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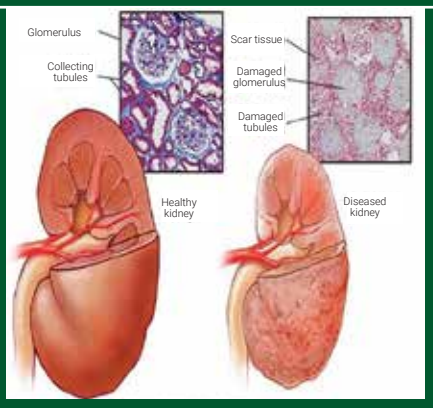

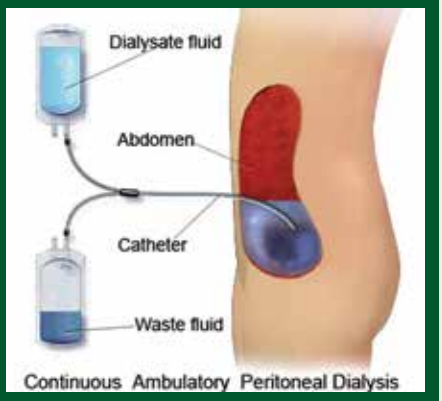

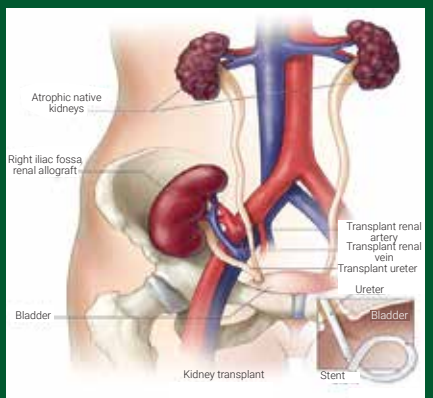

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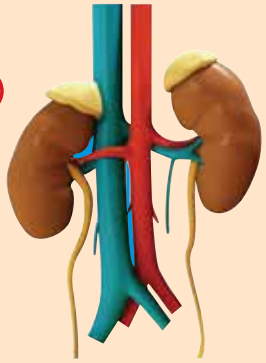

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Editorial

From the Desk of Editor-in-Chief

This is the 2nd volume of the Bangladesh Journal of Kidney Disease (BJKD), July 2024 issue. There are only three original articles, two reviews and one case report. I am hoping that in the coming months, we will be able to further enrich our journal. The article on CAPD is a retrospective study and there are new information on CAPD in Bangladesh. The main problem of CAPD in Bangladesh is the high incidence of infection and cost of treatment. The second article is on Prevalence of Chronic Kidney Disease among healthcare professionals of a specialized Kidney Hospital in Bangladesh: Single Centre Experience. Although the number of health care professionals is small, it gives important information about the prevalence of Chronic Kidney Disease in a specific group of population. The 3rd original article is about comparing antibiotic lock therapy with systemic antibiotics for Prevention of Central Line associated blood stream infection: A single center experience. The result of the study demonstrated that there is no difference between use of prophylactic antibiotic as compared with use of lock solution. The study will save not only money but also reduce the antibiotic resistance. Appropriate prescribing for the patients with kidney disease and kidney failure can make change. Obviously, this is an important but sometimes overlooked issue. The experienced physicians sometimes feel urge to check reference databases before prescribing less familiar medications. For prescribing patients with chronic kidney disease (CKD) or renal replacement therapy (RRT) reference databases should be up-to-dated regularly. Many medicine including antimicrobials are excreted by kidneys, and dose modification is often required in patients with moderate to severe CKD. Many antimicrobials are seen to be administered in standard dose and dose adjustment is ignored in patients with low residual renal function. This scenario is observed in OPD, indoor and even in ICU patients where single or multi-organ failure is a common problem. Many patients are treated with full dose of two or three antibiotics, antiviral and antifungal injections at a time. Therefore, we must be cautious in prescribing antibiotics.

Professor. Dr. Harun Ur Rashid
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Original Article

Continuous Ambulatory Peritoneal Dialysis (CAPD) Perspective in Bangladesh–Single Centre Experience

Arefin MSUZ[1], Begum NAS[2], Bari A[3], Nobi F[4], SK Tasnuva[5], Rashid HU[6]

ABSTRACT:

Over the last 10 years, effort has been made to popularize CAPD in Bangladesh. The incidence and cumulative prevalence of CAPD has increased over the years. In earlier periods, many patients were selected for PD, not as the first choice but because they were not fit for other modalities of renal replacement therapy (RRT). Now, majority of the PD patients are initiated on PD directly. The incidence of peritonitis has decreased from 1 in 14.43 patient months in 2004 to 1 in 41.6 patient months in 2023. The noninfectious complications can be managed conservatively in most cases and does not require catheter removal. There are tremendous opportunities to expand CAPD in Bangladesh. Most of the dialysis centers are in the capital and district towns. Therefore, a vast number of rural and semi-urban people are unable to travel long distances for HD. Hence, CAPD can be an easy approach for RRT. However, cost of CAPD fluid is high making it unaffordable for poor patients.

Key words: Continuous Ambulatory Peritoneal Dialysis, Renal Replacement Therapy, Bangladesh

Introduction

CAPD was first introduced in the world by Popovich and Moncrief in 1976. IPD was started in 1973 and CAPD in 1981 in Bangladesh. PD was performed in seven patients until December 1982. Unfortunately, it could not be continued due to unavailability of PD catheters and PD fluid; then, in 1993 CAPD was restarted (1).

Materials and Methods

This study was conducted at Kidney Foundation Hospital and Research Institute, Dhaka, Bangladesh. It was a retrospective study. Patients who performed CAPD from 2011 to 2023 at Kidney Foundation Hospital were included. Data was collected from patient's file and by contacting patients over phone. Ethical approval was obtained from the Ethical review committee (ERC) of Kidney Foundation Hospital. Data was analyzed using SAS software.

Results

In 1998 the number of new patients starting CAPD was 15 (2). In 2023, the cumulative prevalence of CAPD has increased to 2641 with the number of new patients starting CAPD was 152 in 2022 and 235 in 2023 in Bangladesh.

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At Kidney Foundation Hospital, 40 new patients performed CAPD in 2022 and 22 in 2023.

A total of 578 CAPD patients were studied in this study. The mean age of patients was 68.2±12 years, male 307 (53.1%), female 271 (46.9%).

Among 88 CAPD patients, the causes of ESRD were Diabetic Kidney Disease (DKD) (81.8%), Chronic Glomerulonephritis (CGN) (14.8%), Hypertensive Kidney Disease (HTN) (1.1%) and others (2.3%).

CAPD Technique

All PD catheters were inserted percutaneously (Seldinger technique) by nephrologists. The coiled Tenckhoff catheters were used. The manual exchange was started on 7th postoperative day using twin bag system. During the first 1 week, nephrologists and PD nurses gave education and training to patients and their attendants.

PD Bags

CAPD fluid is imported from Singapore and supplied by Baxter. The solutions are packaged in clear flexible plastic bags. Only 2 L bags of 1.5%, 2.5% or 4.25% dextrose solutions (Dianeal) are available. Very recently Extraneal (icodextrin) from Baxter has become available.

Cost of PD

The cost of PD is higher than HD performed at non-profit dialysis centers like Kidney Foundation. Most of the patients do three exchanges per day, very few perform two exchanges per day due to financial constrain. If three exchanges per day are performed then the cost for one day is around 1380 (USD 12) taka, for 7 days is 9660 taka (USD 82) and for 30 days is 41400 taka (USD 352).

Complications of PD

Infections (exit site infection, tunnel infection and peritonitis) were the most common complication of CAPD. However, the incidence of peritonitis has decreased from 1 in 14.43 patient months in 2004 to 1 in 41.6 patient months in 2023. Table 1 demonstrates the changing rate of peritonitis in CAPD patients in Bangladesh from 2004 to 2023.

Table 1. Evolving rate of peritonitis in CAPD patients in Bangladesh over the years

Year	Peritonitis rate
2004	1 episode per 14.43 patient-months
2009	1 episode per 32.13 patient-months
2021	1 episode per 34.78 patient-months
2022	1 episode per 42.5 patient-months
2023	1 episode per 41.6 patient-months

Among 68 CAPD patients, non-infectious complications were noted in 30.9% cases (21 out of 68). Pain was most commonly reported (19.7%) followed by haemoperitoneum (9.1%), leakage of fluids (7.6%) and malposition of catheter (1.5%).

Outcome and Survival of CAPD Patients

The outcome of 578 patients revealed that 74 patients were continuing CAPD, 12 patients shifted to HD, 7 patients received kidney transplant, 111 patients were lost to follow up and 374 patients died.

Patient survival at 1, 2, 3 and 5 years was found to be 68%, 48%, 38% & 22%, respectively. The cause of death was acute myocardial infarctions, cerebrovascular

disease, pneumonia, malnutrition, peritonitis and others.

Discussion:

The major problem of CAPD is infection, followed by lack of awareness and financial issues. In our study, it is very clear that number of acceptance rate of PD is increasing over the years as compared to haemodialysis and renal transplantation.

Peritonitis is the major drawback for PD in Bangladesh. Iqbal et al., studied the organisms responsible for peritonitis and their sensitivity to antibiotics and found that 77% samples were culture-positive; the organisms isolated were gram-positive bacteria (Staphylococcus and Streptococcus species) in 41%, gram-negative bacteria (Escherichia coli, Pseudomonas, Klebsiella species) in 52% and fungus in 7% of cases (3). Patients with suspected peritonitis are usually advised to come to hospital for treatment. However, those who are unable to come to hospital immediately are advised to start the empirical antibiotics at home.

Non-infectious complications CAPD are classified in two groups on the basis of onset from the time of insertion of catheter: early onset (1-4 months) and late onset (12-24 months). Early onset complications include exit site leakage, catheter malposition, haemoperitoneum, right sided hydrothorax and ultrafiltration failure (UFF). The late-onset complications include abdominal hernia, scrotal swelling, encapsulated peritonitis and catheter cuff protrusion. A study found that pain was the most common noninfectious complication (30.8%), followed by ultrafiltration failure (4.7%), hydrothorax (1.9%), fluid leakage (0.9%) and others (27.1%). Technique failure due to omental wrap, tip migration and fluid leak were reported in about 10% patients, and 5% patients required catheter removal (4-6).

Malnutrition is a common problem in PD patients. While mild to moderate malnutrition is present in 30-70% of PD patients, severe malnutrition develops in 2-9% of patients. The cause is multifactorial and includes delayed dialysis initiation, extreme protein restriction in the pre-dialysis period which often continues even after starting dialysis because of inadequate dietary advice, uremic toxicity, catabolic factors and intercurrent infections.

A number of recent studies have shown that survival rates of HD and PD are similar, and PD patients have better cardiovascular stability than HD patients. A single-center study has shown that 1 & 3-year survival is 90% and 68% respectively (7).

Challenges and Obstacles of PD

The major challenge of CAPD in Bangladesh is peritonitis either alone or in association with exit site and tunnel infections. Unfortunately, culture-negative peritonitis rates are high, which hinder the selection of appropriate antibiotics, and therefore, resolution of infection is sometimes not achieved. This contributes to technique failure and shift from PD to HD. Inadequate sampling, lack of trained and dedicated manpower, lack of automated PD effluent culture system and poor culture technique are the possible reasons for high culture-negative infections. Other major challenges faced are high gram-negative peritonitis rates, infection from multidrug-resistant pathogens, shift from Candida albicans to non-C, albicans and mycelial infections.

Proper training of patients and their relatives about aseptic exchange technique, good exit site care, improvement in catheter insertion technique, strengthening microbiology laboratories and rational use of antibiotics based on local susceptibility data are likely to reduce the peritonitis rate and preserve the peritoneal membrane function, thereby improving clinical outcome of peritonitis and helping PD growth in Bangladesh.

Other obstacles in CAPD are lack of awareness among general people and physicians, lack of confidence and uncertainty among patients and relatives and even in nephrologists, along with high cost of treatment.

Future

There are tremendous opportunities to expand CAPD in Bangladesh. Most of the dialysis centers are in the capital and in large cities. Due to lack of facility, a vast number of rural and semi-urban population are unable to travel long distances to avail HD. Hence, CAPD can be an available and effective form of therapy in this group of population.

Reference:

1. Rashid HU, Alam MR, Khanam A, Rahman MM, Ahmed S, Mostafi M, Arefin SU, Kashem TS, Begum NA, Alam KS, Islam N. Nephrology in Bangladesh. InNephrology Worldwide 2021 (pp. 221-238). Springer, Cham.
2. Rashid HU. Bangladesh Renal Registry 2002-2013. Dhaka, Bangladesh: Kidney Foundation, Bangladesh; 2013.
3. Iqbal MM, Sattar H, Islam MN, Ahmed AH, Rahman MH, Rashid HU, et al. Spectrum of organisms causing peritonitis in peritoneal dialysis patients--experience from Bangladesh. Adv Perit Dial. 2008;24:40-3
4. Arefin MSU. A 2-year follow-up study of patients on continuous ambulatory peritoneal dialysis (CAPD) in specialized hospital in Dhaka, Bangladesh. Journal of Dhaka Medical College. 2015;24(2).
5. Rashid HU. Management of end stage renal disease-Bangladesh perspective. The Open Urology and Nephrology Journal. 2014;7:108-12.
6. Iqbal S, Iqbal MM, Chowdhury TA, Rahim MA, Bhuiyan ASMM, Ananna MA, et al. Experience Managing Adult Patients on Continuous Ambulatory Peritoneal Dialysis in Bangladesh. Adv Perit Dial. 2018;34(2018):38-41.
7. Rashid HU, Arefin S, Hasan S, Alam K. The role of the Kidney Foundation of Bangladesh in promoting kidney care in a resource-limited environment. Clin Nephrol. 2016;86 (2016)(13):64-8

Original Article

Prevalence of Chronic Kidney Disease among Healthcare Professionals of a Specialized Kidney Hospital in Bangladesh: Single Centre Experience

Begum NAS[1], Nobi F[2], Bari A[3], Arefin MSUZ[4], Nomany BMS[5], Akther N[6], Yousuf E[7], Rashid HU[8]

ABSTRACT

Introduction: In Bangladesh, the prevalence of chronic kidney disease (CKD) is increasing day by day. For prevention of CKD, early identification and prompt interventionis the most realistic approach. In our study we screened for CKD and its risk factors among healthcare professionals (HP) of Kidney Foundation Hospital and Research Institute (KFH&RI), Dhaka.

Methods: This is a cross sectional study performed at KFH&RI over 6 months. CKD was defined as an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m2 or the presence of albuminuria (ACR ≥30mg/g). Hypertension was defined as per JNC VII criteria. Participants were considered diabetic if RBS ≥11.1 mmol/l.

Results: A total of 389 HPs were studied. Of them 14.9% (n=58) were found hypertensive and 5.4% (n=21) were diabetic. The prevalence of CKD was 4.9% (18 out of 369), although only 0.54% (2 out of 369) HP was found to have CKD stage ≥3. Microalbuminuria was present in 4.9% participants. Among CKD HP, 27.8% were hypertensive, 16.7% were diabetic and 55.5% had microalbuminuria. Significantly higher number of females (77.8%) had CKD than males (22.2%).

Conclusions: Our study found that nearly 5% HPs of KFH&RI have CKD and hypertension and Diabetes Mellitus were the major risk factors. This knowledge can be used to raise awareness among healthcare professionals and in general population.

Key words: Hypertension, Diabetes and CKD, Healthcare Professionals

1. INTRODUCTION:

Chronic Kidney Disease (CKD) is global public health problem. Worldwide, CKD was the 17th leading cause of death in 1990, surprisingly it has increased dramatically and became the 12th leading cause of death in 2017 [1]. It was estimated that nearly 3 million patients with kidney diseases are on renal replacement therapy worldwide [2] and around 2.4 million people die each year due to CKD [3].

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It is to be noted that, the burden of CKD is higher and is rising in developing nations, particularly in Asia and Africa than that of developed countries [4]. The number of patients with CKD is also increasing day by day in Bangladesh. Unfortunately, it is not yet possible to define the incidence and prevalence of chronic kidney disease in our country to its full extent. However, study from urban disadvantaged people suggested that the prevalence of CKD was 16-18%; of them 11% were in CKD stage III to V [5]. Another recent study reported that the CKD prevalence in rural and peri-urban area of Bangladesh was about 22% [6]. A study in 2010 evaluated the prevalence of proteinuria and CKD among healthcare professionals of Bangladesh which reported that the prevalence of CKD among healthcare providers was 9.9% (Cock-Croft Gault equation) and 7.2% (modification of diet in renal disease (MDRD) study Equation) [7].

Diabetes mellitus (DM), Hypertension (HTN) and Glomerulonephritis are three major causes of CKD. Smoking, obesity and nephrotoxic medications (pain killer, Kabiraji medicine) are other important risk factors of CKD. The number of diabetic patients is rapidly growing in our country. A study in

2014 on 400 patients with type 2 diabetes mellitus (T2DM) in a tertiary diabetes hospital (BIRDEM) showed that the prevalence of diabetic nephropathy was 24.0% (male 27.1%, female 21.8%) [5]. Also, HTN is quite common among our population, but most people are unaware of the presence of HTN and its consequences. In a study among 3000 rural and urban population, the prevalence of hypertension was 18.6% [5].

CKD is usually silent until its later stages, hence in Bangladesh many patients with CKD are unaware of the presence of CKD in them. They only get detected when they reach end stage kidney disease (ESKD) and experience symptoms. It is usually irreversible at that point, and renal replacement therapy becomes the only option for survival. The treatment expense of CKD and ESKD patients including renal replacement therapy is huge. Hospital data showed that more than 70% patients of Bangladesh cannot afford this huge expense and therefore die a premature death [5]. In this circumstance, early identification and reduction of risk factors of CKD, as well as early detection of CKD, would be the most realistic approach to preventing CKD and halting premature mortality and morbidity from CKD. In this study we screened for CKD and its risk factors among healthcare professionals of Bangladesh.

2. METHOD:

This is a cross sectional study performed at Kidney Foundation Hospital and Research Institute, Dhaka over a period of 6 months from April 2022 to September 2022. CKD was defined as an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m2 or the presence of albuminuria (ACR ≥30mg/g). Estimated glomerular filtration rate (eGFR) was calculated using prediction equations of CKD Epidemiology Collaboration (CKD-EPI), 2021.Hypertension was defined as per JNC VII criteria (Normal: Systolic <120 and/or diastolic <80 mm of Hg; Prehypertension: Systolic 120-139 and/or diastolic 80-89 mm of Hg; Stage 1 HTN: Systolic 140-159 and/or diastolic 90-99 mm of Hg; Stage 2 HTN: Systolic ≥160 and/or diastolic ≥100 mm of Hg). Participants were

considered as diabetic if random blood glucose ≥ 11.1mmol/l. Informed consent was obtained from participants. Ethical clearance was obtained from the Ethical Review Committee (ERC) of Kidney Foundation Hospital and Research Institute. Data was analyzed using SPSS software.

