International Journal of Medical Science and Clinical Research Studies

ISSN(print): 2767-8326, ISSN(online): 2767-8342

Volume 03 Issue 12 December 2023

Page No: 3148-3157

DOI: https://doi.org/10.47191/ijmscrs/v3-i12-42, Impact Factor: 6.597

Acute Diarrhea in Early Post-Transplant Period in Living Donor Kidney Transplant Recipients

Khin Phyu Pyar[1], Win Kyaw Shwe[2], Moe Zaw Myint[3], Kyaw Soe Win[3], Aung Myo Saw[3], Zaw Lin Aung[3], Aung Zaw Htet[4], Thurein Wynn[5], Aung Phyoe Kyaw[5], Kaung Myat Oo[6], Zaw Min Htike[7], Aung Khin Sint[8], Kyaw Thet Maung[5], Aung Thu[5], Ye Min Thu[5], Kyaw Zay Ya[5], Myo Thant Kyaw[5], Zay Phyo Aung[5], Han Lin Aung[5], Aung Phyo Latt[5], Zin Zin Aung[9], Myo Maung Maung[9] , Min Aung Hein[10], Kyaw Thurein Lwin[10], Wai Lynn Aung[5], Sitt Min[5]

[1]Professor and Head/Senior Consultant Physician, Department of Medicine/ Department of Nephrology, Defence Services Medical Academy, No. (1) Defence Services General Hospital (1000-Bedded), Yangon, Myanmar
[2]Senior Consultant Nephrologist, No. (2) Defence Services General Hospital (1000-Bedded), Nay Pyi Taw
[3]Senior Consultant Physician, No. (2) Defence Services General Hospital (1000-Bedded), Nay Pyi Taw
[4]Senior Consultant Nephrologist, No. (1) Defence Services General Hospital (1000-Bedded), Yangon
[5]Consultant Physician, No. (1) Defence Services General Hospital (1000-Bedded), Yangon
[6]Consultant Pathologist, No. (1) Defence Services General Hospital (1000-Bedded), Yangon
[7]Consultant Microbiologist, No. (1) Defence Services General Hospital (1000-Bedded), Yangon
[8]Consultant Pharmacologist, No. (1) Defence Services General Hospital (1000-Bedded), Yangon
[9]Consultant Nephrologist, No. (2) Defence Services General Hospital (1000-Bedded), Nay Pyi Taw
[10]Consultant Nephrologist, No. (1) Defence Services General Hospital (1000-Bedded), Yangon

ABSTRACT

Background: Acute diarrhea is common in Myanmar. People are so used to diarrhea at least once a year that they do not think diarrhea as an important problem. Acute diarrhea in early post-operative period in renal transplant recipient may result in pre-renal failure and delay graft function. This study aimed to identify the prevalence of diarrhea, its severity and response to treatment in early post-operative period (3 weeks after transplant) in living donor kidney transplant (LDKT) recipients.

Patients and Methods: LDKT recipients having acute diarrhea in early post-transplant period at two transplant centers (Mingaladon and Nay Pyi Taw) in Myanmar were analyzed over 10 years period; from 2013 to 2023 September. Acute diarrhea is defined as three or more semisolid or liquid stools per day for a minimum of 1 day duration. It was a hospital based observational study. After obtaining diet history and physical examination, laboratory tests were done. Clinical parameters (diet, fever, features of oral candidiasis, features of dehydration, examination of abdomen), stool examination (stool inspection, stool examination for ova and cyst, stool for *Clostridium difficle* toxin, stool culture), blood tests (total WBC count, serum creatinine, liver function tests) and blood trough level for Tacrolimus and mycophenolate mofetil were done. Management was given according to algorithm and their response to treatment was recorded. Dose modification of immunosuppressants were done depending on full blood count and blood level of them.

Results: A total of 230 LDKT recipients were observed; among them, thirteen percent (30/230) of recipients developed acute diarrhea in early post-operative period. The age ranged from 14 to 73 years. A majority of them had mild form; mild dehydration without significant changes in hemodynamic status. The peak onset of diarrhea was 4 to 5 days after transplant; majority resolved over one week. They did not have oral candidiasis. Abdominal examination was normal except mild tenderness over grafted kidney in all of them. Total WBC count and platelet count were normal except in two cases. Stool examination did not show trophozoite or cyst. Stool for *Clostridium difficile* toxin was not identified. With dietary modification and oral rehydration solution, their motion was back to normal in sixteen

ARTICLE DETAILS

Published On:
20 December 2023

percent (5/30). Folic acid therapy with or without probiotics made resolution of diarrhea in 33.3% (10/30). Anti-infective therapy was given in 10% (3/30) of cases; norfloxacin to 2 cases. Intravenous colistin to one case as he had enterocolitis and septicemia due to *Klebsiella pneumonia*. His stool culture as well as blood culture showed Carbepenem resistant *Klebsiella pneumonia*; he was known case of myelodysplastic syndrome.

Blood level of mycophenolate mofetil was normal; however, the dose was reduced in 2 cases owing to leucopenia or thrombocytopenia. Blood tacrolimus trough level was normal in two-third (20/30); and, it was high in one-third of them (20/30). They passed formed stool 24 - 48 hours after dose reduction of tacrolimus.

Conclusion: In this study, 13% of the LDKT recipients had acute diarrhea in early post-operative period. Majority of them had mild form. Half of them recovered with oral rehydration solution, diet modification, folic acid and probiotics. Only one tenth of them had infective in origin and responded to anti-infective therapy. Raised blood tacrolimus trough level was found in one third of LDKT recipients with acute diarrhea; diarrhea improved dramatically after reduction of tacrolimus dose.

KEYWORDS: acute diarrhea, early post-operative period, renal transplant recipients, tacrolimus

Available on:
https://ijmscr.org/

INTRODUCTION

Acute diarrhea is one of the common causes of morbidity and mortality in developing country; it is the 13th leading cause of death in Myanmar. Living donor kidney transplant (LDKT) recipients are in immunocompromised state; therefore, they are vulnerable to infections. Regarding the possible agent of acute diarrhea in early post-transplant period, the source of infection is less likely to be community acquired (Agrawal et al., 2022); it is more likely to be either hospital acquired infection or non-infective in origin.

