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Systematic screening and treatment of asymptomatic bacteriuria in renal transplant recipients

Silvana Fiorante[1], Francisco López-Medrano[1], Manuel Lizasoain[1], Antonio Lalueza[1], Rafael S. Juan[1], Amado Andrés[2], Joaquín R. Otero[3], José M. Morales[2,4] and José M. Aguado[1,4]

[1]*Infectious Diseases Unit, University Hospital 12 de Octubre, Madrid, Spain;* [2]*Department of Nephrology, University Hospital 12 de Octubre, Madrid, Spain and* [3]*Department of Microbiology, University Hospital 12 de Octubre, Madrid, Spain*

We sought to examine the impact of asymptomatic bacteriuria on renal transplant outcome by retrospectively analyzing 189 renal transplant recipients for whom systematic screening uncovered 298 episodes of asymptomatic bacteriuria in 96 recipients. These patients were treated and all were followed for 36 months. Significant risk factors included female gender, glomerulonephritis as the disease that led to transplantation, and double renal transplant. There were no differences in serum creatinine, creatinine clearance, or proteinuria between patients with and without bacteriuria. The incidence of pyelonephritis in these patients was 7.6 episodes per 100 patient-years compared with 1.07 in those without asymptomatic bacteriuria. Between two to five and more than five bacteriuria episodes were significant independent factors associated with pyelonephritis whereas more than five episodes was a significant independent factor associated with rejection. Thus, we found no differences in renal function prognosis between patients who do not develop asymptomatic bacteriuria and those uncovered by systematic screening and who received treatment following kidney transplantation. Despite this treatment, the incidence of pyelonephritis was much higher in the group of patients with detected asymptomatic bacteriuria.

Kidney International (2010) **78,** 774–781; doi:10.1038/ki.2010.286; published online 18 August 2010

KEYWORDS: kidney transplantation; outcomes; pyelonephritis

Correspondence: *Francisco López-Medrano, Infectious Diseases Unit, University Hospital 12 de Octubre, Edificio de Maternidad—Planta 6ª, Avenida de Córdoba s/n, Madrid 28041, Spain. E-mail: flmedrano@yahoo.es*

This study was presented in part at the 47th Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, IL, September 2007 and the 48th Interscience Conference on Antimicrobial Agents and Chemotherapy, Washington, DC, October 2008.

[4]These authors contributed equally to this study.

Received 28 November 2009; revised 27 April 2010; accepted 9 June 2010; published online 18 August 2010

Renal transplantation is the best option for terminal renal insufficiency. In spite of advances in prophylaxis and treatment, infection remains a major cause of morbidity and mortality in this population.[1] Urinary tract infections (UTIs), including asymptomatic bacteriuria, cystitis, and pyelonephritis, are the most common form of bacterial infection in renal transplant recipients.[2–4] These infections are thought to be directly attributable to the exposition of pathogens during the early postoperative period and to immunosuppressive therapy. UTI incidence after renal transplantation has been reduced in recent decades because of improvements in surgical procedures,[5] early removal of urethral catheters,[6] and antibiotic prophylaxis, but it is still higher than in the general population.

The clinical impact of asymptomatic bacteriuria has been extensively studied in different populations such as diabetic patients, patients pending of urological intervention, pregnant women, and the elderly population. Screening for and treatment of asymptomatic bacteriuria are well established before transurethral resection of the prostate (or before other urological procedures in which mucosal bleeding is anticipated) and for pregnant women (recommendation strength grade A-I).[7] Asymptomatic bacteriuria screening and treatment have not been thoroughly evaluated for solid organ recipients, and hence recommendation strength of present guidelines is grade C-III.[7]

In this study we evaluate the role of systematic asymptomatic bacteriuria screening and treatment in the first 3 years after renal transplantation and their impact on pyelonephritis incidence and renal allograft function.

RESULTS

Patients included

Between January 2002 and December 2004, 235 patients received a renal transplant at our institution. A total of 46 patients (19.57%) were excluded from the present study because of incomplete clinical history (25 patients), survival of renal graft for <30 days (12 patients), survival for <30 days (2 patients), and loss of follow-up (7 patients). Finally, 189 patients were included in the cohort and all of them were followed-up for 36 months. The population characteristics are summarized in Table 1. During follow-up, only one

Table 1 | Clinical characteristics of the 189 patients included in the study

Description	No. (%)
Female	75 (39.68%)
Male	114 (60.32%)
Transplant number	189 (100%)
Recipient age	Mean 49 years, range: 20–78 years
Pretransplant serological status:	
Cytomegalovirus, IgG positive	169 (89.42%)
Virus hepatitis B, Ag core positive	26 (13.76%)
Virus hepatitis C, IgG positive	16 (8.47%)
Virus hepatitis C, RNA positive	11 (5.82%)
Transplantation characteristics:	
Cadaveric donor	189 (100%)
First renal transplant	168 (88.89%)
Second renal transplant	21 (11.11%)
Single renal transplant	169 (89.42 %)
Double renal transplant	18 (9.52%)
Simultaneous renal–pancreas transplant	1 (0.53%)
Simultaneous renal–hepatic transplant	1 (0.53 %)
Etiology of renal failure before transplantation	
Glomerulonephritis	46 (24.34%)
Chronic interstitial nephropathy	28 (14.81%)
Diabetic nephropathy	26 (13.76%)
Nephroangiosclerosis	22 (11.64%)
Congenital nephropathy	4 (2.12%)
Polycystic kidney disease	20 (10.58%)
Unknown	36 (19.05%)
Others[a]	7 (3.70%)
Post-transplant cytomegalovirus disease	17 (8.99%)
Post-transplant antibiotic prophylaxis with cotrimoxazol (3 months)	189 (100%)
Urinary tract surgery after transplantation	32 (16.93%)

Abbreviations: Ag, antigen; IgG, immunoglobulin G; RNA, ribonucleic acid.
[a]Söjgren syndrome, systemic lupus erythematosus, and amyloidosis.