3. RESULT:

A total of 389 healthcare professionals (HP) were studied. The mean age was 31.2 ± 10.1 years (range 18 to 77 years). Participants were divided into different age groups. Most of the HP were between 20-40 years age group (82.1%) followed by 40-60 years age group (14.1%), then >60 years age group (2.8%), then <20 years age group (1.0%). Among them, 42.2% (n=164) were male and 57.8% (n=225) female. Mean systolic and diastolic BP was 113.2 ± 13.4 mmHg and 73.1 ± 9.8 mmHg respectively (Table 1).

Table 1: Demographics and history of participants

Total number of participants	389
Mean age (years)	31.2 ± 10.1 years (18 to 77 years)
Age Group	<20 years = 4 (1.0%) 20-40 years = 319 (82.1%) 40-60 years = 55 (14.1%) >60 years = 11 (2.8%)
Male	164 (42.2%)
Female	225 (57.8%)
Mean systolic BP	113.2 ± 13.4 mmHg
Mean diastolic BP	73.1 ± 9.8 mmHg
Obese (BMI>27.5)	69(17.7%)
History of (H/O) painkiller intake	4.6%
H/O taking kabiraji medicine	13.6%
H/O Smoking &betel nut chewing	10.3%; 5.4%
Family H/O kidney disease	13.6%

Of the 389 HP, 14.9% (n=58) were found hypertensive. Among them 63.8% (n=37) knew about their hypertension (HTN) but 36.2% (n=21) were not aware about their HTN. Among the 37 HP who were aware about their HTN, 73.0% (n=27) were taking antihypertensive medications while 27% (n=10) were not. HTN control was good only in 56.8% (n=21) participants whereas in 43.2% (n=16) HP, HTN was uncontrolled.

Diabetes Mellitus (DM) was found in 5.4% participants (n=21). Of them 76.2% (n=16) were known diabetic while 23.8% (n=5) were unaware of their DM. Among known DM patients, majority (93.8%; 15 out of 16) was on anti DM medications and 81.3% had random blood sugar ≤11.1. Amongst HP, mean serum creatinine was 68.3±12.6 µmol/L and mean eGFR was 116.1±13.5 ml/min/1.73 m^2. The prevalence of CKD was 4.9% (18 out of 369), although only 0.54% (2 out of 369) HP was found to have CKD stage ≥3. Albuminuria was present in 4.9% participants. (Fig 1).

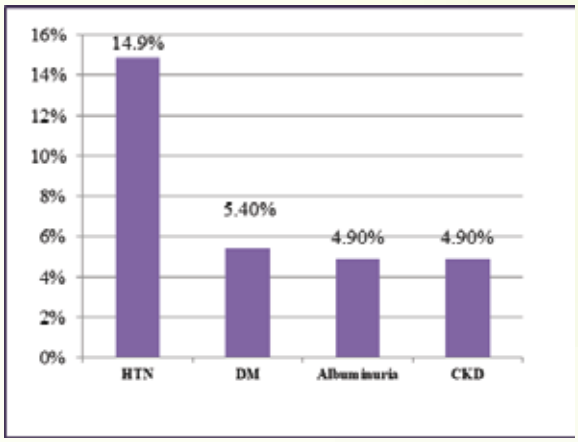

Fig 1: Prevalence of HTN, DM Albuminuria and CKD

Among HP with CKD, 27.8% (5 out of 18) were hypertensive, 16.7% (3 out of 18) were diabetic and 55.5% had albuminuria of undetermined cause (Fig 2).

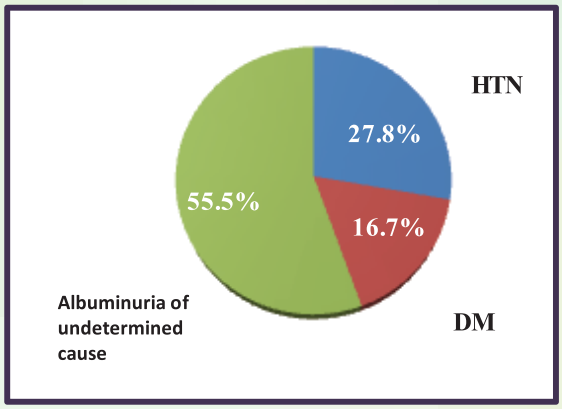

Fig 2: Cause of CKD among HP

Significantly higher number of females (77.8%) had CKD than males (22.2%). Among HP, 17.7% (n=69) were obese (BMI>27.5); 4.6% had history of (H/O) painkiller intake; 13.6% had H/O taking kabiraji medicine; 10.3% had H/O smoking; 5.4% had H/O betel nut chewng and 13.6% had family H/O kidney disease.

4. DISCUSSION:

According to WHO, an estimated 1.28 billion adults aged 30–79 years worldwide have hypertension; most (two-thirds) living in low- and middle-income countries [8]. A recent systematic review found that the prevalence of HTN among general population of Bangladesh was 20% [9]. Our study demonstrated that the prevalence of HTN among HP was 14.9%. A recent study from India reported that the prevalence of HTN among HP was 14.8%which was similar to our study [10].

International Diabetes Federation (IDF) reported that worldwide around537 million (10.5%) adults aged 20-79 years are living with diabetes and in Bangladesh the prevalence of DM among adults is 12.5% [11]. Our study found that Diabetes Mellitus (DM) was present in5.4% HP which is lower than that in general population. The prevalence of DM among hospital employees in India was similar to our study (5.8%) [12].

Kidney diseases are a leading cause of death worldwide, yet the problem is undervalued. International Society of Nephrology estimated that more than 850 million people worldwide have some form of kidney disease and the prevalence of CKD is 10.4% among men and 11.8% among women [13]. In Bangladesh, the prevalence of CKD among the general population was reported as 22.4% [14] which is much higher than that in developed countries (14% in USA) [15]. Our study demonstrated that the prevalence of CKD among HP of a tertiary hospital is 4.9%. Another study in Bangladesh reported that the prevalence of CKD among HP of medical university of Dhaka was 7.2% [7].

The prevalence of HTN, DM and CKD among HP in our study was lower than that among general population of Bangladesh. This could be because majority of our study population was young in the age group of 20-40 years (82.1%) while prevalence of HTN, DM and CKD generally is higher in the older age group. According to CDC, in USA, the prevalence of CKD in the age group of 18-44 years was 6.3% as compared to 33.7% in the age group of ≥65 years [15]. Nonetheless, more knowledge and awareness regarding because of working in a specialized kidney hospital, participants of our study might have CKD than general people which could have contributed to this lower prevalence of CKD.

Like in general population, HTN and DM were the major risk factors of CKD among HP. In this study, 44.5% CKD patients had either HTN or DM or both. In our study the

prevalence of CKD was significantly higher among female HP than male HP. This difference is also observed among general population [15].

5. CONCLUSION:

Our study found that the prevalence of CKD among HP of a specialized kidney hospital of Bangladesh was 4.9% which is much lower than that among the general population (22.4%) as reported by other studies. Hypertension and Diabetes Mellitus was found to be major risk factors for CKD. This knowledge can be used to raise awareness among healthcare professionals and also among general population of Bangladesh. However, the sample size of our study is small, hence future studies with large sample size is needed for better assessment of CKD among HP.

Reference:

1. Cockwell P, Fisher LA. The global burden of chronic kidney disease. Lancet. 2020 Feb 29;395(10225):662-664.
2. Liyanage T, Ninomiya T, Jha V, Neal B, Patrice HM, Okpechi I, Zhao MH, Lv J, Garg AX, Knight J, Rodgers A. Worldwide access to treatment for end-stage kidney disease: a systematic review. The Lancet. 2015 May 16;385(9981):1975-82.
3. Luyckx VA, Tonelli M, Stanifer JW. The global burden of kidney disease and the sustainable development goals. Bulletin of the World Health Organization. 2018 Jun 1;96(6):414.
4. Abraham G, Varughese S, Thandavan T, Iyengar A, Fernando E, Naqvi SA, Sheriff R, Ur-Rashid H, Gopalakrishnan N, Kafle RK. Chronic kidney disease hotspots in developing countries in South Asia. Clinical kidney journal. 2016 Feb 1;9(1):135-41.
5. Rashid HU, Alam MR, Khanam A, Rahman MM, Ahmed S, Mostafi M, Arefin SU, Kashem TS, Begum NA, Alam KS, Islam N. Nephrology in Bangladesh. InNephrology Worldwide 2021 (pp. 221-238). Springer, Cham.
6. Sarker MH, Moriyama M, Rashid HU, Chisti MJ, Rahman MM, Das SK, Uddin A, Saha SK, Arifeen SE, Ahmed T, Faruque AS. Community-based screening to determine the prevalence, health and nutritional status of patients with CKD in rural and peri-urban Bangladesh. Therapeutic advances in chronic disease. 2021 Jul;12:20406223211035281.
7. Das S, Dutta PK. Chronic kidney disease prevalence among health care providers in Bangladesh. Mymensingh medical journal: MMJ. 2010 Jul 1;19(3):415-21.
8. World Health Organization. Newsroom/Fact sheets/Detail/Hypertension. Available from: https://www.who.int/news-room/fact-sheets/detail/hypertension [Accessed 04.07.2024]
9. Chowdhury MZI, Rahman M, Akter T, Akhter T, Ahmed A, Shovon MA, Farhana Z, Chowdhury N, Turin TC. Hypertension prevalence and its trend in Bangladesh: evidence from a systematic review and meta-analysis. ClinHypertens. 2020 Jun 1;26:10.
10. Kurtul S, Ak FK, Türk M. The prevalence of hypertension and influencing factors among the employees of a university hospital. Afr Health Sci. 2020 Dec;20(4):1725-1733.
11. International Diabetes Federation. About diabetes:Facts & figures. Available from: https://idf.org/about-diabetes/diabetes-facts-figures/[Accessed 04.07.2024]
12. Sharma D, Vatsa M, Lakshmy R, Narang R, Bahl VK, Gupta SK. Study of cardiovascular risk factors among tertiary hospital employees and their families. Indian Heart J. 2012 Jul-Aug;64(4):356-63.
13. International Society of Nephrology (ISN). More than 850 Million Worldwide have some form of Kidney Disease: Help Raise Awareness. International Society of Nephrology (ISN). Available from: https://www.theisn.org/more-than-850-million-worldwide-have-some-form-of-kidney-disease-help-raise-awareness/[Accessed 04.07.2024]
14. Banik S, Ghosh A. Prevalence of chronic kidney disease in Bangladesh: a systematic review and meta-analysis. IntUrolNephrol. 2021 Apr;53(4):713-718.
15. Centers for Disease Control and Prevention (CDC). Chronic Kidney Disease in the United States, 2023. 2024 May. Available from: https://www.cdc.gov/kidney-disease/php/data-research/index.html[Accessed 04.07.2024]

Original Article

Comparing Antibiotic Lock Therapy with Systemic Antibiotics for Prevention of Central Line Associated Blood Stream Infection: A Single Centre Experience

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ABSTRACT

Introduction: Central line–associated bloodstream infection (CLABSI) in haemodialysis (HD) patients is associated with high morbidity, mortality and healthcare costs. In Bangladesh, almost all HD centres are using systemic antibiotics for the prevention of CLABSI. Antibiotic lock therapy (ALT) is considered effective for both prevention and treatment of CLABSI. Use of systemic antimicrobial prophylaxis has been discouraged for the concern of antimicrobial toxicity and resistance. In this study we used ALT and compared its efficacy with the common practice of Bangladesh of using systemic antibiotics for prevention of CLABSI in HD patients.

Method: A total of 88 patients were studied. Patients were randomized into two groups: group A (35 patients) received ALT after each HD and group B (53 patients) received continuous systemic antibiotic (intravenous ceftazidime 500mg daily). Strict aseptic techniques and infection control measures were applied to both groups.

Result: In group A, 2 patients (5.7%) were suspected to develop CLABSI while in group B, 3 patients (5.7%) were suspected to develop CLABSI. The overall incidence of suspected CLABSI in our patients was 4.2 per 1000 catheter days. The incidence of suspected CLABSI in ALT group was 4.4 per 1000 catheter days and in systemic antibiotic group was 4.1 per 1000 catheter days.

Conclusion: Our results demonstrated that for the prevention of CLABSI, ALT is non-inferior to systemic antibiotic. The rate of suspected CLABSI is lower in our study than that reported in previous studies of Bangladesh. Our study results might help improve the practice of Bangladesh.

Key words: Antibiotic Lock Therapy, Systemic Antibiotics, Central Line Associated Blood Stream Infection

1. INTRODUCTION:

In developing countries, a large number of end stage renal disease (ESRD) patients start haemodialysis (HD) as an emergency management through a short-term non-cuffed non-tunneled central venous catheter (CVC) [1]. Due to lack of education, low socioeconomic condition, and lack of financial support, majority patients agree to construct fistula only after starting dialysis. As a consequence, patients have to continue HD through the temporary catheter for at least 4-8 weeks and sometimes longer. A proportion of them will develop infections related to these lines either exit site infections, bacteraemia, septicaemia or metastatic infections such as endocarditis or discitis [2]. Central line–associated bloodstream infection (CLABSI) or Catheter-related bloodstream infection (CRBSI) imposes a substantial cost both in terms of morbidity and financial resources expended [2].

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In US hospitals, a total of 250,000 cases of catheter-related infections have been estimated to occur annually [3]. About 37,000 bloodstream infections occurred in 2008 in hemodialysis patients with central lines [4].

In Bangladesh, a study conducted at two tertiary care hospitals reported that the CRBSI rate was 11% and CVC colonization rate 43% [5]. Another study conducted in Bangladesh demonstrated that the rate of CRBSI and catheter colonization were 14% and 42.1% respectively [6]. In Bangladesh, healthcare professionals are struggling to tackle this overwhelming burden of CRBSI among haemodialysis patients. Almost all dialysis centres are using systemic antibiotics for the prevention of CRBSI.

Centers for Disease Control and Prevention (CDC) and Healthcare Infection Control Practices Advisory Committee (HICPAC) updated their guidelines in 2011 to provide evidence-based recommendations for preventing intravascular catheter-related infections [2].In CDC guideline, strategies like education and training regarding appropriate infection control measures, aseptic technique, hand hygiene, exit site care, use of antibiotic ointments to reduce nasal colonization were highlighted.CDC guideline suggested that antibiotic lock therapy can be used as prophylaxis for patients with long-term catheters and a history of multiple catheter-related infections despite maximal efforts to follow aseptic technique. Due to the concern of antimicrobial resistance, they strongly discouraged use of systemic antimicrobial prophylaxis routinely before insertion or during use of an intravascular catheter to prevent catheter colonization or CRBSI [2].

Clinical practice guidelines also recommend antibiotic lock therapy (ALT) for both prevention and treatment of catheter-related infections (CRI) [7]. Guidelines from the Infectious Diseases Society of America (IDSA) for the diagnosis and management of CRI recommend antibiotic locks as adjunctive therapy specifically for catheter salvage in cases where the catheter is not removed. However, CVC removal remains first-line therapy for the management of catheter-related infections [7].

Antibiotic lock therapy (ALT): In general, antibiotic lock solutions combine a highly concentrated antibiotic (100–1,000 times planktonic MIC) with an anticoagulant to allow for local instillation into the catheter lumen. The solution is allowed to dwell or is "locked" while the CVC is not in use to prevent colonization and subsequent CRBSI or sterilize a previously infected catheter [8].

In this study we used ALT and compared its efficacy with the common practice of Bangladesh of using systemic antibiotics for prevention of CRBSI in haemodialysis patients. Also, we emphasized on aseptic precautions and hygienic measures in both groups to reduce the overall incidence of CRBSI.

2. METHODS:

It was a randomized trial done at Kidney Foundation Hospital and Research Institute, Dhaka, Bangladesh over a period of 12 months from January 2018 to December 2018.This study was approved by the ethical review committee of Kidney Foundation Hospital.

2.1. Inclusion and Exclusion Criteria:

Patients who started haemodialysis with a short-term non-cuffed non-tunneled CVC inserted at Kidney Foundation Hospital with aseptic technique were included in the study. Patients who showed signs of infection before catheter insertion, who were already on systemic antibiotic therapy for any other infection, patient who were receiving HD with a diagnosis of suspected AKI and patient who had a catheter inserted outside Kidney Foundation were excluded from the study. Patients were informed in detail by the investigators regarding the study and informed written consent was obtained.

2.2. Study groups:

A total of 88 patients were studied. Patients were randomized into two groups: group A (35 patients) who had ALT after each haemodialysis and group B (53 patients) who received continuous systemic antibiotic (intravenous ceftazidime 500mg daily).

2.3. Antibiotic lock solution preparation:

Antibiotic lock solution was prepared at Kidney Foundation Hospital with Vancomycin 5 mg/mL and Heparin 2500 units/ml. At first Vancomycin 500 mg was diluted with 50 mL of NS (10mg/mL). This solution was labeled as "solution A". Then 2 mL of heparin 5,000 units/mL was taken into a syringe and mixed with 2 mL of solution A (vancomycin 10mg/ml) for a 4 mL of final solution. The final concentration of this solution was Vancomycin 5 mg/mL and Heparin 2500 units/ml. Solution A (Vancomycin 10 mg/ml) was stored in a refrigerator at 2-8°C and mixed with heparin just before instillation into the catheter. Diluted vancomycin was discarded after 72 hours of preparation.

2.4. Antibiotic lock solution administration:

Prior to the start of dialysis, antibiotic lock solution from the catheter lumen was withdrawn. Then dialysis was performed. After completion of dialysis, catheter was first flushed with normal saline and then antibiotic lock solution was instilled to fill catheter lumen (1.8 ml in each catheter lumen). This solution was allowed to dwell until next dialysis. Again, the antibiotic lock solution was aspirated from the catheter lumen just before the start of the next dialysis.

2.5 Other preventive measures:

Following aseptic techniques and infection control measures were applied to both groups:

1. Patients were educated regarding infection control (wear clean cloths, do not touch catheter). Patients and attendants were advised to perform hand washing with soap and water twice daily.
2. Maximal sterile barrier precautions, including the use of a cap, mask, sterile gown, sterile gloves, and a sterile full body drape were used during the insertion of the CVC.
3. To reduce nosocomial colonization, mupirocin ointment was applied at the nose of patient and attendants daily.
4. Dressing over the catheter exit site was changed twice a week. Provide one iodine antiseptic ointment was applied at the catheter exit site after catheter insertion and after dressing change.

2.6. Management of suspected CLABSI:

When patients showed signs of infection (temperature >99.5°F, tachycardia, hypotension, chills and rigors during dialysis), they were clinically examined to look for source (lungs, urine, skin, heart). Complete

blood count (CBC), chest X-ray, urine R/E and urine culture was performed. Unfortunately, blood cultures could not be performed due to financial and logistic problems. Prophylactic systemic antibiotic or antibiotic lock therapy was continued. For the treatment of suspected line infection, the empirical antibiotic policy at our centre was intravenous (IV) Co-amoxiclav 1.2gm stat followed by 600mg IV daily. If there was no clinical improvement after 48 hours, we switched to 2nd line treatment with IV Meropenam 500mg daily. Line removal was considered if no improvement occurred with antibiotic therapy.