The incidence of chronic kidney disease is expected to be 10% of World's population; and the number end stage renal disease (ESRD) is increasing. Kidney transplant is accepted as preferred treatment option among three renal replacement therapies: hemodialysis, peritoneal dialysis and renal transplant. Immunosuppressants play a key role to prevent rejection of grafted kidney; combinations of steroids, mycophenolate mofetil and tacrolimus have been used as immunosuppressants for more than 20 years.

The effect of immunosuppressant therapy on bone marrow is anemia (mycophenolate mofetil), leucopenia (mycophenolate mofetil) and thrombocytopenia (mycophenolate mofetil). Moreover, the induction agents like ATG and Basiliximab have bone marrow suppressant effect through immune mediated mechanism. Acute diarrhea may be one of the gastrointestinal manifestations of untoward effect of mycophenolate mofetil; and, they are reported at 3-4 months after transplant. Moreover, hypersensitivity reaction of both immunosuppressants and induction agents may cause diarrhea. Acute diarrhea may be due to pseudomembranous colitis caused by *Clostridium difficile*; it is common side effect of antibiotics like ciprofloxacin and clindamycin. Howevere, it may be very rarely due to tacrolimus(Sharma & Holder, 1998).

According to studies on diarrheal diseases in Myanmar, the etiology of acute diarrhea was usually infective; viral in origin (Hossian et al., 2021). In children, nearly half of the cases with diarrhea were due to Rota virus infection (Myat et al., 2021) (Moe et al., 2005). Furthermore, Moe et al highlighted that water sanitation, health hygiene and food hygiene played essential role prevalence of diarrheal diseases in Myanmar (Moe et al., 2005).

The reported etiology of chronic diarrhea in kidney transplant recipients was infective; mainly viral infection (Ghusson & Vasquez, 2018) (Gras et al., 2021); rarely parasites like cryptosporidium (Raja et al., 2014) (ISMAIL & FADL, 2019); bacterial infection (Agrawal et al., 2022)(Sharma & Holder, 1998); tuberculosis (García-Padilla et al., 2022); giardiasis; immunosuppressants (Gioco et al., 2020) (Calogero et al., 2020); and, gut dysbiosis (Lee et al., 2019). However, the report on acute diarrhea in (LDKT) living donor kidney transplant recipients in early post-operative period was rarely mentioned. Therefore, this study aimed to identify the prevalence, its severity and response to management of treatment algorithm of acute diarrhea in LDKT recipients in early post-operative period (3 weeks after transplant) in Myanmar.

METHODS

Study design and participants

A hospital based descriptive/observational study was conducted among living donor kidney transplant (LDKT) recipients at two transplant centers in Myanmar- Yangon and Nay Pyi Taw, from February 2018 to September 2023. All recipients in early post-transplant period (3 weeks after transplant) were observed and they were included in this study if they diarrhea. All patients received standard treatment according to hospital transplant guideline; steroids, mycophenolate mofetil and tacrolimus, nystatin, ceftazidime-sulbactam, oxygen, fluid therapy, nutritional support and supportive care. They also got the induction agents like ATG and/or Basiliximab depending on their immunological risks. Informed consent was taken from recipients or from one of the parents if recipient was under 18 years with appropriate documentation by the investigator. If they had diarrhea, they

were managed according to local guideline for acute diarrhea (acute diarrhea algorithm). And, the response to management was recorded. The data were recorded and final analysis was done.

The following is the local guideline for acute diarrhea (acute diarrhea algorithm) for LDKT recipients with acute diarrhea. It was illustrated in figure (1).

Dietary modification and oral replacement therapy with oral rehydration solution will be done as 'Step 1'. And, the response will be observed.

As 'Step 2', oral folic acid with or without probiotics will be added if diarrhea does not respond to 'Step 1' for 24 to 48 hours. And, the response will be observed.

If there is no response or improvement in next 24 -48 hours, stool for microscopy will be done at 'Step 3'. If it shows bacteria with pus cells more than 5 -10 per high power field, oral anti-infective therapy (norfloxacin) will be given. And, oral anti-amoebic therapy (metronidazole/danzolic) will be prescribed if it reveals trophozoite form of *Entamoeba histolytica*. Deworming with appropriate ant-helminthics will be done if the eggs are seen in microscopic examination. And, the response will be observed.

As 'Step 4', stool culture or stool for *Clostridium difficle* toxin will be sent if there is no response in next 24 to 48 hours. They will be treated according to culture results. If stool for *Clostridium difficle* toxin is positive, parenteral metronidazole will be given. And, the response will be observed.

Blood trough level of tacrolimus with or without blood trough level mycophenolate mofetil will be sent in all cases.

For this study, team discussion (either in person or viber) is done on daily basis; team members are nephrologists, physicians, microbiologists, pathologists, pharmacologists, nursing staffs and administrators. Clinical parameters (diet, fever, features of oral candidiasis, features of dehydration, examination of abdomen), stool examination (stool inspection, stool examination for ova and cyst, stool for *Clostridium difficle* toxin, stool culture), blood tests (total WBC count, serum creatinine, liver function tests) and blood trough level for Tacrolimus and mycophenolate mofetil were analyzed.

This study was approved by the hospital research and ethics committee of No.(1) Defence Services General Hospital (1000-Bedded) Mingalardon, Yangon.

Study area

This study was carried out at two purposively selected transplant centers; No.(1) Defence Services General Hospital (1000-Bedded) Mingalardon, Yangon and No.(2) Defence Services General Hospital (1000-Bedded) Nay Pyi Taw, Myanmar.

Operational definitions

'Acute diarrhea' was defined as three or more semisolid or liquid stools per day for a minimum of 1 day duration.

'Early post-transplant period' was defined as 3 weeks after transplant surgery.

