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ORIGINAL ARTICLE

Diagnosis and management of asymptomatic bacteriuria in kidney transplant recipients: a survey of current practice in Europe

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ABSTRACT

Background. Asymptomatic bacteriuria is frequent in kidney transplant recipients (KTRs). However, there is no consensus on diagnosis or management. We conducted a European survey to explore current practice related to the diagnosis and management of asymptomatic bacteriuria in adult KTRs.

Methods. A panel of experts from the European Renal Association–European Dialysis Transplant Association/Developing Education Science and Care for Renal Transplantation in European States working group and the European Study Group for Infections in Compromised Hosts of the European Society of Clinical Microbiology and Infectious Diseases designed this cross-sectional, questionnaire-based, self-administered survey. Invitations to participate were e-mailed to European physicians involved in the care of KTRs.

Results. Two hundred and forty-four participants from 138 institutions in 25 countries answered the survey (response rate 30%). Most participants [72% (176/244)] said they always screen for asymptomatic bacteriuria in KTRs. Six per cent (15/240) reported never treating asymptomatic bacteriuria with antibiotics. When antimicrobial treatment was used, 24% of the participants (53/224) said they would start with empirical antibiotics. For an episode of asymptomatic bacteriuria caused by a fully susceptible microorganism and despite no contraindications, a majority of participants (121/223) said they would use a fluoroquinolone ($n = 56$), amoxicillin/clavulanic acid ($n = 38$) or oral cephalosporins ($n = 27$).

Conclusions. Screening for and treating asymptomatic bacteriuria are common in KTRs despite uncertainties around the benefits and harms. In an era of antimicrobial resistance, further studies are needed to address the diagnosis and management of asymptomatic bacteriuria in these patients.

Keywords: antimicrobial stewardship, asymptomatic bacteriuria, questionnaire, transplantation, urinary tract infection

INTRODUCTION

Kidney transplantation is the renal replacement treatment of choice for many patients living with end-stage kidney disease. According to a report from the Global Observatory on Donation and Transplantation (World Health Organization), nearly 85 000 people worldwide received a kidney transplant in 2015 [1].

Asymptomatic bacteriuria, defined as bacteriuria without signs or symptoms of urinary tract infection (UTI), is a

common finding in kidney transplant recipients (KTRs), occurring in 17–51% of these patients [2, 3]. In individuals who have not had a kidney transplant, available data do not support screening for or treating asymptomatic bacteriuria with antibiotics except in pregnant women and patients awaiting transurethral resection of the prostate [4]. In KTRs, there is no consensus on the diagnosis and management of asymptomatic bacteriuria [3–10]. Because signs and symptoms of symptomatic UTI (e.g. acute pyelonephritis) are impaired as a result of transplant denervation and the use of antirejection medications [11], some transplant physicians screen for and treat asymptomatic bacteriuria in KTRs under the unproven assumption that this approach will reduce the incidence of subsequent symptomatic UTI and improve patient and graft outcomes [2, 12].

However, antibiotic use also has harmful effects. Above all, antimicrobial use is a key driver for antimicrobial resistance selection [13]. This issue is of particular importance in the field of transplantation, where antimicrobial resistance is a rapidly evolving and worrisome issue [14]. Indeed, in the last few years, we and others have observed a rapid increase in antimicrobial resistance rates in KTRs with bacteriuria [15–17]. In addition, antimicrobial use is associated with direct adverse effects, including fluoroquinolone-induced tendinopathy, and promotes *Clostridium difficile*–associated diarrhoea. Furthermore, antibiotics increase the costs of patient care.

Despite the frequency of asymptomatic bacteriuria after kidney transplantation and the risks of promoting antimicrobial resistance and other adverse events by using antibiotics, there is very little information on current practices regarding the management of asymptomatic bacteriuria after kidney transplantation. The results of three additional trials that have investigated the effects of screening for and treating asymptomatic bacteriuria in KTRs will soon become available, so better knowledge of current practice would be useful to help determine how strategies will need to change in the future in order to optimize antibiotic use and patient outcomes [18–20].

