Non antibiotic prophylaxis with D-Mannose for UTI in the novo kidney trasplant recipients.

The Manotras study

Am Rau Lertora, A Santelli, L Oliveras Pages, C Couceiro Monteagudo, F Gomez Preciado, M Fiol, B Etcheverry, M Martin, Jm Cruzado Garrit, E Melilli

Servicio de Nefrología, microbiología y Urología. Hospital Universitario de Bellvitge

BACKGROUND

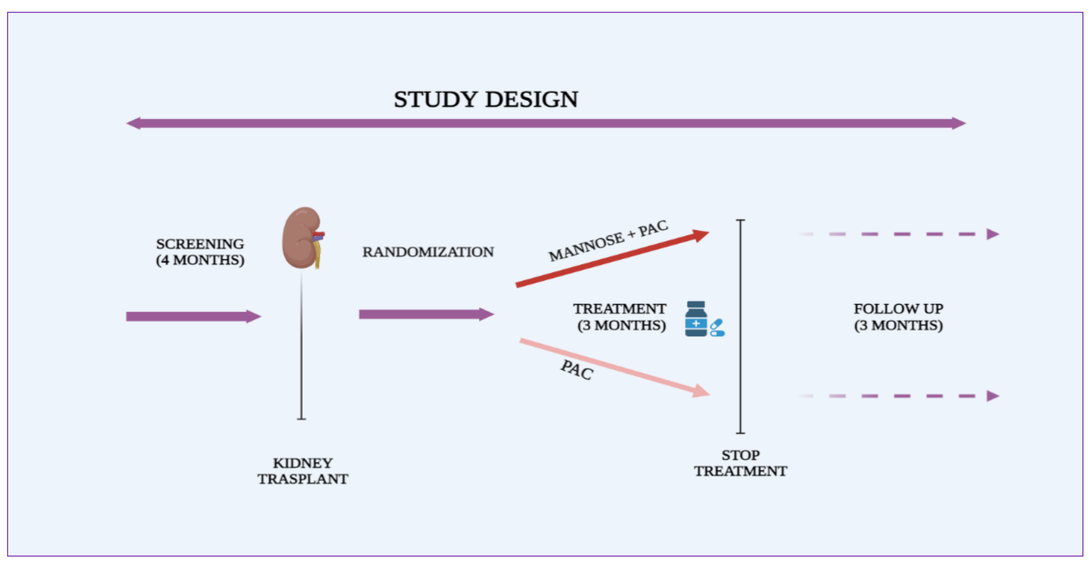
Urinary tract infections are one of the most frequent complications in the first six months after kidney transplantation, both late and early UTIs increase significantly the morbidity and mortality. They also seem to have an impact on long term graft survival.

The role of non-antibiotic prophylaxis in this special population is poorly studied. D-Mannose, a simple sugar and Proanthocyanins acts inhibiting bacterial attachment to the urothelium. Both have shown promising results in reducing the risk of UTI in healthy women; but its efficacy has not been evaluated in kidney transplant population yet.

STUDY DESIGN

Primary Objective: The primary outcome was the incidence of UTI during the first 6 months after kidney transplantation. We showed UTI incidences according 3 period: period 1 from first day after kidney transplantation to double J removal, period 2 from double J removal to last day of study treatments (meaning ending of supplements intakes) and period 3 from last day of study treatments to end of study (6 months).

Study design: Unicentric prospective, pilot, randomized, double-blind, parallel study group (1:1 ratio)



BASELINE CHARACTERISTICS

Supplementary table 2.

Baseline demographics and clinical characteristics depending on treatment group

Characteristic	Mannose+PAC n = 27	PAC n=27	P
Sex, (F/M), n %	13/14 (48/52 %)	12/15 (44/55 %)	0.78
Age (years) median (IQR)	62 [49-69]	57 [50-70]	0.68
Waiting time on dialysis (months), median (IQR)	31 [20-54]	27 [17.7-39]	0.35
Cause of ESKD			0.83
Undetermined, n (%)	5 (18%)	6 (22%)	
Diabetes, n (%)	3 (11,1%)	3 (11,1%)	
Vascular nephropathy, n (%)	2 (7,4%)	2(7,4%)	
Tubulo-interstitial nephritis, n (%)	3 (11,1%)	0 (0 %)	
ADPKD, n (%)	2 (7,4%)	7 (25,9%)	
Glomerulonephritis, n (%)	8 (29,96%)	7 (25,9%)	
Others, n (%)	4 (14,1%)	2 (7,4%)	
Type of donor, n (%)			0.58
Living donor	1 (4%%)	2 (8%)	
DBD	10 (37%)	13 (52%)	
DCD	16 (59%)	12 (40%)	
Induction Therapy, n (%)			0.26
Basiliximab	18 (66%)	14 (52%)	
Thymoglobulin	9 (33%)	13 (48%)	

PAC, proanthocyanins; ESKD, end stage kidney decease; ADPKD, autosomic dominant kidney decease; CMV, cytomegalovirus;

OUTCOMES

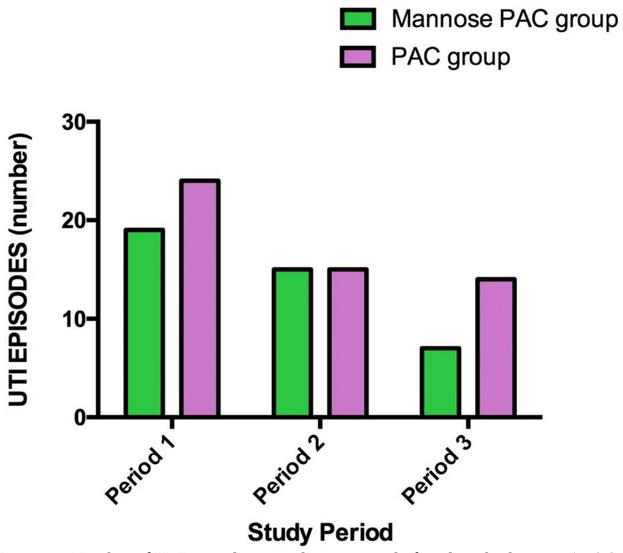


Figure 1. Number of UTI episodes according to period of study in both group (p. 0.8 for period 1, p. 0.6 for period 2 and p. 0.2 for period 3).