'Hospital Transplant guideline/ the Standard treatment' included steroids, mycophenolate mofetil and tacrolimus, oral nystatin for 2 weeks, ceftazidime-sulbactam for 5 days, oxygen, fluid therapy, nutritional support and supportive care. 'Induction agents' included ATG and/or Basiliximab, given depending on immunological risks.

'Onset of diarrhea' was defined in 'Days' after transplant surgery. Day of transplant surgery was defined as 'Day 0". Next day after transplant surgery was defined as 'Day 1'. Next day after 'Day 1' was defined as 'Day2' and so on.

'Severity of diarrhea' was classified as mild, moderate and severe. 'Mild form of diarrhea' was defined as 'frequency of motion was less than 5 times/day with features of mild dehydration (dry tongue, thirst, reduced skin elasticity without tachycardia or reduction in blood pressure)'. 'Moderate form of diarrhea' was defined as 'features of mild plus tachycardia and reduction in blood pressure'. 'Severe form of diarrhea' was defined as 'features of moderate plus cold clammy extremities and hypovolemic shock'.

'Symptomatic therapy' was defined as 'replacement with oral rehydration solution'.

Dietary modification was defined as "advice to withhold new diet (milk or milk product) or to withhold unhygienic diet (salads, unsterile water and fruits without removable skin like grapes)".

'Probiotic therapy' was defined as 'bioflor therapy'.

'Anti-infective therapy' was defined as 'either oral quinolone or azithromycin'.

Response to management was defined as 'Yes' or 'No'. 'Yes' was 'Resolution of diarrhea'; it was defined as ' passage of semisolid or formed stool less than 2 times per day'. 'No' was 'No resolution of diarrhea'; it was defined as ' passage of semisolid or liquid stool more than 2 times per day'.

'Dosage of steroid' was 'intravenous methyl prednisolone 500 mg daily for 3 days followed by oral prednisolone 1 mg per kg per day'.

'Tacrolimus dose 'is calculated as 0.05 mg/Kg twice a day for 2 days. Then, it is increased to Initial half of Daily dose 0.1 mg/Kg . If creatinine is 50% of pre-transplant value, daily dose is 0.1 mg/Kg.

'Tacrolimus trough level' was defined as ' the amount of tacrolimus measured in the blood of recipient taken 30 minutes before next oral dose'. It was measured 48 hours after full dose. Target was 7-10 ng/ml; it was usually kept as 8-9 ng/ml.

'Dosage of mycophenolate mofetil' was '1 gram 12 hourly'.

'Therapeutic level mycophenolate mofetil' was defined as ' the amount of mycophenolic acid (MPA) measured'at post-transplant 7^{th} day. Plasma concentrations of mycophenolic acid at time points immediately before drug administration, 0.5 hours, and 2 hours post dose (C_0, $C_{0.5}$, and C_2) were determined by validated HPLC-UV method. The estimated MPA $AUC_{0\text{-}12hr}$ was calculated by using the validated limited

sampling strategy equation from the three plasma concentration time points measured ($7.75 + 6.49 \times C_0 + 0.76 \times C_{0.5} + 2.43 \times C_2$). in the blood of recipient taken 30 minutes before next oral dose'.

DATA COLLECTION AND PROCEDURES

Supervised treatment was done; and, both clinical and laboratory data were collected by using standardized forms and analysis was done.

LDKT recipients having acute diarrhea in early post-transplant period (3 weeks) at two transplant centers (Mingaladon and Nay Pyi Taw) in Myanmar were analyzed as a hospital based observational study over 10 years period; from 2013 to 2023 September. They were included in study after getting informed consent if they had acute diarrhea; three or more semisolid or liquid stools per day for a minimum of 1 day duration. Detailed history on currently taken diet including drinking water was obtained; new diet like milk and milk products, unhygienic food, unsterile water and fruits without removable skin like grapes. Physical examination was done daily till resolution of diarrhea; temperature, pulse rate, blood pressure, features of oral candidiasis, signs of dehydration, abdominal examination and urine output. Stool was inspected daily. Laboratory tests like renal function tests, liver function tests and full blood count were done in addition to blood level of mycophenolate mofetil and tacrolimus. Management was done according to different steps in algorithm; and, their response to treatment was recorded after each step of management as demonstrated in figure (1).

'Step 1' (dietary modification and oral replacement therapy with oral rehydration solution) was done to all cases having diarrhea. And, the response was observed. If diarrhea did not respond to 'Step 1' for 24 to 48 hours, 'Step 2', oral folic acid with or without probiotics was added. Next, the response was recorded. If there was no response or improvement within another 24 -48 hours, stool for microscopy was done at 'Step 3'. If it showed bacteria, oral anti-infective therapy (norfloxacin) was given. And, oral anti-amoebic therapy (metronidazole/danzolic) was prescribed if it revealed trophozoite form of *Entamoeba histolytica*. Deworming with appropriate ant-helminthics was done if eggs were seen in microscopic examination. After 'Step 3', the response was observed again. 'Step 4', stool culture or stool for *Clostridium difficle* toxin was sent if there was no response in next 24 to 48 hours. They were treated accordingly depending on culture results. If stool for *Clostridium difficle* toxin was positive, parenteral metronidazole was given. Then, the response was noted. Blood trough level of tacrolimus with or without blood level mycophenolate mofetil was sent in all cases.

Team discussion (either in person or viber) was done on daily basis. Clinical parameters (diet, fever, features of oral candidiasis, features of dehydration, examination of abdomen), stool examination (stool inspection, stool examination for ova and cyst, stool for *Clostridium difficle* toxin, stool culture), blood tests (total WBC count, serum creatinine, liver function tests) and blood trough level for Tacrolimus and mycophenolate mofetil were analyzed.

Stool samples for microbiological examination (red cells, pus cells, bacteria, ova, trophozoite and cyst) was done if diarrhea did not resolve with diet modification, probiotics/folic acid therapy (Step 2).

Dose modification of immunosuppressants were done depending on full blood count, blood level of mycophenolate mofetil and tacrolimus. If there was leucopenia and thrombocytopenia, the dose of mycophenolate mofetil was reduced. If the trough level of tacrolimus was high, the dose of tacrolimus was decreased. The nature of stool and frequency following response to individualized treatment in each step was recorded.