This survey aims to assess the current status of diagnosis and management of asymptomatic bacteriuria in adult KTRs in Europe.

MATERIALS AND METHODS

Survey content

A panel of experts from the European Renal Association–European Dialysis Transplant Association (ERA-EDTA) Developing Education Science and Care for Renal Transplantation in European States (DESCARTES) working group and the European Study Group for Infections in Compromised Hosts (ESGICH) of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) designed a cross-sectional, questionnaire-based, self-administered survey that was approved by the board members of both working groups. The survey content was based on a review of the literature and adapted by consensus to require ∼5 min for completion. Pretesting was conducted on a sample of colleagues from our departments and we subsequently modified the survey in order to limit misinterpretations of questions and errors. The online survey was created using SurveyMonkey (Palo Alto, CA, USA; https://www.surveymonkey.com). A paper version of our questionnaire can be found in the Appendix provided as Supplementary Material. Briefly, the questionnaire included 17 items subdivided into three sections: 6 questions concerning participants' characteristics (Section 1), 5 questions on the diagnosis of asymptomatic bacteriuria after kidney transplantation (Section 2) and 6 questions regarding its management (Section 3). Ethics committee approval was deemed unnecessary for this study, as our survey only collected the personal opinions of physicians and did not contact patients or require any specific patient data.

Survey participants

Our target population was European physicians directly involved in the care of adult KTRs, including not only nephrologists, but also transplant surgeons and infectious disease physicians. An invitation message including the survey link was emailed to 649 physicians from 33 European countries using the ERA-EDTA/DESCARTES official e-mail address. This mailing list was created by merging the lists of the members of the ERA-EDTA/DESCARTES and ESCMID/ESGICH working groups with two databases previously used to conduct European studies focusing on transplant infectious diseases [21, 22]. The mailing list was checked before sending the invitation e-mails. Reminder e-mails were sent by the survey coordinators to non-respondents to increase the survey response rate. We offered no money for survey participation. Physicians who do not personally take care of adult kidney transplant recipients on a regular basis were asked not to answer the survey. The survey was open online between 27 June and 5 October 2017.

Data collection and statistical analysis

All the entered data were checked before the final analysis. If we received more than one completed survey from a transplant centre, they were all included for analysis, because practice may vary not only from one transplant centre to another but also from one physician to another within a transplant centre. A survey was considered complete if answers were given to all three sections of the questionnaire and partially complete if only the first two sections of the questionnaire were completed. The response rate was defined as the ratio of the number of respondents (partial and complete responses obtained from invited candidates) to the total number of invited candidates ($n = 649$). Surveys in which only the first section of the survey was completed were excluded from the analysis. Categorical variables are presented as numbers and percentages.

RESULTS

Response rate and characteristics of survey participants

A total of 244 (240 complete and 4 partial) responses were obtained from physicians from 138 institutions in 25 European countries. Of these 244 respondents, 196 (80%) had received the survey link from our invitation e-mail [response rate 30% (196/649)]. We also received 48 responses from physicians who had not been directly invited by e-mail to participate in the

Table 1. Number of participants per country

Country	Number of invitations	Number of participants	Number of participating institutions
France	114	49	22
Spain	67	36	19
Belgium	49	36	15
Italy	82	25	19
Greece	10	19	10
Switzerland	23	16	7
UK	53	15	11
Germany	82	9	8
Poland	33	8	4
Albania	3	5	2
The Netherlands	18	5	2
Denmark	26	4	3
Croatia	5	2	2
Czech Republic	10	2	2
Luxembourg	2	2	1
Andorra	0	1	1
Austria	8	1	1
Bosnia and Herzegovina	2	1	1
Cyprus	2	1	1
Ireland	3	1	1
Macedonia	3	1	1
Montenegro	3	1	1
Portugal	6	1	1
Romania	10	1	1
Serbia	5	1	1
Slovakia	4	1	1
Finland	2	0	0
Hungary	5	0	0
Iceland	2	0	0
Lithuania	1	0	0
Malta	1	0	0
Norway	6	0	0
Slovenia	1	0	0
Sweden	8	0	0
Total number	649	244	138

A total of 244 responses were obtained from physicians in 138 institutions from 25 European countries. Of these respondents, 196/244 (80%) participated directly following receipt of our invitation message [response rate 30% (196/649)]. We also obtained 48 responses from physicians who were not directly invited by e-mail to participate in the study but had been forwarded the questionnaire by a colleague.