Table 2 | Frequency of microorganisms isolated in urine culture in asymptomatic bacteriuria episodes

Bacterium	Frequency (no.)	Percentage (%)
Escherichia coli	200	58.31
Enterococcus faecalis	38	11.08
Klebsiella pneumoniae	32	9.33
Streptococcus agalactiae	18	5.25
Proteus mirabilis	12	3.50
Staphylococcus epidermidis	8	2.33
Pseudomonas aeruginosa	7	2.04
Morganella morganii	6	1.75
Klebsiella oxytoca	5	1.46
Enterococcus faecium	5	1.46
Acinetobacter baumannii	2	0.58
Citrobacter freundii	2	0.58
Streptococcus viridans	2	0.58
Enterobacter cloacae	2	0.58
Stenotrophomonas maltophila	2	0.58
Corynebacterium striatum	1	0.29
Streptococcus gordonii	1	0.29

patient died and another required transplant nephrectomy. Appointment date was respected in 98% of the occasions. Urine sample was correctly collected at every medical visit. In 90 of 298 episodes of asymptomatic bacteriuria (30%), antibiotic treatment was not administered. There were no reported cases in which more than one consecutive episode of asymptomatic bacteriuria was not treated with antibiotics.

Development of asymptomatic bacteriuria

Among 189 renal transplant recipients, 96 (50.79%) patients presented 298 episodes of asymptomatic bacteriuria (one episode in 36, between two and five episodes in 45, and more than five episodes in 15 patients) and 93 did not experience any episode of asymptomatic bacteriuria, throughout the 36 months of follow-up. *Escherichia coli* was the most frequently isolated bacteria (58.3% of the episodes), followed by *Enterococcus faecalis* (11.8%), *Klebsiella pneumoniae* (9.3%), and *Streptococcus agalactiae* (5.2%). Table 2 contains the complete list of isolated microorganisms. In 152 of the 298 episodes of asymptomatic bacteriuria (51%), the isolated bacteria were trimethoprim-sulfamethoxazole resistant. No major adverse effects were recorded related to antibiotic administration for asymptomatic bacteriuria treatment.

The time pattern of the different types of UTI episodes is shown in Figure 1. Asymptomatic bacteriuria episodes occurred all through the 36 months of follow-up, but mostly in the first 12 months. Most of pyelonephritis episodes occurred in the first year after transplantation.

Asymptomatic bacteriuria-associated risk factors

Risk factors for the development of asymptomatic bacteriuria are analyzed in Table 3. The variables that were independently related to the development of asymptomatic bacteriuria in the final multivariate model were female sex of the recipient (odds ratio (OR) 4.397; confidence interval 2.307–8.379; $P = 0.0001$), glomerulonephritis as the disease that led to transplantation (OR 2.075; confidence interval 1.001–4.302; $P = 0.0497$), and double renal transplant (OR 4.011; confidence interval 1.68–13.775; $P = 0.0273$).

Long-term influence of asymptomatic bacteriuria on renal graft function

We found no significant differences in serum creatinine, creatinine clearance, or proteinuria throughout the 36 months of follow-up between those patients who developed asymptomatic bacteriuria and those who did not (Figure 2). Patients were arbitrarily classified into four groups according to the number of asymptomatic bacteriuria episodes during follow-up: no episode (93 patients), 1 episode (36 patients), 2–5 episodes (45 patients), and >5 episodes (15 patients). No differences in renal function (assessed by serum creatinine, creatinine clearance, and proteinuria) were found when the number of asymptomatic bacteriuria episodes was taken into account. Asymptomatic bacteriuria influence on survival of both the allograft and the patient was impossible to calculate as only one patient died and only one lost the graft during follow-up.