Stool for *Clostridium difficle* toxin and stool culture were done if they did not respond to above treatment (Step 3). Response to management was recorded accordingly.

The clinical outcome of the patients was evaluated daily till 4 weeks after treatment. Data were collected in standardized proforma and confidentiality was maintained. The data were checked by two medical officers and then, supervision, completeness, and consistency of collected data were performed by the principle investigator. Statistical evaluation was done.

RESULTS

LDKT recipients were kept in intensive care units for one week; immediate post-operative period to 'Day 7' after kidney transplant. Then, they were shifted to renal medical unit for another 7 to 14 days. They went home 2 to 3 weeks after transplant. If they had diarrhea and the cause of diarrhea was infective, they were isolated and barrier nursing was done.

In two transplant centers (Mingaladon and Nay Pyi Taw) in Myanmar, a total of 230 cases underwent living donor kidney transplant (LDKT) in the past 10 years, from 2018 to 2023 September. In early post-transplant period, 3 weeks after transplant surgery, a total of 30 recipients (13%, 30/230) had diarrhea. The youngest was 14 years and the eldest was 73 years old. Male were 55% and female was 45%. The time of onset of diarrhea was 4 to 5 days after transplant. They did not have fever. A majority of them had mild form of diarrhea; mild dehydration; no tachycardia nor hypotension. They did not have oral candidiasis. They did not feel abdominal pain. Abdominal examination did not reveal features of acute abdomen; only mild tenderness over grafted kidney was noted in all cases.

Their stool did contain blood in naked inspection; microscopy did not reveal red blood cells. Blood for total WBC count was normal except in two cases; leucopenia and thrombocytopenia. Stool examination did not show trophozoite or cyst. Stool for *Clostridium difficile* toxin was not identified.

After reviewing dietary history thoroughly, physical examination and stool for inspection were done. Then, dietary modification, and oral replacement therapy with oral rehydration solution were given according to 'Step 1" in management algorithm. Table (1) described each step and corresponding response. The loose motion was back to formed stool in 16% (5/30) of them.

In remaining 25 recipients, diarrhea persisted. Therefore, folic acid therapy with or without probiotics was added as 'Step 2'. And, the response was observed for another 48 hours. 'Step 2' made resolution of diarrhea in 33.3% (10/30) of them.

As stool for microscopy demonstrated bacteria and pus cells in 3 cases (10%=3/30), anti-infective therapy was given as 'Step 3'. Norfloxacin was prescribed to 2 cases. Intravenous colistin was initiated to one case as his stool culture showed Carbepenem resistant *Klebsiella pneumonia*. He was known case of myelodysplastic syndrome and he also had *Klebsiella pneumonia* septicemia.

Two-third of them (20/30) had normal blood tacrolimus trough level and the remaining (10/30) had raised tacrolimus level. Therefore, dose reduction of tacrolimus was done as 'Step 4'. Twenty-four to forty-eight hours after dose reduction of tacrolimus, they passed formed stool. Three cases of them required hemodialysis due to delayed graft function.

Blood level of MPA (mycophenolic acid) was within normal range in all of them. However, dose reduction of mycophenolate mofetil was done as 2 cases (6.6%). One case had leucopenia and another case had thrombocytopenia. Therefore, only 3 cases (10%) in this study required antibiotics.

Table (1) Frequency of response to different steps of management (n=30)

Serial number	Management Steps	Number	Percent	Remarks (indication)
1	Response to 'Step 1' (Diet + ORS)	5	16	
2	Response to 'Step 2' (Folic acid +/- Probiotics)	10	33.3	
3	Response to 'Step 3' (oral anti-infective therapy)	2	6.6	Pus & bacteria in stool microscopy
4	Response to 'Step 4' (stool culture or stool for *Clostridium difficle* toxin)	1	3.3	Stool culture positive
5	Response to dose reduction of Tacrolimus	10	33	Raised tacrolimus level
6	Response to dose reduction of MMF	2	6.6	Leucopenia & thrombocytopenia
	Total number of cases with diarrhea	30	100	