Table 2. Characteristics of the 244 survey participants

Characteristics	*n* (%)
Specialty	
Nephrology	213 (87.3)
Infectious diseases	17 (7)
Transplant surgery	7 (2.9)
Transplant infectious diseases	4 (1.6)
Other	3 (1.2)
Level of medical experience	
Junior doctor	5 (2)
Staff physician for <5 years	36 (14.8)
Staff physican 5–20 years	111 (45.5)
Staff physician for >20 years	92 (37.3)
Years of clinical experience with KTRs ($n = 242$)	
<1	1 (0.4)
1–5	48 (19.8)
5–20	111 (45.9)
>20	82 (33.9)
Number of kidney transplants performed last year in the institution ($n = 242$)	
<25	22 (9.1)
25–50	38 (15.7)
50–100	81 (33.5)
100–150	49 (20.2)
150	24 (9.9)
Centre where transplant recipients are followed up but no transplants are performed	28 (11.6)
Number of KTRs personally managed every week, as in- or outpatients	
<5	45 (18.4)
6–14	70 (28.7)
15–24	53 (21.7)
≥25	76 (31.1)

study but had the questionnaire forwarded to them by a colleague (Table 1). The characteristics of survey participants are shown in Table 2. Most participants were nephrologists [87% (213/244)] and had at least 5 years experience with KTRs [80% (193/242)]. Fifty-five per cent of respondents (134/244) worked in one of the five largest European countries in terms of population (i.e. Germany, France, the UK, Italy and Spain, which have a total population of ∼320 million).

Diagnosis of asymptomatic bacteriuria after kidney transplantation

Most participants [72% (176/244)] replied that they always screen for asymptomatic bacteriuria in KTRs attending the outpatient clinic; 18% (44/244) screened only in the first months after transplantation (Table 3). Thus 10% of participants (24/244) said they never screen for asymptomatic bacteriuria. When screening for asymptomatic bacteriuria, half of the participants [51% (110/214)] said they proceeded directly with urine culture and the other half [49% (104/214)] first performed a dipstick test and used urine cultures only if the dipstick test suggested the presence of bacteriuria. One in two participants (108/215) said they used a threshold of ≥100 000 colony forming units (CFU)/mL to discriminate between 'true bacteriuria' and urine contamination in asymptomatic KTRs. Other participants used either a lower threshold [22% (47/215)] or did not use a fixed threshold [28% (60/215)]. Last, 41% of participants declared that KTRs were not systematically educated in their institution in order to ensure that skin cleansing and midstream collection are performed when providing samples for urinalysis.

Management of asymptomatic bacteriuria after kidney transplantation

Six per cent of the participants (15/240) reported never treating asymptomatic bacteriuria with antibiotics in KTRs (Table 4). Fifteen per cent of participants (37/240) said they treated asymptomatic bacteriuria always or most of the time. The majority of participants said they would treat asymptomatic bacteriuria in selected situations, such as when a KTR has a urinary device [50% (121/240)], when the patient is early after transplantation [43% (103/240)], if the serum level of C-reactive protein (CRP) is increased [42% (102/240)], if the patient had a recent history of symptomatic UTI [42% (101/240)] or if the urine leucocyte count is elevated [27% (65/240)]. When a

Table 3. Answers obtained regarding diagnosis of asymptomatic bacteriuria after kidney transplantation