2. RESULT:

A total of 88 patients were studied who started haemodialysis (HD) through a temporary venous catheter. Among them 35 patients received antibiotic lock therapy (group A) and 53 patients received IV Ceftazidime (group B). In group A, male was 60% and female 40% and in group B, male 55% and female 45%. Average age of patients in group A was 51.5 years (range from 23 to 75 years) and in group B was 51.5 years (range from 23 to 75 years). In group A, 97% patients received HD through jugular venous catheter (JVC) and 3% patients received HD through femoral venous catheter (FVC). In group B, 91% patients received HD through JVC and 9% patients received HD through FVC. The causes of ESRD in group A patients were diabetic nephropathy (57%), chronic glomerulonephritis (26%) and hypertension (17%). The causes of ESRD in group B patients were diabetic nephropathy (42%), chronic glomerulonephritis (28%), Hypertension (24%) and others (6%). Average observation period in group A patients was 12.9 ± 4.6 days (range 7 to 21 days) and in group B patients was 13.9 ± 6.0 days (range 7 to 27 days). Basic demographics of patients are summarized in table 1.

Table 1: Basic Demographics of patients

Parameters		Group A (ALT)	Group B (systemic antibiotic)
Number (Total = 88)		35	53
Mean Age (years)		51.5 (range, 23 to 75)	51.5 (range 23 to 75)
Sex	Male	60%	55%
	Female	40%	45%
Cause of ESRD	DM	57%	42%
	GN	26%	28%
	HTN	17%	24%
Catheter site	Jugular	97%	91%
	Femoral	3%	9%
Observation period (days)		12.9±4.6 (range 7 to 21)	13.9±6.0 (range 7 to 27)

ALT: antibiotic lock therapy, ESRD: end stage renal disease, DM: diabetes mellitus, GN: glomerulonephritis, HTN: hypertension

Out of the 88 patients studied, 09 patients (10.2%) experienced persistent fever during the observation period. In group A, 14.3% (05 out of 35) patients experienced persistent fever and in group B, 7.5% (04 out of 53) patients experienced persistent fever.

Patients who developed fever were further investigated to find out the source of infection. In group A, out of the 05 patients who developed fever, 02 patients (5.7%) were suspected to develop CLABSI. Among them 01 patient had suspected CLABSI along with pneumonia and urinary tract infection (UTI)

as chest x-ray showed consolidation and urine culture grew E. coli. Patient received intravenous antibiotics but only became afebrile after catheter removal. Another patient also had suspected CLABSI who self-discharged with intravenous antibiotics and was lost to follow up. The source of infection in the remaining 03 patients was chest. All of them had symptoms and signs and radiological evidence of chest infection and improved with intravenous antibiotics without requiring catheter removal. In group B, 03 patients (5.7%) were suspected to develop CLABSI. Two of them required removal of catheter and another patient improved with intravenous antibiotics only. The source of infection in the remaining one patient was UTI. There was no difference in the incidence of suspected CLABSI between these two groups (5.7% vs 5.7%, p=0.99) (Table 2). The overall incidence rate of suspected CLABSI in our study group was 4.2 episodes per 1000 catheter days. The incidence of suspected CLABSI in ALT group was 4.4 episodes per 1000 catheter days and in systemic antibiotic group was 4.1 episodes per 1000 catheter days. It was noted that the incidence of overall infection rate was higher in ALT group compared to systemic antibiotic group (14.3% vs 7.5%, p=0.31). However, this was not statistically significant.

Table 2: Incidence of infection in two groups

Parameters	Group A (ALT) n=35	Group B (systemic antibiotic) n=53	P value
Suspected CLABSI	5.7%	5.7%	p=0.99
Chest infection	11.4%	nil	
UTI	2.9%	1.9%	p=0.77
Overall infection	14.3%	7.5%	p=0.31
Catheter removal	2.9%	3.8%	p=0.82

ALT: antibiotic lock therapy' CLABSI: central line–associated bloodstream infection, UTI: urinary tract infection

In our study we found that the rate of suspected CLABSI among diabetic nephropathy (DN) patients was higher than that among non-DN patients (7.1% vs 4.3%, p=0.577) but it was not statistically significant. Also, the rate of overall infection was higher among DN patients than that among non-DN patients (11.9% vs 8.7%, p=0.624).

3. DISCUSSION:

Catheter-related bloodstream infection (CRBSI) in dialysis patients is associated with high morbidity, mortality and healthcare costs [2]. In Bangladesh like other developing countries, patients with ESRD usually initiate hemodialysis as an emergency through a non-tunneled non-cuffed temporary hemodialysis catheter. These catheters are associated with a high incidence of CRBSI. A study by Oliver et al. reported that the incidence of CRBSI was 5.4% after three weeks of placement in JVC and 10.7% after one week in FVC [9]. A recent study from India also reported that incidence of CRBSI in temporary catheters was 5.37 episodes per 1000 catheter days [10]. Studies also suggested that the incidence of CRBSI is higher with un-cuffed temporary catheters than that with tunneled cuffed catheters (TCC). Weimar et al demonstrated that the rate of CRBSI for TCCs was 2.9 per 1000 catheter days, for un-cuffed jugular catheters was 15.6 per 1000 catheter days and for un-cuffed femoral catheters it was 20.2 per

1000 catheter days [11]. For the prevention of CRBSI the practice in almost all tertiary hospitals in Bangladesh is to use continuous systemic antibiotics either oral or intravenous. However, concerns regarding antibiotic resistance, cost of antibiotic and side effects of antibiotics remain. In our study we used antibiotic lock therapy for the prevention of CRBSI and compared its efficacy with the usual practice of continuous intravenous antibiotic. In our study, the incidence of overall suspected CLABSI was 4.2 per 1000 catheter days. A study conducted at two tertiary care hospitals of Dhaka, Bangladesh, reported that the rate of CRBSI was 8 per 1000 and 11 per 1000 catheter days [5]. Another study conducted at a tertiary care hospital of Bangladesh demonstrated that the rate of CRBSI was 16 per 1000 catheter days [6]. The reason the rate of suspected CLABSI is lower in our study than that reported in previous studies of Bangladesh may be because we reinforced on strict antiseptic precautions like aseptic technique during insertion of catheters; hand hygiene; twice weekly change of dressing, use of antiseptic ointment at exit site and use of antibiotic ointments into nose to reduce nasal colonization. A recent study from India found that the incidence of CLABSI was 7.34 episodes per 1000 catheter days and they have hypothesized that poor hygiene might have contributed to this high incidence [1].

Our study showed that the rate of suspected CLABSI in ALT group was 4.4 per 1000 catheter days where as the rate of suspected CLABSI in continuous systemic antibiotic group was 4.1 per 1000 catheter days. Our results demonstrated that for the prevention of CLABSI, ALT is non-inferior to systemic antibiotic. To the best of our knowledge this is the first study that compared ALT with systemic antibiotic for prevention of CLABSI. A study compared the efficacy of ALT with conventional catheter care for prevention of CRBSI in tunneled cuffed catheter and shown that the rate of infection was significantly lower in ALT group (4.39/1000 dialysis sessions) compared to conventional catheter care group (11.69/1000 dialysis sessions) [12]. Our antibiotic lock solution consisted of vancomycin 5 mg/ml and heparin 2500 units/ml. Several studies have investigated the combination of vancomycin and heparin for the prevention and management of CRBSI. Different doses of vancomycin have been used in different studies ranging from 0.025mg/ml to 10mg/ml [8]. A mixture of vancomycin 5 mg/mL with heparin 2500 units/ml was found compatible and stable for 72-96 hours or longer [13]. The advantages of using ALT over systemic antibiotic include a lower risk of antibiotic toxicity and antibiotic resistance and low cost. The cost of ALT using our protocol is 50 taka ($0.57) per person per week while the cost of administering systemic antibiotic is 910 taka ($10) per person per week. However, some theoretical risks of using AL Have been assumed [8]. As the lock solution is allowed to dwell in the catheter lumen, occlusion of the catheter might happen. This risk is reduced as the solution also contains heparin. No incidence of catheter occlusion was note din our patients during the study period. Also, patients may become exposed to concentrated antibiotic and anticoagulants if the lock solution is flushed into the circulation [8]. We minimized this risk by aspirating the lock solution before each dialysis session started.

Patients with end stage renal disease (ESRD) who are on dialysis are at high risk of getting infection and infection related death due to their immunosuppressed state, underlying diseases (diabetes mellitus, peripheral vascular disease, etc.) uremic condition, malnutrition, or dialysis access and dialysis process. Haemodialysis vascular-access devices (HVADs) are a major source of infection in these patients. A study by Berman et al reported that the rate of infection among dialysis patients was 5.7 episodes per 1000 dialysis days and the important sources of infections were HVADs (20.5%), infections below the knee (19.3%) pneumonia (13%), and skin and soft-tissue infections (9%), urinary tract infections, intra-abdominal infections, etc. [14]. In our study we noted that the incidence of infection irrespective of the source was higher in ALT group in comparison to systemic antibiotic group (14.3% vs 7.5%, p=0.31). This phenomenon is expected and understandable, because ALT is not supposed to prevent infection other than CLABSI like chest infection or UTI whereas systemic antibiotic is expected to prevent or treat those infections unless resistant. Therefore, for a patient with a temporary catheter who develops infection, it is first to suspect and investigate for CLABSI, but it is also very important to look for other sources of infection at the same time. In our study we noted that the rate of suspected CLABSI among diabetic nephropathy (DN) patients was higher than that among non-DN patients (7.1% vs 4.3%, p=0.577) but it was not statistically significant. Menegueti et al described that diabetes was significantly associated with the development of catheter related infection [15].

In Bangladesh, although ALT has been suggested by Bangladesh Society of Medical Microbiologists [16], to the best of our knowledge, ALT has never been used before. Our results demonstrated that for the prevention of CLABSI, ALT is non-inferior to systemic antibiotic.

4. LIMITATIONS:

In this study the organism responsible for CLABSI could not be isolated due to financial and logistical problems. One study performed in Bangladesh found that the most common bacteria causing CRBSI was Klebsiella spp. (36.4%) followed by Acinetobacter spp. (27.3%), Pseudomonas spp. (18.2%) and E. coli (18.2%). Most of the isolated bacteria causing CRBSI were resistant to commonly used antibiotics [5]. Another study of Bangladesh found that the most common causative pathogens causing CRBSI were Pseudomonas sp. (23.7%), Acinetobacter sp. (18.4%), Staphylococcus aureus (13.2%) and Enterobacteriaceae (10.5%) [6].

5. CONCLUSION

To conclude, CRBSI in dialysis patients is associated with high morbidity, mortality and healthcare costs. For prevention of CRBSI, guidelines have recommended use of ALT and strongly discouraged use of systemic antibiotics. Our study demonstrated that for the prevention of CLABSI, ALT is non-inferior to systemic antibiotics. The advantages of using ALT over systemic antibiotic include a lower risk of antibiotic toxicity and antibiotic resistance and low cost. However, the overall incidence of infection was higher with ALT than with systemic antibiotics which might misguide clinicians to use systemic antibiotic for prevention of CRBSI. To influence the practice of

Bangladesh in future, large scale randomized controlled trials comparing the efficacy of ALT with systemic antibiotics are required.

References:

1. Agrawal V, Valson AT, Mohapatra A, David VG, Alexander S, Jacob S, Bakthavatchalam YD, Prakash JA, Balaji V, Varughese S. Fast and furious: a retrospective study of catheter-associated bloodstream infections with internal jugular non tunneled hemodialysis catheters at a tropical center. Clinical kidney journal. 2019;12(5):737-44.
2. O'grady NP, Alexander M, Burns LA, Dellinger EP, Garland J, Heard SO, Lipsett PA, Masur H, Mermel LA, Pearson ML, Raad II. Guidelines for the prevention of intravascular catheter-related infections. Clinical infectious diseases. 2011;52(9):e162-93.
3. Maki DG, Kluger DM, Crnich CJ. The risk of bloodstream infection in adults with different intravascular devices: a systematic review of 200 published prospective studies. In Mayo Clinic Proceedings 2006;81(9):1159-71.
4. Centers for Disease Control and Prevention (CDC).Vital Signs. Making Health Care Safer: Reducing Bloodstream Infections.[pdf] Atlanta, GA: Centers for Disease Control and Prevention. 2011. Available from: https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6008a4.htm [Accessed 21.05.2022]
5. Afroz Z, Jobayer M, Ahmed S, Anwar S, Mia MR. Central venous catheter-related bloodstream infections (CVC-BSI) in patients of clinically suspected septicemia. Bangladesh Medical Research Council Bulletin. 2015;41(2):89-94.
6. Mansur FJ, Barai L, Karim MM, Haq JA, Fatema K, Faruq MO. Intravascular catheter related infections and antimicrobial susceptibility pattern of isolated bacteria in a tertiary care hospital of Bangladesh. Indian Journal of Medical Microbiology. 2014;32(1):68-71.
7. Mermel LA, Allon M, Bouza E, Craven DE, Flynn P, O'Grady NP, Raad II, Rijnders BJ, Sherertz RJ, Warren DK. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 Update by the Infectious Diseases Society of America. Clinical infectious diseases. 2009;49(1):1-45.
8. Justo JA, Bookstaver PB. Antibiotic lock therapy: review of technique and logistical challenges. Infection and drug resistance. 2014;7:343.
9. Oliver MJ, Callery SM, Thorpe KE, Schwab SJ, Churchill DN. Risk of bacteremia from temporary hemodialysis catheters by site of insertion and duration of use: a prospective study. Kidney international. 2000;58(6):2543-5.
10. Chandra A, Das A, Sen M, Srivastava D. Haemodialysis catheter-related blood stream infection in ESRD patients: incidence, outcome and antibiogram of the isolated organisms. Int J Adv Med. 2016;3(4):912-9.
11. Weijmer MC, Vervloet MG, ter Wee PM. Compared to tunnelled cuffed haemodialysis catheters, temporary untunnelled catheters are associated with more complications already within 2 weeks of use. Nephrology Dialysis Transplantation. 2004;19(3):670-7.
12. Al-Hwiesh AK. Tunneled catheter-antibiotic lock therapy for prevention of dialysis catheter-related infections: a single center experience. Saudi journal of kidney diseases and transplantation. 2008;19(4):593.
13. Bookstaver PB, Rokas KE, Norris LB, Edwards JM, Sherertz RJ. Stability and compatibility of antimicrobial lock solutions. American journal of health-system pharmacy. 2013;70(24):2185-98.
14. Berman SJ, Johnson EW, Nakatsu C, Alkan M, Chen R, LeDuc J. Burden of infection in patients with end-stage renal disease requiring long-term dialysis. Clinical infectious diseases. 2004;39(12):1747-53.
15. Menegueti MG, Betoni NC, Bellissimo-Rodrigues F, Romão EA. Central venous catheter-related infections in patients receiving short-term hemodialysis therapy: incidence, associated factors, and microbiological aspects. Revista da SociedadeBrasileira de Medicina Tropical. 2017;50:783-7.
16. Roy CK. Antibiotic Lock Therapy: Paradism of saving lives and antibiotics. Bangladesh Journal of Medical Microbiology. 2016;10(2):1-3.

Review article

Pre- and Post-Transplant Vaccination for Solid Organ Transplant Recipients

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Summary

Solid-organ transplant (SOT) candidates are at an increased risk for infections, some of which are preventable by vaccines. In post-transplant immunosuppressed individuals, certain infections are more complicated with poorer outcomes. Patients should ideally be immunized early in the course of their disease, or during pre-transplant evaluation. Vaccination schedules should be completed at least 2 weeks for killed vaccines and at 4 weeks for live vaccines before SOT. Live vaccines are not advised after transplantation due to immunosuppression and risk of vaccine induced disseminated infection (i.e., measles, mumps, rubella, varicella, live zoster, polio, yellow fever and dengue vaccines). Post-transplant vaccines are initiated 3–6 months after transplant. They often have lower rates of serological conversion, lower mean antibody titers, and diminishing immunity with time and may need for repeat vaccination. Serological conversion can be documented by at least 4 weeks after vaccination. Blood products transfusion can interfere with the response to live vaccines and should be deferred for 3 months. There is no risk to the SOT candidates, if family members or close household contacts receive live vaccines except oral polio vaccines. Pets should also be fully immunized. Therefore, transplant providers should include appropriate vaccination protocol in their management strategies.

Key words: Solid-organ transplant candidates, immunosuppressed individuals, infections, vaccination, repeat vaccination.

Infection is an important cause of morbidity and mortality in solid organ transplant recipients (SOTRs). According to Transplant data from Global Observatory on Donation and Transplantation, about 13700 living and deceased SOTs were done in South Asia (SA) in 2019.

Majority were kidney transplants (92%), followed by liver (19%), heart (2%), lungs (0.8%), and pancreas (0.18%) (1). SA is a home of many tropical diseases (infectious, malnutritional, genetic, environmental). SOT candidates are at an increased risk for infections, some of which are preventable by vaccines. In post- transplant immune compromised individuals, certain infections are more common, more complicated and have poorer outcomes (2). As a part of routine pre-transplant immunization, serologies for certain infections should also be done to guide vaccine planning, e.g., anti-HBs antibody titre (3,4).

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However, one viral infection increases the risk of other opportunistic infections by releasing various cytokines that deepen immunosuppression. T cell response to viral infection can lead to organ rejection through heterologous immunity (e.g., molecular mimicri) to donor antigens (5). Therefore, vaccination for prospective transplant recipients should be advised accordingly.

How vaccines work?

Vaccines have poor pathogenecity but strong immunogenecity and can protect from future infection. Vaccine just imitates an infection and teaches the body immune system how to fight off future infections. Sometimes, after getting a vaccine, body responds by causing minor symptoms, such as fever. These kinds of minor symptoms are due to building of immunity.It takes a few weeks for building up full immune response. Therefore, a person can be infected with a disease just before or just after getting vaccinated. It is also possible to get a disease even when vaccinated, with less severity. Some vaccines require more than one doses to be fully effective and to give the most protection.

General Guidelines of Vaccination for SOT Candidates

There is no consensus on the time or stage of chronic kidney disease (CKD) that is ideal for vaccination. But vaccination in the earlier stage of the disease usually results in better immunologic response (3,4). Vaccination schedules should be completed at least 2 weeks for killed vaccines and 4 weeks for live vaccines before solid organ transplantation. Live vaccines are not advised after transplantation due to immunosuppression and risk of vaccine induced disseminated infection. Live vaccines include: BCG, Measles, mumps and rubella (MMR), Oral polio, oral typhoid, Yellow fever, Influenza nasal spray, Varicella-zoster (Shingles). Post-transplant (non-live) vaccines may be initiated 3–6 months after transplant, once baseline immunosuppression is achieved. They often have lower serological response and antibody titers, and diminishing immunity with time and may need repeat vaccination. In general practice, vaccines should be re-started a year after SOT, except for influenza and severe acute respiratory syndrome-coronavirus-2 vaccines. Multiple vaccines can be given at a single setting. Pre-transplant live vaccines may be given on the same day, if not possible, at a 4 or more weeks interval to achieve higher antibody titers. Inactive vaccines can be given at any time of interval. To ensure protection, serological response can be documented by measuring of antibody titer at least 4 weeks after vaccination.

Vaccination of Close Contacts:

There is little or no risk to the transplant recipient, if family members or close household contacts receive live vaccines. The exception is oral polio vaccines. Therefore, family members or close household contacts should be immunized with injectable polio vaccine. Frequent hand washing for a 2-week is recommended for household contacts receiving live influenza vaccine.