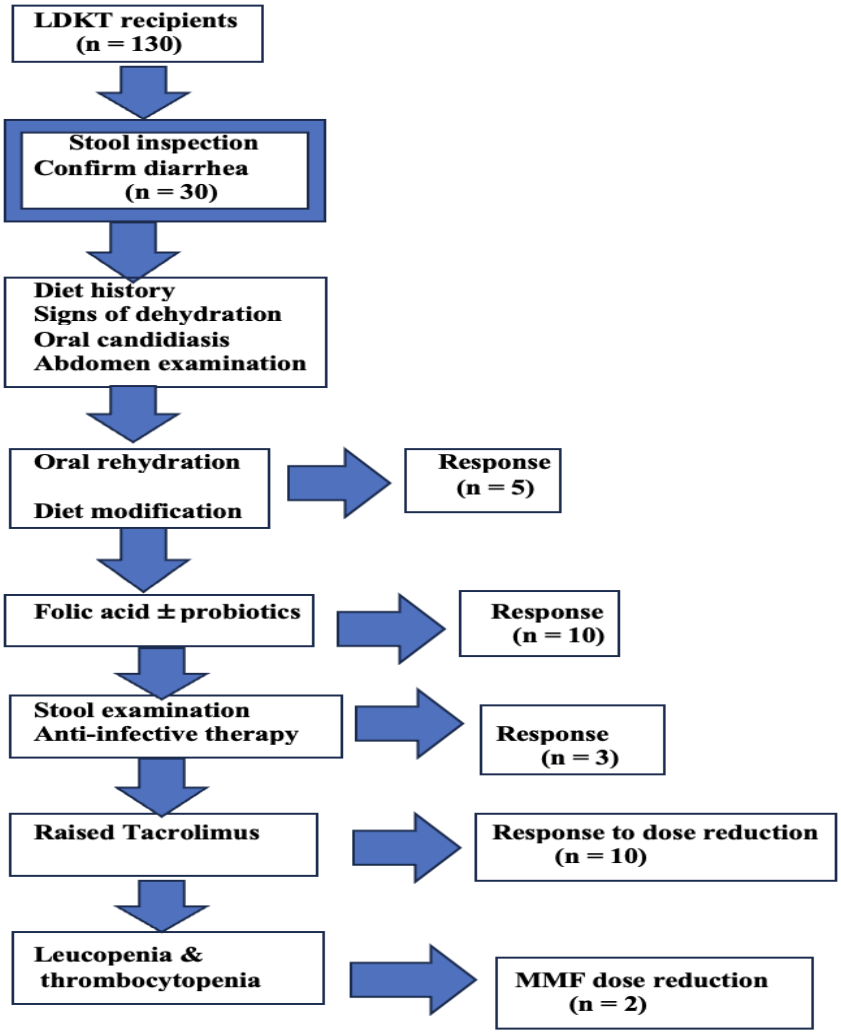

Figure (1) Management algorithm for LDKT recipients with acute diarrhea

DISCUSSION

Acute diarrhea is a common problem in developing countries. In 2020, deaths due to diarrheal diseases occupied 2% of total deaths in Myanmar (WHO, 2020). Therefore, having acute diarrhea in early post-transplant period should not be ignored. The fluids and electrolytes loss in LDKT recipients may lead to pre-renal failure and delayed graft function. This hospital-based descriptive study was done over 10 years in 2 transplant centers in Myanmar. It was found that 13% of 130 LDKT recipients had acute diarrhea within first 3 weeks of transplant.

The studies on acute diarrhea in immunocompetent person in Myanmar revealed that the majority were due to virus. The cause of acute diarrhea in LDKT recipients with immunocompromised status in early post-transplant period should be analyzed whether the etiology is the same as immunocompetent person or not. Development of diarrhea in early post-operative period was related with surgical technique; On the other hand, the causes of chronic diarrhea in kidney transplant recipients were reported as giardiasis (Vyas et al., 2021), cryptosporiosis (Raja et al., 2014) (Castellano Carrasco et al., 2017) (Vyas et al., 2021) (ISMAIL & FADL, 2019), bacteria (Agrawal et al., 2022) (Echenique et al., 2015), CMV virus (García-Padilla et al., 2022) (Echenique et al., 2015), Rota virus (Shin & Chandraker, 2017) (Yin et al., 2015), Norovirus (Ghusson & Vasquez, 2018) (Shin & Chandraker, 2017) (Echenique et al., 2015), Adeno virus (Shin & Chandraker, 2017), Sapo virus (Ghusson & Vasquez, 2018), Hu No virus (Gras et al., 2021), gut dysbiosis (Lee et al., 2019), tuberculosis (García-Padilla et al., 2022), and anti-rejection drugs related MMF(Fatly et al., n.d.) (Gioco et al., 2020) (Calogero et al., 2020).

Timely identification of the cause of diarrhea was essential and it must be focused to save the graft kidney as well as the recipient himself (Angarone & Snydman, 2019). Molecular tools significantly improved the detection of single and multiple enteric infections by comparison to classical techniques; and, they became the key element in the management of severe acute diarrhea in transplant recipients (Coste Jean-François et al., 2020). The molecular tools were very important for microbiological diagnosis to detect exact organism in them (Coste et al., 2013) and they were user

friendly. The accessibility of the molecular tools in low resource setting was questionable. We agreed the fact that identification of the cause of diarrhea timely and focused (Angarone & Snydman, 2019).

Therefore, the guideline for acute diarrhea (acute diarrhea algorithm) for LDKT recipients with acute diarrhea was developed locally to preserve resources as much as possible. It was based mainly on clinical skills: focused history, physical examination and bed side stool examination. It was very cost effective because it tailored the investigation. Moreover, it aimed at maintaining proper hydration status. Furthermore, it identified the cause diarrhea timely; it supported the important points raised by Angarone et Al (Angarone & Snydman, 2019). This is one reason to share the guideline for management of acute diarrhea in LDKT recipients in early post-operative period.

Rodrigues et al suggested that dietary factors played an important role in chronic diarrhea in kidney transplant recipients (Rodrigues et al., 2021). Here, dietary modification made improvement of diarrhea.

According to the study done in India, infective etiology was identified in nearly half of solid organ transplant recipients having chronic diarrhea; they developed diarrhea 6 months after transplant. Parasites attributed 70% of infection; drugs related diarrhea was 30%; etiology was not identified in 20% (Vyas et al., 2021). *Clostridium difficile* was as commonly identified bacteria causing diarrhea in transplant recipients in majority of the studies (Echenique et al., 2015)(Sharma & Holder, 1998b). Stool for *Clostridium difficile* toxin was not identified in this study. Carbepenem resistant *Klebsiella pneumonia* was detected stool culture in this study; the patient was known case of myelodysplastic syndrome and he also had *Klebsiella pneumonia* septicemia. Common site of infection for *Klebsiella pneumonia* was respiratory tract; it caused enterocolitis through blood stream spread. We would like to highlight the point that the natural habitant of bacteria might change in non-immunocompetent person or it might change de no vo. It is another reason to learn from this study.

In early post-transplant period, 3 weeks after transplant surgery, a total of 30 recipients (13%, 30/230) had diarrhea. The onset of diarrhea was 4 to 5 days after transplant surgery. The prevalence of acute diarrhea as well as peak onset of diarrhea was not comparable with other studies because their studies were done not in early post-operative period. They did at least 6 months after transplant (Fatly et al., n.d.) (Vyas et al., 2021).

In this study, only 3 cases (10%) were due to bacterial infection and 90% of cases were non-infective in origin. Therefore, it supported the findings 'one-half of episodes of diarrhea in kidney transplant recipients were non-infectious in origin'(Sonambekar et al., 2020). In addition, Fatly and colleagues pointed out that diarrhea was found to be one of the troublesome gastrointestinal symptoms 6 months after transplantation in the majority of kidney transplant recipients with tacrolimus and mycophenolate mofetil; diarrhea only improved over time by mouth 15 particularly after discontinuing mycophenolate mofetil; diarrhea only improved over time by mouth 15 particularly after discontinuing mycophenolate mofetil (Aulagnon et al., 2014) (Fatly et al., n.d.)