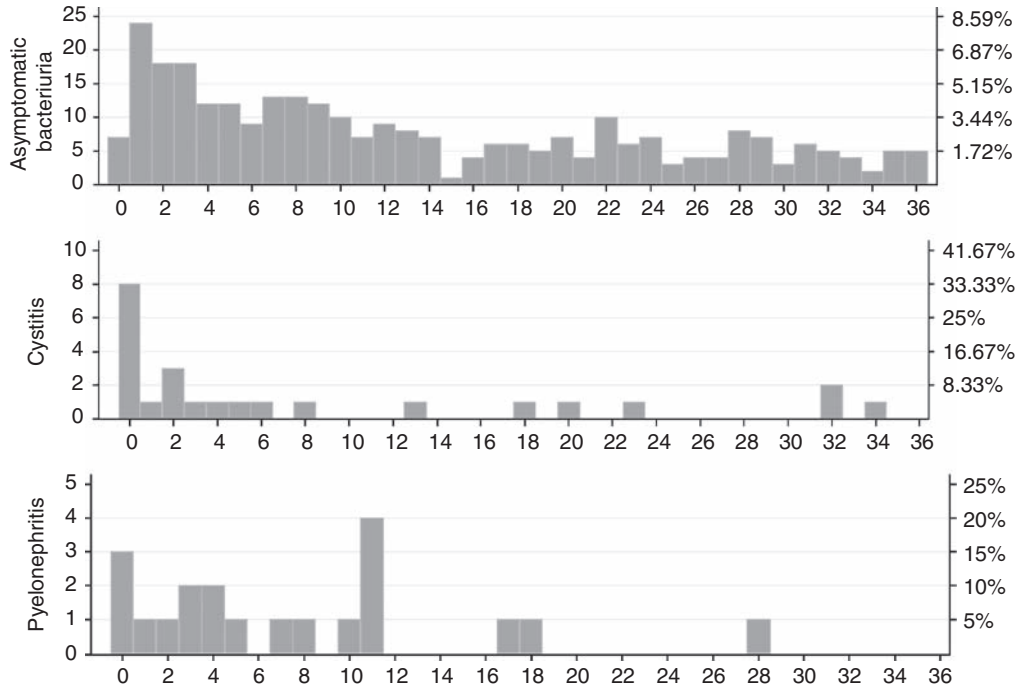

Figure 1 | Time pattern of asymptomatic bacteriuria, cystitis, and pyelonephritis episodes throughout the 36 months of follow-up (expressed as percentage of total number of episodes for each category).

Table 3 | Univariate and multivariate analyses of risk factors for asymptomatic bacteriuria development among the 189 renal transplant recipients of the cohort

	Univariate analysis			Multivariate analysis		
Variable	OR	95% CI	*P*-value	OR	95% CI	*P*-value
Age (>60)	0.95	0.49–1.86	0.90			
Female sex	2.51	1.35–4.70	<0.0001	4.39	2.30–8.37	0.0001
HCV infection	0.52	0.26–2.06	0.55			
Kidney disease before Tx:						
Glomerulonephritis	1.93	0.97–3.83	0.058	2.07	1.00–4.30	0.049
Chronic interstitial nephropathy	1.91	0.83–4.40	0.12			
Diabetic nephropathy	0.96	0.42–2.20	0.93			
Nephroangiosclerosis	0.77	0.30–1.95	0.58			
Congenital nephropathy	0.31	0.03–3.09	0.32			
Kidney polycystosis	0.77	0.30–1.95	0.58			
Non-filiated kidney disease	0.63	0.30–1.32	0.22			
Double transplant	2.87	0.88–9.39	0.079	4.01	1.16–13.77	0.027
First renal transplant	0.75	0.30–1.87	0.53			
Second renal transplant	1.68	0.48–4.84	0.33			
Urinary tract surgery after Tx	2.08	0.94–4.61	0.06			
Nephrostomy after Tx	1.37	0.52–3.58	0.51			
Cytomegalovirus disease after Tx	2.51	0.84–7.43	0.09			

Abbreviations: CI, confidence interval; HCV, hepatitis C virus; OR, odds ratio; Tx, renal transplantation.

Relationship between asymptomatic bacteriuria and rejection

An analysis was made to establish risk factors for organ rejection (Table 4). The presence of one or more asymptomatic bacteriuria episodes was significantly correlated with rejection development in univariate analysis. Only the presence of >5 asymptomatic bacteriuria episodes remained as an independent factor associated with rejection in multivariate analysis (OR 3.46; $P<0.03$; Table 4).

Relationship between asymptomatic bacteriuria and cystitis

During follow-up, the total amount of cystitis episodes diagnosed was 23 in the 189 subjects of the cohort: 19 episodes in 19 patients with asymptomatic bacteriuria