Frequent hand washing

Protective factors against influenza includes higher hand washing score, providing soap or hand cleaner beside the hand-washing basin, avoiding touching eyes, nose and mouth, receiving influenza vaccine and other good hygienic habits. Regular hand-washing (for 20 seconds or more) and good hygienic habits are associated with a reduced risk of influenza

transmission in health care and community setting (6).

Blood products and vaccination:

Blood products like packed cell transfusion, platelet transfusion, intravenous immune globulin (IVIG), fresh frozen plasma (FFP) can interfere with the response to live vaccines. Live vaccines should be deferred for 3 months after receiving of blood products

Pet vaccination

Like caregivers, pets should also be fully immunized. Immunization of pets with live vaccines (e.g., canine Bordet ella bronchiseptica intranasal vaccine) poses little or no risk of transmission to SOT recipient (4).

Vaccination and tuberculin skin test:

Live vaccines can interfere with the tuberculin skin test (TST). TST should be done on the same day of the live vaccine administration or 4–6 weeks after vaccination.

Travel medicine:

The SOTRs should preferably restrict their travels for the first 12 months' post-transplantation. In the meantime, their health and the graft function become stable (7). All SOTRs should be seen by a travel medicine specialist prior to traveling to destinations with higher rates of infection (8). Malaria chemoprophylaxis should be taken before travelling to malaria endemic regions.

Transplant tourism

Medical tourism refers to the crossing of international borders for the purpose of receiving medical care. Transplant tourism involves traveling for transplant. Transplant tourism has 4 models.

1: Donor and recipient from the same country travel to another country for transplantation;

2: Donor travels to the country where the recipient resides;

3: Recipient travels to the country that the donor resides;

4: Donor and recipient from different countries travel to the third country for transplantation (9, 10). Transplant tourism has always generated controversy about the source of transplant organs, post-transplant care of the donors and recipients, donor-derived infections (DDI), local and opportunistic infections in recipients and overall clinical outcomes in organ recipients. Appropriate vaccination may limit the infection and improve the outcome of SOTRs.

Vaccination for tuberculosis in SOTR

BCG is a live attenuated vaccine form of Mycobacterium bovis and is contraindicated in after SOT. BCG vaccination after infancy may show positive TST (>10 mm) (11). IGRA (Quantiferon TB Gold test) should be used to interpret positive TSTs in persons with a history of BCG vaccination or intra vesicle BCG for bladder cancer, as IGRA is not affected by BCG administration (12). TB is 20 to 74 times more frequent and carries a high mortality in SOTRs. TB can be transmitted via the transplanted organs (13). Living donor with active TB should be accepted after adequate treatment for at least 2 months of intensive therapy with 4 drugs, including rifampicin and documentation of clinical and radiological response. Treatment should be extended in incomplete clinical or radiological response. The recipient should be given isoniazid prophylaxis for 6 months. Deceased donors with known or suspected active TB should not be accepted (14). If active TB is found in the transplanted organ, then the recipient should be initiated on full

anti-tubercular treatment (Ethumbutol, INH, Pyrazinamide, Levofloxacin for 3 months, followed by Ethumbutol, INH, Pyrazinamide or, Levofloxacin for 9 months), and the risk should be notified to the recipients of other organs (15). Transplant recipients traveling to SA are advised to use N95 masks when close to a person with active TB, avoid prolonged and close contact with active TB patients, avoid crowded place with poor ventilation.

Influenza vaccine

Post-transplant influenza is common and is associated with higher morbidity and mortality. It is also associated with an increased risk of rejection in kidney transplant recipients. Vaccinated patients have significantly lower complications and better graft and patient survival (16). In tropical countries, like Bangladesh, flu is not seasonal and can occur throughout the year. Both the killed and the live attenuated vaccines are equally effective. Live vaccine can be given to patient in pre-transplant period, at least 4 weeks prior to the surgery (4). The live vaccine is not recommended post-transplant. Flu vaccine is recommended annually. But the immunogenicity may be reduced in the first 3–6 months after transplant. Influenza revaccination after 1–3 months of SOT is recommended, since missing a dose might put the patient in risk in influenza season (17). In community influenza outbreak, the vaccination can be done 1 month after transplantation, and re-vaccination should be done 3–6 months later if outbreak persists (4). Household and close contacts of transplant recipients should also receive the flu vaccine annually, particularly the inactivated vaccine.

Pneumococcal vaccine

Transplant recipients are at increased risk of invasive pneumococcal disease. There are two formulations of the pneumococcal vaccine: A13-valent conjugate vaccine and 23-valent polysaccharide vaccine. The conjugate vaccine is recommended as part of the childhood vaccination, but only a limited population are vaccinated in past decade (18). There is a trend for greater vaccine immunogenicity with the conjugate vaccine (higher antibody titer) (19). All candidates need the conjugate vaccine, followed 2 months later by the polysaccharide vaccine. If the candidate has received the polysaccharide vaccine (PPSV23) initially, the conjugate vaccine (PCV13) is recommended after 1 year. A repeat of the polysaccharide vaccine is recommended after 5 years in both situations (19). **Diphtheria, tetanus, pertussis vaccine.** Diphtheria, tetanus, pertussis (DPT) vaccination is universal in children in South Asian region (20). Recent outbreaks of pertussis are believed to be due to diminished immunity in adulthood after childhood vaccination. All adults who have had their childhood immunization schedule are otherwise advised tetanus and diphtheria boosters every 10 years. **To boost pertussis immunity, a single dose of DPT vaccine is recommended for all adults over the age of 18 years (21). Measles, mumps, rubella vaccine.** MMR vaccination is given universally to all children in the region of South Asia (22). However due to a poor uptake of childhood MMR vaccination, all transplant candidates should have either proper documentation of two doses of vaccine or have their serologies checked for measles, mumps and rubella before transplant and

immunized, if indicated. (4) **Two doses of MMR vaccine 4 weeks apart are indicated for susceptible persons.** Since it is a live vaccine, it is contraindicated after transplant. Transplant should be deferred for 4 weeks after the vaccine. Household and close contacts of transplant recipients should also receive the vaccine (4). **Meningococcal vaccine.** Transplant recipients are not at an increased risk of meningococcal infections. Specific recommendations are made for high-risk situations, like Hajj or Sub-Saharan Africa travelers, elective splenectomy, military camping and patients receiving complement inhibitor eculizumab (23,24). The vaccine is recommended at least 2 weeks before the first dose of eculizumab. Two doses of the quadrivalent conjugate vaccine, 2 months apart are recommended. A booster may be advised after 5 years. The immunologic response of the polysaccharide vaccine is only 40% in SOT recipients (25).

Hepatitis B vaccine

Bangladesh comes under the intermediate prevalence (2%–5%) area for Hepatitis B, with similar rates in South Asia. Hepatitis B vaccine should be given to all candidates as a standard 3-dose series at 0, 1, and 6 months. An accelerated schedule can be given at 0, 1, 2 months, and 6 months (with a double-dose) for patients with CKD5 patients on dialysis (3). Hepatitis B antibody titers should be routinely monitored 4–8 weeks after the last dose (3). Revaccination is recommended if HBs antibody titers fall <10 IU/ml (non-responders) (26). CKD, HIV, T1DM, CLD, drug abuse, thalassemia, vaccine in buttocks, obesity, smoking may lead to a high rate of nonresponse to hepatitis B vaccination. Dialysis patients should always receive a double-dose vaccination and extended vaccination protocols. But even with the most recent vaccines, nearly 20% of patients do not develop protective antibody levels (27). This impaired response led to the development of specifically intradermal administration protocols (weekly 8 doses X 5 to 10 microgram) with improved seroprotection in former non responders (28). Skin is more immunogenic barrier against infection by dendritic cells (APCs).

Hepatitis A vaccine

South and south-east Asia are areas of end emicity for hepatitis A. Other risk factors include poor sanitation, lack of safe water, homeless persons, international travelers, use of recreational drugs, being a sexual partner of someone with acute hepatitis A infection, sex between men, and certain ethnic or close religious groups. Hepatitis A is not part of the routine childhood vaccination. The inactivated vaccine schedule includes 2 doses, 6 months apart. This provides lifelong immunity, though the antibody response is poorer in SOT recipients (29). This vaccine is also recommended to SOT recipients traveling to South Asia (30). The live attenuated hepatitis A vaccine (Biovac-A) is not recommended in transplant recipients but could be given at least a month before transplant.

Human papilloma virus vaccine

Both cervical and anogenital warts and cancer caused by the human papilloma virus are seen more commonly in SOT recipients (31). Two formulations of the vaccine are available: A quadrivalent vaccine and a bivalent vaccine that are recommended between 9 and 26 years of age (32). A 3-dose prophylactic vaccine schedule is recommended prior to transplant

at 0, 2, and 6 months. If the doses are not completed pre-transplant, they can be resumed post-transplant. Immunogenicity may be sub-optimal in adult transplant recipients (33).

Polio vaccine

Bangladesh was certified as polo-free by the Global Polio Eradication Initiative (GPEI) in 2014. But people are still vulnerable to the virus, because it remains endemic in Afghanistan and Pakistan. Total 20 and 6 WPV polio cases were found in Pakistan in 2022 and 2023, respectively (34). A booster dose of inactivated polio vaccine as IM injection can be given for all SOT recipients. The oral live-attenuated virus vaccine is contraindicated for all transplant recipients and their household contacts. Because faeco-oral transmission of viruses can occur, with risk of prolonged shedding with stool and also reversal to pathogenic virus.

Varicella vaccine

Varicella-zoster infection after SOT is associated with increased morbidity and mortality. Varicella vaccine is a live attenuated virus vaccine that is indicated pre-transplant in those who are not yet immunocompromised. The vaccine is given as 2 doses 4 weeks apart. Post-vaccination serology can be performed in certain situations, and seroconversion occurs up to 95% before transplantation (35). It is LAV, and is avoided post-transplant (36). For nonimmune transplant recipients exposed to a patient with VZ virus infection, immune-prophylaxis with either acyclovir or varicella-zoster immune globulin (VZIG) is recommended within 10 days following the exposure.

Herpes zoster vaccine

Reactivation of VZ (Herpes Zoster) is common after SOT. Herpes Zoster vaccine is a live-attenuated virus vaccine indicated in those older than 50 years to prevent shingles and post herpetic neuralgia. Zostavax is a live-attenuated vaccine given as a single dose. It is contraindicated post-transplant. But it can be used at least 4 weeks before in the pre-transplant setting, assuming they are not otherwise on immunosuppression.

Typhoid vaccine

Typhoid is endemic in several parts of South and Southeast Asia. Two formulations of typhoid vaccine are available: a polysaccharide and a conjugate vaccine. Both vaccines are safe and reasonably effective. The polysaccharide vaccine is recommended every 3 years whereas one dose of the conjugate vaccine is believed to offer a more robust and prolonged immunogenicity (37). The typhoid vaccine does not protect against paratyphoid. Therefore, other protection measures such as food and water hygiene before consumption are necessary after transplantation. A third formulation of oral live attenuated vaccine is not currently available in Bangladesh.

COVID vaccine

Organ transplant recipients are at heightened risk for severe COVID-19 infection, hence there is a paramount need for vaccination in this vulnerable population (38). Prospective transplant recipients and their household members should receive any COVID-19 vaccine that is authorized or approved by designated advisory authority. Countries in the Southeast Asian Region are administering Astra Zeneca, Moderna, Sinopharm, Sinovac, Sputnik V, and Pfizer following emergency

use authorization being granted by their national regulatory authorities (39). Efficacy and safety of COVID-19 vaccine in SOTs have been scientifically documented only for few mRNA vaccines and many are still under clinical trial (40). The current data suggest there may be a diminished antibody response in this population. Post-transplant immunosuppression should be maintained throughout the vaccination period and not reduced (41). Some countries are recommending a third dose of mRNA vaccine for transplant recipients.

Yellow fever vaccine

The yellow fever vaccine requirements are regulated by international law. It is a live-attenuated virus vaccine that is contraindicated in the post-transplant setting. Yellow fever is not endemic in south Asia. The vaccine is recommended to all immunocompetent susceptible individuals traveling to endemic areas. A single dose of yellow fever vaccine is sufficient to provide life-long immunity in immune-competent hosts (42). SOT recipients who travel to YF risk areas should be counseled on mosquito bite prevention measures. Avoid going to Africa and South America if not vaccinated. If travel is necessary, travel with yellow card with stamp and reason of not vaccinated.

Rabies vaccine

South and South-east Asia are endemic for rabies and have the most rabies-related deaths. Transplant recipients should be advised to avoid exposure to these animals during their travel. However, transplant recipients expecting intense exposure to rabies are advised preexposure rabies vaccination (0 and 7 days). Post vaccination titers should be checked. In the event of a suspected rabid animal bite, 4 doses on day 0, 3, 7, and 14/28 is recommended. For those who have not had a preexposure vaccine, immunoglobulin (RIG), and the complete vaccine course should be given, regardless of the severity of the bite or animal status (43).

Dengue vaccine

Dengue is mosquito-borne flaviviral infection. Currently, a live-attenuated virus tetravalent chimeric vaccine is available with an estimated efficacy of 56.6% (44). Dengue vaccine is contraindicated post-transplant as it is a live vaccine. The vaccine is indicated in countries where dengue sero-prevalence is >70%. In Bangladesh it is nearly 80% (45).

Malaria: Chemoprophylaxis for transplant travelers:

Last minute chemoprophylaxis is not sufficient at all. Doxycycline for MDR plasmodium falciparum: 100mg daily; starting 1-2 days before travel, and continue 4 weeks after returning. Efficacy rate is 96% for P.falciparum and 98% for P.vivax. The targets are blood schizonts. Mefloquine for chloroquine resistant plasmodium falciparum: 250mg (1 tablet) once a week; starting at least 2 weeks before travel, and continue for 4 weeks after returning. Chloroquine (or hydroxychloroquine): 500mg (2 tab) once a week. Start 1 week before travel, and continue 4 weeks after returning home (46). Caution should be taken with ciclosporin as chloroquine can increase blood ciclosporin levels. Chloroquine sensitive plasmodium falciparum are only found in middle-east, the Caribbeans, Central America (west of Panama Canal).

Cholera vaccine

Cholera vaccine is currently indicated for travelers to endemic areas during cholera

outbreaks. Three orally administered vaccines are available. A Killed cholera vaccine offers cross-protection to Enterotoxigenic E. coli. 2 dose series 1 week apart is practiced. A live cholera vaccine is contraindicated in SOT recipients.

Conclusion

Vaccination can provide protection against numerous infections in low immuned transplant patients. Pre-transplant evaluation of vaccine status is important to update vaccines. Live vaccines should not be given after Transplant. All vaccines show lower immunologic response and therefore, SOTRs may need repeat vaccination. Last minute vaccination and chemoprophylaxis are not enough for protecting the transplant travelers. The transplant providers should cover good enough vaccination protocol to reduce morbidity and mortality in the patients.

Reference:

1. Global Observatory on Donation and Transplantation. Reports. WHO-ONT Collaboration. Available at http://www.transplant-observatory.org. Accessed May 31, 2022.
2. Bansal SB, Sethi S, Prasad N, Kotton CN, et al.Pre and Posttransplant Vaccination for Solid Organ Transplant Recipient and in South Asia - Expert Group Opinion. Indian J Transplant 2022;16:S106-11.
3. Rubin LG, Levin MJ, Ljungman P, Davies EG, Avery R, Tomblyn M, et al 2013 IDSA clinical practice guideline for vaccination of the .immunocompromised host. Clin Infect Dis 2014;58:e44–100.
4. Danziger-Isakov L, Kumar DAST ID Community of Practice. Vaccination of solid organ transplant candidates and recipients: Guidelines from the American society of transplantation infectious diseases community of practice. Clin Transplant 2019;33:e13563.
5. Higdon L E, Tan J C, Maltzman JS. Infection, rejection and the connection. Transplantation; March 2023. 107(3).
pp 584-595.
6. Mingbin Liu, Jianming Ou et al. Protective effect of hand-washing and good hygeinic habits against seasonal influenza. Medicine (Baltimore). 2016 Mar; 95 (11): e3046.
7. Available from: https:// wwwnc.cdc.gov /travel/yellowbook/2020/travelers-with-additional-considerations
/immunocompromised-travelers. [Last accessed on 2021 Sep 15]
8. Buchan CA, Kotton CN, AST Infectious Diseases Community of Practice. Travel medicine, transplant tourism, and the solid organ transplant recipient-Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. Clin Transplant. 2019;33(9):e13529.
9. Shimazono Y. The state of the international organ trade: a provisional picture based on integration of available
information. Bull World Health Organ 2007; 85: 955-962).
10. Ritesh N, Pahnwat TT, Humayun A, Salim S.Current state of medical tourism involving liver transplantation-the risk of infections and potential complications.World J Hepatol 2021 July 27; 13(7): 717-722).
11. Mancuso JD, Mody RM, Olsen CH, et al. The long-term effect of Bacillus Calmette Guerin vaccination on
tuberculin skin testing: A 55-year-follow up study. Chest. 2017 Aug;152(2):282-294.
12. Chika N. Okafor, Ayesan Rewane, Ifeanyi I. Momodu. Bacillus Calmette Guerin. StatPearls [Internet]. Last Update: July 3, 2023.
13. Bumbacea D, Arend SM, Eyuboglu F, et al. The risk of tuberculosis in transplant candidates and recipients: a
TBNET consensus statement. Eur Respir J. 2012;40:990–1013.
14. Morris MI, Daly JS, Blumberg E, et al. Diagnosis and management of tuberculosis in transplant donors: a donor-
derived infections consensus conference report. Am J Transplant. 2012;12:2288–2300.
15. Shyam B B, Venktasubramnian R, Narayan P, Neeraj S., et al. South Asian Transplant Infectious Disease
Guidelines for Solid Organ Transplant Candidates, Recipients, and Donors. Transplantation. September 2023. Vol107. No 9. pp1910.
16. Hurst FP, Lee JJ, Jindal RM, Agodoa LY, Abbott KC. Outcomes associated with influenza vaccination in the first year after kidney transplantation. Clin J Am Soc Nephrol 2011;6:1192–7.

17. Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group. KDIGO clinical practice guideline for the care of kidney transplant recipients. Am J Transplant 2009;9 Suppl 3:S1–155.
18. Available from: https://iapindia.org/pdf/124587-IAP-GUIDE-BOOK-ON-IMMUNIZATION-18-19.pdf. [Last accessed on 2021 Sep 15]

19. Blanchard-Rohner G, Enriquez N, Lemaître B, Cadau G, Giostra E, Hadaya K, et al Pneumococcal immunity and PCV13 vaccine response in SOT-candidates and recipients. Vaccine 2021;39:3459–66.
20. Available from: https://iapindia.org/pdf/124587-IAP-GUIDE-BOOK-ON-IMMUNIZATION-18-19.pdf. [Last accessed on 2021 Sep 15]
21. Guidelines for vaccination in normal adults in India. Indian J Nephrol 2016;26 Suppl 1:S7–14.
22. Available from: https://iapindia.org/pdf/124587-IAP-GUIDE-BOOK-ON-IMMUNIZATION-18-19.pdf. [Last accessed on 2021 Sep 15]
22. Struijk GH, Bouts AH, Rijkers GT, Kuin EA, ten Berge IJ, Bemelman FJ. Meningococcal sepsis complicating eculizumab treatment despite prior vaccination. Am J Transplant 2013;13:819–20.
23. Rubin LG, Levin MJ, Ljungman P, Davies EG, Avery R, Tomblyn M, et al 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. Clin Infect Dis 2014;58:e44–100.
24 .Shyam B B, Venktasubramanian R, Sidharth S, Narayan P, Camille N K. Pre and Posttransplant Vaccination for Solid Organ Transplant Recipient and in South Asia - Expert Group Opinion. Indian Journal of Transplantation. Vol16, Supplement Issue 1, 2022. pp S106-110.)
25. Weinbaum CM, Williams I, Mast EE, Wang SA, Finelli L, Wasley A, et al Recommendations for identification and public health management of persons with chronic hepatitis B virus infection. MMWR Recomm Rep 2008;57:1–20.
26. Janssen RS, Mangoo-Karim R, Pergola PE, et al. Immunogenicity and safety of an investigational hepatitis B vaccine with a toll-like receptor 9 agonist adjuvant (HBsAg-1018) compared with a licensed hepatitis B vaccine in patients with chronic kidney disease. Vaccine. 2013;31:5306–5313.
27. Barraclough KA, Wiggins KJ, Hawley CM, et al. Intradermal versus intramuscular hepatitis B vaccination in hemodialysis patients: a prospective open-label randomized controlled trial in nonresponders to primary vaccination. Am J Kidney Dis. 2009;54:95.
28. Jeon HJ, Ro H, Jeong JC, Koo TY, Han M, Min SI, et al Efficacy and safety of hepatitis A vaccination in kidney transplant recipients. Transpl Infect Dis 2014;16:511–5.
29. Available from: https:// wwwnc.cdc.gov //travel/yellowbook/2020/travelers-with-additional-considerations/immunocompromised-travelers. [Last accessed on 2021 Sep 15].
30. Wieland U, Kreuter A, Pfister H. Human papillomavirus and immunosuppression. Curr Probl Dermatol 2014;45:154–65.
31. Guidelines for vaccination in normal adults in India. Indian J Nephrol 2016;26 Suppl 1:S7–14.
32. Kumar D, Unger ER, Panicker G, Medvedev P, Wilson L, Humar A. Immunogenicity of quadrivalent human
papillomavirus vaccine in organ transplant recipients. Am J Transplant 2013;13:2411–7.
33. Pakistan Polio Eradication Programme. National Emergency Operation Centre. Prime Minister Health Complex, Chak Shahzah, 44000, Islamabad.
34. Broyer M, Tete MJ, Guest G, Gagnadoux MF, Rouzioux C. Varicella and zoster in children after kidney
transplantation: Long-term results of vaccination. Pediatrics 1997;99:35–9.
35. Posfay-Barbe KM, Pittet LF, Sottas C, Grillet S, Wildhaber BE, Rodriguez M, et al Varicella-zoster
immunization in pediatric liver transplant recipients: Safe and immunogenic. Am J Transplant 2012;12:2974–85.
36. Sahastrabuddhe S, Saluja T. Overview of the typhoid conjugate vaccine pipeline: Current status and future plans.
Clin Infect Dis 2019;68:S22–6.
37. Akalin E, Azzi Y, Bartash R, Seethamraju H, Parides M, Hemmige V, et al COVID-19 and kidney transplantation. N Engl J Med 2020;382:2475–7.
38. Available from: https://www.who.int/southeastasia/news/detail/06-08-2021-over-half-a-billion-covid-19-
vaccine-doses-administered-in-who-south-east-asia-region-as-countries-scale-up-vaccination-efforts. [Last accessed on 2021 Sep 11]
39. Cucchiari D, Egri N, Bodro M, Herrera S, Del Risco-Zevallos J, Casals-Urquiza J, et al Cellular and humoral response after MRNA-1273 SARS-CoV-2 vaccine in kidney transplant recipients. Am J Transplant 2021;21:2727–39.
40. Stock PG, Henrich TJ, Segev DL, Werbel WA. Interpreting and addressing suboptimal immune responses after
COVID-19 vaccination in solid-organ transplant recipients. J Clin Invest 2021;131:151178.
41. Who. Vaccines and vaccination against yellow fever: WHO position paper, June 2013 – Recommendations.
Vaccine 2015;33:76–7.

42. World Health Organization. Rabies vaccines: WHO position paper, April 2018 - Recommendations. Vaccine
2018;36:5500–03.
43. Schwartz LM, Russell PK. Protective and immunological behaviour of chimeric yellow fever dengue vaccine.
Vaccine 2016;34:1643–7.
44. Government of the People's Republic of Bangladesh, Ministry of health and family Welfare, 2017.
45. Elizabeth Devos, Noel Dunn. Malaria prophylaxis. [Last update: July 3, 2023] In StatPearls (internet). Treasure Island (FL): StatPearls publishing; 2024 Jan-. Available from: https: // www.ncbi.nlm.nih.gov/books/NBK551639.

Review article

Renal Stone Disease – A Circle of Influence for the Nephrologists

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Summary:

Recurrent or long-standing renal stone disease is one of the top five causes of chronic kidney disease and ESRD. The prevalence increases with obesity, insulin resistance, and type 2 DM (1). Highest incidence is found in the third and fourth decades of life. Men suffer more than women. The risk for CKD from renal stone disease is greater in women below 50 years. Optimum management should cover a multidisciplinary approach by nephrologists, urologists and dieticians are necessary. Medical management of pain, infection and underlying etiology, lithotripsy, different types of surgical interventions, dietary advices and life style modification all are important for holistic management. Drinking plenty plain water, fewer intakes of animal protein and avoiding unnecessary calcium containing medication is the mainspring of prophylactic management of renal stone disease.

Key words: Renal stone disease, chronic kidney disease, calcium oxalate, multidisciplinary approach.

Introduction:

There are two professional circles for the physicians, one is circle of concern (CC) and another is circle of influence (CI). Circle of concern covers the issues of knowledge only that a person cannot change, like time and climate. Circle of influence covers those issues one can change, like life style modification, prevention and management of diseases. Renal stone disease is a circle of influence for the nephrologists. In the next few pages, we will try to prove it. The prevalence of renal stone disease increases day by day, especially with obesity, insulin resistance, and type 2 DM (1). Highest incidence is found in the third and fourth decades of life. Men suffer more than women (2). The increased incidence rates may be due to hot climate, and greater sunlight exposure with heavy sweating and concentrated urine (3). Kidney stones are associated with chronic kidney disease (CKD), coronary heart disease with greater aortic calcification, osteoporosis and higher risk of bone fracture (4). The risk for CKD from renal stone disease is greater in women below 50 years (5).

Pathogenesis:

Stones occur in urine that is supersaturated with the ionic components of the stone. Supersaturation depends on the product of the free ion activities, which can be affected by the concentration of crystals, urine P^H and presence of inhibitors. These inhibitors (e.g., citrate) may result in a decrease in free ion activity even with higher total concentration. Several genetic polymorphisms have been implicated in the pathogenesis of calcium stones. They include genes regulating calcium and phosphate reabsorption in tubules, genes preventing calcium salt precipitation, and genes for aquaporins (6,7).

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Clinical Manifestations

Pain and hematuria are most common symptoms. Six presentations of renal stone disease:

1. Pain -- loin pain, flank pain, fixed renal or lumbar pain, ureteric colic, dysuria.
2. Hematuria—gross or microscopic
3. Urinary tract infection --recurrent, chronic infection, pyelonephritis.
4. Asymptomatic—Microcopic hematuria, proteinuria, sterile pyuria.
5. Interrupted urinary stream or anuria by stone.
6. Acute kidney injury (AKI): If stones cause bilateral obstruction or unilateral obstruction in a single functing kidney.

Renal pain

The classic manifestation is ureteric colic. Sudden severe flank or loin pain is of abrupt onset and intensifies over time, resolves only with stone passage or removal. The pain may radiate anteriorly along the abdomen and inferiorly to the groin, testicles, or labia majora as the stone moves toward the ureterovesical junction. Gross hematuria, urinary urgency, frequency, nausea, and vomiting may occur. Stones <5 mm usually pass spontaneously with hydration, but larger stones may require urologic intervention (Fig 1) (8).

Fig 1: This gentleman presented with left loin pain with radiation to groin

Ureteric colic may also occur with the passage of clots from hematuria (clot colic) or necrosed papillae. Renal stone also may provoke poorly localized pain to the kidney with wide differential diagnoses. Staghorn calculi may be asymptomatic and discovered during the investigation for unrelated abdominal pain or musculoskeletal symptoms. Obstructive uropathy caused by calculi also may be painless. Therefore, stone disease always should be considered in the differential diagnosis of unexplained kidney failure. The finding of a stone on radiologic examination does not exclude the non-renal cause of pain.

Clinical evaluation of stone disease

Basic Evaluation:

Stone history

- Number of stones formed
- Frequency of stone formation Age at first onset: Stones that develop at a young age may be caused by cystinuria or primary hyperoxaluria.
- Size of stones passed or still present: Large staghorn calculi do not pass spontaneously, recur despite frequent surgical intervention and more consistent with struvite stones. Kidney involved (left, right, or both). If stones recur frequently in a single kidney, a congenital abnormality in that kidney should be excluded, such as megacalyx or medullary sponge kidney.
- Stone type, if known
- Need for urologic intervention such as ESWL or PCNL.
- Response to intervention. Cystine stones do not fragment well with lithotripsy.

- Association of stones with urinary tract infections

Family history

- Family history of stone disease is important in familial hypercalciuria cystine stones and nephrocalcinosis. (9)

Occupational history:

- Residence (e.g., Middle East).
- Occupation and lifestyle: Those who engage in vigorous physical activities may not rehydrate adequately, producing excessively concentrated urine and renal stone diseases.

Fluid intake and diet:

- The patient should be asked about sodium-containing foods, as well as quantities of calcium, animal protein, purine, and oxalate.
- Many patients are erroneously instructed to eliminate all calcium from their diet, a suggestion that increases the risk of stone formation.
- Sugar rich soda appears to be associated with a greater risk for stone formation.
- Consumption of coffee and tea appears to be associated with a lower risk. (10)

Medications:

- Loop diuretics, corticosteroids, vitamin D and calcium tablets may cause calciuria and calcium stone formation.
- Acetazolamide and topiramate cause metabolic acidosis, lower urine citrate and increase calcium phosphate stone formation.
- Salicylates may predispose to uric acid stone formation.

Past medical history:

- Any disease that can lead to hypercalcemia including malignancy, hyperparathyroidism, and sarcoidosis) can result in hypercalciuria and increase the risk for calcium stone formation.

- A number of gastrointestinal disorders with malabsorption syndrome (e.g., Crohns' disease and celiac disease) can result in calcium oxalate stone formation from high oxalate in blood and urine and dehydration.

- Uric acid stones often occur in patients with a history of gout and insulin resistance. (11)

Physical examination

- Evidence of systemic causes (e.g., tophi in uric acid stone)
- Podagra
- Obesity: Central obesity is associated with metabolic syndrome and uric acid stones.
- Paraplegic patients with a chronic indwelling bladder catheter may have chronic UTI and struvite stones.

Laboratory data

- **Urinalysis:**
  - Examination of the urine may reveal red blood cells along with characteristic crystals. The high specific gravity will confirm inadequate fluid intake in many patients.
  - Urine is acidic in patients with uric acid and calcium oxalate stones.
  - Urine is generally alkaline in patients with struvite and calcium phosphate stones.

- Bacteriuria with urine pH greater than 7.0 suggests struvite stones.

- **Urine culture:**
  Urine should be cultured. As many urine bacteria produce urease even when bacterial colony counts are low, the microbiology laboratory should be instructed to type the organism even if there are fewer than 10^5 colony-forming units/ml.

- **Blood chemistry:**
- Creatinine, sodium, potassium, chloride, bicarbonate, calcium, phosphorus, uric acid.
- A low potassium or bicarbonate level may indicate renal tubular acidosis with hypocitraturia.
- Intact parathyroid hormone level: if calcium elevated or at the upper limit of normal especially if the serum phosphorus is low.
- **Stone analysis:**
  Chemical analysis of stone may help to find out the metabolic abnormality and to the guide treatment strategies.
- **Abdominal radiograph:**
  Plain radiography of the kidneys, ureters, and bladder (KUB) may reveal calcium, cystine, or struvite stones (Fig 2). Uric acid and xanthine calculi are radiolucent and will not be visible on plain films.

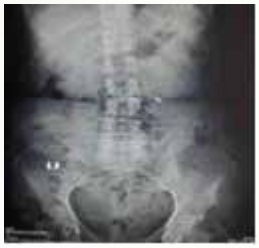

Fig 2: X-ray KUB showing left ureteric stone

- **Ultrasound (generally recommended) (Fig 3):**
  Kidney ultrasound does not expose patients to ionizing radiation and is less expensive. Ultrasonography is the first-line imagining modality for pregnant women and patients below 14 years. The combination of ultrasound and X-ray KUB is more sensitive in detecting stones than either test alone, with minimizing radiation.

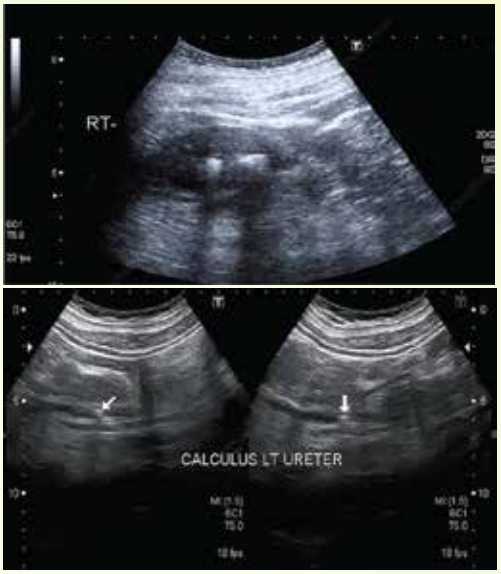

Fig 3: Ultrasonography showing stone in kidney and left ureter.

- **Non-contrast computed tomography (Fig 4):**
  CT urography has replaced IVU, because it is more sensitive and specific, and avoids the need for contrast. Results from CT urography are available in minutes in the emergency setting. But CT imaging is not free from disadvantages: radiation of CT is nearly three times more than conventional IVU, more expensive and is associated with more incidental but clinically insignificant findings. CT urography should be avoided in children and pregnant women (12).

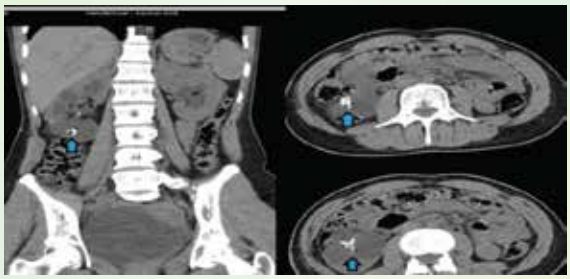

Fig 4: CT scan KUB showing stone in right kidney.

Complete Evaluation

A complete evaluation should be arranged for patients with multiple stones, metabolically active stones, non-calcium containing stones, in all children (13). The complete evaluation should include 24-hour urine volume and the quantity of calcium, phosphorus, oxalate, uric acid, sodium, citrate, and creatinine excreted in a 24-hour urine (Table 1)**.** Patients should stop taking any vitamin C for at least 5 days before the urine collection because it may interfere with the assay.

Table 1: Optimal 24-hour urine values in recurrent renal stone disease

24-Hour urine values	Men	Women
Urine volume	2 to 2.5 L	2 to 2.5 L
Calcium	<4 mg/Kg (0.1 mmol/Kg)// <300 mg	<250 mg
Oxalate	<40 mg	Same
Uric acid	<800 mg	<750 mg
Sodium	<2000 mg	Same
Phosphorus	<1100 mg	Same
Citrate	>320 mg	Same
Creatinine (as evidence of complete collection of urine specimen)	>15 mg/Kg	>10 mg/Kg

Medical Management

Modifications in diet and increased fluid intake decrease in stone recurrence. The non-pharmacologic measures are: Increase fluid intake for daily UO >2.5L/day. Restriction of dietary sodium, which leads to a reduction of urine calcium excretion. Restriction of animal protein leads to a reduction of urine calcium and uric acid excretion and an increase in excretion of the calcification inhibitor citrate. Ingestion of an appropriate amount of dietary calcium, which will bind oxalate in the intestine, preventing its absorption. Dietary calcium restriction is not beneficial and can actually increase the rate of stone formation and can promote osteopenia (14).

Fluid intake: Urine volume 2 to 2.5 L daily reduces the incidence of stones. Urine should not appear dark and concentrated, rather clear. Drink a large glass of water at specific times during the day. Keep a large bottle of water at the workplace and sip from it regularly. Drink two full glasses of water at each meal (one before, one after). Drink before bedtime. Aim to provoke nocturia at least once per night. Patients should avoid sugar-containing beverages which may lead to stone formation. (15)

Salt intake

More urine sodium excretion results in more urine calcium excretion. Therefore, less dietary salt intake is associated with less urine calcium excretion. Patients should be instructed to limit daily sodium intake to a maximum of 2 gram. Educate patients to understand salt content labeling on foods.

Dietary protein

Increased animal protein ingestion increases the frequency of kidney stone formation. Aim is 0.8–1.0g/kg/day animal protein (meat, poultry, fish, eggs, cheese, yogurt), and advise for non-animal protein substitutes (lentils, peas, kidney beans, butter beans, baked beans). The metabolic acidosis from excess protein ingestion causes calcium release from bone and a higher calciuria. Amino acids make urinary calcium ions less soluble.(16) Acidosis leads to a decrease in citrate excretion in urine. Acidic urine with increased uric acid excretion from animal protein results in uric acid stone formation. Such patients should consume less amount of protein and fructose.

Dietary calcium

Dietary calcium reduces renal stone formation due to intestinal binding of ingested oxalate and preventing oxalate absorption (17). The calcium tablets result in transient hypercalciuria and may not be safe. Women taking calcium tablets also may be at higher risk for vascular calcification, cardiovascular disease and death (18). Higher-calcium diet results in greater fall in urinary oxalate in the men on low-sodium and low–animal protein diet (19). Appropriate calcium intake, best derived from dairy products is recommended, as stone formation is reduced with normal calcium intake and there is a risk for bone demineralization and osteoporosis with low-calcium diet (9, 20).

Vitamin D

No association has been found between vitamin D supplementation and stone formation in hypercalciuric patients. Thus, vitamin D therapy should not be withheld in patients with vitamin D deficiency (25-(OH) D levels <20 ng/ml) on the basis of kidney stone disease (21).

Specific types of renal stone

There are four important types of renal stone. The majority of stones are calcium oxalate and calcium phosphate (70 to 80%). Magnesium ammonium phosphate stones cover 10% to 15% of stones formed. Nearly 10% are uric acid stones. Cystine stones are 1% to 2% only. In the Middle East, about 75% of stones are composed of uric acid (11).

Calcium Stones:

Most stones are composed of calcium oxalate with or without calcium phosphate or uric acid (22). Calcium-based stones most often develop from hypercalciuria. Other causes of calcium stones are hyperoxaluria, hyperuricosuria, hypocitraturia, renal tubular acidosis, medications, and congenital abnormalities of the genitourinary tract.