We analyzed UTI episodes incidence according to 3 different period and we didn't observe significant differences between groups (Figure 1). As expected, UTI were more frequent in the first 3 months after kidney transplantation compared with months 3 to 6 one compared (n. 73 vs 21 episodes).

Table 1

Graft and Transplant related outcomes depending on treatment group

Outcomes	Mannose + PAC n = 27	PAC n=27	p.
DGF, n (%)	7 (26%)	6 (22%)	0.75
Acute allograft rejection, n (%)	1 (3,7%)	1 (3,7%)	1
Urological complications:	5 (18.5%)	7 (25.9%)	0.74
Acute urine retention	1	2	
Ureteral reintervention	1	1	
Lithiasis	1	1	
Obstructive Lymphocele	3	2	
eGFR (umol/L) 6 months, median (IQR)	46±16	51±16	0.17
Time until catheter extraction, median (IQR)	24 [22-27]	24 [21-26]	0.99
CMV viremia, n (%)	8 (29,6%)	8 (29,6%)	0.99

PAC, proanthocyanins; DGF, delay graft function; eGFR, estimated glomerular filtration rate; PT, post transplantation.

Table 1 shows the main graft and urological related outcomes depending on treatment group. No major differences were observed.

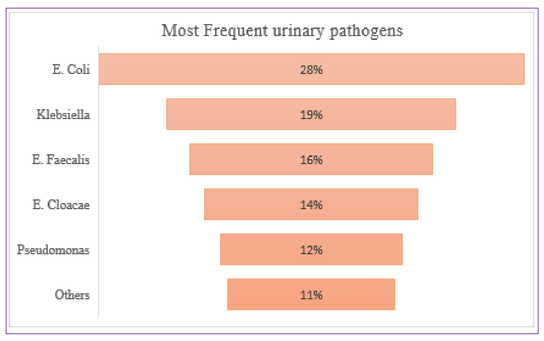
Table 3.

UTI by treatment group

UTI	Mannose+PAC	PAC	p.
Asymptomatic Bacteriuria, n %	18 (66)	15 (48)	0.40
Cystitis, n %	2 (7)	3 (11)	1
Pyelonephritis, n %	4 (14)	5 (18)	1
With bacteremia	4 (14)	3 (11)	1
Number of UTI (total) episodes, n	41	53	0.4
Recurrent UTI (3 episodes), n %	5 (18)	9 (33)	0.2
Recurrent UTI (2 episodes) n. %	12 (46)	14 (52)	0.6
Contaminate culture, n %	38 (52)	35 (56)	1

UTI, urinary tract infections; PAC, proanthocyanins; E. Coli, Escherichia Coli

There was 94 UTI episodes in 34 patients (3.4 UTI episodes for patient/year). 33 patients had at least one episode of asymptomatic bacteriuria (61%), 5 patients had cystitis (9.3%) and 9 patients had acute pyelonephritis (17%). Six pyelonephritis episodes appeared after urinary manipulation (2 occurred after the double J ureteral stent removal, 3 after the bladder stent removal and 1 after nephrostomy placement). Sixteen patients (30 %) had recurrent UTI (≥ than 3 episodes



Escherichia Coli was the most frequent pathogen, observed in 28 % of UTI's episodes. The frequency of uropathogens isolated in the urine culture is showed in figure 2. No differences in frequency of patients with UTI episodes according bacteria type were observed among study groups.

In terms of tolerance, the reported adverse events were minor and mainly gastrointestinal (GI) Therefore, the addition of mannose was not associated with more adverse events. . In total 50% of patients presented adverse effects; being 51.9 % in those treated with PAC alone and 48.1% of those treated with Mannose (p= 0.7).

CONCLUSIONS

With the present study we have provided valuable information on a prophylactic strategy that has proven to be effective in non-transplanted population. Unfortunately, the use of D-mannose in the early post-transplant period, even though is safe and well tolerated, seems not add any protective effect, confirming once again the complexity of pathogenesis in kidney transplant population and the unmet need for preventive strategies for UTIs.

BIBLIOGRAPHY

Alangaden GJ, Thyagarajan R, Gruber SA, Morawski K, Garnick J, El-Amm JM, et al. Infectious complications after kidney transplantation: current epidemiology and associated risk factors. Clin Transplant 2006;20(4):401-409; Britt NS, Hagopian JC, Brennan DC, Pottebaum AA, Santos CA, Gharabagi A, et al. Effects of recurrent urinary tract infections on graft and patient outcomes after kidney transplantation. Nephrology Dialysis Transplantation 2017;32(10):1758-1766; Abbott KC, Swanson SJ, Richter ER, Bohen EM, Agodoa LY, Peters TG, et al. Late urinary tract infection after renal transplantation in the United States. American journal of kidney diseases 2004;44(2):353-362.; Ariza-Heredia EJ, Beam EN, Lesnick TG, Cosio FG, Kremers WK, Razonable RR. Impact of urinary tract infection on allograft function after kidney transplantation. Clin Transplant 2014;28(6):683-690.; Bojana Kranjcec B, Papes D, Altarac S. D-mannose powder for prophylaxis of recurrent urinary tract infections in women: a randomized clinical trial. World J Urol.doi 2013;10.