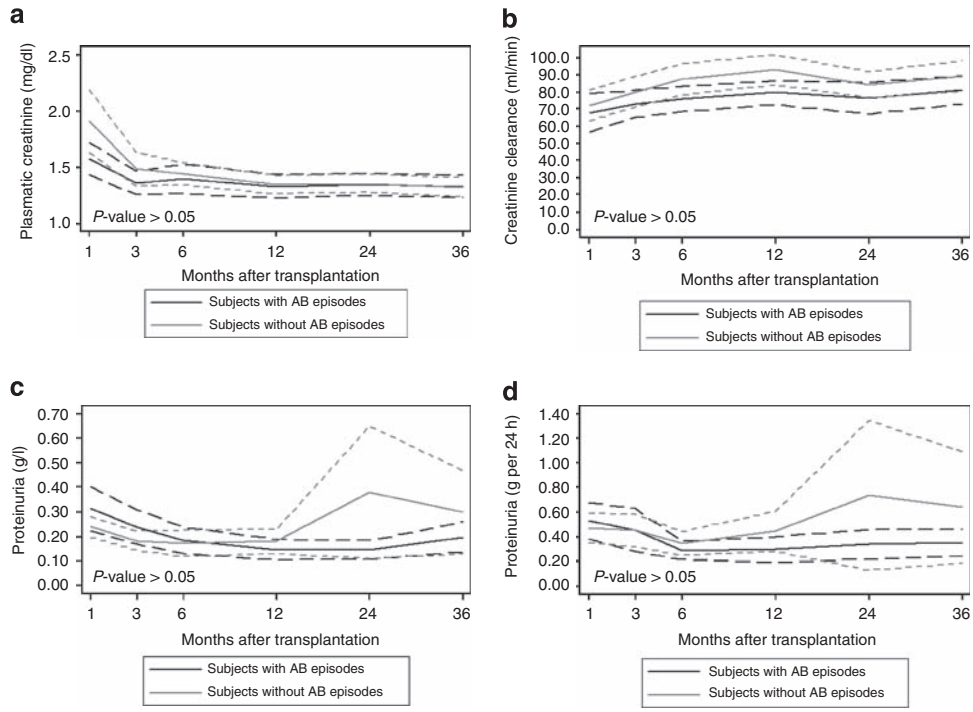

Figure 2 | Relationship between asymptomatic bacteriuria (AB) and renal function throughout the 36 months of follow-up. This relationship was assessed by: (**a**) serum creatinine level (mg/dl); (**b**) creatinine clearance (ml/min); (**c**) level of proteinuria (g/l); and (**d**) level of proteinuria (g per 24 h) throughout the 36 months of follow-up. ANOVA test for repeated measures. Dashed lines denote the s.d.

Table 4 | Univariate and multivariate analyses of factors associated with kidney allograft rejection

	Univariate analysis			Multivariate analysis		
Variable	**OR**	**95% CI**	***P*-value**	**OR**	**95% CI**	***P*-value**
Age (>60)	0.95	0.49–1.86	0.90			
HCV infection	3.88	1.04–14.39	0.42			
Kidney disease before Tx:						
Glomerulonephritis	1.93	0.97–3.83	0.058			NS
Chronic interstitial nephropathy	1.05	0.83–4.40	0.12			
Diabetic nephropathy	0.96	0.42–2.20	0.93			
Nephroangiosclerosis	0.77	0.30–1.95	0.58			
Congenital nephropathy	0.31	0.03–3.09	0.32			
Kidney polycystosis	0.77	0.30–1.95	0.58			
Non-filiated kidney disease	0.63	0.30–1.32	0.22			
Double transplant	2.87	0.88–9.39	0.07			NS
First renal transplant	0.75	0.30–1.87	0.53			
Second renal transplant	1.68	0.58–4.84	0.33			
Urinary tract surgery after Tx	2.12	1.02–4.41	0.06			NS
Nephrostomy after Tx	1.37	0.52–3.58	0.51			
Cytomegalovirus disease after Tx	2.51	0.84–7.53	0.09			
>5 Episodes of AB vs 0	22.74	3.89–32.86	0.0005	3.46	1.07–11.18	0.037
2–5 Episodes of AB vs 0	7.83	1.99–8.514	0.0021	1.30	0.52–3.24	NS
1 Episode of AB vs 0	1.68	0.99–2.54	0.019	1.25	0.46–3.38	NS

Abbreviations: AB, asymptomatic bacteriuria; CI, confidence interval; HCV, hepatitis C virus; NS, not significant; OR, odds ratio; Tx, renal transplantation.

episodes and 4 episodes in 4 patients without asymptomatic bacteriuria episodes. All the cystitis episodes resolved uneventfully under antibiotic treatment.

Relationship between asymptomatic bacteriuria and pyelonephritis

The total amount of pyelonephritis episodes diagnosed was 25 in the 189 subjects of the cohort (global incidence of 4.4 episodes per 100 patient-years): 22 episodes in 17 patients with asymptomatic bacteriuria and 3 episodes in 2 patients without asymptomatic bacteriuria. The relationship between the asymptomatic bacteriuria episodes and the pyelonephritis episodes was as follows: 8 episodes occurred in the first fortnight after transplantation—when the asymptomatic bacteriuria detection strategy was not yet effective; 3 of the pyelonephritis episodes occurred in patients who had

Table 5 | Univariate and multivariate analyses of risk factors for pyelonephritis

	Univariate analysis			Multivariate analysis		
Variable	OR	95% CI	*P*-value	OR	95% CI	*P*-value
1 AB episode	5.686	0.994–32.541	0.0508	—	—	NS
2–5 AB episodes	9.836	1.994–48.514	0.0050	7.703	1.429–41.509	0.0175
>5 AB episodes	22.746	3.894–132.864	0.0005	13.516	1.975–92.496	0.0080
Glomerulonephritis	4.136	1.563–10.941	0.0042	4.474	1.426–14.034	0.0102
⩾1 Acute rejection	3.537	1.308–9.562	0.0128	3.524	1.075–11.558	0.0376
Simple renal transplant	0.194	0.064–0.591	0.0039	0.193	0.052–0.712	0.0135
Double renal transplant	3.855	1.092–13.601	0.0360	—	—	NS
Cotrimoxazol prophylaxis	1.179	1.018–1.365	0.0275	—	—	NS
⩾2 Urinary tract surgeries	3.384	1.215–9.425	0.0196	—	—	NS
Recurrent UTI	7.042	2.513–19.728	0.0002	—	—	NS
Relapsing UTI	4.376	1.634–11.720	0.0033	—	—	NS