Hypercalciuria:

Some patients excrete more calcium than they consume. This calcium must be derived from the bones with higher risk of osteopenia. The cause of higher calcium transport is increased number of biologically active vitamin D receptors (23). Metabolic disorders with higher levels of serum calcium, parathyroid hormone, or 1,25-dihydroxyvitamin D result in hypercalciuria.

Treatment:

Thiazide diuretics increase calcium reabsorption at distal renal tubules and reduce urinary calcium. Once daily 25 to 50 mg chlorthalidone may be the drug of choice. Indapamide 1.25 to 2.5 mg/day may be preferred for patients with cardiac risk factors or elevated serum lipids. Patients should be

instructed to increase their dietary potassium intake. Serum potassium level should be monitored 7 to 10 days later. If serum potassium is low, oral potassium supplementation should be initiated. Potassium citrate (20 to 40 mmol = 2 to 4 tablets daily) is generally preferred over potassium chloride (KCl). Potassium citrate may increase the serum bicarbonate level and urinary pH above normal and, can promote calcium phosphate stone formation. Potassium chloride may be used in calcium phosphate stones. The 24-hour urine calcium, sodium, and citrate should be rechecked after several weeks. If the calcium excretion remains elevated, the thiazide dose should be increased. If the sodium excretion remains high (>100 mEq/day), patients should be encouraged to limit their sodium intake further. If serum potassium remains low despite supplementation, addition of a potassium-sparing diuretic may be required. Amiloride with a starting dose 5 mg/day is the preferred treatment for thiazide-induced hypokalemia (6).

Hyperoxaluria

Normally urinary oxalate excretion is < 40 mg/24 h (0.45 mmol/24 h). High urinary oxalate results from dietary oxaluria due to excessive dietary intake (e.g. high vitamin C intake), enteric oxaluria due to gastrointestinal malabsorption syndrome with colonic absorption (e.g. tropical sprue, chronic pancreatitis, biliary obstructon, celiac disease), or primary hyperoxaluria from an inherited enzyme enzyme defects in the liver. (24).

In primary hyperoxaluria, huge oxalate production leads to widespread calcium oxalate deposition throughout the body resulting in **congestive cardiac failure** (dyspnoea, edema), **bone marrow failure** (pancytopenia), and **renal failure**.

Treatment of dietary and enteric hyperoxaluria:

Treatment of dietary oxaluria consists of dietary oxalate restriction. The low-oxalate diet and mealtime calcium carbonate for dietary oxaluria is helpful. Calcium-containing diet binds intestinal oxalate and prevent its absorption. To evaluate the success of dietary restriction, 24-hour urine oxalate can be measured.

Specific therapy for the malabsorption syndrome is the first-line treatment for enteric hyperoxaluria, such as a gluten free diet for sprue. For steatorrhea, a low-fat diet, cholestyramine, and medium-chain triglycerides (e.g. cow's milk, goat's milk, butter and cheese, dried coconut, coconut oil, palm oil, etc.) may reduce fat malabsorption and oxalate absorption.

The diarrhea may result in low urine volumes, hypokalemia, hypocitraturia, and hypomagnesuria. Patients should increase their fluid and potassium citrate intake. Magnesium is a urinary stone inhibitor and can be given as magnesium oxide 400 mg every 12 hours.

Treatment of primary hyperoxaluria (PH)

Primary hyperoxaluria type 1 (PH1) is cured only with liver transplantation to replace the defective hepatic enzyme. Oxalate production can be reduced by pyridoxine (vitamin B6) in doses ranging from 2.5 to 15 mg/kg/day (e.g. Tab. Pyridoxine 20 mg 2+2+2). Calcium and oxalate can be made more soluble in the urine

with citrate and magnesium. Oxalate is poorly excreted in CKD and very poorly removed by dialysis. Kidney transplantation improves oxalate excretion and systemic oxalosis.(8)

Lumasiran injection is used subcutaneously to treat primary hyperoxaluria to reduce oxalate production in the liver and to lower oxalic acid in the urine and blood. This molecule is designed for specific uptake into liver, the main site of oxalate overproduction. Thus lumasiran reduces the risk of oxalate stone formation, kidney failure and systemic oxalosis in both children and adults. (25)

Hypocitraturia

Low citrate in urine favors stone formation, which may be found with excessive protein intake, hypokalemia, hypomagnesemia, metabolic acidosis, infections, androgens, starvation, and acetazolamide.

Treatment should cover underlying pathology and potassium citrate supplementation. Potassium citrate 10 to 20 mmol (1 to 2 tablets) two to three times daily is required. Serum potassium should be monitored for risk of hyperkalemia (8).

Distal Renal Tubular Acidosis (dRTA): There is impaired distal tubular excretion of H^+ with normal anion gap metabolic acidosis and alkaline urine. The acidosis causes calcium and phosphate to be released from bone with increased loss in urine (16). The acidosis also increases citrate reabsorption by the proximal tubule with lower urinary citrate (<100 mg/24 h). Calcium precipitates with phosphorus in the alkaline tubular fluid leading to nephrocalcinosis. The metabolic acidosis and hypocitraturia should be treated with a combination of sodium bicarbonate and/or potassium citrate. If urinary citrate is below 150 mg/day, dose of potassium citrate is 60 mg/day orally (2+2+2). If urinary citrate is above 150 mg/day, dose potassium citrate is 30 mg/day orally (1+1+1). Maintain urinary P^H 6 to 7.

Hyperuricosuria

Calcium oxalate crystals often precipitate around uric acid crystals. Hyperuricosuria contributes to 10% to 15% of calcium stone disease. Therapy consists of increased fluid intake and reduced dietary purine intake. If uric acid remains elevated, allopurinol or febuxostat or dotinurad should be initiated (23).

Uric Acid Stones

Uric acid stones are radiolucent and poorly visible on plain radiographs. They are detectable on ultrasound and CT and as filling defects on IVU. Factors associated with uric acid stone formation:

1. Low Urine pH (≤5.5): High animal protein diet, diarrhea, insulin resistance (high BMI, metabolic syndrome, T2DM). The urinary acidosis is a result of impaired ammoniagenesis. Uric acid is poorly soluble at pH below 5.5. Solubility increases with urine alkalinity at urine pH 6.5 or more (11, 26).

2. Low Urine Volume: Inadequate fluid intake, excessive extra renal fluid losses.

3. Hyperuricosuria: Excessive dietary purine or protein intake, cellular breakdown (tumor lysis syndrome, myeloproliferative disorders, hemolytic anemia), gout, uricosuric medications (Salicylates), certain inborn errors of metabolism, and excessive fructose intake.

Treatment

Alkalinization of urine can prevent uric acid stone formation as well as result in stone dissolution. To raise urine pH, potassium citrate is recommended. Sodium bicarbonate also alkalinizes the urine and increases uric acid solubility, but sodium serves as a nidus for calcium oxalate precipitation. Potassium citrate 30 to 60 mmol/day (3 to 6 tablets daily) in divided doses is given, to achieve a urine pH of 6.5 to 7.0 with dipsticks. If urine pH remains acidic with potassium citrate >100 mmol/day or patient develops hyperkalemia, acetazolamide (carbonic anhydrase inhibitor) may be added to make urine alkaline. Urine pH above 7.0 is a risk factor for calcium phosphate precipitation. A low-purine and low–animal protein diet is also useful in raising urinary pH and decreasing uric acid excretion. If uric acid excretion remains high, febuxostat should be prescribed, 40 to 80 mg/day.

Reduce dietary purine intake: Meat (particularly liver, kidney, heart), crab, oily fish, shrimp, certain vegetables (including cauliflower, peas, spinach), mushrooms, lentils, kidney beans, beer, etc.

Struvite Stone

Struvite stones are sepsis-related stones. Struvite is a mineral that's produced by bacteria in the urinary tract, more often in women because of an increased risk of UTI. Struvite stones are composed of magnesium ammonium phosphate and calcium carbonate. The stones grow rapidly to a large size, can reduce GFR in the affected kidney, are associated with co-morbid condition (e.g. urosepsis), and are difficult to eradicate. Most large calculi penetrate renal calyx. Their formation requires the presence of urease-producing bacteria in the urine, e.g. Proteus, Haemophilus, Yersinia, Staphylococcus epidermidis, Pseudomonas, Klebsiella, Citrobacter, Ureaplasma. If there is a strong suspicion for struvite stones but no organism is detected in the urine, a specific culture should be requested for Ureaplasma urealyticum (27). Other predisposing factors for struvite stones are indwelling urinary catheters, neurogenic bladders, genitourinary tract anomalies, and spinal cord lesions. An alkaline urine (pH ≥7.0), urine culture of urease-producing bacteria, and large stones suggest the diagnosis of struvite nephrolithiasis (27).

Treatment

Antibiotic therapy is important to reduce further stone growth and for stone prevention. Bacteria in the stone gaps will continue to grow unless chronic antibiotic suppression is maintained or the calculi are completely eradicated. Stones smaller than 2 cm may respond well to ESWL. But larger stones need percutaneous nephrolithotomy (PCNL), with or without ESWL. Any stone fragments should be cultured for specific antibiotics. Once the urine is sterile, usually after 2 weeks, the dose is halved. Monthly urine cultures should be obtained, and if they remain sterile for 3 consecutive months, antibiotics may be discontinued. (28)

Cystine Stones

Cystine stones account for about 1 to 2% of kidney stone in adults and 6% to 8% in children. Cystinuria is a tubular defect in amino acid transport, resulting in increased cystine, ornithine, lysine, and arginine excretion. The mode of inheritance may be AR or AD. The stone disease is usually

clinically manifested by the second and third decades of life. Because of the high sulfur content of the cystine molecule, the stones are apparent on plain radiographs and often will manifest as multiple bilateral stones or as staghorn calculi. Normal cystine excretion is 30 to 50 mg per day. Cystinurics excrete higher amount of cystine per day (>250 mg/day).

Treatment: It is impractical to reduce intake, as cystine and methionine are essential amino acids. Dietary restriction of animal protein is helpful. Increasing urine volume up to 4L is necessary to ensure the solubility. A low-sodium diet may reduce urine cystine excretion (29).

Potassium citrate or sodium bicarbonate increase urinary P^H between 7 to 7.5 and increase the solubility of cystine. D-penicillamine binds cystine and reduce urinary supersaturation. The angiotensin-converting enzyme inhibitor captopril may be effective to make cystine more soluble.

Conservative (Nonsurgical) Management:

Stones with a diameter of 4 mm pass. spontaneously in up to 80% of patients. Stones with a diameter of more than 7 mm, the chance of spontaneous passage is low (30).The location is also important; up to 70% of distal ureteral, 45% of midureteral and 25% of proximal ureteral stones pass spontaneously. Intervention is recommended with persistent pain for >72 hours despite adequate analgesia, persistent obstruction with risk for impaired kidney function, bilateral obstruction, or associated urinary tract sepsis.

Medical expulsive therapy (MET)

MET with tamsulosin 400 µg once daily or nifedipine (calcium channel blocker) 30 mg once daily, is sometimes used to aid stone passage, particularly for distal ureteral stones. MET is beneficial for management of distal ureteral stones less than 10 mm and is still recommended in most guidelines.(31, 32, 33, 34, 35).Chemolysis or dissolving of stone is only effective for uric acid stones and some drug-induced calculi, with **oral potassium citrate**, or with **sodium bicarbonate solution** instilled directly into the urinary tract via PCN tube.

Acute Surgical Intervention

If the patient is well enough for general anesthesia, ureteroscopic stone destruction using laser lithotripsy can be attempted. Alternatively, a D-J ureteral stent can be inserted to relieve obstruction until definitive treatment is performed (Fig 5).

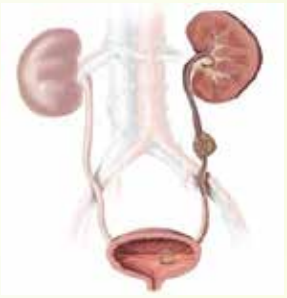

Fig 5: A left sided D-J ureteral stent passed through an ureteric obstruction with stone.

Acute ESWL is increasingly being used for ureteral stones in stable patients without superimposed infection. However, in the setting of UTI resulting from an obstructing stone, decompression of the urinary tract and free drainage of urine are more important. There is little difference in the outcomes

between an antegrade (i.e., PCN) or retrograde (i.e., D-J stent) approach (36). However, PCN is generally the preferred option because it can be performed with local anesthesia with less chance of bacteremia.

Extracorporeal Shock Wave Lithotripsy (ESWL):

ESWL is the **first-line treatment** for more than 75% of stone patients that require an intervention. During ESWL, shock wave is delivered to a stone under fluoroscopic and/or ultrasound guidance (fig 6). Treatment can be repeated at intervals of 10 to 14 days. Stones up to 20 mm in size can be treated effectively. However, ESWL is operator dependent.

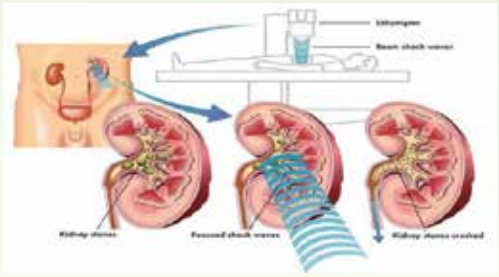

Fig 6: Extracorporeal Shock Wave Lithotripsy (ESWL).

Outcome is influenced by the size, composition, and location of the stone and the type of lithotripter used. Cystine and calcium oxalate stones are especially resistant. Targeting of the stone is difficult in obesity and skeletal deformity patients. ESWL is contraindicated in patients with aortic or renal artery aneurysm, uncontrolled UTI, coagulation disorders/receiving anticoagulation treatment, pregnant persons, and obstruction distal to the stone being treated. A D-J ureteral stent is sometimes placed before or after ESWL treatment to prevent stone fragments from obstructing the distal ureter. Other acute complications of ESWL include hemorrhage, infection, and injury to adjacent organs.

Percutaneous Nephrolithotomy (PCNL)

During PCNL, a tract through the kidney parenchyma is made between the skin and the collecting system of the kidney. Stone fragmentation is undertaken by ultrasound, pneumatic, or laser devices (fig 7).

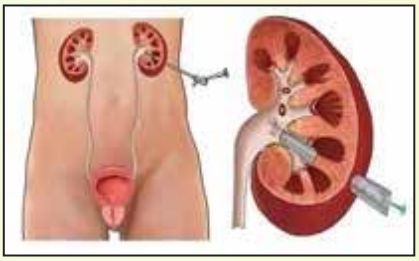

Fig 7: Percutaneous Nephrolithotomy (PCNL)

An RCT has shown that for lower pole stones greater than 10 mm, PCNL has much better clearance rates than ESWL (92% vs. 23%) (39). Complications include hemorrhage, sepsis; fluid overload; injury to spleen, pleura, or colon; and extravasation (37).

Open Stone Surgery

Approximately 2% of stone patients are treated with open surgery, mainly with difficult anatomical situation. Other indications include complex stone burden, pelviureteral junction obstruction, and stones within a nonfunctioning kidney. Here nephrectomy is more appropriate.

Ureteroscopy (URS)

Flexible ureteroscopes allows access for the ureter, renal pelvis and calyces (fig 8).

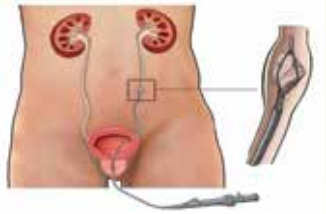

Fig 8: Ureteric stone removal with ureteroscope and basket.

Stone fragmentation can be achieved by laser which is equally effective for all types of stones with less tissue injury. Success rate is nearly 80%. Advances in laser technology now enable stones to be reduced to dust-like particles, reducing the need for graspers and baskets and hence reducing complications. For lower pole kidney stones, flexible ureteroscopes can access the lower pole to facilitate treatment, and the stone-free rate in comparative studies is similar to that of ESWL (38, 39). Complications of ureteroscopy include mucosal injury, perforation, hematuria, infection and stricture. In the event of failed stone clearance after ureteroscopy, PCNL is commonly used next and is likely to remain an essential treatment for lower pole stones.

Management of Staghorn Calculus:

Usually a staghorn calculus is managed by intervention. Patient age and GFR heavily influence treatment decision making. The primary treatment option for a patient with preserved kidney function is PCNL. The treatment option for a staghorn calculus in a nonfunctioning kidney is partial or total nephrectomy. For total stone clearance, ESWL or ureteroscopy can be used as an adjunct to PCNL. This is called multimodal approach. Very rarely, open surgical removal of the stone may be indicated.

Stones in Transplanted Kidney:

Single functioning transplant kidney makes the management more challenging. Retrograde access to the ureter and kidney is more difficult due to pelvic location. Prophylactic stenting, ureteroscopy, and PCNL are preferred. ESWL may be difficult due to mistargeting of stone. Open surgery may be indicated in few cases. Early active intervention is important.

