Should we treat asymptomatic bacteriuria after renal transplantation?

Julien Coussement¹ and Daniel Abramowicz²

¹Department of Nephrology, Dialysis and Kidney Transplantation, Hôpital Erasme – Université Libre de Bruxelles, Brussels, Belgium and ²Department of Nephrology-Hypertension, Universitair Ziekenhuis Antwerpen, Edegem, Belgium

Correspondence and offprint requests to: Julien Coussement; E-mail: julien.coussement@erasme.ulb.ac.be

Infections remain a major cause of morbidity and mortality in the modern kidney transplantation era [1]. Symptomatic urinary tract infections (UTIs), which are defined as the association of a positive urine culture with the presence of symptoms or signs referable to UTI, are usually divided into lower tract (cystitis) and upper tract (pyelonephritis) infections. It is the most common infection in this population, both short-term as well as long-term post-transplantation [2]. As a consequence, UTI is the leading cause of antibiotic administration in kidney transplant recipients [3]. The highest incidence of symptomatic UTIs occurs during the first months after transplantation [4, 5]. In a registry study conducted by the Spanish Network for Research on Infection in Transplantation (RESITRA) in 2052 kidney transplant recipients with at least 1 year of follow-up, symptomatic UTIs occurred in 150 patients (7.3%) with an incidence rate of 0.45 episodes per 1000 transplantation days [4]. Escherichia coli and Enterococcus are known to account for more than half of bacterial UTIs post-kidney transplantation [2–5].

In a time of increasing resistance to antimicrobial agents and rising health-related costs, factors that trigger UTIs need to be understood, and if possible prevented. As in the general population, female gender is the strongest risk factor for UTI in kidney transplant recipients [4, 6, 7]. In comparison with men, the shorter urethra contributes to this phenomenon. Other risk factors such as advanced age, diabetes mellitus, primary end-stage renal disease, urinary tract abnormalities, cadaveric donor kidney, graft dysfunction and rejection, CMV infection and prolonged time on dialysis prior to transplantation have been pinpointed in some series [2, 6–10]. Identification of treatable risk factors is of interest as it may lead to a reduction in the frequency of symptomatic UTIs.

Whether asymptomatic bacteriuria is a modifiable risk factor for symptomatic episodes and could impact the global prognosis of the transplanted patient (and should therefore be screened for and treated) remains controversial [11]. The Infectious Diseases Society of America (IDSA) defines asymptomatic bacteriuria as isolation of a specified quantitative count of bacteria (≥10⁵ CFU/mL) in an appropriately collected urine sample obtained from a person without symptoms or signs referable to a UTI [12]. While a single urine specimen is sufficient to define asymptomatic bacteriuria in men, it is usually defined in women as two consecutively voided urine specimens with isolation of the same bacterial strain in quantitative counts ≥10⁵ CFU/mL. This definition stems from a study showing that, in non-transplanted women, when the first specimen contains at least 10⁵ bacteria per millilitre of urine, there is an 80% probability that the patient has true bacteriuria [13]. That 20% of women have a negative second culture is thought to reflect transient bacteriuria rather than contamination [14].

Asymptomatic bacteriuria is a common event after renal transplantation. For instance, Fiorante et al. showed that 51% of the recipients develop asymptomatic bacteriuria—as defined by the IDSA guidelines—during the 3 years following transplantation [15]. Therefore, the question of its management remains a daily unsolved problem for transplant physicians. Antibiotic overuse could lead to the emergence of bacterial resistance and antimicrobial agents’ side effects. In addition, important costs are associated with the strategy of systematic screening and treatment of post-kidney transplantation asymptomatic bacteriuria, such as the costs of urinalyses, antibiotics and even hospitalization of asymptomatic patients. This is a matter of concern in a time of limited health-care resources.

To date, no study has demonstrated a clear benefit in treating asymptomatic bacteriuria with antimicrobial agents in kidney transplant recipients [15–17]. Of the studies published addressing this question, only one was prospective. This small trial, conducted in 88 Iranian patients, did not show a statistically significant decreased rate of symptomatic UTIs when kidney transplant recipients with asymptomatic bacteriuria were treated with a 10-day course of antibiotics [17]. Nine of the 43 treated patients (21%) developed symptomatic UTI during the 9–12 months of follow-up, in comparison with 14
of 45 patients in the untreated arm (31%, P > 0.05). In addition to being underpowered, the lack of data concerning any chronological or microbiological link between asymptomatic and symptomatic episodes limits the quality and generalizability of these results. More recently, a retrospective study showed that of 67 untreated episodes of asymptomatic Escherichia coli or Enterococcus faecalis bacteriuria (defined as a specimen containing 10^6 or more bacteria per millilitre of urine) occurring in kidney transplant recipients, only one was followed by a symptomatic UTI [16]. Moreover, Green et al. recently reported in a retrospective study of 112 kidney transplant recipients with asymptomatic bacteriuria that the risk of developing symptomatic UTI at 6 months after asymptomatic bacteriuria was significantly increased in treated patients compared to those who remained untreated [18].