Abbreviations: AB, asymptomatic bacteriuria; CI, confidence interval; NS, not significant; OR, odds ratio; UTI, urinary tract infection.

not presented previous asymptomatic bacteriuria episodes; in 11 cases, the routine urine culture performed for detection of asymptomatic bacteriuria detection was sterile just before the patient developed the pyelonephritis episode; in 2 episodes, asymptomatic bacteriuria was detected and adequately treated immediately before pyelonephritis development (in both cases the asymptomatic bacteriuria episode and the subsequent pyelonephritis episode were produced by *E. coli* with the same antibiotic susceptibility pattern); in the 4 remaining cases of pyelonephritis, the strategy was not correctly applied (in 2 cases the patient refused the asymptomatic bacteriuria treatment and in 2 cases the attending physician missed the asymptomatic bacteriuria episode treatment). The microorganisms isolated in these cases were *Pseudomonas aeruginosa*, *E. faecium*, *Morganella morgagni*, and coagulase-negative *Staphylococcus*. In the four cases, the same specie was isolated in the asymptomatic bacteriuria episode and in the subsequent pyelonephritis episode. The incidence of pyelonephritis was 7.6 episodes per 100 patient-years in patients presenting asymptomatic bacteriuria versus 1.07 episodes of pyelonephritis per 100 patient-years in patients who did not. The risk factors for pyelonephritis are analyzed in Table 5. The presence of one or more episodes of asymptomatic bacteriuria was significantly correlated with the development of pyelonephritis in univariate analysis. The detection of 2–5 episodes of asymptomatic bacteriuria (OR 7.7; $P<0.01$) or >5 episodes of asymptomatic bacteriuria remained as independent factors associated with pyelonephritis in multivariate analysis (OR 13.5; $P<0.008$; Table 5).

DISCUSSION

Systematic screening and treatment of asymptomatic bacteriuria has been related to a reduction in pyelonephritis rate in pregnant women and in those subjects who undergo transurethral prostate resection (level of evidence A-I for both categories).[7] On the other hand, asymptomatic bacteriuria treatment in diabetic women has not shown any protective effect neither in the development of pyelonephritis nor in the mortality rate or the progression to diabetic complications such as nephropathy. Systematic screening for asymptomatic bacteriuria is not recommended in this group (level of evidence A-I).[7] For renal transplant recipients there is scarce information regarding the benefit of systematic asymptomatic bacteriuria screening and treatment in terms of reduction in pyelonephritis incidence or prevention of allograft nephropathy development. Recent guidelines affirm that it is not possible to make a recommendation for systematic screening or treatment of asymptomatic bacteriuria in renal transplant recipients (level of evidence C-III)[7] and no reference to asymptomatic bacteriuria is made in recent guidelines for outpatient surveillance in renal transplant recipients.[8] Previous studies have focused their attention on the influence of UTI as a whole on the prognosis of renal transplant recipients[3,4,9,10] rather than on the influence of asymptomatic bacteriuria. There is no doubt about the need for treatment of symptomatic UTI. The controversy remains around the convenience of systematically treating asymptomatic episodes. Some researchers[11] have recommended asymptomatic bacteriuria treatment based on the possibility that UTI, even asymptomatic, could lead to renal allograft scarring in the context of vesicoureteric reflux.

Only two previous studies have addressed the problem of asymptomatic bacteriuria in renal transplant recipients.[12,13] One of them was published in 1979[12] and included 65 patients in whom 59 episodes of asymptomatic bacteriuria were detected. The follow-up of these patients was 14 months after transplantation. The other study was published in 1985[13] and included 281 patients in whom 177 episodes of asymptomatic bacteriuria were detected. The follow-up of these patients ranged between 1 month and 16 years. In neither of these studies[12,13] is the frequency of asymptomatic bacteriuria screening specified, nor the parameters established to evaluate renal function.

The protocol of our hospital for renal allograft recipient management establishes that asymptomatic bacteriuria must be systematically screened and treated for a long period after transplantation. This gave us a unique opportunity to study its effect on pyelonephritis development and on renal function prognosis. To our knowledge, there are no previous studies that have evaluated this effect.

We found some risk factors independently associated with the development of asymptomatic bacteriuria in the patients of the cohort: female sex, glomerulonephritis as the disease

that produced the renal failure that led to transplantation, and double renal transplant. Female sex has been recognized as a risk factor for UTI in general population.[14] Glomerulonephritis before transplantation was a risk factor for both asymptomatic bacteriuria ($P<0.05$) and pyelonephritis ($P<0.01$). The rationale for this not previously described association is not clear. The role of immunocompromising co-morbidities (that is, lupus or systemic vasculitis) or the amount and duration of pre- and post-transplant immunosuppression in this subgroup of patients may be hypothesized. A relationship between the use of azathioprine or mycophenolate mofetil and the development of UTI has been previously described.[9,15,16] Double renal transplantation implies the presence of more renal parenchyma and more anastomosis in the urinary tract, which could increase the risk of infection. Special surveillance must be kept on these groups of patients taking into account the potential risk of developing UTI.