Reference:

1. Chewcharat A, Curhan G. Trends in the prevalence of kidney stones in the United States from 2007 to 2016. Urolithiasis. 2021;49(1):27–39.
2. Scales Jr CD, Smith AC, Hanley JM, et al. Prevalence of kidney stones in the United States. Eur Urol. 2012;62(1):160–165.
3. Moe OW. Kidney stones: pathophysiology and medical management. Lancet. 2006;367(9507):333–344.
4. Shavit L, Girfoglio D, Vijay V, et al. Vascular calcifcation and bone mineral density in recurrent kidney stone formers. CJASN. 2015;10(2):278–285.
5. Alexander RT, Hemmelgarn BR, Wiebe N, et al. Kidney stones and kidney function loss: a cohort study. BMJ. 2012;345:e5287.
6. Bushinsky DA. Nephrolithiasis. In: Goldman S, ed. Goldman-Cecil, Medicine. Elsevier; 2020:776–781.
7. Arcidiacono T, Mingione A, Macrina L, et al. Idiopathic calcium nephrolithiasis: a review of pathogenic mechanisms in the light of genetic studies. Am J Nephrol. 2014;40(6):499–506.
8. Coe FL, Evan A, Worcester E. Kidney stone disease. J Clin Invest. 2005;115(10):2598–2608.
9. Moe OW, Bushinsky DA. Genetic hypercalciuria: a major risk factor in kidney stones. In: Thakker RVW,MP, Eisman JA, Igarashi T, eds. Genetics of Bone Biology and Skeletal Disease. Academic Press; 2013:585–604.
10. Ferraro PM, Taylor EN, Gambaro G, et al. Soda and other beverages and the risk of kidney stones. Clin J Am Soc Nephrol. 2013;8(8):1389–1395.
11. Maalouf NM, Cameron MA, Moe OW, et al. Novel insights into the pathogenesis of uric acid nephrolithiasis. Curr Opin Nephrol Hyper. 2004;13(2):181–189.
12. Brisbane W, Bailey MR, Sorensen MD. An overview of kidney stone imaging techniques. Nat Rev Urol. 2016;13(11):654–662.
13. Pozdzik A, Maalouf N, Letavernier E, et al. Meeting report of the Symposium on kidney stones and mineral metabolism: calcium kidney stones in 2017. J Nephrol. 2019;32(5):681–698.\

14. Bushinsky DA. Kidney stones. In: Malmed P, Larsen and Kronenberg, eds. William's Textbook of Endocrinology. 14th ed. Philadelphia: Elsevier; 2019:689–703.
15. Ferraro PM, Taylor EN, Gambaro G, et al. Soda and other beverages and the risk of kidney stones. Clin J Am Soc Nephrol. 2013;8(8):1389–1395.
16. Bushinsky DA, Kriefer NS. Effect of acid on bone. Kidney Int. 2022;101:1160–1170.
17. Jackson RD, LaCroix AZ, Gass M, et al. Calcium plus vitamin D supplementation and the risk of fractures. New Engl J Med. 2006;354(7):669–683.
18. Bolland MJ, Avenell A, Baron JA, et al. Effect of calcium supplements on risk of myocardial infarction and cardiovascular events: meta-analysis. BMJ. 2010;341.
19. Borghi L, Schianchi T, Meschi T, et al. Comparison of two diets for the prevention of recurrent stones in idiopathic hypercalciuria. New Engl J Med. 2002;346(2):77–84.
20. Michaelsson K, Melhus H, Warensjo E, et al. Long term calcium intake and rates of all cause and cardiovascular mortality: community based prospective longitudinal cohort study. BMJ. 2013;346.
21. Leaf DE, Korets R, Taylor EN, et al. Effect of vitamin D repletion on urinary calcium excretion among kidney stone formers. Clin J Am Soc Nephrol. 2012;7(5):829–834.
22. Bushinsky DA, Coe FL, Moe OW. Nephrolithiasis BM B. In: The Kidney. Philadelphia: W.B. Saunders; 2012:1455–1507.
23. Frick KK, Asplin JR, Favus MJ, et al. Increased biological response to 1,25(OH)(2)D-3 in genetic hypercalciuric stone-forming rats. Am J Physiol-Renal. 2013;304(6):F718–F726.
24. Asplin JR. Hyperoxaluric calcium nephrolithiasis. Endocrin Metab Clin. 2002;31(4):927.
25. Garrelfs SF, Frishberg Y, Hulton SA, et al. Lumasiran, an RNAi therapeutic for primary hyperoxaluria type 1. N Engl J Med. 2021;384(13):1216–1226.
26. Cameron MA, Maalouf NM, Adams-Huet B, et al. Urine composition in type 2 diabetes: predisposition to uric acid nephrolithiasis. J Am Soc Nephrol. 2006;17(5):1422–1428.
27. Rodman JS. Struvite stones. Nephron. 1999;81:50–59.
28. Flannigan R, Choy WH, Chew B, et al. Renal struvite stones-pathogenesis, microbiology, and management strategies. Nat Rev Urol. 2014;11(6):333–341.
29. Goldfarb DS, Coe FL, Asplin JR. Urinary cystine excretion and capacity in patients with cystinuria. Kidney Int. 2006;69(6):1041–1047.
30. Shah TT, Gao C, Peters M, et al. British Urology Researchers in Surgical Training (BURST) Collaborative MIMIC Study Group. Factors associated with spontaneous stone passage in a contemporary cohort of patients presenting with acute ureteric colic: results from the Multi-centre cohort study evaluating the role of Inflammatory Markers in patients presenting with acute ureteric Colic (MIMIC) study. BJU Int. 2019;124(3):504–513.
31. Assimos D, Krambeck A, Miller N, et al. American Urological Association/ Endourological Society Guideline: Surgical Management of Stones; 2016. https://www.auanet.org/guidelines/kidney-stones-surgical-management guideline.
32. Turk C (Chair), Neisius A, Petrik A, et al. European Association of Urology Guidelines on Urolithiasis; 2020. www.uroweb.org/guideline/urolithiasis.
33. National Institute for Health and Care Excellence. Renal and Ureteric Stones: Assessment and Management; 2019. NICE guideline [NG118] https://www.nice.org.uk/guidance/ng118.
34. Campschroer T, Zhu Y, Duijvesz D, et al. Alpha-blockers as medical expulsive therapy for ureteral stones. Cochrane Database Syst Rev. 2014;(4):CD008509.
35. Barrionuevo Moreno P, Asi N, Benkhadra K, et al. Surgical Management of Kidney Stones: A Systematic Review. Mayo clinic; 2015.
36. Pearle MS, Pierce HL, Miller GL, et al. Optimal method of urgent decompression of the collecting system for obstruction and infection due to ureteral calculi. J Urol. 1998;160(4):1260–1264.
37. Webb DR, Fitzpatrick JM. Percutaneous nephrolithotripsy: a functional and morphological study. J Urol. 1985;134:587–591.
38. Galvin DJ, Pearle MS. The contemporary management of renal and ureteric calculi. BJU Int. 2006;98:1283–1288.
39. Pearle MS, Lingeman JE, Leveillee R, et al. Prospective, randomized trial comparing shock wave lithotripsy and ureteroscopy for lower pole caliceal calculi 1 cm or less. J Urol. 2005;173:2005. –2009.

Case Report

Varicella Zoster Virus and Cytomegalovirus Coinfection in a Live Related Kidney Transplant Recipient: A Case Report

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Abstract

Infections are common complications in kidney transplant recipients owing to the lifelong immunosuppression. Cytomegalovirus (CMV) and Varicella Zoster Virus (VZV) infections are quite common in the post-transplant period. Coinfection with both however has been reported only once. The immunomodulatory effect of CMV makes their interaction with other organisms like VZV potentially sinister. This is a case of a young woman who developed coinfection with HZV and CMV in the first month following a live related kidney transplantation from her mother.

Key words: Varicella Zoster Virus, Cytomegalovirus, Kidney Transplant Recipient

Introduction

Kidney transplant is the best long-term treatment option for end stage kidney disease (ESKD) patients at the moment. It restores the entire spectrum of kidney function and provides a better quality of life than any other modality of renal replacement therapy (RRT)(1). But this comes at the cost of lifelong immunosuppressive therapy in order to ensure graft survival, making infection the third commonest cause of death with a functioning graft following the first year of kidney transplantation(2). Although infection and infection related mortality rates are lower in kidney transplant recipients compared to other solid organ transplants, it remains a significant source of mortality and morbidity (3). Infection pattern and organisms vary with periods after transplant. Opportunistic infections predominate in the first six months, especially viral infections. Organisms from the Herpesviridae family are among the common pathogens.

Varicella Zoster virus (VZV) and Cytomegalovirus (CMV) are both members of the Herpesviridae. Compared to other solid organ transplants, CMV infection occurs less frequently following kidney transplants. Surprisingly, VZV infection occurs more frequently (4). Their infection rates range from 8-32% and 4-12%(5). Simultaneous infections with multiple viruses are much less common. There have been few cases of CMV, BK Virus and Human Herpes Virus (HHV) 6 and 7 coinfection(6-10). But there has been only one reported case ofCMVnephritis and VZV coinfection to our knowledge(11).

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Here we report a case of a VZV and CMV coinfection in a 32-year-old female in the first month following a live related kidney transplantation.

Case Report

A 32-year-old woman, with a presumptive diagnosis of glomerulonephritis, hypertension and chronic kidney (CKD) underwent live-related kidney transplantation from her mother following a period of hemodialysis via arteriovenous fistula for 8 months. There was one haplotype match and T cell cross match was <10%. CMV DNA was undetected in both donor and recipient prior to transplantation. The donor being mother and considering the financial condition of the patient, no depleting or non-depleting induction therapy was not given. Immunosuppression consisted of intravenous (IV) Methylprednisolone 500 mg, 250 mg and 125 mg on 3 consecutive days starting on the day of transplant surgery, followed by oral prednisolone 20 mg/day. This was accompanied by oral Mycophenolate Sodium 1080 mg/day and Tacrolimus 4 mg/day, which was started 2 days before the transplant. During pre-transplant evaluation, she was found to be anti-HCV positive. Liver function tests were normal and HCV RNA was undetected. Therefore, a combination of Sofusbuvir and Velpatasvir was also started immediately prior to transplantation at a prophylactic dose of 400/100 mg/day and continued. CMV or Pneumocystis carinii (PCP) prophylaxis was not started. The surgery was uneventful. Donor had dual renal arteries and single vein of normal course and caliber. The warm ischemic time (WIT) was 37 seconds and the cold ischemic time (CIT) was 58 minutes 25 seconds. The patient had good urine output following the surgery ranging from 4 to 6 liters/day, recovered well clinically and did not need any dialysis. However, the kidney function did not become normal following the surgery, reaching a nadir of 2 mg/dl on the 13thpost-operative day (POD) and rising after that. Tacrolimus trough level was 8.1 ng/ml. Graft biopsy was done and 2 doses of 500 mg IV Methylprednisolone were given, suspecting acute rejection. Unfortunately, the biopsy sample underwent ischemic necrosis due to a complication during storage and tissue processing. She did not consent to a repeat biopsy. She developed repeated asymptomatic urinary tract infections from the 20th POD, which were treated with multiple IV and oral antibiotics. 25 days after transplant, she developed fever, which was low grade with a highest recorded temperature of 101 degrees Fahrenheit. CMV-DNA for polymerase chain reaction (PCR) was sent to rule out CMV infection. 2 days later, she developed pain and vesicular eruptions involving the dermatomal distribution of the ophthalmic division of the trigeminal nerve (V1) on the left. It was not preceded by any other prodromal symptoms. Anti-VZV antibodies and fluid analysis from the blisters were planned, but the patient could not afford the investigations. Since patient had a history of chicken pox in childhood and clinically the lesion was pathognomonic of VZV, treatment was immediately started with oral Acyclovir 2400 mg/day, Acyclovir ointment and Ganciclovir eye gel, along with topical Fusidic acid cream to prevent secondary infections. Temporarily stopping MMF was discussed with the patient along with its pros and cons, but considering the raised Creatinine, she did not want to risk a rejection and decided to continue. A week later, serum CMV DNA result came back positive yielding 300 copies/ml and Acyclovir was replaced with oral Valganciclovir 450

mg/day to address both infections. Serum Creatinine rose to 3.2 mg/dl and total white blood cell count fell to 2×10^9/L. But the patient was clinically improving and with this treatment regimen. Her fever subsided and the skin lesions resolved over a period of 2 weeks. Serum creatinine came down to baseline. Total count also became normal. However, she developed post-herpetic neuralgia, which was managed with oral Pregabalin. Other follow-up investigations were not done due to financial constraints.

Discussion

VZV is a common infection after kidney transplantation. The incidence is about 28 per 1000 person-years (12). The median time of onset ranges from about 6 months to 2 years(13, 14). It can manifest in several ways in kidney transplant recipients – localized involving a dermatome, disseminated cutaneous, visceral etc.(13, 15).Usually, primary infection results in disseminated and reactivation results in dermatomal involvement (16). In our patient it was localized involving the V1 dermatome. Involvement of the facial dermatomes carries the additional risks of complications like Ramsay Hunt Syndrome, which did not occur in our case (13). Several risk factors have been associated with VZV infection following kidney transplantation. Although these vary among studies, increasing age of the recipient, induction therapy with depleting agents, intensification of immunosuppressive therapy suspecting rejection and seronegativity to VZV at the time of transplant are associated with increased risk (12, 17). Intensification of steroid regiment is applicable in our case.

Anti-VZV IgM, Tzanck smear and VZV DNA are all excellent diagnostic tools for confirming VZV infection. But more often than not, feasibility becomes an issue in a resource poor setting like ours. Also, anti-VZV IgM has low sensitivity. With the textbook dermatomal skin lesions, we decided to rely on our clinical judgement and start treatment without any delays(13, 18). VZV infection needs to be treated promptly in renal transplantation patients since complications are common. Some of the complications are hepatitis, pneumonitis, pancreatitis, cerebritis, disseminated intravascular coagulation, post-herpetic neuralgia (PHN) etc. Disseminated infection carries a mortality risk of 34%(13, 15, 19). In our case, being a localized disease, the patient responded well to Acyclovir and did not develop any such complication other than PHN. PHN incidence ranged from around 8 to 28% in other studies(14, 20). Another complication observed in few cases was acute kidney injury (AKI)(21, 22). Although our patient did develop deterioration of kidney function, which later improved upon initiation of therapy, it is difficult to pick VZV infection, CMV infection, rejection or UTI as the underlying cause without a proper biopsy report.

CMV is the commonest viral infection following any solid organ transplant (3).Although our patient did not demonstrate any localizing evidence of CMV infection, CMV DNA detection and reduced WBC count confirmed this diagnosis. Without disseminated VZV infection, no evidence of secondary infection and a resolved UTI, it would also explain the fever. Rather than being another co-infection, CMV may have played a more significant role in the VZV infection. CMV has an immunomodulatory effect. It affects the B cell, T cell, macrophage

and phagocytic function, most notably the T cells. As in our patient, where we observed leukopenia, this can make the patient vulnerable to another infection like VZV(10, 23). The role of ongoing anti-viral prophylaxis for CMV is less clear. Few studies have reported lower risk of VZV infection with ongoing prophylaxis, and few have found no association(12, 20). CMV and VZV both being common infections in kidney transplant patients and with CMV's immunomodulatory effect, we could have expected CMV and VZV co-infection to occur. But although multiple cases of BK virus, HHV 7 and possibly 6 coinfections were reported with CMV, there has been only one reported case of CMV nephritis and coinfection with VZV to our knowledge(6-9, 11).

Conclusion

Infections after kidney transplant is often difficult to diagnose, manage and cure, especially in the immediate post-transplant period. Weighing the pros and cons of altering the immunosuppressive regimen, starting antimicrobials with potential nephrotoxicity is a difficult task and needs to be tailored for individual scenarios. Our case of VZV and CMV coinfection was not any different. Early diagnosis, early start of anti-viral therapy, decision regarding continuing routine immunosuppressives while closely monitoring the patient for signs of dissemination and worsening eventually culminated in a good overall outcome for the patient's graft and her life.

Reference:

1. Sawinski D, Poggio ED. Introduction to Kidney Transplantation: Long-Term Management Challenges. Clin J Am Soc Nephrol. 2021;16(8):1262-3.
2. Ying T, Shi B, Kelly PJ, Pilmore H, Clayton PA, Chadban SJ. Death after Kidney Transplantation: An Analysis by Era and Time Post-Transplant. J Am Soc Nephrol. 2020;31(12):2887-99.
3. van Delden C, Stampf S, Hirsch HH, Manuel O, Meylan P, Cusini A, et al. Burden and Timeline of Infectious Diseases in the First Year After Solid Organ Transplantation in the Swiss Transplant Cohort Study. Clin Infect Dis. 2020;71(7):e159-e69.
4. Gourishankar S, McDermid JC, Jhangri GS, Preiksaitis JK. Herpes zoster infection following solid organ transplantation: incidence, risk factors and outcomes in the current immunosuppressive era. Am J Transplant. 2004;4(1):108-15.
5. Patel R, Paya CV. Infections in solid-organ transplant recipients. Clin Microbiol Rev. 1997;10(1):86-124.
6. Cukuranovic J, Ugrenovic S, Jovanovic I, Visnjic M, Stefanovic V. Viral infection in renal transplant recipients. ScientificWorldJournal. 2012;2012:820621.
7. Tong CY, Bakran A, Williams H, Cheung CY, Peiris JS. Association of human herpesvirus 7 with cytomegalovirus disease in renal transplant recipients. Transplantation. 2000;70(1):213-6.
8. Chapenko S, Folkmane I, Tomsone V, Amerika D, Rozentals R, Murovska M. Co-infection of two beta-herpesviruses (CMV and HHV-7) as an increased risk factor for 'CMV disease' in patients undergoing renal transplantation. Clin Transplant. 2000;14(5):486-92.
9. Kidd IM, Clark DA, Sabin CA, Andrew D, Hassan-Walker AF, Sweny P, et al. Prospective study of human betaherpesviruses after renal transplantation: association of human herpesvirus 7 and cytomegalovirus co-infection with cytomegalovirus disease and increased rejection. Transplantation. 2000;69(11):2400-4.
10. Kotton CN, Fishman JA. Viral infection in the renal transplant recipient. J Am Soc Nephrol. 2005;16(6):1758-74.
11. Visuttichaikit S. CMV NEPHRITIS WITH MULTI-DERMATOMAL HERPES ZOSTER CO-INFECTION IN A KIDNEY TRANSPLANT RECIPIENT: A CASE REPORT AND REVIEW OF THE LITERATURE. The Southeast Asian Journal of Tropical Medicine and Public Health. 2021;52(2).
12. Arness T, Pedersen R, Dierkhising R, Kremers W, Patel R. Varicella zoster virus-associated disease in

adult kidney transplant recipients: incidence and risk-factor analysis. Transpl Infect Dis. 2008;10(4):260-8.
13. Milinkovic M, Jovicic-Pavlovic S, Lausevic M, Durutovic O, Naumovic R. Epidemic varicella zoster virus reactivation in renal transplant recipients: a case report. Transplant Proc. 2015;47(1):146-50.
14. Mustapic Z, Basic-Jukic N, Kes P, Lovcic V, Bubic-Filipi L, Mokos I, et al. Varicella zoster infection in renal transplant recipients: prevalence, complications and outcome. Kidney Blood Press Res. 2011;34(6):382-6.
15. Rommelaere M, Maréchal C, Yombi JC, Goffin E, Kanaan N. Disseminated varicella zoster virus infection in adult renal transplant recipients: outcome and risk factors. Transplant Proc. 2012;44(9):2814-7.
16. Abad CL, Razonable RR. α Herpes Virus Infections Among Renal Transplant Recipients. Semin Nephrol. 2016;36(5):344-50.
17. Pavlopoulou ID, Poulopoulou S, Melexopoulou C, Papazaharia I, Zavos G, Boletis IN. Incidence and risk factors of herpes zoster among adult renal transplant recipients receiving universal antiviral prophylaxis. BMC Infect Dis. 2015;15:285.
18. Devin A, Renoult E, Roger M, Hébert MJ. Herpes Zoster in Kidney Transplant Recipients: Detection of VZV DNA in Blood During the Prodromal Phase. Transplant Direct. 2018;4(6):e351.
19. Fehr T, Bossart W, Wahl C, Binswanger U. Disseminated varicella infection in adult renal allograft recipients: four cases and a review of the literature. Transplantation. 2002;73(4):608-11.
20. Fernández-Ruiz M, Origüen J, Lora D, López-Medrano F, González E, Polanco N, et al. Herpes zoster in kidney transplant recipients: protective effect of anti-cytomegalovirus prophylaxis and natural killer cell count. A single-center cohort study. Transpl Int. 2018;31(2):187-97.
21. Bourbigot B, Quillien MC, Airiau J, Hardy E, Guiserix J, Leroy JP, et al. Renal failure in the course of reactivation of varicella-zoster virus infection in a renal transplant recipient. J Infect. 1986;13(2):159-62.
22. Toprak O, Turan OF, Bozyel EA, Alp B, Ucdu GZ. Dialysis-requiring acute kidney injury and electrolyte imbalances as a result of prodromal herpes zoster in a kidney transplant recipient. Transpl Infect Dis. 2021;23(4):e13578.
23. Singh N. Interactions between viruses in transplant recipients. Clin Infect Dis. 2005;40(3):430-6.

Medical Quiz

This 60-year-old-gentleman getting maintenance hemodialysis 3 sessions per week for long has developed ascites in last 3 months (Figure 1). For respiratory distress he was admitted in KFH and about 5L of ascitic fluid was aspirated percutaneously. Biochemical and radiological examinations excluded liver and significant cardiac diseases for ascites. What is your diagnosis?

Fig 1: A 60-year-old-man on maintenance hemodialysis with ascites.