Therefore, the causal link between asymptomatic and symptomatic episodes of UTI in kidney transplantation is questionable. Asymptomatic bacteriuria, which has been considered in the last decades as a risk factor for symptomatic UTIs in this population, may therefore only be a risk marker. In other words, it would identify patients who are at higher risk of later developing a symptomatic UTI, possibly with another pathogen, regardless of the prior asymptomatic infection having been treated or not. This hypothesis is supported by a recent retrospective study from Fiorante et al. that showed that pyelonephritis and cystitis were more common in kidney transplant recipients with asymptomatic bacteriuria, even if this condition was usually treated in this series [15]. Because the treatment of a risk marker is usually not associated with any benefit, whether there is anything to be gained from treating asymptomatic bacteriuria in kidney transplant patients has to be clarified.

Understanding asymptomatic bacteriuria condition in non-transplanted individuals may help to appropriately manage this process in our specific population. For instance, antimicrobial treatment of asymptomatic bacteriuria among pregnant women significantly decreased the frequency of acute pyelonephritis, low-birth weight infants and preterm delivery [12]. Nevertheless, this finding has not been reproduced in other patient populations. Indeed, prospective randomized studies showed that treatment of asymptomatic bacteriuria in populations where this condition is frequent, such as diabetic women [19], elderly ambulatory non-hospitalized women [20], institutionalized residents of long-term care facilities [21] and spinal-cord injured subjects [22] did not reduce the rate of symptomatic UTIs. Recently, a prospective randomized study that included more than 600 sexually active premenopausal women with recurrent symptomatic UTIs documented that treatment of asymptomatic bacteriuria is not only unnecessary but also possibly counterproductive, as it resulted in a statistically significantly higher incidence of symptomatic episodes during the 1-year follow-up [23].

These clinical findings may be correlated with molecular studies that have highlighted the role of host-pathogen interactions in the urinary tract. In immunocompetent patients, many fitness and virulence factors are now well described in pathogens such as E. coli [24], including fimbriae, toxins, flagella and nutrient acquisition factors such as iron and zinc uptake systems. These microbial phenotypes partly explain the clinical difference observed between asymptomatic bacteriuria and symptomatic UTI, with low-virulence strains typically associated with asymptomatic events. Even if only a few studies have evaluated the role of virulence factors in kidney transplant recipients, Rice et al. showed that E. coli isolates expressing P-fimbriae were significantly associated with renal allograft injury [25]. Lastly, asymptomatic bacteriuria could even prevent symptomatic episodes by a process called bacterial interference [26], by which non-pathogenic bacterial strains compete with disease-causing microorganisms.

What is the present clinical practice among renal transplant physicians faced with asymptomatic bacteriuria? As immunosuppressive agents can mask clinical signs of UTI and as kidney graft pain can be absent in the denervated graft, most physicians treat asymptomatic bacteriuria with antibiotics. However, in 2005, the IDSA decided not to issue a recommendation on this topic because of a lack of evidence [12]. Likewise, in view of the lack of robust evidence in the field, the 2009 Kidney Disease: improving Global Outcomes (KDIGO) Clinical Practice Guideline on the Monitoring, Management and Treatment of Kidney Transplant Recipients did not make any recommendation concerning asymptomatic bacteriuria neither [27]. Along the same line, the American Society of Transplantation Infectious Diseases Community of Practice advised avoiding treating asymptomatic bacteriuria that occurs beyond 3 months post-transplant, unless there is an associated rise in creatinine [11].

It is therefore welcome that three prospective studies that compare antibiotics to no treatment in kidney transplant recipients with asymptomatic bacteriuria are currently underway [28–30]. The results of these trials are eagerly awaited as they will likely provide important data for the management of this common problem.

In conclusion, asymptomatic bacteriuria is common in kidney transplant patients, and ongoing randomized trials may help to better understand its meaning, and possibly redefine the approach to screening and antimicrobial treatment in this population.

**AUTHORS’ CONTRIBUTIONS**

J.C. and D.A. equally contributed in the writing of the manuscript.

**ACKNOWLEDGEMENTS**

We thank Dr Michel Abramowicz and Dr James Anstey for their expert reading of the article.

**CONFLICT OF INTEREST STATEMENT**

None declared.
REFERENCES