Question	*n* (%)
In stable, asymptomatic adult KTRs attending the outpatient clinic, do you test the urine (dipstick test and/or urine culture) to screen for bacteriuria?	
Yes, always	176 (72.1)
Yes, but only during the first 2 months after transplantation	16 (6.6)
Yes, but only during the first 6 months after transplantation	15 (6.1)
Yes, but only during the first 12 months after transplantation	13 (5.3)
Never	24 (9.8)
How do you usually screen for asymptomatic bacteriuria? ($n = 214$)	
I first perform a urine test strip (i.e. a dipstick test). If the test is abnormal (e.g. suggests the presence of leucocytes), I proceed to urine culture	104 (48.6)
I do not use urine test strips (i.e. dipstick tests), but proceed directly with urine culture	110 (51.4)
When a urine culture shows asymptomatic bacteriuria (e.g. >100 000 CFU/mL) of *E. coli*), do you immediately perform a second urine culture to confirm the result? ($n = 215$)	
No, I consider this single result as positive	101 (47)
Only in female KTRs	8 (3.7)
Only if, after questioning the patient, contamination is suspected because of inappropriate urine collection (e.g. no clean catch midstream urine sample)	85 (39.5)
Yes, always	36 (16.7)
What threshold of CFU/mL do you use to discriminate between 'true bacteriuria' and urine contamination in asymptomatic KTRs? ($n = 215$)	
>1000 CFU/mL	7 (3.3)
>10 000 CFU/mL	33 (15.3)
>50 000 CFU/mL	7 (3.3)
≥100 000 CFU/mL	108 (50.2)
I do not use a fixed threshold	60 (27.9)
Are KTRs educated in order to ensure that skin cleansing and midstream collection are performed when providing samples for urinalysis? ($n = 216$)	
Yes, KTRs are systematically educated (e.g. at time of transplant)	128 (59.3)
Occasionally (information provided on a case-by-case basis rather than systematically)	64 (29.6)
No, patients are not educated	11 (5.1)
I do not know	13 (6)

This section of the questionnaire focused on stable adult KTRs who do not have urinary devices such as bladder catheters or JJ stents.

Table 4. Answers obtained regarding management of asymptomatic bacteriuria after kidney transplantation

Question	*n* (%)
Do you treat asymptomatic bacteriuria (e.g. >100 000 CFU/mL of *E. coli*) with antibiotics in adult KTRs? ($n = 240$)	
Never	15 (6.2)
Yes, in patients who are early after transplantation (e.g. within the first 6 months)	103 (42.9)
Yes, in patients who have urinary devices (e.g. bladder catheter or JJ stent)	121 (50.4)
Yes, in patients who are expected to have a urological procedure (e.g. removal of JJ stent) or a kidney graft biopsy in the next few days	181 (75.4)
Yes, in patients with a recent history of symptomatic UTI	101 (42.1)
Yes, in patients with a raised urine leucocyte count	65 (27.1)
Yes, in patients with an increased serum level of CRP	102 (42.5)
Yes, most of the time	30 (12.5)
Yes, always	7 (1.9)
If you decide to treat an episode of asymptomatic bacteriuria after kidney transplantation, when do you start antibiotics? ($n = 224$)	
I start antibiotics before the results of antimicrobial susceptibility testing are available and subsequently adapt the therapy (empirical therapy)	53 (23.7)
I wait for antimicrobial susceptibility testing results before starting therapy	171 (76.3)
If you have decided to treat an episode of asymptomatic bacteriuria caused by a fully susceptible microorganism (e.g. wild-type *E. coli*), what is your preferred oral treatment in the absence of any contraindication? ($n = 223$)	
Fluoroquinolone	56 (25.1)
Fosfomycin	40 (17.9)
Amoxicillin/clavulanic acid	38 (17)
Oral cephalosporin	27 (12.1)
Amoxicillin	25 (11.2)
Nitrofurantoin	8 (3.6)
Cotrimoxazole (i.e. trimethoprim–sulfamethoxazole)	6 (2.7)
Pivmecillinam	6 (2.7)
I do not have a preferred oral agent	17 (7.6)
If you have decided to treat an episode of asymptomatic bacteriuria in a stable KTR but the microorganism is not treatable using available oral antibiotics (e.g. carbapenemase-producing *Klebsiella* spp.), what do you do? ($n = 221$)	
I give no antibiotics and arrange a follow-up visit	130 (58.8)
I arrange hospital admission for parenteral antibiotics	47 (21.3)
I prescribe parenteral antibiotics at home or at the outpatient clinic	44 (19.9)
What duration of antimicrobial therapy do you use in the majority of cases of asymptomatic bacteriuria in female KTRs? ($n = 225$)	
<5 days	63 (28)
5–9 days	136 (60.4)
10–14 days	24 (10.7)
>14 days	2 (0.9)
What duration of antimicrobial therapy do you use in the majority of cases of asymptomatic bacteriuria in male KTRs? ($n = 225$)	
<5 days	34 (15.1)
5–9 days	121 (53.8)
10–14 days	63 (28)
>14 days	7 (3.1)