Ans. Hemodialysis-associated ascites or in short, dialysis-associated ascites (DAA).

Q. What is dialysis-associated ascites (DAA)?
Ans. Dialysis-associated ascites, also called nephrogenic ascites is a rare condition that develops in patients on long-term hemodialysis. It is characterized by rapidly accumulating ascites that is often recurrent and resistant to standard treatment. This is the diagnosis of exclusion.

Q. What are the challenges in DAA?
Ans. These patients usually have poor hemodynamics. There are frequent episodes of hypotension due to third-spacing loss. This limits the fluid removal during dialysis. Patient needs serial therapeutic paracenteses to relieve symptoms. Moreover, coagulopathy, malnutrition, and encephalopathy complicate the issue.

Q. What are the other options for management of DAA?
Ans. Renal transplantation is the only definitive treatment. Peritoneal dialysis (PD) also provides hemodynamic stability and better volume management. PD eliminates the need for large volume paracentesis (LVP). (1)

Q. What are the advantages of PD in patients with DAA?
Ans. Advantages are better hemodynamic stability, no need for anticoagulation, no risk of hepatitis B and C virus transmission, continuous drainage of ascites and provision of calorie.

Q. What are the disadvantages of PD in patients with DAA?
Ans. Disadvantages are protein loss in dialysate effluent, risk of peritonitis, pericatheter leaks, hernia, and other mechanical complications.

Q. How the PD catheter is placed with ascites?
Ans. Nephrologists can place PD catheters similarly in patient without ascites. Bleeding and intestinal perforations have not been occurred more in patients with ascites.

Q. How PD is initiated in ascitic environment?
Ans. Urgency of starting PD should be determined based on volume status and uremic symptoms. If there is no immediate need to initiate PD, initiation can be delayed

2-4 weeks to promote healing of the surgical site and reduce the risks of catheter complications. (2). However, even if PD initiation is delayed, the ascitic fluid should be frequently drained and the catheter concomitantly flushed to ensure patency and monitor any leaks. Drain ascites and flush PD catheter 1-3 times/week.

Q. How urgent PD is initiated with ascites?

Ans. Drain ascites at first. Fill low volume (500-750 mL) in recumbent position. Exchange should be 2-4 times over 4-8 hours/day and 3-5 days/week.

Q. What is the amount of ascites fluid to be initially drained?

Ans. 5-6 L of ascitic fluid is drained on the initial visit in patients with tense ascites. On subsequent visits, some centers have drained 10% to 20% extra fluid over the fill volume (FV) with every exchange. Others have drained nearly 500 mL above the FV until the ascitic fluid is completely drained. (3).

Q. What are the number and frequency of PD exchanges in these patients?

Ans. When urgent start is needed, typically 3-5 exchanges over 3-5 hours a day are performed by the PD nurse, 3-5 days a week. If urgent start is not needed, PD flushes with concurrent ascites fluid drainage should be done 1-3 times a week.

Q. What is the ultimate management of dialysis-associated ascites?

Ans. The initial management covers salt and fluid restriction, increased frequency of hemodialysis, intermittent paracentesis for symptomatic ascites, and improved nutritional intake. Most of the patients are not suitable for renal transplantation. Renal transplantation often leads to complete resolution of ascites within six weeks. Ascites often recurs after the graft failure.

References:

1. Nilum Rajora, Lucia De Gregorio, and Ramesh Saxena. Peritoneal Dialysis Use in Patients With Ascites: A Review Am J Kidney Dis. 78(5):728-735. Published online June 16, 2021. doi: 10.1053/j.ajkd.2021.04.010.
2. Ranganathan D, John GT, Yeoh E, et al. A randomized controlled trial to determine the appropriate time to initiate peritoneal dialysis after insertion of catheter (Timely PD Study). Perit Dial Int. 2017;37(4):420-428.
3. Lee SM, Son YK, Kim SE, An WS. Clinical outcomes of peritoneal dialysis in end-stage renal disease patients with liver cirrhosis: a propensity score matching study. Perit Dial Int. 2017;37(3):314-320.

Information for the Authors about Writing Scientific Articles

Introduction

Many research workers are reluctant to publish their articles after completing the academic degrees. Sometimes they make an unacceptable delay in writing articles for publications in local or international journals. In many instances, the manuscript is written after several years, and many recognized journals do not accept the article for publication. Scientific articles must be published in time to make the research results acceptable to the professionals and to use the results by greater scientific community.

Guidelines for the Authors:

The Kidney Foundation Hospital and Research Institute Journal provides publication (six monthly) of articles in nephrology, pediatric nephrology, renal histopathology, renal imaging, transplant medicine and urology. The Journal welcomes the submission of manuscript that meets the general criteria of significance and scientific excellence. Papers must be submitted with the understanding that they have not been published elsewhere (except in the form of an abstract or as part of a published lecture, review, or thesis) and are not currently under consideration by another journal published by international research journals or any other publisher. The submitting (corresponding) author is responsible for ensuring that article's publication has been signed and approved by all the other co-authors.

Writing protocol of scientific article is different

Writing of the scientific article should be started as soon as the research has been completed. Actually, writing article is an art which has to be achieved by practice. There are some differences between writing thesis and research paper or research report. One may write a thesis of 160 pages but it may not be possible to publish a single article from that thesis in a peer reviewed journal having impact factor. On the other hand, more than one article may be prepared from some thesis having quality contents and data.

Peer-reviewed journal

Most clinical and scientific discovery is published in peer-reviewed journals. Peer-reviewed journals are those that utilize a process by which an author's peers (experts) in the respective contents evaluate the manuscript. The main objective of peer review is unbiased, independent and critical assessment of research papers by experts on the topic who are not involved in editorial office. Peer review helps editors to select the right article to publish in a journal. It also helps the author and the editor to improve the quality of the manuscript. Following peer reviewing, the manuscript is recommended for publication, revision or rejection.

Different types of scientific articles

There are several types of articles written to publish in journals: a) Editorials, b) original article, c) review article, d) case report, and e) letter to the editors.

a) **Editorials:** It will be preferably written invited only and usually covers a single topic of contemporary interest.
b) **Original research article:** Examples of original articles are research carried out in

laboratory, in the field or in the hospitals, or on a part of population by direct participation of the researchers. **O**riginal article contents are those that have been directly observed by the investigators. The article is written from the research carried out by a group of researchers by active participation in research activities.

c) **Review articles:** Review articles are those that are prepared from many published articles on a particular topic mentioning or citing the references of authors of the original articles. In review article the reviewer cannot show any data from his/her own if it is not published before.
d) **Case Report:** Case report is another form of publication of original data. An atypical presentation of an existing disease or a common or uncommon presentation of a rare disease may be published as a case report.
e) **Letter to editors:** A new discovery of public importance and the data needs to be disseminated urgently to benefit the community. This may be published as letter to the editor. A new finding of a research work having no sufficient strength to be a full article or it will take time to publish as full article, may also be published as letter to the editor. Full articles are kept in queue after acceptance to accommodate in any of the future issues. Publishing article in a quality peer reviewed journal may take a year. But letters to editor are published in the immediate next issue. Decision regarding acceptance of letter to editors are also taken after peer review but in relatively faster process.

All forms of manuscripts are to be submitted in a journal following the instructions for authors of that journal.

Acceptance and rejection of submitted manuscript

Nearly 85% submitted manuscripts by the novice researcher are rejected by a recognized journal. So manuscript rejection should not invite frustration. After rejection by peer reviewers, the comments are usually sent to the author mentioning the problems and pitfalls in the manuscript which may guide the author to improve for next submission in another journal with greater chance of acceptance. For peer review manuscript publication repeated practice can improve the performance of the author.

Acceptance criteria

The reviewers usually follow the criteria for accepting the manuscripts: 1) timeliness, relevance, importance, and prevalence of the addressed topics; 2) appropriate, detailed, rigorous, and comprehensive study design to achieve the objectives; 3) thoughtful, focused, and up-to-date literature review; 4) sample size is sufficiently large; 5) accurately constructed tables and figures; and 6) accurately and sufficiently described statistical analysis, 7) the text is grammatically correct, well-written, clear, straightforward and logical.

Rejection criteria

The following are the main rejection criteria: 1) irrelevant, unimportant and insufficiently addressed problem; 2) use of inappropriate and insufficiently described populations or instruments; 3) text is poorly written and grammatically incorrect; 4) incomplete, inaccurate, or outdated review of the

literature; 5) inaccurate, inconsistent and insufficient data presented; 6) inappropriate and insufficiently described statistical analysis; 7) small sample size or biased samples; 8) over-interpretations of study results; and 9) defective tables or figures.

Submission of completely prepared manuscript

Do not submit the partially prepared article. Read the article repeatedly before submission so that error(s) can be identified and corrected. Grammar, tense, and spelling mistakes are often a cause of rejection by reviewers. Despite the good content, these errors suggest that the authors have written the manuscript with less attention with incorrect findings. So, the manuscript should preferably be checked by a mentor before submission for publication. The articles have several sections: Title, Abstract, Introduction, Methods, Results, and Discussion.

Title:

Title should be attractive to the readers. Most of the readers take decision whether he/she will read the article or not by observing the title.

Abstract or summary

Abstract or summary of an article should contain 200-300 words. After reading the abstract the reader determines if the remainder of the article is worth reading. The abstract is a summary of the article allowing the readers to get a quick glance of the contents. It is better to submit structured abstracts containing back ground, objectives, methods, results and conclusion. The message in the abstract should be clean and precise to the readers.

Introduction

Introduction should be in present tense. The necessity of the present study is presented to the reader by describing the information reported in different studies. Introduction should cover the following points: a) significance of the topic, b) the knowledge gap in the available reports on the topic, 3) selection of some questions on the topic and discuss literature in support of the questions, 4) finding of justification, objectives and hypotheses. Don't try to review all available knowledge on the topic in introduction. Try to adhere to the topic strictly. Literature review is not your prime work and don't write too broad literature review. Describe the literature in such a way that rationale of the study is established. From the last few sentences of introduction, the readers should understand the knowledge gap on the present topic, the purpose and objectives of the study, possible outcome and implications of the study results. Last paragraph may be like this: "No systematic study on urosepsis has been carried out in the hospital. The purpose of the study was to find out bacterial causes of urosepsis in a tertiary care hospital and to observe the role of effective antibiotics in reducing mortality". In scientific article, 1st person language may be accepted such as 'we', 'our'. If any abbreviation is used, it should be written in full with abbreviation in bracket at first, followed by abbreviations only in subsequent paragraphs.

Materials and methods

The materials and methods (M & M) section is the heart of a scientific paper. After initial screening, the editors decide whether the manuscript should be sent for external review or not. Therefore, this section should be the

most elaborated and detailed. M & M should contain the study question/hypothesis.

M & M should cover the explanation of the procedures in detail, the study design, place of study, the research population, inclusion and exclusion criteria which help the reader to understand the population used, sample size, sample collection procedure, data collection instrument/sheet, data management and data analysis.

Next paragraphs should be more detailed in describing the procedures. It is to be written in such a clean way that an appropriately trained researcher can be able to replicate the experiments. There should be complete transparency when describing the study. A researcher should be honest in doing research work and publishing scientific article.

Methodology section should cover the equipments and reagents used in the study, name of the manufacturing company and country, procedures done during the study with the instruments, the protocol used, the outcomes and the methods used for data analysis including the name of the test. Procedure of data collection, type of data collection (retrospectively or prospectively), place of data collection are also mentioned.

Approval from an appropriate ethical review committee should be included in methodology section. Example: under the subheading of "ethical issues" "informed written consent was taken from each participant and ethical clearance was obtained from the ethical review committee of the institute" should be mentioned.

Many editorial offices claim for the certificate of ERC and raw data for checking authenticity of the research work. If any research involves experiment with animals, a statement regarding kind handling of animal should be inserted as "animal experiment was carried out following the guidelines of international Animal Experimentation Ethics Committee (AEEC) and a clearance was obtained from AEEC".

Results

The results are actual statements of observations, shown in tables, figures, graphs and statistics.

Table should be constructed accurately and each table should stand alone and self-explanatory. Tables should not have internal vertical and horizontal lines; data should not be in boxes in the table or a table should not be in one row or column. The title of the table should be just above the table. Inappropriately prepared table indicates that the manuscript is also prepared inappropriately.

Results should be written in past tense. In the text, all the results should not be shown in table; write the important points only with reference of table in parentheses. Example: Most (82%) of the isolated bacteria were resistant to ceftriaxone and ciprofloxacin (table-2); 35% were positive for ESBL gene (table-3; fig-2). Write all means with standard deviation (+SD). Do not begin a sentence with digit, always spell out; and always spell out '1' as 'one". Example: "Seventy five percent of clinically suspected patients with renal cell carcinoma had microscopic hematuria." All the figures should be numbered consecutively and should have a figure legend. Figure legend is the description of the figure and it should be just below a figure. Table number(s) should be different from figure numbers. If a manuscript has 5 tables and 3 figures, the tables will be

numbered as table-1 to table 5. Similarly figure numbers should be figure 1 to figure 3. Many formats for graphic presentation are acceptable, including graphs, charts, and pictures. Photograph should be clear, free of irrelevant background. Color photographs are preferred but need charges to publish in many journals. Digital figures (Scans or existing files and photographs) must be at least 300dpi. All the tables and figures should be in separate sheets and photographs should be provided as separate files ('jpeg' or 'tif'). The editorial office decides where the tables and figures should be inserted in the published article. Some new researchers submit the raw figure and photographs without following instructions of the journal and it may be a cause of rejection of the article.

Don't ignore negative results

Negative and inconclusive results along with positive results should be mentioned. Do not suppress results which do not support your hypothesis and objectives. Example: suppose your study objective was "to find out renal complications like acute kidney injury (AKI) and proteinuria among the admitted COVID-19 cases." Many Covid 19 patients having pulmonary involvement and some having cardiac complications were observed. But you did not find any COVID-19 patient having acute kidney injury (AKI) and proteinuria during study period. In this case you may write as "although a good number of COVID-19 patients developed pulmonary and cardiac complications but none developed acute kidney injury (AKI) and proteinuria during study period."

Discussion

This section should cover the research results with interpretations only. Any additional results, not mentioned in the results section should not be discussed here. At first, the results should be presented and then discussed with relevant interpretations. Discussion should not simply be a repeat of the results section. Results can broadly be discussed in two ways: 1) comparison with other published reports on the same topic, where the research information is similar or different; 2) if other reports are different from the data, the reasons of such different results in other studies should be explained. In this connection all the possible hypotheses should be explained without biasness to support and establish the ongoing research hypothesis and objectives.

In discussion section, one of the major problems is making very strong statements or overestimating the significance of findings. The problem can be minimized by using soft words. Example: it is better to say: "It might be due to …" or "Observations of this study speculate …." or "Findings of the current study support…." or "these findings suggest…." rather than, "It is due to……" or "Observations of this study indicate…" or "Finding of the current study prove that…" or "this means that….". All no research findings are beyond the questions and criticisms. Therefore, word selection should be done carefully maintaining a sense of humbleness in writing discussion, like "might be" "suggests" "possibly" or "likely" to express the interpretations of results in a polite manner. These words actually express that some other explanations might also be there besides what are mentioned here and thereby the criticisms about the research findings may be minimized.

Only discuss the ideas, concepts, or information covered by the research only

without discussing any other irrelevant ideas, not covered by this topic. Carefully address all relevant results, not just the statistically significant ones, supporting the hypothesis only. In places where you have to give your opinion you may write " from the observations of the study on hemodialysis patients, the authors therefore speculate that" or " in our opinion, the sudden death of the hemodialysis patients might be due to…..".

In any section of the article statement like "no research on this topic has been done in the country before or this is the first scientific paper or report on this topic in the country/world" should be avoided. This may be considered as over interpretation/overstatement.

Conclusion

Conclusion is not just a restatement of the research results, rather this is the final finishing, summary statements that reflect the flow and outcomes of the entire paper with the objectives. It should not contain any reference. Based upon the study findings, a statement about potential changes in clinical practice or future research opportunities can be added here. Conclusion paragraph should not be too long and should be covered in 3-6 sentences.

Acknowledgement

The researcher should acknowledge the supervisor or mentor of the research work, people who contributed in completing research by providing monitory fund by any funding agency, providing technical support, access to instruments and reagents which are not available in the department. The data collectors or nurses who were appointed on payment need not to be acknowledged.

How to cite references:

There are two referencing styles are commonly followed in scientific writing in biomedical research: Vancouver referencing style (1,2,3, etc) and Harvard referencing style (Faisal et al, 2018).

Citation of an article in a journal should be in modified Harvard style. Example: Nomany BMS, Rashid HU, Alam MR. Fasting Ramadan in Chronic Kidney Disease, Kidney Transplant and Dialysis Patients. Bangladesh Renal Journal, July 2023; 5(2):60-64. When citing in the text, introduction, discussion should be: "Muslims who have moderate to severe chronic kidney diseases and take regular medications may harm their health by fasting. (Nomany BMS et al, 2023)."In list of references it will appear as "Nomany BMS, Rashid HU, Alam MR. Fasting Ramadan in Chronic Kidney Disease, Kidney Transplant and Dialysis Patients. Bangladesh Renal Journal, July 2023; 5(2):60-64."

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Online Journal Article example: Khan, AKM.' Corona virus in Bangladesh', Virology Journal [online], 2020. Available at: https:// www dmcj. com/reference-management/ reference-manager (Accessed: 15 June, 2020)

Authorship criteria

According to the authorship criteria of the International Committee of Medical Journal Editors (ICMJE), an author has to participate in all of the following three areas: "(1) conception of the reach idea OR data collection OR data analysis and interpretation of the findings, plus (2) drafting the manuscript OR critically reviewing it, plus (3) evaluation of the manuscript." For being author, it is not mandatory to be involved in the very beginning section of the research work, e.g., data collection. A co-author can participate from the data analysis and in the later part of the study. Friends, family members and funding agency cannot be the authors of a study.

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A scientific article should be up to 5000 words including end notes and references. The scientific articles should be written in a concise format and word count should usually be around 3000 words, excluding summary and references. Short communication, comments on a published paper should not be more than 2000 words including end notes and references.

ABBREVIATIONS

Angstrom	A
body surface area	BSA
body weight	body wt.
centimeter	cm
celius	C
complement components	C1, C2, C3
Correclation coefficient	r
creatinine clearance	Ccr.
curie (s)	Ci
Equivalents	Eq
Fahrenheit	F
Glomerular fitration rate	GFR
gram (s)	g
Grams per cent	g/100mi
half-time	tfl/2
hour (s)	hr

inch	inch
International Unit (s)	IU
Intramuscular	im.
intraperioneal	i.p.
intravenous	i.v.
inulin clearance	Cln
Kilogram (s)	kg
liter (s)	L
meter (s) or milli	m
microns (s) or micro	µ
milligram (s) per cent	mg/100ml
minutes (s)	min
molar	M
mole (s)	mole (s)
Molecular weight	molwt
nanogram (s) (millimicrogram)	ng

nanoliter (s) (millimicroliter)	Nl
normal (concentration)	N
not significant	NS
optical density	OD
osmole (s)	Osm
probanility	P
second (s)	sec

standard deviatation	SD
standard error	SE
standard error of the mean	SEM
ultraviolet	UV
unit (s)	U
volt	V

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