There are no previous studies evaluating the repercussion of asymptomatic bacteriuria on renal function prognosis in patients with kidney transplants. Our study shows that when asymptomatic bacteriuria is systematically screened and treated during the first 36 months after renal transplantation, renal function prognosis is similar to the group of patients who do not present asymptomatic bacteriuria during follow-up. When the number of asymptomatic bacteriuria episodes was taken in consideration, no differences were found. The retrospective character of the present study did not allow us to determine the influence of untreated asymptomatic bacteriuria in the renal allograft prognosis. Although this scientific information is not available, we have decided to keep the protocol of systematic screening and treatment of asymptomatic bacteriuria after renal transplantation at our hospital.

When UTI was considered as a whole (asymptomatic bacteriuria plus cystitis plus pyelonephritis), adverse impact on long-term graft function was not found, provided that asymptomatic episodes were systematically treated (also analyzed by analysis of variance (ANOVA) test for repeated measures).

The relationship between asymptomatic bacteriuria and rejection episodes was studied. We found that, even when systematically treated, repetition of asymptomatic bacteriuria episodes was an independent factor associated with rejection. We could not determine causality of this relationship, as not all the episodes of rejection were preceded by asymptomatic bacteriuria episodes. Previous studies have found a clinical[15,17,18] and pathogenic[19] relationship between pyelonephritis and rejection in kidney transplant recipients.[15,17,18] In our study, pyelonephritis was significantly more frequent in patients with asymptomatic bacteriuria episodes. This association of events could justify the relationship found between asymptomatic bacteriuria and rejection. From a clinical point of view, it could be important to consider that asymptomatic bacteriuria identifies a high-risk subgroup for rejection development among kidney graft recipients.

The relationship between asymptomatic bacteriuria and pyelonephritis was studied. We found that, even when systematically treated, repeated asymptomatic bacteriuria episodes were an independent factor associated with pyelonephritis. In this relationship also we could not determine causality. However, pyelonephritis incidence was more than seven times higher in the group of patients who presented asymptomatic bacteriuria (7.6 episodes per 100 patient-years)—even when systematically treated—than in the group of patients without asymptomatic bacteriuria (1.07 episodes per 100 patient-years). Previous studies in renal transplant recipients have reported a pyelonephritis incidence of 8.8 episodes per 100 patient-years[15] (when asymptomatic bacteriuria was systematically treated during the first 3 months after transplantation) and between 12[18] and 26[20] episodes per 100 patient-years when asymptomatic bacteriuria was not screened or treated after transplantation. If these results are compared with those of the present study, treating asymptomatic bacteriuria could be an option for lowering pyelonephritis incidence, although it will remain higher than in the group of patients who do not develop asymptomatic bacteriuria. Recent studies have found a worse prognosis for renal transplant recipients who develop pyelonephritis.[19] This probable extra benefit of the strategy of systematic screening and treatment of asymptomatic bacteriuria is another argument to maintain this protocol in the renal transplant program of our hospital.

The strengths of this study are the number of transplant recipients that were followed up (in every case up for 36 months) and the fact that on every visit asymptomatic bacteriuria was systematically screened. But there are also some drawbacks that deserve specific consideration, mainly because of the retrospective nature of the study. Not in every case was the asymptomatic bacteriuria episode treated with antibiotics. Nevertheless, the study target was the validation of a strategy for the whole kidney transplant program of a hospital, rather than the strategy for an individual patient. The definition of relapse was based on the isolation of the same bacterium with same resistance pattern, whereas molecular analysis of the strains was not made. No major adverse effects were recorded related to the antibiotic administration but minor adverse effects were not systematically recorded for this study.

Our data suggest that there are no differences in renal allograft prognosis between those who do not develop asymptomatic bacteriuria and those who do develop asymptomatic bacteriuria and are systematically treated. Moreover, systematic treatment of asymptomatic bacteriuria may reduce pyelonephritis incidence. Prospective studies comparing treatment versus non-treatment of asymptomatic bacteriuria and its influence on allograft prognosis or pyelonephritis incidence should be undertaken.

MATERIALS AND METHODS

The study was carried out at the 12 de Octubre University Hospital 12, a 1300-bed teaching hospital in Madrid, Spain. The study was

approved by the local ethics committee of the hospital. We retrospectively selected all the patients who had received a renal transplantation at our institution between 1 January 2002 and 31 December 2004. The follow-up period was 36 months for every patient. A standard technique was used for the allograft implantation. A urethral catheter was inserted before transplantation and systematically removed 3 to 4 days after surgery.

Immunosuppressive treatment

A single 250 mg dose of intravenous prednisolone was given intraoperatively at anesthesia induction and a 250 mg dose at the moment of reperfusion. After surgery, a 0.5 mg/kg dose of prednisone was given daily and progressively tapered to a total dose of 5 mg/day. Steroids were associated with a combination of tacrolimus (dose was adjusted for a therapeutic range of 10–15 ng/ml in the induction period and 5–10 ng/ml in maintenance) or cyclosporine (dose was adjusted for a therapeutic range of 100–300 ng/ml in the induction period and 50–200 ng/ml in maintenance) with mycophenolate mofetil (dose was adjusted for a therapeutic range of 2–4 μg/ml) or azathioprine (1.5 mg/kg every 24 h). Rapamycin (5 mg per 24 h) was used in some cases.