decision was made to use antimicrobial treatment, 24% of the participants (53/224) said they would start with empirical antibiotics (i.e. initiation of antimicrobial therapy before the results of antimicrobial susceptibility testing are available). In the hypothetical case of an episode of asymptomatic bacteriuria caused by a fully susceptible microorganism (e.g. wild-type *Escherichia coli*) and despite the absence of any contraindication, a majority of the participants (54%) said they would use either a fluoroquinolone (56/223), amoxicillin/clavulanic acid

(38/223) or an oral cephalosporin (27/223). In the hypothetical case of an episode of asymptomatic bacteriuria caused by a microorganism not treatable using available oral antibiotics (e.g. carbapenemase-producing *Klebsiella* spp.), most participants said they would not give antibiotics and would arrange a follow-up visit [59% (130/221)]. However, 41% of the respondents said they would administer parenteral antibiotics, either in the hospital or at home. In our sample, participants were more likely to use ≥10 days of antimicrobial therapy for asymptomatic bacteriuria in male KTRs compared with female patients [31% (70/225) versus 12% (26/225)].

DISCUSSION

Our results suggest that screening for and treating asymptomatic bacteriuria after kidney transplantation are common in Europe. The two main findings of our survey are that most participants (72%) said they always screen for asymptomatic bacteriuria in KTRs attending the outpatient clinic and only 6% of the participants said they would never treat asymptomatic bacteriuria with antibiotics in KTRs.

To date, there have been two interventional studies comparing antibiotic administration versus no treatment for asymptomatic bacteriuria in KTRs [23, 24]. In a recent Cochrane systematic review of these two studies, in which the incidence of symptomatic UTI was 25% in patients who were not treated, the effects of the antibiotics on the incidence of symptomatic UTI were unclear [risk ratio 0.86 (95% confidence interval 0.51–1.45)] [10]. The conclusions of this systematic review were that there is insufficient evidence to support the use of antibiotics in this situation due to scarce data and low-quality evidence [10]. Despite this, 15% of participants in our survey systematically treat asymptomatic bacteriuria. Moreover, a large number of participants said they would treat asymptomatic bacteriuria in selected situations, such as when KTRs have urinary devices, when they have a recent history of symptomatic UTI or when the urine leucocyte count is elevated. Interestingly, studies conducted in non-transplant patients showed that these three conditions (i.e. presence of urinary devices, increased urine leucocyte count and recent history of symptomatic UTI) are not indications for treating asymptomatic bacteriuria with antibiotics [4, 25]. In our survey, other indications for treating asymptomatic bacteriuria included an increased serum level of CRP or occurrence within the first months after transplantation. More research is needed to investigate whether these specific situations are indications for treating asymptomatic bacteriuria in KTRs.

