faced, and requires collaboration and cultivation of the patient's hopes, aspirations, interests, and values. Efforts are needed to ensure that structural biases, discrimination, and disparities in the health care system also need to be identified, so all patients are given the opportunity to have a voice.

THE ROLE OF CARE-PARTNER

A care-partner is often an informal caregiver who is also a family member of the patient with CKD.[11] They may take on a wide range of responsibilities including coordinating care (including transportation to appointments), administration of treatment including medications, home dialysis assistance, and supporting dietary management. Caregivers of patients with CKD have reported depression, fatigue, isolation, and also burnout.The role of the care-partner has increasingly become more important in CKD care given the heightened complexity in communicative and therapeutic options including the expansion of telemedicine under the coronavirus disease 2019 (COVID-19) pandemic and given the goal to achieve higher life expectancy with CKD.[12] The experience of caring for a partially incapacitated family member with progressive CKD can represent a substantial burden on the care-partner and may impact family dynamics. Not infrequently, the career goals and other occupational and leisure aspects of the life of the care-partner are affectedbecause of CKD care partnership, leading to care-partner overload and burnout. Hence, the above-mentioned principles of life participation need to equally apply to care-partners as well as all family members and friends involved in CKD care.

LIVING WITH KIDNEY DISEASE IN LOW-INCOME REGIONS

In low and lower-middle-income countries (LICs and LMICs) including in sub-Saharan Africa, South East Asia, and Latin America, patient's ability to self-manage or cope with the chronic disease vary but may often be influenced by internal factors including spirituality, belief system, and religiosity, and external factors including appropriate knowledge of the disease, poverty, family support system, and one's grit and social relations network. The support system comprising healthcare providers and caregivers plays a crucial role as most patients rely on them

Table 1. *Suggested Strategies for "Living Well with CKD" Using a Strengths-Based Approach*

Strengths-Based Approach	Suggested Strategies
Build resilience	• Identify or provide strategies and resources to manage stress and functioning when encountering challenges, adversity and trauma (e.g. commencement of dialysis)
Harness social connections	• Facilitate connections with other patients to learn coping strategies and for support • Support family members/caregivers
Build awareness and knowledge	• Provide education (including practical advice) on diet and lifestyle modifications • Understand, identify, and address the potential impacts of CKD (e.g. cognitive function). • Encourage patients to ask questions. • Encourage the use of knowledge to empower and prepare for the future.
Facilitate access to support	• Refer to allied health care professionals (e.g. dietitian, social worker, mental health professionals, occupation therapists) • Provide support that enables the patient to participate in important life activities e.g. work.
Establish confidence and control in self-management	• Support informed and shared decision-making (including dialysis, kidney transplantation, conservative or non-dialytic care) • Encourage patients to learn to "get in tune" with what works well for them and to voice any concerns, and work together to develop better management strategies to enable patients to feel better. • Provide strategies to prevent or manage complications (e.g. infection) • Support open communication regarding goals, concerns, and priorities

CKD: Chronic kidney disease (not receiving kidney replacement therapy)

in making decisions, and for the necessary adjustments in their health behavior.[13] In LIC regions, wherethere are often a relatively low number of physiciansand even lower number of kidney care providers per population especially in rural areas, a stepwise approach can involvelocal and national stakeholders including both non-governmental organizations and government agencies by 1) extending kidney patient education in rural areas, 2) adapting telehealth technologies if feasible to educate patients and train local community kidney care providers and 3) implementing effective retention strategies for rural kidney health providersincluding adapting career plans and competitive incentives.

Many patients in low resource settings present in very late stage needing to commence emergency dialysis.[14] The very few fortunate ones to receive kidney transplantation may acquire an indescribable chance to normal life again, notwithstanding the high costs of immunosuppressive medications in some countries. For some patients and care-partners in low-income regions, spirituality and religiosity may engender hope, when ill they are energized by the anticipation of restored health and spiritual well-being. For many patients, informing them of a diagnosis of kidney disease is a harrowing experience both for the patient (and caregivers) and the healthcare professional. Most patients present to kidney physicians (usually known as "renal physicians" in many of these countries) with trepidations and apprehension. It is rewarding therefore to see the patient's anxiety dissipate after reassuring him or her of a diagnosis of simple kidney cysts, urinary tract infection, simple kidney stones, solitary kidneys, etc., that would not require extreme measures like kidney replacement therapy. Patients diagnosed with glomerulonephritis who have an appropriate characterization of their disease from kidney biopsies and histology; who receive appropriate therapies and achieve remission are relieved and are very grateful. Patients are glad to discontinue dialysis following resolution of acute kidney injury (AKI) or acute on CKD.

Many CKD patients who have residual kidney function appreciate being maintained in a relatively healthy state with conservative measures, without dialysis. They experience renewed energy when their anemia is promptly corrected using erythropoiesis-stimulating agents. They are happy when their peripheral oedema resolves with treatment. For those on maintenance hemodialysis who had woeful stories from emergency femoral cannulations, they appreciate the construction of good temporary or permanent vascular accesses. Many patients in low resource settings present in very late stage needing to commence emergency dialysis. Patients remain grateful forwaking from a uremic coma or recovering from recurrent seizures when they commence dialysis.