Definition of acute rejection

Acute rejection was suspected in the case of an elevation of serum creatinine (without an evident alternative diagnosis) and diagnosed by histological examination if possible. If biopsy was not technically possible, 'intended-to-treat' episodes that respond to antirejection therapy were also taken into account. *Graft loss* was defined as the requirement for dialysis and/or loss of a functioning graft because of death of the renal transplant recipient.

Treatment for acute rejection episodes

Intravenous corticosteroid boluses were administered for 5 consecutive days followed by antithymocytic globulin in the event of corticosteroid resistance (manifested as the persistence or exacerbation of elevated serum creatinine after the last bolus and the absence of histological improvement).

Antibiotic prophylaxis

All the patients received 2 g of intravenous cefazolin intraoperatively. Postoperative antibiotic prophylaxis consisted of 160/800 mg of trimethoprim–sulfamethoxazole administered three times a week for the first 3–6 months to prevent *Pneumocystis jiroveci* pneumonia and other infections. Ganciclovir or valganciclovir were administered as prophylaxis or pre-emptive treatment for cytomegalovirus infection according to the Spanish guidelines.[21]

Infectious disease definitions

Bacteriuria was defined as two consecutive voided urine specimens with isolation of the same bacterial strain in quantitative counts $>10^5$ colony-forming units (cfu/ml) in asymptomatic women. A single, clean-catch voided urine specimen with one bacterial species isolated in a quantitative count of $>10^5$ cfu/ml defined asymptomatic bacteriuria in men. A single catheterized urine specimen with one bacterial species isolated in a quantitative count of $>10^2$ cfu/ml identified bacteriuria in women or men. Asymptomatic bacteriuria was defined by the presence of bacteriuria in the absence of any symptoms of lower or upper UTI. Cystitis was defined by the presence of bacteriuria and clinical manifestations as dysuria, frequency, or urinary urgency in the absence of pyelonephritis criteria. Pyelonephritis was defined by the simultaneous presence of a urine bacteria count of more than 10^5 cfu/ml and/or bacteremia and fever with one or more of the following four categories: lumbar pain, over graft pain, chills, criteria for cystitis (bacteriuria and clinical manifestations such as dysuria, frequent urination, or urinary urgency).[14] Reinfection was defined by a new episode of infection with the isolation of a bacteria other than the one that caused the previous infection or the same bacteria with different antibiotic sensitivity pattern.[22] Relapse was defined as the isolation of the same microorganism that caused the preceding infection, with the same antibiotic sensitivity pattern, in a urine culture obtained $\geqslant 2$ weeks after finishing the previous treatment. Recurrent infection was defined as $\geqslant 3$ UTI in a 12-month period.

Antibiotic treatment

According to the protocol, every episode of asymptomatic bacteriuria should be treated with antibiotics. Every episode of symptomatic UTI was treated with antibiotics. Asymptomatic bacteriuria and cystitis were treated with an oral antibiotic for 5–7 days, according to the antibiotic susceptibility of the microorganism isolated. The antibiotics recommended for asymptomatic bacteriuria treatment, in order of preference, were: ciprofloxacin 250 mg per 12 h for 3 days; cefuroxime 250 mg per 12 h for 7 days; amoxicillin–clavulanate 500–125 per 8 h for 7 days; and fosfomicin 3 g in a single dose and a repeated dose 72 h later In the event of pyelonephritis, the antibiotic was administered intravenously, according to the antibiotic susceptibility of the microorganism isolated, until the patient was afebrile and then orally for a total of at least 14 days.

Visiting schedule and monitoring of asymptomatic bacteriuria

Asymptomatic bacteriuria was systematically investigated in every patient over a 3-year follow-up period. A urine sample was processed every fortnight in the first trimester after transplantation, monthly between months 4 and 12, every 2 months between months 13 and 18, and every 3 months from months 19 to 36. In every visit, the patient was clinically questioned, physically explored, and a blood sample and a urine midstream specimen were obtained for urine culture and determination of serum creatinine (mg/ml), creatinine clearance (ml/min), and proteinuria (calculated both in g/dl and g per 24 h). Samples were also taken in the event of symptomatic UTI and blood cultures were drawn in the event of fever. In every episode of asymptomatic bacteriuria, cystitis, or pyelonephritis, a postreatment-control urine culture was performed 2 weeks later. Urological evaluation was carried out for patients who developed a second episode of pyelonephritis. Long-term renal graft function was evaluated by means of serum creatinine, creatinine clearance, and proteinuria throughout follow-up.