Regarding the type of antimicrobial treatment used for asymptomatic bacteriuria in KTRs, our survey provided surprising results. First, about a quarter of participants said they used empirical therapy for the treatment of asymptomatic bacteriuria (i.e. initiation of antimicrobial therapy before the results of antimicrobial susceptibility testing are available). This strategy is likely to be associated with harmful effects and the potential benefits are questionable. Second, in the hypothetical case of an episode of asymptomatic bacteriuria caused by a fully susceptible organism (e.g. wild-type *E. coli*) and despite the absence of any contraindication, a majority of the participants (54%) selected antibiotics known to have an important impact on the gut microbiota and associated with the emergence of antimicrobial resistance, such as fluoroquinolones, amoxicillin/clavulanic acid or oral cephalosporins [26]. Moreover, the use of fluoroquinolones is associated with a significant risk of tendon injury in patients with renal disease and/or taking corticosteroids [27]. Because there is no evidence that treating asymptomatic bacteriuria with antibiotics is beneficial in KTRs, it is of course not possible to recommend one antimicrobial drug over another. Third, when we gave the example of a stable KTR with asymptomatic bacteriuria not treatable using available oral antibiotics, we were surprised to find that 41% of respondents decided to initiate parenteral antibiotics.

Regarding the criteria used to diagnose asymptomatic bacteriuria, our survey revealed several discrepancies between the 2005 guidelines from the Infectious Diseases Society of America [4] and current European practice in kidney transplant patients. First, the threshold of ≥100 000 CFU/mL, which is recommended to discriminate between 'true bacteriuria' and urine contamination in non-catheterized individuals, was used by only half of our participants. Second, 41% of participants declared that KTRs were not systematically educated in their institution in order to ensure that skin cleansing and midstream collection are performed when providing samples for urinalysis. As a consequence, there is a risk of urine contamination and misdiagnosis of asymptomatic bacteriuria, possibly leading to unnecessary antibiotic prescription. Finally, it was surprising that half of the participants said they use a dipstick test to screen for asymptomatic bacteriuria (i.e. limiting the use of urine cultures to situations in which the dipstick test showed abnormal results). To our knowledge, the usefulness of dipstick tests has not been demonstrated for the diagnosis of bacteriuria in KTRs [8, 28].

Our survey has several limitations. First, the non-response rate of 70% may have significantly biased our findings. However, high response rates are difficult to achieve in transplantation and ours is relatively good compared with recently published European questionnaire-based surveys focusing on infectious diseases in transplant patients [22, 29, 30]. The fact that we obtained responses from a large number of participants from 138 institutions in 25 European countries and the characteristics of participants suggest that our survey provides a reasonable snapshot of current European practice regarding asymptomatic bacteriuria after kidney transplantation. It is difficult, however, to precisely measure the effect of non-response on the representativeness of our survey. For instance, we were unable to compare the characteristics of participants with those of non-respondents due to a lack of information on people not participating. One could say that most participants came from western Europe and, as a result, our findings may not adequately reflect current practice in underrepresented areas, such as central or northern Europe. Ideally, future surveys on kidney transplantation practices in Europe should have a more balanced representation across Europe. To achieve this target, including one survey coordinator per European country might be useful.

In conclusion, screening for and treating asymptomatic bacteriuria after kidney transplantation is common in Europe

despite uncertainties around their benefits and harms. It is welcome and reassuring that three additional randomized controlled trials comparing antibiotics versus no therapy for asymptomatic bacteriuria in KTRs are ongoing [18–20]. Their results are likely to change and improve current practice in this field.

SUPPLEMENTARY DATA

Supplementary data are available at ndt online.

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AUTHORS' CONTRIBUTIONS

J.C. conceived the study and drafted the protocol, with help from all other authors. All authors participated to the collating of an up-to-date mailing list and checked the mailing list before sending invitation e-mails. J.C. checked and analysed the results. J.C. drafted the manuscript with the help of all other authors, who revised it critically. All authors approved the final version of the manuscript.

CONFLICT OF INTEREST STATEMENT

None declared.

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