Majority had mild form of diarrhea in this study and they did not require parenteral fluid therapy. Severe diarrhea in LDKT recipients may result in significant morbidity including dehydration, increased toxicity of medications, and acute rejection. In this study, only one tenth of them were due to bacterial infection. The reverse was seen in the study done in Belgium; their cases had severe form of diarrhea and they were treated with anti-infectives, changes to concomitant medication and other empirical treatments (Maes et al., 2006). Therefore, the etiology of mild form of diarrhea was less likely to be infective. And, severe form was more likely to be infective according to this study and Belgium study.

Blood trough level of tacrolimus was raised in 10 recipients (33%) with acute diarrhea in this study; surprisingly, their motion was back to normal 24 to 48 hours after dose reduction of tacrolimus. Hochleitner et al found an elevated tacrolimus trough level (peak 20–60 ng/ml) after onset of gastroenteritis in solid organ transplant recipients. With symptomatic therapy and adequate adjustment of tacrolimus dose, the gastroenteritis stopped and tacrolimus levels returned to the therapeutic range. Therefore, they recommended to monitor tacrolimus blood level during diarrhea in order to prevent intoxication (Hochleitner et al., 2001) (Lemahieu et al., 2005). On the other hand, one study, 'effect of mild diarrhea on tacrolimus exposure', mentioned that there was no evidence for the presence of hidden tacrolimus overexposure in renal transplant recipients with mild diarrhea while on treatment with tacrolimus and mycophenolate mofetil (van Boekel et al., 2012). However, one case report pointed out that increase in tacrolimus trough levels was infrequently recognized as a potential cause of the adverse effect of severe diarrhea; the patient was 32 years old male who developed severe diarrhea 8 months after renal transplant (Asano et al., 2004). Most of the studies on chronic diarrhea in solid organ transplant recipients mentioned that mycophenolate mofetil was the culprit and it improved with dose reduction of mycophenolate mofetil (Aulagnon et al., 2014) (Fatly et al., n.d.) (Gioco et al., 2020) (Calogero et al., 2020). Therefore, further studies are required particularly in early post-transplant period for better understanding of etiologies of acute diarrhea; it will provide timely treatment and appropriate choice of immunosuppressive regimen.

Three cases of them required hemodialysis due to delayed graft function in this study; and, all cases had satisfactory renal function at 3 to 4 weeks after transplant. Recovery of graft function to baseline was seen in a majority of cases with the resolution of diarrhea (Sonambekar et al., 2020).

In this study, the management algorithm was based on clinical assessment, stool microscopy and culture were done in selected cases only. Even in rich countries, the cause of

diarrhea was unclear in half of renal transplant recipients having diarrhea after one year of renal transplantation (G. Gowthaman et al., 2019).

There were several limitations in this study. Being resource limited country, stool for Clostridium difficile toxin was not done in all recipients. Stool culture was expensive. Stool for viral PCR like Rotavirus, Norovirus, Adenovirus, Sapovirus as well as molecular tests for parasites were not available. Stool for CMV viral load should be studied; however, it was very expensive.

CONCLUSION

In this study, one-tenth of the LDKT recipients developed acute diarrhea in early post-transplant period. Majority of them had mild form of diarrhea and onset of diarrhea was 'Day 4'. Majority of them resolved over one week. Dietary modification, oral rehydration solution, folic acid with or without probiotics caused resolution of diarrhea in half of them. Infective cause was identified in 10% of them. High trough level of tacrolimus with improvement of diarrhea after dose reduction of tacrolimus was seen in one-third of them. Awareness of acute diarrhea and providing appropriate management are important to protect graft kidney.

RECOMMENDATION

Further study on relation between blood tacrolimus level and occurrence of diarrhea in early post-transplant period in kidney transplant recipient should be done. For better understanding of etiology of acute diarrhea, molecular PCR tests for stool should be encouraged to detect exact virus, bacteria and protozoa.

ACKNOWLEDGEMENT

We are thankful to Professor Ko Ko Lwin, Professor Kyaw Zay Ya, Professor Aung Myat Kyaw, Professor Thet Aung, Professor Myint Zaw and Professor Thet Naing for their administrative support; Professor Yu Aye Latt for anaesthesia & intensive care; Professor Than Aye for urosurgery; Professor Khin Maung Maung Than for academic support; Professor Tin Moe Mya for laboratory support; Professor Khine Khine Su for microbiology support; Professor Ohmar Hlaing for radiological support; and, Professor Khin Ohmar Kyaing for pharmacokinetic support. We are also grateful to all health professionals and kidney transplant recipients involved in this study.

DECLARATION OF CONFLICT OF INTEREST

The authors declared no potential conflicts of interests with respect to authorship and publication of this article.

ETHICAL APPROVAL

This study was approved by Hospital Research and Ethic Committee from Defence Services General Hospital (1000-Bedded) Mingaladon, Myanmar. Informed consent was also taken from each recipient.

FUNDING

The authors received no financial support for publication of this article.