Data analysis

Continuous variables were expressed as the mean ($\pm$ s.d.) for those values with a normal distribution and as the median (mostly for those with a skewed distribution). Discrete variables were expressed as percentages. Student's unpaired *t*-test was used to compare continuous variables, the Mann–Whitney *U*-test was used to compare continuous variables with non-normal distribution, and the χ^2 or Fisher's exact test was used to compare proportions. All statistical tests were two tailed and the threshold of statistical significance was $P<0.05$. ORs were calculated for variables with statistically significant differences between patients with or without asymptomatic bacteriuria. Binary logistic regression was applied

individually to each variable to obtain the OR in the univariate analysis. Statistically significant variables ($P<0.05$) in the univariate analysis were introduced in a multivariate model by the use of forward stepwise logistic regression, to identify the independent risk factors for asymptomatic bacteriuria. Additionally, those factors with P-values <0.1 that were considered clinically relevant were forced in the multivariate model to investigate their effect. Long-term repercussion of asymptomatic bacteriuria in the renal graft function, determined as evolutive tendencies of serum creatinine, creatinine clearance, and proteinuria, was assessed by variance analysis (two-way ANOVA test for repeated measures). Using a standard ANOVA in this case is not appropriate because it fails to model the correlation between the repeated measures: the data violate the ANOVA assumption of independence. ANOVA test was used for comparing the means in creatinine, creatinine clearance, and proteinuria between the groups of patients who did or not did develop asymptomatic bacteriuria episodes throughout the follow-up period. The SPSS statistical software, version 13.0 (Chicago, IL, USA), was used for performing calculations.

DISCLOSURE

All the authors declared no competing interests.

ACKNOWLEDGMENTS

S Fiorante was supported by a grant of the Spanish International Cooperation Agency (AECI-Ministerio de Asuntos Exteriores). F López-Medrano was supported by a grant of Fundación Mutua Madrileña. We thank Martin Smyth, for the revision of the English version of the manuscript.

REFERENCES

1. Fishman JA. Infection in solid-organ transplant recipients. *N Engl J Med* 2007; **357**: 2601–2614.
2. Rubin RH, Tolkoff-Rubin NE. The impact of infection on the outcome of transplantation. *Transplant Proc* 1991; **23**: 2068–2074.
3. Takai K, Aoki A, Suga A *et al.* Urinary tract infections following renal transplantation. *Transplant Proc* 1998; **30**: 3140–3141.
4. Schmaldienst S, Dittrich E, Horl WH. Urinary tract infections after renal transplantation. *Curr Opin Urol* 2002; **12**: 125–130.
5. Odland MD. Surgical technique/post-transplant surgical complications. *Surg Clin North Am* 1998; **78**: 55–60.
6. Rabkin DG, Stifelman MD, Birkhoff J *et al.* Early catheter removal decreases incidence of urinary tract infections in renal transplant recipients. *Transplant Proc* 1998; **30**: 4314–4316.
7. Nicolle LE, Bradley S, Colgan R *et al.* Infectious Diseases Society of America guidelines for the diagnosis and treatment of asymptomatic bacteriuria in adults. *Clin Infect Dis* 2005; **40**: 643–654.
8. Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). *Kidney Int Suppl* 2009: S1–130.
9. Chuang P, Parikh CR, Langone A. Urinary tract infections after renal transplantation: a retrospective review at two US transplant centers. *Clin Transplant* 2005; **19**: 230–235.
10. Abbott KC, Swanson SJ, Richter ER *et al.* Late urinary tract infection after renal transplantation in the United States. *Am J Kidney Dis* 2004; **44**: 353–362.
11. Dupont PJ, Psimenou E, Lord R *et al.* Late recurrent urinary tract infections may produce renal allograft scarring even in the absence of symptoms or vesicoureteric reflux. *Transplantation* 2007; **84**: 351–355.
12. Ramsey DE, Finch WT, Birtch AG. Urinary tract infections in kidney transplant recipients. *Arch Surg* 1979; **114**: 1022–1025.
13. Prat V, Horcickova M, Matousovic K *et al.* Urinary tract infection in renal transplant patients. *Infection* 1985; **13**: 207–210.
14. Nicolle LE. Uncomplicated urinary tract infection in adults including uncomplicated pyelonephritis. *Urol Clin North Am* 2008; **35**: 1–12, v.
15. Kamath NS, John GT, Neelakantan N *et al.* Acute graft pyelonephritis following renal transplantation. *Transpl Infect Dis* 2006; **8**: 140–147.
16. Staskewitz A, Kirste G, Tonshoff B *et al.* Mycophenolate mofetil in pediatric renal transplantation without induction therapy: results after 12 months of treatment. German Pediatric Renal Transplantation Study Group. *Transplantation* 2001; **71**: 638–644.
17. Muller V, Becker G, Delfs M *et al.* Do urinary tract infections trigger chronic kidney transplant rejection in man? *J Urol* 1998; **159**: 1826–1829.
18. Pelle G, Vimont S, Levy PP *et al.* Acute pyelonephritis represents a risk factor impairing long-term kidney graft function. *Am J Transplant* 2007; **7**: 899–907.
19. Audard V, Amor M, Desvaux D *et al.* Acute graft pyelonephritis: a potential cause of acute rejection in renal transplant. *Transplantation* 2005; **80**: 1128–1130.
20. Valera B, Gentil MA, Cabello V *et al.* Epidemiology of urinary infections in renal transplant recipients. *Transplant Proc* 2006; **38**: 2414–2415.
21. Torre-Cisneros J, Fortun J, Aguado JM *et al.* [Consensus document from GESITRA-SEIMC on the prevention and treatment of cytomegalovirus infection in transplanted patients]. *Enferm Infecc Microbiol Clin* 2005; **23**: 424–437.
22. Ronald AR, Pattullo AL. The natural history of urinary infection in adults. *Med Clin North Am* 1991; **75**: 299–312.