WORLD KIDNEY DAY 2021 ADVOCACY

World Kidney Day 2021 theme on 'Living Well with Kidney Disease' is deliberately chosen to have the goals to redirect more focus on plans and actions towards achieving patient-centred wellness. "*Kidney Health for Everyone, Everywhere*" with emphasis on patient-centred wellness should be a policy imperative that can be successfully achieved if policymakers, nephrologists, health care professionals, patients, and care partners place this within the context of comprehensive care. The requirement of patient engagement is needed. WHO in 2016 put out an important document on patient empowerment (WHO 2016): 'Patient engagement is increasingly recognized as an integral part of health care and a critical component of safe people-centred services. Engaged patients are better able to make informed decisions about their care options. In addition, resources may be better used if they are aligned with patients' priorities and this is critical for the sustainability of health systems worldwide. Patient engagement may also promote mutual accountability and understanding between patients and health care providers. Informed patients are more likely to feel confident to report both positive and negative experiences and have increased concordance with mutually agreed care management plans. This not only improves health outcomes but also advances learning and improvement while reducing adverse events.' In the ISN Community Film Event at World Congress of Nephrology (WCN) 20 (ISN Community Film Event 2020), it is good to see a quote in the film from patients: "*Tell me. I will forget; Show me. I will remember; Involve me. I will understand.*" ISN Global Kidney Policy Forum 2019 included a patient speaker Nicki Scholes-Robertson from New Zealand: 'Culturally appropriate and sensitive patient information and care are being undertaken in New Zealand to fight inequities in kidney health, especially in Maori and other disadvantaged communities.'

World Kidney Day 2021 would like to promote to the policy makers on increasing focus and resources on both drug and non-drug programmes in improving patient wellness. Examples include funding for erythropoiesis-stimulating agents and anti-pruritic agents for managing anemia and itchiness respectively, just name but a few.[15,16] Home dialysis therapies have been consistently found to improve patient autonomy and flexibility, quality of life in a cost-effective manner, enhancing life participation. Promoting home dialysis therapies should tie in with appropriate 'assisted dialysis' programs to reduce patient and care partner fatigue and burnout. Also, examples like self-management programmes, cognitive behavioural therapy, and group therapies for managing depression, anxiety, and insomnia should be promoted before resorting to medications.[17] The principle of equity recognizes that different people with different levels of disadvantage require different approaches and resources to achieve equitable health outcomes. The kidney community should push for adapted care guidelines for vulnerable and disadvantaged populations. The involvement of primary care and general physicians especially in LICs and LMICs would be useful in improving the affordability and access to services through the public sector in helping the symptom management of CKD patients and improve their wellness. In the overall wellness program for kidney disease patients, the need for prevention should be reiterated. Early detection with a prolonged course of wellness despite kidney disease, after an effective secondary prevention program, should be promoted.[18] Prevention of CKD progression can be attempted by lifestyle and diet modifications such as a plant-dominant low protein diet and by means of effective pharmacotherapy including administration of sodium-glucose transport protein 2 (SGLT2) inhibitors.[19] WKD 2021 continues to call for increased awareness of the importance of preventive measures throughout populations, professionals, and policy makers, applicable to both developed and developing countries.[18]

CONCLUSION

Effective strategies to empower patients and their care-partners strive to pursue the overarching goal of minimizing the burden of CKD related symptoms in order to enhance patient satisfaction, health-related quality of life, and life participation.World Kidney Day 2021 theme on "*Living Well with Kidney Disease*" is deliberately chosen to have the goals to redirect more focus on plans and actions towards achieving patient-centered wellness. Notwithstanding the COVID-19 pandemic that had overshadowed many activities in 2020 and beyond, the World Kidney Day Steering Committee has declared 2021 the year of "*Living well with Kidney Disease*" in an effort to increase education and awareness on the important goal of effective symptom management and patient empowerment. Whereas the World Kidney Day continues to emphasize the importance of effective measures to prevent kidney disease and its progression,[18] patients with preexisting kidney disease and their care-partners should feel supported to live wellthrough concerted efforts by kidney care communities and other stakeholders throughout the world even during a world-shattering pandemic as COVID-19 that may drain many resources.[20] Living well with kidney disease is an uncompromisable goal of all kidney foundations, patient groups, and professional societies alike, to which the International Society of Nephrology and the International Federation of Kidney FoundationWorld Kidney Alliance are committed at all times.

ACKNOWLEDGMENT

The authors has taken permission of reprinting this article in mutiple journals in order to spread awareness by the Steering Committee.

CONFLICTS OF INTEREST

K.K.-Z. reports honoraria from Abbott, Abbvie, ACI Clinical, Akebia, Alexion, Amgen, Ardelyx, Astra-Zeneca, Aveo, BBraun, Cara Therapeutics, Chugai, Cytokinetics, Daiichi, DaVita, Fresenius, Genentech, Haymarket Media, Hospira, Kabi, Keryx, Kissei, Novartis, Pfizer, Regulus, Relypsa, Resverlogix, Dr Schaer, Sandoz, Sanofi, Shire, Vifor, UpToDate, and ZS-Pharma. P.K.T.L. reports personal fees from Fibrogen and Astra-Zeneca. G.S. reports personal fees from Multicare, Novartis, Sandoz, and Astra-Zeneca. V.L. reports nonfinancial support from Genesis Pharma.

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