REFERENCES

I. Agrawal, A., Ison, M. G., & Danziger-Isakov, L. (2022). Long-Term Infectious Complications of Kidney Transplantation. *Clinical Journal of the American Society of Nephrology*, *17*(2). https://journals.lww.com/cjasn/fulltext/2022/02000/long_term_infectious_complications_of_kidney.17.aspx

II. Angarone, M., & Snydman, D. R. (2019). Diagnosis and management of diarrhea in solid-organ transplant recipients: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. *Clinical Transplantation*, *33*(9), e13550. https://doi.org/10.1111/ctr.13550

III. Asano, T., Nishimoto, K., & Hayakawa, M. (2004). Increased tacrolimus trough levels in association with severe diarrhea, a case report. *Transplantation Proceedings*, *36*(7), 2096–2097. https://doi.org/10.1016/j.transproceed.2004.06.026

IV. Aulagnon, F., Scemla, A., Dewolf, S., Legendre, C., & Zuber, J. (2014). Diarrhea After Kidney Transplantation: A New Look at a Frequent Symptom. *Transplantation*, *98*. https://doi.org/10.1097/TP.0000000000000335

V. Calogero, A., Gallo, M., Sica, A., Peluso, G., Scotti, A., Tammaro, V., Carrano, R., Federico, S., Lionetti, R., Amato, M., Carlomagno, N., Dodaro, C. A., Sagnelli, C., & Santangelo, M. (2020). *Gastroenterological complications in kidney transplant patients*. *15*(1), 623–634. https://doi.org/10.1515/med-2020-0130

VI. Castellano Carrasco, R., Torres Sánchez, M. J., de Teresa Alguacil, F. J., & Osuna Ortega, A. (2017). Diarrhea and malnutrition in kidney transplant recipient: A case of infection by cryptosporidiosis. *Nefrología (English Edition)*, *37*(3), 338–339. https://doi.org/10.1016/j.nefroe.2017.05.004

VII. Coste Jean-François, Vuiblet Vincent, Moustapha Betoul, Bouin Alexis, Lavaud Sylvie, Toupance Olivier, de Rougemont Alexis, Benejat Lucie, Megraud Francis, Wolak-Thierry Aurore, Villena Isabelle, Chemla Cathy, Le Magrex Elisabeth, de Champs Christophe, Andreoletti Laurent, Rieu Philippe, & Leveque Nicolas. (2020). Microbiological Diagnosis of Severe Diarrhea in Kidney Transplant Recipients by Use of Multiplex PCR Assays. *Journal of Clinical Microbiology*, *51*(6), 1841–1849. https://doi.org/10.1128/jcm.03366-12

VIII. Coste, J.-F., Vuiblet, V., Moustapha, B., Bouin, A., Lavaud, S., Toupance, O., de Rougemont, A.,

Benejat, L., Megraud, F., Wolak-Thierry, A., Villena, I., Chemla, C., Le Magrex, E., de Champs, C., Andreoletti, L., Rieu, P., & Leveque, N. (2013). Microbiological diagnosis of severe diarrhea in kidney transplant recipients by use of multiplex PCR assays. *Journal of Clinical Microbiology*, *51*(6), 1841–1849. https://doi.org/10.1128/JCM.03366-12

IX. Echenique, I. A., Penugonda, S., Stosor, V., Ison, M. G., & Angarone, M. P. (2015). Diagnostic Yields in Solid Organ Transplant Recipients Admitted With Diarrhea. *Clinical Infectious Diseases*, *60*(5), 729–737. https://doi.org/10.1093/cid/ciu880

X. Fatly, Z. A., Betjes, M. G., van Gestel, J., Verschragen, M., & de Weerd, A. E. (n.d.).G. Gowthaman, N. D. Srinivasaprasad, K. Thirumalvalavan, S. Sujith, M. Edwin Fernando, & R. Selvi. (2019). DIARRHEA IN RENAL TRANSPLANT RECIPIENTS – A CROSS SECTIONAL STUDY. *Medico Research Chronicles*, *6*(1), 34–39.

XI. García-Padilla, P., Contreras, K., Serrano, P. P., Sánchez Leon, N., & Lucero Pantoja, O. (2022). Mycobacterium tuberculosis and Cytomegalovirus Colitis in a Renal Transplant Patient: A Case Report. *Journal of Investigative Medicine High Impact Case Reports*, *10*, 23247096221139269. https://doi.org/10.1177/23247096221139269

XII. Ghusson, N., & Vasquez, G. (2018). Successfully Treated Norovirus- and Sapovirus-Associated Diarrhea in Three Renal Transplant Patients. *Case Reports in Infectious Diseases*, *2018*, 6846873. https://doi.org/10.1155/2018/6846873

XIII. Gioco, R., Corona, D., Ekser, B., Puzzo, L., Inserra, G., Pinto, F., Schipa, C., Privitera, F., Veroux, P., & Veroux, M. (2020). Gastrointestinal complications after kidney transplantation. *World Journal of Gastroenterology*, *26*(38), 5797–5811. https://doi.org/10.3748/wjg.v26.i38.5797

XIV. Gras, J., Abdel-Nabey, M., Dupont, A., Le Goff, J., Molina, J.-M., & Peraldi, M. N. (2021). Clinical characteristics, risk factors and outcome of severe Norovirus infection in kidney transplant patients: A case-control study. *BMC Infectious Diseases*, *21*(1), 351. https://doi.org/10.1186/s12879-021-06062-2

XV. Hochleitner, B.-W., Bösmüller, C., Nehoda, H., Steurer, W., Königsrainer, A., Margreiter, R., Frühwirt, M., Simma, B., Ellemunter, H., & Hochleitner, E. O. (2001). Increased tacrolimus levels during diarrhea. *Transplant International*, *14*(4), 230–233. https://doi.org/10.1111/j.1432-2277.2001.tb00050.x

XVI. Hossian, M. E., Islam, M. M., Miah, M., Haque, W., Vinjé, J., Rahman, M. Z., Faruque, A. S. G., Khan, A. I., Ahmed, T., & Rahman, M. (2021). Viral Etiology of Acute Gastroenteritis Among Forcibly Displaced Myanmar Nationals and Adjacent Host Population in Bangladesh. *The Journal of Infectious Diseases*, *224*(12 Suppl 2), S864–S872. https://doi.org/10.1093/infdis/jiab466

XVII. ISMAIL, M. A. M., & FADL, H. O. (2019). CYCLOSPORA INFECTION IN RENAL TRANSPLANT RECIPIENT. *Journal of the Egyptian Society of Parasitology*, *49*(3), 727–730. https://doi.org/10.21608/jesp.2019.68083

XVIII. Lee, J. R., Magruder, M., Zhang, L., Westblade, L. F., Satlin, M. J., Robertson, A., Edusei, E., Crawford, C., Ling, L., Taur, Y., Schluter, J., Lubetzky, M., Dadhania, D., Pamer, E., & Suthanthiran, M. (2019). Gut microbiota dysbiosis and diarrhea in kidney transplant recipients. *American Journal of Transplantation*, *19*(2), 488–500. https://doi.org/10.1111/ajt.14974

XIX. Lemahieu, W., Maes, B., Verbeke, K., Rutgeerts, P., Geboes, K., & Vanrenterghem, Y. (2005). Cytochrome P450 3A4 and P-glycoprotein Activity and Assimilation of Tacrolimus in Transplant Patients with Persistent Diarrhea. *American Journal of Transplantation*, *5*(6), 1383–1391. https://doi.org/10.1111/j.1600-6143.2005.00844.x

XX. Maes, B., Hadaya, K., De Moor, B., Cambier, P., Peeters, P., De Meester, J., Donck, J., Sennesael, J., & Squifflet, J.-P. (2006). Severe Diarrhea in Renal Transplant Patients: Results of the DIDACT Study. *American Journal of Transplantation*, *6*(6), 1466–1472. https://doi.org/10.1111/j.1600-6143.2006.01320.x

XXI. Moe, K., Hummelman, E. G., Oo, W. M., Lwin, T., & Htwe, T. T. (2005). Hospital-based surveillance for rotavirus diarrhea in children in Yangon, Myanmar. *The Journal of Infectious Diseases*, *192 Suppl 1*, S111-113. https://doi.org/10.1086/431509

XXII. Myat, T. W., Thu, H. M., Tate, J. E., Burnett, E., Cates, J. E., Parashar, U. D., Kyaw, Y. M., Khaing, T. E. E., Moh, K. M., Win, N. N., Khine, W. K., Kham, M. M. Z., Kyaw, T., Khine, Y. Y., Oo, K. K., & Aung, K. M. (2021). Rotavirus infection among children under five years of age hospitalized with acute gastroenteritis in Myanmar during 2018–2020 – Multicentre surveillance before rotavirus vaccine introduction. *Vaccine*, *39*(47), 6907–6912. https://doi.org/10.1016/j.vaccine.2021.10.014

XXIII. Raja, K., Abbas, Z., Hassan, S. M., Luck, N. H., Aziz, T., & Mubarak, M. (2014). Prevalence of cryptosporidiosis in renal transplant recipients presenting with acute diarrhea at a single center in Pakistan. In *J Nephropathol* (Vol. 3, Issue 4, pp. 127–131).

XXIV. Rodrigues, F. G., Swarte, J. C., Douwes, R. M., Knobbe, T. J., Sotomayor, C. G., Blokzijl, H., Weersma, R. K., Heilberg, I. P., Bakker, S. J. L., de

Borst, M. H., & TransplantLines Investigators. (2021). Exhaled Hydrogen as a Marker of Intestinal Fermentation Is Associated with Diarrhea in Kidney Transplant Recipients. *Journal of Clinical Medicine*, *10*(13). https://doi.org/10.3390/jcm10132854

XXV. Sharma, A. K., & Holder, F. E. (1998a). Clostridium difficile Diarrhea After Use of Tacrolimus Following Renal Transplantation. *Clinical Infectious Diseases*, *27*(6), 1540–1541. https://doi.org/10.1086/517744

XXVI. Sharma, A. K., & Holder, F. E. (1998b). Clostridium difficile Diarrhea After Use of Tacrolimus Following Renal Transplantation. *Clinical Infectious Diseases*, *27*(6), 1540–1541. https://doi.org/10.1086/517744

XXVII. Shin, H. S., & Chandraker, A. (2017). Causes and management of postrenal transplant diarrhea: An underappreciated cause of transplant-associated morbidity. *Current Opinion in Nephrology and Hypertension*, *26*(6), 484–493. https://doi.org/10.1097/MNH.0000000000000368

XXVIII. Sonambekar, A., Mehta, V., Desai, D., Abraham, P., Almeida, A., Joshi, A., Gupta, T., Sirsat, R., & Kothari, J. (2020a). Diarrhea in kidney transplant recipients: Etiology and outcome. *Indian Journal of Gastroenterology*, *39*(2), 141–146. https://doi.org/10.1007/s12664-020-01022-1

XXIX. Sonambekar, A., Mehta, V., Desai, D., Abraham, P., Almeida, A., Joshi, A., Gupta, T., Sirsat, R., & Kothari, J. (2020b). Diarrhea in kidney transplant recipients: Etiology and outcome. *Indian Journal of Gastroenterology : Official Journal of the Indian Society of Gastroenterology*, *39*(2), 141–146. https://doi.org/10.1007/s12664-020-01022-1

XXX. van Boekel, G. A. J., Aarnoutse, R. E., van der Heijden, J. J., Hoogtanders, K. E. J., & Hilbrands, L. B. (2012). Effect of Mild Diarrhea on Tacrolimus Exposure. *Transplantation*, *94*(7). https://journals.lww.com/transplantjournal/fulltext/2012/10150/effect_of_mild_diarrhea_on_tacrolimus_exposure.15.aspx

XXXI. Vyas, V. D., Parameswaran, S. A., Paramasivan, P., Sankaranarayanan, K., Palaniswamy, K. R., Mohan, A. T., Srinivas, U., Dhus, U., Muthuswamy, H., Revathy, M. S., Natarajan, M., Karunakaran, P., Venkatesh, S., Mahalingam, P., & Patel, A. (2021). Etiological profile of diarrhea in solid organ transplant recipients at a tertiary care center in Southern India. *Transplant Infectious Disease : An Official Journal of the Transplantation Society*, *23*(4), e13584. https://doi.org/10.1111/tid.13584

XXXII. Yin, Y., Metselaar, H. J., Sprengers, D., Peppelenbosch, M. P., & Pan, Q. (2015). Rotavirus in Organ Transplantation: Drug-Virus-Host Interactions. *American Journal of Transplantation*, *15*(3), 585–593. https://doi.org/10.1111/ajt.13135